STUDY PROTOCOL

A Phase 3, Multicenter, Expanded Access Study of Ibalizumab Plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected With Multi-Drug Resistant (MDR) HIV-1

PROTOCOL NUMBER: TMB-311
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Proprietary Notice:	This document contains mainly unpublished data and is the sole property of TaiMed Biologics, Inc. Therefore, it is provided to you in strict confidence as an investigator, potential investigator, or consultant. The information may be reviewed by you, your staff, and your institutional review board/independent ethics committee. It is understood that this information will not be disclosed to others without written authorization from TaiMed Biologics, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.
Ethics Statement:	The study will be completed according to the International Conference on Harmonisation guidelines E6(R1): 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 patients 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).

Table of Contents

Appendices

Appendices to this protocol are presented in a separate document titled:
"Appendices to Protocol TMB-311: A Phase 3, Single Arm, Multicenter, Expanded Access Study of Ibalizumab Plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected With Multi-Drug Resistant (MDR) HIV-1"

The Appendices include the following:

Appendix A: CDC Classification System for HIV Infection

Appendix B: Division of AIDS: Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, November 2014

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

PROTOCOL SUMMARY

Protocol Number:	TMB-311
Title:	A Phase 3, Multicenter, Expanded Access Study of Ibalizumab Plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected With Multi-Drug-Resistant (MDR) HIV-1
Sponsor:	TaiMed Biologics, Inc. 2 Executive Circle, Suite 280 Irvine, CA 92614
Study Phase:	3
Patients and Investigator Sites:	Anticipated enrollment is approximately 100 patients from approximately 40 sites in North America and the European Union; however, the numbers of participating patients will not be limited and may exceed 100 and the number of sites will not be limited and may exceed 40.
Study Drug Dosage and Route of Administration:	The investigational product, ibalizumab, is a humanized IgG4 monoclonal antibody (MAb) administered via intravenous infusion (IV). Patients will be enrolled in one of two Cohorts (Cohort 1 and Cohort 2). Cohort 1 patients will continue their current dosage of ibalizumab (800 mg every 2 weeks or 2,000 mg every 4 weeks). Cohort 2 patients will receive a 2,000 mg loading dose at Baseline/Day 0 followed by 800 mg maintenance doses every 2 weeks. All patients will receive an OBR, which is a standard-of-care regimen selected by the investigator based on treatment history and the results of viral resistance testing.
Control Drug, Dosage, and Route of Administration:	None
Objectives:	The primary objectives of this study are to: Cohort 1 ■ Continue to provide ibalizumab to patients currently receiving ibalizumab treatment under Investigator-sponsored INDs or TaiMed-sponsored protocols ■ Demonstrate the safety and tolerability of ibalizumab in human immunodeficiency virus (HIV)-positive patients with MDR HIV infection Cohort 2 ■ Provide access to ibalizumab for qualifying MDR HIV-1-infected patients with limited treatment options ■ Demonstrate the safety and tolerability of ibalizumab in HIV-

	positive patients with MDR HIV infection The secondary objectives of this study are to: ■ Demonstrate the antiviral activity of ibalizumab in HIV-positive patients with MDR HIV infection ■ Characterize HIV-1 sensitivity/susceptibility changes associated with protocol-defined virologic failure after ibalizumab administration in combination with the OBR ■ Determine the presence and significance of anti-ibalizumab antibodies associated with protocol-defined virologic failure after ibalizumab administration, if any (immunogenicity of ibalizumab)
Patient Population: ***Inclusion Criteria***	Patients will be enrolled in one of two Cohorts (Cohort 1 and Cohort 2) Patients may be enrolled in Cohort 1 if they meet both of the following criteria: 1. Are currently receiving ibalizumab via other TaiMed-sponsored or Investigator-sponsored IND protocol 2. Are capable of understanding and have voluntarily signed the informed consent document Patients may be enrolled in Cohort 2 if they meet all of the following criteria: 1. Are 18 years of age or older 2. Are capable of understanding and have voluntarily signed the informed consent document 3. Have documented HIV-1 infection by official, signed, written history (e.g., laboratory report); otherwise, an HIV-antibody test will be performed 4. Are able and willing to comply with all protocol requirements and procedures 5. Have a viral load >1,000 copies/mL and documented resistance to at least one antiretroviral medication from each of three classes of antiretroviral medications as measured by previous viral resistance testing (resistance testing is not provided by the study for qualification purposes) 6. Have a history of at least 6 months on antiretroviral treatment 7. Are receiving a failing antiretroviral regimen OR have failed and are off therapy

	8. Have viral sensitivity/susceptibility to at least one antiretroviral agent other than ibalizumab, as determined by a previous resistance test performed within 6 months of Screening, and be willing and able to be treated with at least one agent to which the patient's viral isolate is fully sensitive/susceptible according to the Screening resistance tests as a component of the OBR 9. If sexually active, are willing to use an effective method of contraception during the study and for 30 days after the last administration of the study drug
Patient Population: ***Exclusion Criteria***	There are no Exclusion Criteria for patients meeting the Inclusion Criteria for Cohort 1. For Cohort 2, patients having or meeting any of the following conditions or characteristics will be excluded from the study: 1. Eligible for participation in other TaiMed Biologics-sponsored clinical trials of ibalizumab 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 patient from participating in the study 3. Any significant acute illness within 1 week before the first administration of investigational medication on the study 4. Any active infection secondary to HIV requiring acute therapy; however, patients who 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 4 weeks before Day 0 6. Any prior exposure to ibalizumab (formerly TNX-355 and Hu5A8) 7. Any vaccination within 7 days before Day 0 8. Any female patient who is pregnant, intends to become pregnant, or is currently breastfeeding 9. Any current alcohol or illicit drug use that, in the investigator's opinion, will interfere with the patient's ability to comply with the study schedule and protocol evaluations 10. Any previous clinically significant allergy or hypersensitivity to any excipient in the ibalizumab formulation 11. Any radiation therapy during the 28 days before first administration of investigational medication on this study

	12. Any clinically significant 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
Study Design:	This Phase 3, multicenter, expanded access study will evaluate the safety and tolerability of ibalizumab in treatment-experienced patients infected with MDR HIV-1. Patients will be enrolled in one of two Cohorts (Cohort 1 and Cohort 2): Cohort 1 (continuing treatment) ■ Patients will continue on an ibalizumab-containing regimen at their current dosage in combination with a current OBR. Cohort 2 (initiating ibalizumab) ■ On Day 0 patients will receive one 2,000 mg dose (loading dose) of ibalizumab. An OBR that is selected based on resistance test results and antiretroviral history will be initiated on Day 0 and must include at least one agent to which the patient's virus is susceptible. ■ Beginning at Day 14, 800 mg of ibalizumab will be administered every 2 weeks through the remainder of the study. Virologic failure is defined as two consecutive measurements beginning at Week 24 or later if less than a 0.5 $\log_{10}$ decline in viral load from Baseline viral load. Patients may be discontinued from the study: ▪ At the patient's or investigator's request ▪ If the patient becomes pregnant ▪ For protocol violation ▪ For experiencing virologic failure ▪ For treatment-related serious or intolerable adverse events (AEs) (DAIDS criteria, see Appendix B) ▪ For toxicity (defined as two consecutive laboratory results, at least 14 days apart, with a $CD4^+$ cell count below 200 cells/mm^3 that also represents a 50% reduction from the baseline $CD4^+$ cell count) ▪ Upon commercial availability of ibalizumab

Safety and Effectiveness Assessments:	Primary safety and effectiveness variables: Cohort 1 and Cohort 2 ■ Safety and tolerability of ibalizumab as assessed by AEs and Discontinuations Cohort 2 only ■ Proportion of patients achieving a ≥0.5 log_{10} decrease from Baseline in viral load at Day 7 Secondary safety and effectiveness variables: Cohort 1 and Cohort 2 ■ HIV-1 sensitivity/susceptibility changes associated with virologic failure after administration of ibalizumab Cohort 2 only ■ Proportion of patients with HIV-1 RNA levels <50 copies/mL and <400 copies/mL at assessment time points ■ Mean change from Baseline in viral load at Day 7 and all assessment time points ■ Proportion of patients achieving a ≥0.5 log_{10} and ≥1.0 log_{10} decrease from Baseline in viral load at all assessment time points
Safety Assessments:	Safety assessments will include the following: ■ Physical examinations ■ Vital sign measurements ■ Clinical laboratory parameters (hematology, serum chemistry, and urinalysis) ■ Monitoring of AEs and concomitant medications ■ Incidence of Class C events as defined by the CDC Classification System for HIV Infection (Appendix A) ■ Anti-ibalizumab antibody levels (immunogenicity of ibalizumab)

Statistical Considerations:	**Sample Size:** A sample size of approximately 100 patients is anticipated to be enrolled, though the number of participating patients will not be limited and may exceed 100. 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. **Effectiveness:** (Cohort 2 only) The primary effectiveness endpoint of the study is the proportion of patients achieving a ≥ 0.5 $\log_{10}$ decrease from Baseline in viral load at Day 7. **Safety Analyses:** The safety analyses will include descriptions of treatment-emergent AEs (TEAEs), Class C events per the CDC Classification System for HIV Infection, clinical laboratory test results, physical examination findings, vital sign results, and immunogenicity of ibalizumab.

ABBREVIATIONS

ABBREVIATION	TERM
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
CD4	glycoprotein expressed on the surface of T-helper cells
$CD4^+$	type of white blood cell, also called T-lymphocytes, T-cells, or T-helper cells
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CRF	case report form
CT	computed tomography
DAIDS	Division of AIDS
DSMB	data and safety monitoring board
EC	ethics committee
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
HAART	highly active antiretroviral therapy
HHS	Department of Health and Human Services
HIV-1	human immunodeficiency virus type-1
HTE	heterogeneous treatment effect
ICH	International Conference on Harmonisation
ID	identification
IND	Investigational New Drug
IRB	institutional review board
ITT	intention-to-treat
IV	intravenous
LLOQ	lower limit of quantitation
MAb	monoclonal antibody
MDR	multi-drug resistant
MEdDRA	Medical Dictionary for Regulatory Activities
MEF	missing equals failure
MESF	molecules of equivalent soluble fluorescence
mITT	modified intention-to-treat
Mu5A8	murine progenitor of ibalizumab
OBR	optimized background regimen
PK	pharmacokinetics
q2wk	every 2 weeks
q4wk	every 4 weeks
QOL	quality of life
RNA	ribonucleic acid
SAE	serious adverse event
SAF	safety dataset for analysis

ABBREVIATION	TERM
SD	standard deviation
TEAE	treatment-emergent adverse event
TFDA	Taiwan Food and Drug Administration
US	United States
USP	United States Pharmacopoeia
WHODD	WHO Drug Dictionary

1. Introduction

1.1 Background

Antiretroviral medications for treatment of human immunodeficiency virus (HIV) have evolved tremendously over recent years. Efficacy and tolerability have improved as well as the convenience of treatment regimens. The percentage of patients on treatment who maintain viral suppression approaches 75%-80%.[1,2] Unfortunately, some patients harbor strains of HIV that are resistant to currently available therapies. Patients with multi-drug resistant (MDR) HIV have limited or no treatment options. Department of Health and Human Services (HHS) HIV treatment guidelines encourage these patients to seek clinical trials and expanded access programs.[3]

TaiMed Biologics is currently developing ibalizumab for treatment of HIV. Ibalizumab is a monoclonal antibody that binds to a conformational epitope on domain 2 of the extracellular portion of the CD4 receptor. Ibalizumab binding reduces HIV replication by inhibiting viral entry into $CD4^+$ T-cells. With this novel mechanism of action, ibalizumab has no known cross-resistance with other antiretroviral medications. Ibalizumab in combination with other antiretroviral medications has demonstrated safety and durable antiviral activity in clinical trials in HIV-1-infected, treatment-experienced patients with MDR HIV. Ibalizumab has been awarded Orphan Drug and Breakthrough Drug designations by the US Food and Drug Administration (FDA). Still, the clinical trial and regulatory approval process can take several years to complete; some patients who are in urgent need of treatment cannot wait for ibalizumab to secure approval. An expanded access to clinical trial is needed to provide potentially life-saving access for patients with MDR HIV and limited or no available treatment options.

1.2 Clinical Studies

Prior studies have been conducted in HIV-positive individuals using the IV formulation of ibalizumab, and are summarized here. In addition, a study of ibalizumab administered subcutaneously (TMB-108) to HIV-negative at-risk volunteers has been completed. Another study (TMB-121) exploring both subcutaneous and intramuscular administration routes in both HIV-negative and HIV-positive participants is ongoing.

Results from the Phase 1a clinical trial (Hu5A8.01) demonstrated that IV administration of a single dose of ibalizumab to HIV-infected patients 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 (TNX-355.02), ibalizumab was given to HIV-infected patients as a single agent (monotherapy) or added to failing highly active antiretroviral therapy (HAART). Multiple doses of ibalizumab 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 (TNX-355.03) evaluated the safety, efficacy, and pharmacokinetics (PK) activity of two ibalizumab dose regimens (10 mg/kg and 15 mg/kg) in combination with an optimized background regimen (OBR) versus placebo with an OBR in treatment-experienced patients. As in the Phase 1 program, the Phase 2a study clearly demonstrated the antiviral activity of ibalizumab. Viral load reductions in the treatment arms were statistically significantly different from placebo, with approximately 1 $\log_{10}$ reductions seen in the ibalizumab-containing arms at 24 weeks (primary endpoint) and 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 ibalizumab 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 patients. When compared to placebo (Phase 2a) the incidences, spectrum, and intensity of AEs were similar between the active treatment arms and the placebo arm. While a statistically significant difference in incidence was not 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 monoclonal antibody (MAb) medications.[4] The administration of ibalizumab was not associated with immunosuppression, as evidenced by the lack of any increase in infections or malignancies in the study population treated with ibalizumab. Intradermal skin tests performed on a subset of patients were also similar between active treatment arms and placebo. Anti-ibalizumab antibodies have been detected transiently and at low titers in a small number of patients (2.4%). The observation of anti-ibalizumab antibody activity was not associated with any AEs and appeared to have no impact on antiviral efficacy. The significance of anti-ibalizumab antibodies is not known.

A Phase 2b clinical trial in 113 HIV-infected patients was also completed. Heavily treatment-experienced patients enrolled in this study received IV doses of 800 mg of ibalizumab every 2 weeks (q2wk) or 2,000 mg every 4 weeks (q4wk) in combination with an OBR. The key primary efficacy endpoint was the proportion of patients with HIV-1 ribonucleic acid (RNA) levels below the assay limit (<50 copies/mL) at Week 24. The percentages of patients with <50 copies/mL at Week 24 were 44% and 28% for the 800 mg q2wk arm and the 2,000 mg q4wk arm respectively, in the most stringent intention-to-treat (ITT) missing equals failure (MEF) analysis. Other noteworthy efficacy endpoints included mean change from Baseline in HIV-1 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 2,000 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 2,000 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 2,000 mg q4wk arms in viral load outcomes at 24 weeks.

Similar to previous studies, ibalizumab in combination with the 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 patients, 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 patients 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 patients 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 2,000 mg q4wk dose demonstrated safety and efficacy in this treatment-experienced HIV-positive patient population.

A subcutaneous formulation of ibalizumab has been developed and an initial Phase 1 clinical trial (TMB-108) conducted. TMB-108 was a randomized, placebo-controlled, double-blind, multi-dose sequential escalating dose study. The dosing cohorts were 120 mg, 240 mg, and 480 mg each given weekly. Each subject received weekly doses of ibalizumab subcutaneously for 4 weeks. Subjects who withdrew prior to completion of dosing for non-safety-related reasons were replaced.

No SAEs and no discontinuations due to AEs were reported on the protocol. No Grade 4 AEs were reported. One Grade 3 AE, "headache," was reported. This AE was treated with over-the-counter medications and resolved within one day of onset. Headache was also the most frequently reported AE, with all other reports of headache being mild to moderate in intensity. In addition to headache, AEs reported in more than one patient were cough, sinus/nasal congestion, and pruritis. No injection site reactions were reported. Taken together, the reported results of completed clinical studies suggest that ibalizumab is safe and has potent activity against HIV in humans.

The phase 3 registrational study (TMB-301) was a single arm, multicenter study, conducted in 40 treatment-experienced HIV-infected patients with multi-drug resistant HIV-1. Patients were treated with antiretrovirals for at least 6 months and were failing or had recently failed (i.e., in the last 8 weeks) therapy to determine baseline viral load with documented HIV viral load of >1,000 copies/mL.

During Days 0 through 6, "the control period", patients were monitored on current failing background regimen (or no therapy, if the patient had failed and discontinued treatment within the 8 weeks preceding Screening). During Days 7 through 13, "the essential monotherapy period", patients continued on current failing therapy and received one 2000 mg dose (loading dose) of ibalizumab on Day 7. Day 7 was Baseline for the treatment period (Day 7-Week 25). On Day 14, viral load was assessed for the primary end point, thereafter the background regimen was optimized to include at least one agent to which the patient's virus was susceptible. Beginning at Day 21, 800 mg of ibalizumab was administered every 2 weeks through Week 23, the "maintenance period". Thirty-one patients completed the Week 25/ End of Study Visit. The primary effectiveness endpoint was the proportion of patients achieving a ≥0.5 log10 decrease in viral load from Day 0 to Day 7 and from Day 7 to Day 14.

At Baseline, median viral load and CD4+ T cell counts were 4.55 log10 copies/mL (35,350 copies/mL) and 73 cells/mm3, respectively. Baseline Overall Susceptibility Scores (OSS) was were 0, 1, 2, or ≥2, for X (X13%), XX (X35%), XXX (X45%), and 3% of patients, for 0, 1, and ≥2, respectively.

In the ITT population, a statistically significant difference was observed between the proportion of patients achieving a 0.5 log10 decrease in viral load from Day 0 to Day 7 (Control period; 2.5%; 95% CI: 0.0006, 0.1316) and compared with the proportion achieving a 0.5 log10 decrease from Day 7 to Day 14 after receiving a 2000 mg loading dose of ibalizumab (82.5%; 95% CI: 0.6722,

0.9266; p<0.0001). Sixty Fifty five percent of patients achieved ≥1.0 log10 reduction in viral load after receiving the 2000 mg loading dose, during the essential monotherapy period (Day 7 to Day 14), and 55%after receiving the 2000 mg loading dose. maintained a ≥1.0 log10 reduction in viral load after receiving the and 800 mg q wk dose at once weekly through Week 25, during the maintenance period. during the essential monotherapy period (Day 7 to Day 14). The mean change in viral load from Baseline to Day 14 was a 1.07 log 10 reduction and to Week 25 was a 1.64 log 10 reduction at Day 14 was a 1.07 log10 reduction.

An increase in the mean number of CD4+ T-cells of 63 cell/μL was observed from Baseline to Week 25. This increase in CD4+ T-cells is indicative of the therapeutic effect over 24 weeks.
At Week 25 after treatment with the 800 mg a 2wk maintenance dose, the mean change in viral load from Day 7 was 1.6 log10 reduction with 55% and 48% of patients having a ≥1 log10 and ≥2 log10 reduction, respectively. Viral load <50 and <200 HIV-1 RNA copies/mL was reached in 43% and 50% of patients, respectively.

The most common adverse reactions (all Grades) reported in at least 5% of subjects were diarrhea, dizziness, nausea, and rash. Table 1 shows the frequency of adverse reactions occurring in 5% or more of subjects.

Table 1. Adverse Reactions (All Grades) Reported in ≥5% of Subjects Receiving ibalizumab and Optimized Background Regimen for 23 Weeks in Trial TMB-301

	Percent of All TMB-301 Subjects (N=40) n (%)
Diarrhea	3 (8%)
Dizziness	3 (8%)
Nausea	2 (5%)
Rash*	2 (5%)

*Includes pooled terms "rash", "rash erythematous", "rash generalized", "rash macular", "rash maculopapular", and "rash papular"

Most (90%) of the adverse reactions reported were mild or moderate in severity. Two subjects experienced severe adverse reactions: one subject had a severe rash and one subject developed immune reconstitution inflammatory syndrome manifested as an exacerbation of progressive multifocal leukoencephalopathy.

Laboratory Abnormalities

Table 2. Selected Laboratory Abnormalities (≥Grade 3) in Trial TMB-301

	% Subjects N=40
Bilirubin (≥ 2.6 x ULN)	5%
Direct Bilirubin (> ULN)	3%
Creatinine (>1.8x ULN or 1.5x baseline)	10%
Blood Glucose (> 250 mg/dL)	3%
Lipase (>3.0 x ULN)	5%
Uric Acid (>12 mg/dL)	3%
Hemoglobin (< 8.5 g/dL)	3%
Platelets (< 50,000/mm^3)	3%
Leukocytes (< 1.5 10^9 cells/L)	5%
Neutrophils (<0.6 10^9 cells/L)	5%

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ibalizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. All subjects enrolled in clinical trial TMB-301 and trial TMB-202 (a Phase 2b clinical trial that studied ibalizumab administered intravenously as 2,000 mg every 4 weeks or 800 mg every 2 weeks; the safety and effectiveness of this dosing regimen has not been established), were tested for the presence of anti-ibalizumab IgG antibodies throughout their participation. One sample tested positive with low titer anti-ibalizumab antibodies. No adverse reaction or reduced efficacy was attributed to the positive sample reported in this subject.

1.3 Pharmacokinetic Profile

IV administration of escalating single doses of ibalizumab (Protocol Hu5A8.01) demonstrated that serum concentrations of ibalizumab generally peaked at the end of the infusion period. Ibalizumab PKs were dose-dependent, as both systemic exposure and elimination half-life increased disproportionately with increasing dose. This indicated that the elimination of ibalizumab is capacity limited and saturable at higher doses. A similar conclusion was reached after a multiple-dose study of IV ibalizumab (Protocol 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 ibalizumab relative to endogenous IgG4 molecules. In the IV ibalizumab studies conducted to date, there was a correlation between ibalizumab 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. Similar observations were made after subcutaneous administration of ibalizumab in HIV-negative volunteers, in which dose-dependent systemic exposure indicated saturable elimination with the same correlation between serum concentrations and CD4 receptor occupancy. A new study (TMB-121) of parenterally administered ibalizumab (subcutaneous and intramuscular) has been initiated to evaluate viral load responses in HIV-infected patients.

2. Study Objectives

2.1 Primary Objectives

The primary objectives of this study are to:

Cohort 1

- Continue to provide ibalizumab to patients currently receiving ibalizumab treatment under Investigator-sponsored IND or TaiMed-sponsored protocols
- Demonstrate the safety and tolerability of ibalizumab in HIV-positive patients with MDR HIV infection

Cohort 2

- Provide access to ibalizumab for qualifying MDR HIV-1-infected patients with limited treatment options
- Demonstrate the safety and tolerability of ibalizumab in HIV-positive patients with MDR HIV infection

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Demonstrate the antiviral activity of ibalizumab in HIV-positive patients with MDR HIV infection
- Characterize HIV-1 sensitivity/susceptibility changes associated with protocol-defined virologic failure after ibalizumab administration in combination with the OBR
- Determine the presence and significance of anti-ibalizumab antibodies associated with protocol-defined virologic failure after ibalizumab administration, if any (immunogenicity of ibalizumab)

3. Study Plan

3.1 Overall Design

This Phase 3, multicenter, expanded access study will evaluate the safety and tolerability of ibalizumab in treatment-experienced patients infected with MDR HIV-1. Eligible patients will include (1) those currently receiving ibalizumab under a TaiMed-sponsored or Investigator-sponsored IND protocol and (2) treatment-experienced patients with no history of ibalizumab treatment who are on a failing regimen, or who have failed and are off treatment.

Patients will be enrolled in one of two Cohorts (Cohort 1 and Cohort 2):

Cohort 1 (continuing treatment)

- Patients will continue on an ibalizumab containing regimen at their current dosage in combination with a current OBR.

Cohort 2 (initiating ibalizumab)

- On Day 0/Baseline, patients will receive one 2,000 mg dose (loading dose) of ibalizumab. The OBR will be initiated on Day 0/Baseline and must include at least one agent to which the patient's virus is susceptible.

- Beginning at Day 14, an 800 mg of ibalizumab will be administered every 2 weeks through the remainder of the study.

Virologic failure is defined as two consecutive measurements at Week 24 or later if less than a 0.5 $\log_{10}$ decline from the Baseline viral load (see Section 9.4 for the definition of Baseline).

Patients will be discontinued from the study at the patient's request or if the patient becomes pregnant, at investigator request, for protocol violation, for virologic failure, for treatment-related serious or intolerable AE(s) (Division of AIDS [DAIDS] criteria, see Appendix B), or for toxicity (defined as two consecutive laboratory results, at least 14 days apart, with a $CD4^+$ cell count below 200 cells/mm^3 that also represents a 50% reduction from the Baseline $CD4^+$ cell count).

3.2 Discussion of Trial Design

This study is designed to assess the safety and tolerability of IV ibalizumab. In addition, all patients will receive a standard of care OBR consisting of antiretroviral medications selected by the Principal Investigator based upon the patient's treatment history and the results of viral resistance testing. The effectiveness of the treatment regimen will also be assessed (Cohort 2 only). Safety and tolerability will be evaluated by the occurrence of AEs and discontinuations. The primary evaluation of effectiveness will be at Day 7. Additional secondary evaluations will be conducted at Day 7 and other assessment time points.

This is an open-label safety study to provide early access to IV ibalizumab for HIV-1-infected patients who have no or limited treatment options on commercially available antiretroviral therapy (ART) and who are ineligible for participation in any other TaiMed Biologics-sponsored trial of ibalizumab. The safety and tolerability of IV ibalizumab in combination with an OBR in MDR HIV-1-infected patients with limited or no treatment options will be assessed. Eligible patients already approved for Investigator-sponsored ibalizumab INDs (Cohort 1) will remain on Investigator-sponsored INDs until they can be transitioned to this protocol. Upon enrollment, patients will continue to receive treatment with the previously assigned regimen: either ibalizumab 800 mg IV every 2 weeks with an OBR, or ibalizumab 2,000 mg IV every 4 weeks with an OBR. Treatment will continue until treatment-limiting toxicity, virologic failure, loss to follow-up, withdrawal from the trial, pregnancy, discontinuation of ibalizumab development, or commercial availability of ibalizumab.

Eligible patients participating in TaiMed Protocol TMB-301 (who will enroll in Cohort 1 of this study) will continue to receive treatment with ibalizumab 800 mg IV every 2 weeks with an OBR while enrolled in this study. Treatment will continue until treatment-limiting toxicity, virologic failure, loss to follow-up, withdrawal from the trial, pregnancy, discontinuation of ibalizumab development, or commercial availability of ibalizumab.

Eligible patients who are not participating in an Investigator-sponsored or TaiMed-sponsored ibalizumab IND (Cohort 2 of this study) will undergo a Screening period of, at most, 6 weeks. Patients will start treatment with ibalizumab 2,000 mg IV (loading) on Day 0 and then 800 mg IV (maintenance) on Day 14 and every 2 weeks thereafter. All patients will also receive an OBR beginning at Day 0. Treatment will continue until treatment-limiting toxicity, virologic failure, loss to

follow-up, withdrawal from the trial, pregnancy, discontinuation of ibalizumab development, or commercial availability of ibalizumab.

3.3 Dose Selection

Both dosages of IV ibalizumab (2,000 mg every 4 weeks and 800 mg every 2 weeks) were evaluated in the TMB-202 Phase 2b study. The results of that study indicated that higher serum concentrations and maximum receptor occupancy were achieved more rapidly with the 2,000 mg dose. Conversely, a higher percentage of patients on the 800 mg dose administered every 2 weeks achieved and maintained HIV RNA levels below 50 copies at Week 24 compared to patients on the 2,000 mg dose administered every 4 weeks. This observation may have been associated with the trend toward higher trough concentrations observed with the 800 mg dose. As the AE profile of both dosages was similar, the dosage regimen selected for Cohort 2 (patients initiating ibalizumab) in this study reflects the optimal PK features of each dose studied in TMB-202: A single 2,000 mg loading dose will be followed by 800 mg maintenance doses administered every 2 weeks. This dose regimen is designed to combine the maximal initial drug exposure of a 2,000 mg dosage with the more durable exposure of the 800 mg q2week dosage. Cohort 1 patients (continuing treatment) will continue on their current successful dosing regimens.

3.4 Schedule of Events

The Schedule of Events is presented in Tables 3-1 and 3-2 for Cohort 1 patients receiving ibalizumab 800 mg every 2 weeks, in Tables 3-3 and 3-4 for Cohort 1 patients receiving ibalizumab 2,000 mg every 4 weeks, and in Tables 3-5 and 3-6 for patients in Cohort 2. Throughout the study, patients are not required to fast before collection of blood samples for safety or effectiveness. However, patients should adhere to dietary recommendations as suggested for the components of their OBR or other concomitant medications.

Table 3-1. Schedule of Events: Cohort 1 – 800 mg every 2 weeks, Screening through Week 4

	Study Visit		
	Screening/ Day 0	Day 14	Week 4
Visit window (days)	N/A	±1	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION			
Discuss the inclusion/exclusion criteria	X		
Obtain a signed informed consent form	X		
Record demographics, medical history (general and HIV), height	X		
Record all prior ART exposure; record all other medications within the last 30 days	X		
Assess adherence to the OBR			X
Record results of a complete physical examination	X		
Record vital sign measurements	X	X	X
Record the patient's weight	X		
Record AEs	X[4]	X	X
Record concomitant medications		X	X
BLOOD [1] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION			
Hepatitis serology, C-reactive protein	X		
Hematology, serum chemistry, urinalysis (see Section 7.2.2)	X		
Archive sample	X		
Serum for pregnancy test for females of childbearing potential [2]	X		
Urine for pregnancy test for females of childbearing potential			X
HIV-1 RNA (viral load)	X		
HIV-1 viral resistance sample [3]	X		
$CD4^+$ T-cell count [5]	X		
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [5]	X		
STUDY DRUG ADMINISTRATION AND AFTER			
Administer study medication	X	X	X
Record vital sign measurements and observe (15 min.) after infusion	X	X	X
Record AEs	X	X	X

[1] Patients need not fast before blood sampling.

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

[3] Viral resistance testing will include assessments of reverse transcriptase, protease, integrase, and envelope (entry) genes and chemokine coreceptor utilization; the samples will be collected and stored, and testing will only be performed for patients who experience virologic failure while on the study.

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

[5] Samples to be drawn within 1 hour before the start of the infusion (if infusion is scheduled for that visit).

Abbreviations: AE = adverse event; ART = antiretroviral therapy; $CD4^+$ = helper T-cell; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; OBR = optimized background regimen

Table 3-2. Schedule of Events: Cohort 1 – 800 mg every 2 weeks, Week 6 through end of study

Week	Study Visit										
	6	8	10	12	14	16	18	20	22	24	26
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION											
Record results of a complete physical examination										X	
Record results of an abbreviated physical examination [1]				X							
Record the patient's weight				X						X	
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X
Record AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR		X		X						X	
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION											
Hepatitis serology, C-reactive protein										X	
Hematology, serum chemistry, urinalysis (see Section 7.2.2)				X						X	
Archive sample				X						X	
Serum for pregnancy test for females of childbearing potential										X	
Urine for pregnancy test for females of childbearing potential		X		X		X		X			
HIV-1 RNA (viral load)				X						X	
HIV-1 viral resistance sample [3]				X						X	
$CD4^+$ T-cell count [4]				X						X	
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]										X	
STUDY DRUG ADMINISTRATION AND AFTER											
Administer study medication	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs and observe (15 min.) after infusion	X	X	X	X	X	X	X	X	X	X	X

Table 3-2. Schedule of Events: Cohort 1 – 800 mg every 2 weeks, Week 6 through end of study (Continued)

Week	Study Visit												
	28	30	32	34	36	38	40	42	44	46	48	50	52
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION													
Record results of a complete physical examination											X		
Record results of an abbreviated physical examination [1]					X								
Record the patient's weight					X						X		
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	X
Records AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR					X						X		
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION													
Hepatitis serology, C-reactive protein											X		
Hematology, serum chemistry, urinalysis (see Section 7.2.2)					X						X		
Archive sample					X						X		
Serum for pregnancy test for females of childbearing potential											X		
Urine for pregnancy test for females of childbearing potential	X		X		X		X		X				X
HIV-1 RNA (viral load)					X						X		
HIV-1 viral resistance sample [3]					X						X		
$CD4^+$ T-cell count [4]					X						X		
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]											X		
STUDY DRUG ADMINISTRATION AND AFTER													
Administer study medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs and observe (15 min.) after infusion	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3-2. Schedule of Events: Cohort 1 – 800 mg every 2 weeks, Week 6 through end of study (Continued)

Week	Study Visit												
	54	56	58	60	62	64	66	68	70	72	74	76	78
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION													
Record results of a complete physical examination										X			
Record results of an abbreviated physical examination [1]				X									
Record the patient's weight				X						X			
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	X
Records AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR				X						X			
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION													
Hepatitis serology, C-reactive protein													
Hematology, serum chemistry, urinalysis (see Section 7.2.2)				X						X			
Archive sample				X						X			
Serum for pregnancy test for females of childbearing potential										X			
Urine for pregnancy test for females of childbearing potential		X		X		X		X				X	
HIV-1 RNA (viral load)				X						X			
HIV-1 viral resistance sample [3]				X						X			
$CD4^+$ T-cell count [4]				X						X			
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]										X			
STUDY DRUG ADMINISTRATION AND AFTER													
Administer study medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs and observe (15 min.) after infusion	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3-2. Schedule of Events: Cohort 1 – 800 mg every 2 weeks, Week 6 through end of study (Continued)

Week	Study Visit												
	80	82	84	86	88	90	92	94	96	98	100	102	104
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION													
Record results of a complete physical examination									X				
Record results of an abbreviated physical examination [1]													
Record the patient's weight									X				
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	X
Records AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR			X						X				
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION													
Hepatitis serology, C-reactive protein									X				
Hematology, serum chemistry, urinalysis (see Section 7.2.2)									X				
Archive sample									X				
Serum for pregnancy test for females of childbearing potential									X				
Urine for pregnancy test for females of childbearing potential	X		X		X		X				X		X
HIV-1 RNA (viral load)									X				
HIV-1 viral resistance sample [3]									X				
$CD4^+$ T-cell count [4]									X				
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]									X				
STUDY DRUG ADMINISTRATION AND AFTER													
Administer study medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs and observe (15 min.) after infusion	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3-2. Schedule of Events: Cohort 1 – 800 mg every 2 weeks, Week 6 through end of study (Continued)

Week	Study Visit												
	106	108	110	112	114	116	118	120	122	124	126	128	130
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION													
Record results of a complete physical examination								X					
Record results of an abbreviated physical examination [1]													
Record the patient's weight								X					
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	X
Records AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR		X						X					
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION													
Hepatitis serology, C-reactive protein													
Hematology, serum chemistry, urinalysis (see Section 7.2.2)								X					
Archive sample								X					
Serum for pregnancy test for females of childbearing potential													
Urine for pregnancy test for females of childbearing potential		X		X		X		X		X		X	
HIV-1 RNA (viral load)		X						X					
HIV-1 viral resistance sample [3]		X						X					
$CD4^+$ T-cell count [4]		X						X					
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]								X					
STUDY DRUG ADMINISTRATION AND AFTER													
Administer study medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs and observe (15 min.) after infusion	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3-2. Schedule of Events: Cohort 1 – 800 mg every 2 weeks, Week 6 through end of study (Continued)

Week	Study Visit								
	132	134	136	138	140	142	144/ EOS	150/ Follow up	Early Withdrawal[5]
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION									
Record results of a complete physical examination							X	X	X
Record results of an abbreviated physical examination [1]									
Record the patient's weight							X	X	X
Record vital sign measurements	X	X	X	X	X	X	X	X	X
Records AEs and concomitant medications	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR	X						X	X	X
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION									
Hepatitis serology, C-reactive protein								X	X
Hematology, serum chemistry, urinalysis (see Section 7.2.2)								X	X
Archive sample							X	X	X
Serum for pregnancy test for females of childbearing potential									X
Urine for pregnancy test for females of childbearing potential	X		X		X		X	X	
HIV-1 RNA (viral load)	X						X	X	X
HIV-1 viral resistance sample [3]	X						X	X	X
$CD4^+$ T-cell count [4]	X						X	X	X
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]							X	X	X
STUDY DRUG ADMINISTRATION AND AFTER									
Administer study medication	X	X	X	X	X	X	X		
Record vital sign measurements and AEs and observe (15 min.) after infusion	X	X	X	X	X	X	X		

[1] Abbreviated physical examination will include an examination of lymph nodes, respiratory and cardiovascular systems, abdomen, extremities, and nervous system.

[2] Patients need not fast before blood sampling.

[3] Viral resistance testing will include assessments of reverse transcriptase, protease, integrase, and envelope (entry) genes and chemokine coreceptor utilization; the samples will be collected and stored, and testing will only be performed for patients who experience virologic failure while on the study.

[4] Samples to be drawn within 1 hour before the start of the infusion (if infusion is scheduled for that visit).

[5] Patients who withdraw or are withdrawn at any time prior to the Week 150 visit should have Early Withdrawal procedures performed.

Abbreviations: AE = adverse event; ART = antiretroviral therapy; $CD4^+$ = helper T-cell; EOS = end of study; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; OBR = optimized background regimen

Table 3-3. Schedule of Events: Cohort 1 – 2,000 mg every 4 weeks, Screening through Week 8

	Study Visit		
	Screening/ Day 0	Week 4	Week 8
Visit window (days)	N/A	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION			
Discuss the inclusion/exclusion criteria	X		
Obtain a signed informed consent form	X		
Record demographics, medical history (general and HIV), height	X		
Record all prior ART exposure; record all other medications within the last 30 days	X		
Assess adherence to the OBR		X	X
Record results of a complete physical examination	X		
Record vital sign measurements	X	X	X
Record the patient's weight	X		
Record AEs	X	X	X
Record concomitant medications		X	X
BLOOD [1] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION			
Hepatitis serology, C-reactive protein	X		
Hematology, serum chemistry, urinalysis (see Section 7.2.2)	X		
Archive sample	X		
Serum for pregnancy test for females of childbearing potential [2]	X		
Urine for pregnancy test for females of childbearing potential		X	X
HIV-1 RNA (viral load)	X		
HIV-1 viral resistance sample [3]	X		
$CD4^+$ T-cell count [4]	X		
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]	X		
STUDY DRUG ADMINISTRATION AND AFTER			
Administer study medication	X	X	X
Record vital sign measurements and observe (15 min.) after infusion	X	X	X
Record AEs	X	X	X

[1] Patients need not fast before blood sampling.

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

[3] Viral resistance testing will include assessments of reverse transcriptase, protease, integrase, and envelope (entry) genes and chemokine coreceptor utilization; the samples will be collected and stored, and testing will only be performed for patients who experience virologic failure while on the study.

[4] Samples to be drawn within 1 hour before the start of the infusion (if infusion is scheduled for that visit).

Abbreviations: AE = adverse event; ART = antiretroviral therapy; $CD4^+$ = helper T-cell; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; OBR = optimized background regimen

Table 3-4. Schedule of Events: Cohort 1 – 2,000 mg every 4 weeks, Week 12 through end of study

Week	Study Visit											
	12	16	20	24	28	32	36	40	44	48	52	56
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION												
Record results of a complete physical examination				X						X		
Record results of an abbreviated physical examination [1]	X						X					
Record the patient's weight	X			X			X			X		
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR	X			X			X			X		
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION												
Hepatitis serology, C-reactive protein				X						X		
Hematology, serum chemistry, urinalysis (see Section 7.2.2)	X			X			X			X		
Archive sample	X			X			X			X		
Serum for pregnancy test for females of childbearing potential				X						X		
Urine for pregnancy test for females of childbearing potential	X	X	X		X	X	X	X	X		X	X
HIV-1 RNA (viral load)	X			X			X			X		
HIV-1 viral resistance sample [3]	X			X			X			X		
$CD4^+$ T-cell count [4]	X			X			X			X		
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]				X						X		
STUDY DRUG ADMINISTRATION AND AFTER												
Administer study medication	X	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs and observe (15 min.) after infusion	X	X	X	X	X	X	X	X	X	X	X	X

Table 3-4. Schedule of Events: Cohort 1 – 2,000 mg every 4 weeks, Week 12 through end of study (Continued)

Week	Study Visit											
	60	64	68	72	76	80	84	88	92	96	100	104
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION												
Record results of a complete physical examination				X						X		
Record results of an abbreviated physical examination [1]	X											
Record the patient's weight	X			X						X		
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR	X			X			X			X		
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION												
Hepatitis serology, C-reactive protein				X						X		
Hematology, serum chemistry, urinalysis (see Section 7.2.2)	X			X						X		
Archive sample	X			X						X		
Serum for pregnancy test for females of childbearing potential				X						X		
Urine for pregnancy test for females of childbearing potential	X	X	X		X	X	X	X	X		X	X
HIV-1 RNA (viral load)	X			X						X		
HIV-1 viral resistance sample [3]	X			X						X		
$CD4^+$ T-cell count [4]	X			X						X		
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]				X						X		
STUDY DRUG ADMINISTRATION AND AFTER												
Administer study medication	X	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs and observe (15 min.) after infusion	X	X	X	X	X	X	X	X	X	X	X	X

Table 3-4. Schedule of Events: Cohort 1 – 2,000 mg every 4 weeks, Week 12 through end of study (Continued)

Week	Study Visit											
	108	112	116	120	124	128	132	136	140	144 EOS	150 Follow up	Early Withdrawal[5]
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION												
Record results of a complete physical examination				X						X	X	X
Record results of an abbreviated physical examination [1]												
Record the patient's weight				X						X	X	X
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR	X			X			X			X	X	X
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION												
Hepatitis serology, C-reactive protein											X	X
Hematology, serum chemistry, urinalysis (see Section 7.2.2)				X							X	X
Archive sample				X						X	X	X
Serum for pregnancy test for females of childbearing potential												X
Urine for pregnancy test for females of childbearing potential	X	X	X	X	X	X	X	X	X	X	X	
HIV-1 RNA (viral load)	X			X			X			X	X	X
HIV-1 viral resistance sample [3]	X			X			X			X	X	X
$CD4^+$ T-cell count [4]	X			X			X			X	X	X
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]				X						X	X	X
STUDY DRUG ADMINISTRATION AND AFTER												
Administer study medication	X	X	X	X	X	X	X	X	X	X		
Record vital sign measurements and AEs and observe (15 min.) after infusion	X	X	X	X	X	X	X	X	X	X		

[1] Abbreviated physical examination will include an examination of lymph nodes, respiratory and cardiovascular systems, abdomen, extremities, and nervous system.

[2] Patients need not fast before blood sampling.

[3] Viral resistance testing will include assessments of reverse transcriptase, protease, integrase, and envelope (entry) genes and chemokine coreceptor utilization; the samples will be collected and stored, and testing will only be performed for patients who experience virologic failure while on the study.

[4] Samples to be drawn within 1 hour before the start of the infusion (if infusion is scheduled for that visit).

[5] Patients who withdraw or are withdrawn at any time prior to the Week 150 visit should have Early Withdrawal procedures performed.

Abbreviations: AE = adverse event; ART = antiretroviral therapy; $CD4^+$ = helper T-cell; EOS = end of study; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; OBR = optimized background regimen

Table 3-5. Schedule of Events: Cohort 2, Screening through Day 14

	Screening	Study Visit		
	Weeks -6 to -1	Day 0 Baseline	Day 7	Day 14
Visit window (days)	N/A	N/A	±1	±1
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION				
Discuss the inclusion/exclusion criteria	X			
Obtain a signed informed consent form	X			
Record demographics, medical history (general and HIV), height	X			
Record all prior ART exposure or changes to ART; record all other medications within the last 30 days[1]	X	X		
Obtain documentation of HIV-1 infection [2]	X			
Obtain documentation of viral resistance, if available (within 6 months of Screening); select OBR	X			
Initiate the selected OBR		X		
Assess adherence to the OBR			X	
Record results of a complete physical examination	X	X		
Record results of an abbreviated physical examination [3]			X	
Record vital sign measurements	X	X	X	X
Record the patient's weight	X	X		
Record AEs	X[4]	X [4]	X	X
Record concomitant medications			X	X
BLOOD [5] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION				
Hepatitis serology, C-reactive protein	X			
Hematology, serum chemistry, urinalysis (see Section 7.2.2)	X	X	X	
Archive sample		X	X	
Serum for pregnancy test for females of childbearing potential [6]	X			
Urine for pregnancy test for females of childbearing potential		X		
HIV-1 RNA (viral load)	X	X	X	X
HIV-1 antibody level, if written documentation not provided	X			
HIV-1 viral resistance sample [7]	X	X	X	X
$CD4^+$ T-cell count [8]	X	X	X	X
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [8]		X		

Table 3-5. Schedule of Events: Cohort 2, Screening through Day 14 (Continued)

	Screening		Study Visit	
	Weeks -6 to -1	Day 0 Baseline	Day 7	Day 14
STUDY DRUG ADMINISTRATION AND AFTER				
Administer study medication [9]		X		X
Record vital sign measurements after infusion[10]		X		X
Record AEs		X		X

[1] All prior ART will be recorded at Screening; Day 0 visit will only record changes to ART.

[2] An HIV antibody test will be completed at Screening if official, signed, written documentation is unavailable.

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

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

[5] Patients need not fast before blood sampling.

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

[7] Viral resistance testing will include assessments of reverse transcriptase, protease, integrase, and envelope (entry) genes and chemokine coreceptor utilization; the samples will be collected and stored, and testing will only be performed for patients who experience virologic failure while on the study.

[8] Samples to be drawn within 1 hour before the start of the infusion (if infusion is scheduled for that visit).

[9] All patients in Cohort 2 must be observed for 1 hour after the completion of study drug administration. If the patient does not experience an AE(s) related to the infusion (local or systemic) through and including the second infusion on Day 14, then the observation time can be reduced to 15 minutes thereafter.

[10] Record vital signs after infusion (if infusion is completed at that visit).

Abbreviations: AE = adverse event; ART = antiretroviral therapy; $CD4^+$ = helper T-cell; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; OBR = optimized background regimen

Table 3-6. Schedule of Events: Cohort 2, Week 4 through end of study

Week	Study Visit											
	4	6	8	10	12	14	16	18	20	22	24	26
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION												
Record results of a complete physical examination	X										X	
Record results of an abbreviated physical examination [1]					X				X			
Record the patient's weight	**X**				X				X		X	
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR	X		X		X				X		X	
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION												
Hepatitis serology, C-reactive protein											X	
Hematology, serum chemistry, urinalysis (see Section 7.2.2)					X						X	
Archive sample					X						X	
Serum for pregnancy test for females of childbearing potential											X	
Urine for pregnancy test for females of childbearing potential	X		X		X		X		X			
HIV-1 RNA (viral load)	X	X	X		X		X		X		X	
HIV-1 viral resistance sample [3]	X	X	X		X		X		X		X	
$CD4^+$ T-cell count [4]	X	X s	X		X		X		X		X	
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]											X	
STUDY DRUG ADMINISTRATION AND AFTER												
Administer study medication [5]	X	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs after infusion	X	X	X	X	X	X	X	X	X	X	X	X

Table 3-6. Schedule of Events: Cohort 2, Week 4 through end of study (Continued)

Week	Study Visit												
	28	30	32	34	36	38	40	42	44	46	48	50	52
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION													
Record results of a complete physical examination											X		
Record results of an abbreviated physical examination [1]			X				X						
Record the patient's weight			**X**		X		X				X		
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	X
Records AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR			X				X				X		
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION													
Hepatitis serology, C-reactive protein											X		
Hematology, serum chemistry, urinalysis (see Section 7.2.2)	X				X						X		
Archive sample	X				X						X		
Serum for pregnancy test for females of childbearing potential											X		
Urine for pregnancy test for females of childbearing potential	X		X		X		X		X				X
HIV-1 RNA (viral load)	X				X						X		
HIV-1 viral resistance sample [3]	X				X						X		
$CD4^+$ T-cell count [4]	X				X						X		
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]											X		
STUDY DRUG ADMINISTRATION AND AFTER													
Administer study medication [5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs after infusion	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3-6. Schedule of Events: Cohort 2, Week 4 through end of study (Continued)

Week	Study Visit												
	54	56	58	60	62	64	66	68	70	72	74	76	78
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION													
Record results of a complete physical examination										X			
Record results of an abbreviated physical examination [1]				X									
Record the patient's weight				X						X			
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	X
Records AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR				X						X			
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION													
Hepatitis serology, C-reactive protein													
Hematology, serum chemistry, urinalysis (see Section 7.2.2)				X						X			
Archive sample				X						X			
Serum for pregnancy test for females of childbearing potential										X			
Urine for pregnancy test for females of childbearing potential		X		X		X		X				X	
HIV-1 RNA (viral load)				X						X			
HIV-1 viral resistance sample [3]				X						X			
$CD4^+$ T-cell count [4]				X						X			
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]										X			
STUDY DRUG ADMINISTRATION AND AFTER													
Administer study medication [5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs after infusion	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3-6. Schedule of Events: Cohort 2, Week 4 through end of study (Continued)

Week	Study Visit												
	80	82	84	86	88	90	92	94	96	98	100	102	104
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION													
Record results of a complete physical examination									X				
Record results of an abbreviated physical examination [1]			X										
Record the patient's weight			X						X				
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	X
Records AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR			X						X				
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION													
Hepatitis serology, C-reactive protein									X				
Hematology, serum chemistry, urinalysis (see Section 7.2.2)			X						X				
Archive sample			X						X				
Serum for pregnancy test for females of childbearing potential									X				
Urine for pregnancy test for females of childbearing potential	X		X		X		X				X		X
HIV-1 RNA (viral load)			X						X				
HIV-1 viral resistance sample [3]			X						X				
$CD4^+$ T-cell count [4]			X						X				
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]									X				
STUDY DRUG ADMINISTRATION AND AFTER													
Administer study medication [5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs after infusion	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3-6. Schedule of Events: Cohort 2, Week 4 through end of study (Continued)

Week	Study Visit												
	106	108	110	112	114	116	118	120	122	124	126	128	130
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION													
Record results of a complete physical examination								X					
Record results of an abbreviated physical examination [1]													
Record the patient's weight								X					
Record vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	X
Records AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR		X						X					
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION													
Hepatitis serology, C-reactive protein													
Hematology, serum chemistry, urinalysis (see Section 7.2.2)								X					
Archive sample								X					
Serum for pregnancy test for females of childbearing potential													
Urine for pregnancy test for females of childbearing potential		X		X		X		X		X		X	
HIV-1 RNA (viral load)		X						X					
HIV-1 viral resistance sample [3]		X						X					
$CD4^+$ T-cell count [4]		X						X					
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]								X					
STUDY DRUG ADMINISTRATION AND AFTER													
Administer study medication [5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Record vital sign measurements and AEs after infusion	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3-6. Schedule of Events: Cohort 2, Week 4 through end of study (Continued)

Week	Study Visit								
	132	134	136	138	140	142	144/ EOS	150/ Follow up	Early Withdrawal[6]
Visit window (days)	±2	±2	±2	±2	±2	±2	±2	±2	
ACTIVITIES TO BE COMPLETED BEFORE STUDY DRUG ADMINISTRATION									
Record results of a complete physical examination							X	X	X
Record results of an abbreviated physical examination [1]									
Record the patient's weight							X	X	X
Record vital sign measurements	X	X	X	X	X	X	X	X	X
Records AEs and concomitant medications	X	X	X	X	X	X	X	X	X
Assess adherence to the OBR	X						X	X	X
BLOOD [2] AND/OR URINE SAMPLES TO BE COLLECTED BEFORE STUDY DRUG ADMINISTRATION									
Hepatitis serology, C-reactive protein								X	X
Hematology, serum chemistry, urinalysis (see Section 7.2.2)								X	X
Archive sample							X	X	X
Serum for pregnancy test for females of childbearing potential									X
Urine for pregnancy test for females of childbearing potential	X		X		X		X	X	
HIV-1 RNA (viral load)	X						X	X	X
HIV-1 viral resistance sample [3]	X						X	X	X
$CD4^+$ T-cell count [4]	X						X	X	X
Immunogenicity of ibalizumab (2 tubes x 3 mL each) [4]							X	X	X
STUDY DRUG ADMINISTRATION AND AFTER									
Administer study medication [5]	X	X	X	X	X	X	X		
Record vital sign measurements and AEs after infusion	X	X	X	X	X	X	X		

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

[2] Patients need not fast before blood sampling.

[3] Viral resistance testing will include assessments of reverse transcriptase, protease, integrase, and envelope (entry) genes and chemokine coreceptor utilization; the samples will be collected and stored, and testing will only be performed for patients who experience virologic failure while on the study.

[4] Samples are to be drawn within 1 hour before the start of the infusion (if infusion is scheduled for that visit).

[5] All patients in Cohort 2 must be observed for 1 hour after the completion of study drug administration. If the patient does not experience an AE(s) related to the infusion (local or systemic) through and including the second infusion on Day 14, then the observation time can be reduced to 15 minutes thereafter.

[6] Patients who withdraw or are withdrawn at any time prior to the Week 102 visit should have Early Withdrawal procedures performed.

Abbreviations: AE = adverse event; ART = antiretroviral therapy; $CD4^+$ = helper T-cell; EOS = end of study; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; OBR = optimized background regimen

3.5 Effectiveness Assessments

The primary effectiveness variable is the proportion of patients achieving a ≥0.5 $\log_{10}$ decrease from Baseline in viral load at Day 7 (assessed for Cohort 2 only).

Secondary effectiveness variables will be the following:

- Proportion of patients with HIV-1 RNA levels <50 copies/mL and <400 copies/mL at assessment time points (assessed for Cohort 2 only)
- Mean change from Baseline in viral load at Day 7 and all assessment time points (assessed for Cohort 2 only)
- Proportion of patients achieving a ≥0.5 $\log_{10}$ and ≥1.0 $\log_{10}$ decrease from Baseline in viral load at all assessment time points (assessed for Cohort 2 only)
- HIV-1 sensitivity/susceptibility changes associated with virologic failure after administration of ibalizumab

3.6 Safety Assessments

Safety assessments will include the results of the following measurements throughout the study:

- Physical examinations
- Vital sign measurements
- Clinical laboratory parameters (hematology, serum chemistry, and urinalysis)
- Monitoring of AEs and concomitant medications
- Incidence of Class C events as defined by the Centers for Disease Control and Prevention (CDC) Classification System for HIV Infection (Appendix A)
- Anti-ibalizumab antibody levels (immunogenicity of ibalizumab)

4. Study Treatments

4.1 Study Drug Dosage and Administration

There are two different ibalizumab IV drug product vial configurations available for use in this study:

Current Drug Lots In Use
(1) vials with a 1.33 mL injection volume and 200 mg ibalizumab per vial (Lots 201509019 and 201505012).

Patients receiving ibalizumab in study TMB-301, who will enroll into Cohort 1 of this study, and patients initiating ibalizumab in Cohort 2 will receive only vials with a 1.33 mL injection volume and 200 mg ibalizumab per vial.

Previous Drug Lot that is Depleted
(2) vials with a 1.2 mL injection volume and 180 mg ibalizumab per vial (Lot 201403001. This information is provided only in the event that Cohort 1 sites, with patients who were previously under Investigator sponsored IND protocols, may still have this lot in their inventory).

All ibalizumab drug product to be used in this study will be at a concentration of 150 mg/mL.

4.1.1 Cohort 1

Patients in Cohort 1 will continue receiving ibalizumab via IV infusion at the currently assigned dosage: either 800 mg q2wk or 2,000 mg q4wk.

(Lots 201509019 and 201505012)
For patients enrolling into this study from study TMB-301, study drug will be provided in open-labeled cartons of 10 vials at 1.33 mL/200 mg each. For the 800 mg q2wk doses, 4 vials are to be

used. Using a sterile syringe, 1.33 mL is withdrawn from each of the vials to be used and injected into a 250 mL infusion bag of normal saline. Administration of the prepared infusion should begin no more than 6 hours after the time of preparation.

(Lot 201403001)
Until the supply of drug product currently allocated for use in Cohort 1 patients enrolling from Investigator-sponsored INDs is exhausted, study drugs for these patients will continue to be provided in open-labeled cartons containing 10 vials at 1.2 mL/180 mg each.

- For the 2,000 mg q4wk doses (adjusted to 2,010 mg for this vial configuration), 13.4 mL total volume of ibalizumab drug product is required for each administration.
- For the 800 mg q2wk doses (adjusted to 810 mg for this vial configuration), 5.4 mL total volume of ibalizumab drug product is required for each administration.

Using a sterile syringe, the required content is withdrawn from each of the vials to be used and injected into a 250 mL infusion bag of normal saline. Administration of the prepared infusion should begin no more than 6 hours after the time of preparation.

When the 1.2 mL, 180 mg/vial drug product is exhausted, patients enrolled in Cohort 1 from Investigator-sponsored INDs will be switched to the 1.33 mL, 200 mg/vial drug product. Study drug will then be provided in open-labeled cartons of 10 vials at 1.33 mL/200 mg each.

- For the 2,000 mg q4wk doses, all 10 vials in a carton are to be used.
- For the 800 mg q2wk doses, 4 vials are to be used.

Using a sterile syringe, 1.33 mL is withdrawn from each of the vials to be used and injected into a 250 mL infusion bag of normal saline. Administration of the prepared infusion should begin no more than 6 hours after the time of preparation.

4.1.2 Cohort 2

(Lots 201509019 and 201505012)
Study drug will be administered via IV infusion at a dose of 2,000 mg on one occasion (Day 0/Baseline), followed 2 weeks later (Day 14) by doses of 800 mg administered once every 2 weeks through the remainder of the study.

Study drug will be provided in open-labeled cartons of 10 vials each.

- For the 2,000 mg doses, all 10 vials in a carton are to be used.
- For the 800 mg doses, four vials are to be used.

Using a sterile syringe, 1.33 mL is withdrawn from each of the vials to be used and injected into a 250 mL infusion bag of normal saline. Administration of the prepared infusion should begin no more than 6 hours after the time of preparation.

4.1.3 Administration

The infusion should be administered in the cephalic vein of the patient's right or left arm. If this vein is not accessible, an appropriate vein located elsewhere can be used. For patients initiating ibalizumab in Cohort 2, the duration of the infusion should be no less than 30 minutes during the first two study drug administrations. If no infusion-associated AEs have occurred after two administrations, the duration of the infusion can be decreased to no less than 15 minutes.

The start and stop times of each infusion will be recorded in an Electronic Data Capture (EDC) system, along with the site of administration. The date of use and the patient's study identification (ID) number and initials will be recorded.

All Cohort 2 patients must be observed for 1 hour after completion of study drug administration for at least the first two administrations (Day 0/Baseline and Day 14). If the patient does not experience an AE(s) related to the infusion (local or systemic) during the first two infusions, then the post-infusion observation time can be reduced to 15 minutes thereafter.

In addition to the study drug, all patients will receive an OBR, which is a standard-of-care regimen selected by the investigator based upon treatment history and the results of recent viral resistance testing. For patients enrolling into Cohort 2, previous resistance testing done within 6 months prior to Screening must demonstrate that the patient's viral isolate is sensitive/susceptible to a minimum of one of the agents selected for the OBR. As part of the OBR, the patient must be willing and able to take at least one of the agents to which their virus is sensitive/susceptible.

4.2 Prohibited Medications and Restrictions

Use of and changes in concomitant medications will be recorded in the patient's source documents and the 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 in Section 4.4.2 for Cohort 2 patients, 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 patient in the EDC system. Complete information is expected for any medication prescribed during the trial.

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

For patients enrolled into Cohort 2 only, the following medications are not to be administered concomitantly:

- Therapeutic HIV vaccines from Screening until study participation ends
- Any vaccines during the 7 days before Day 0/Baseline through Day 14 of the study
- All investigational drugs from 30 days before Day 0/Baseline and throughout the study (except investigational antiretroviral medications as a component of the OBR)

In addition, radiation therapy is not allowed for patients in Cohort 2 from 28 days before first administration of study drug to the last administration of study drug. Patients receiving radiation therapy are not allowed to enter Cohort 2 of the study; however, if a patient in Cohort 2 develops a condition that requires radiation but does not disqualify them from study participation for any other reason, then this event would need to be discussed with the medical monitor.

First-dose, generalized, self-limiting skin rash has been described with therapeutic MAbs.[5,6] Re-challenge in such an event is at the discretion of the investigator. While there is no recommendation for premedication with diphenhydramine, acetaminophen, or corticosteroids, these medications have been used prior to the administration of other MAbs.[7] Any patient who experiences anaphylactoid symptoms that are considered to be related to the study drug (possibly, probably, definitely) must have study drug discontinued and be withdrawn from the study immediately. Severe post-infusion reaction management typically includes corticosteroids, oxygen, and IV fluids, based on the severity and symptoms.[7] 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).

4.3 Measurement of Patient Adherence

Patient adherence will require the availability of the patient at the study site to receive the dose and the patient's willingness/ability to receive the entire dose. The receipt of the entire dose is assured, as each dose is given as an IV infusion by a trained professional from the clinical site and the event is recorded. Adherence to the OBR will also be recorded.

4.4 Missed Doses of Study Drug

4.4.1 Cohort 1

Patients should receive study drug per the Schedule of Events (Section 3.4). A missed dose is defined as any dose of study drug that is not administered within the study visit window. Patients who miss doses of study medication for two consecutive dosing intervals (i.e., >28 days without a study drug infusion) of 800 mg dosage or one and one-half dosing intervals (i.e., >42 days without a study drug infusion) of the 2,000 mg dose may be withdrawn from the study.

Missed Doses. If a dose is missed, the missed dose should be administered at the first opportunity. If an 800 mg dose is missed and cannot be administered at least 3 days before the next scheduled dose, it should be skipped. If a 2,000 mg dose is missed and cannot be administered at least 5 days before the next scheduled dose, it should be skipped.

End of study (EOS) procedures should be performed as soon as possible after the patient qualifies for withdrawal due to missed doses. Patients who are withdrawn from the study for missed doses may not be permitted to participate in other ibalizumab protocols.

4.4.2 Cohort 2

Patients should receive study drug per the Schedule of Events (Section 3.4). A missed dose is defined as any dose of study drug that is not administered within the study visit window. Patients who miss doses of study medication for two consecutive dosing intervals (i.e., >28 days without a study drug infusion) or miss greater than two doses cumulatively will be withdrawn from the study. EOS procedures should be performed as soon as possible after the patient qualifies for withdrawal due to missed doses. Patients who are withdrawn from the study for missed doses may not be permitted to participate in other ibalizumab protocols.

Missed Initial (Loading) Dose. If the initial 2,000 mg dose (loading dose) of study drug is administered outside the treatment window, the dose should be administered at the first available opportunity and the timing of subsequent doses should be adjusted to coincide with the actual administration time of the first dose.

Missed Maintenance Dose (3-7 days). If a dose of 800 mg (maintenance dose) of study drug is missed by going beyond the scheduled dosing day by 3-7 days, a loading dose of 2,000 mg (reload) should be administered at the next available opportunity. The reload dose would substitute for the maintenance dose that was missed. All other visit procedures would not change other than the dose amount administered (i.e., 2,000 mg reload dose substituted for 800 mg maintenance dose). The scheduling of subsequent visits will not be adjusted.

Example: If a patient is scheduled to receive study drug on Day 49 (Week 7) but cannot come in until Day 55, the patient should receive a 2,000 mg loading dose (reload) on Day 55. The subsequent dose should be 800 mg and scheduled for Day 63 (Week 9) (±2 day window). The patient should continue on the original visit schedule.

Missed Maintenance Dose (>7 days and <14 days). If a dose of 800 mg (maintenance dose) of study drug is missed by going beyond the scheduled dosing day by more than 7 days but less than 14 days, the patient should receive a 2,000 mg dose (reload) at the next available opportunity. The missed dose should be recorded as a missed dose/missed visit. A 2,000 mg reload dose administered between >7 days and <14 days beyond the scheduled dosing date will not substitute for the missed dose. The 2,000 mg reload dose will substitute for the next scheduled 800 mg maintenance dose. Study procedures for the visit subsequent to the missed dose/missed visit should be performed along with the administration of the 2,000 mg reload dose. The dosing schedule should be adjusted

such that the following 800 mg maintenance dose should be scheduled 2 weeks after the reload dose was administered. NOTE: Week 102/EOS procedures should be performed without regard to dose window whenever the visit occurs.

Example: If a patient is scheduled to receive study drug on Day 49 (Week 7) but cannot come in until Day 58, the patient should receive a 2,000 mg loading dose (reload) on Day 58. Study procedures for Day 49 (Week 7) are recorded as missed. Study procedures for Day 63 (Week 9) are performed along with the administration of the 2,000 mg reload dose. The dose following the reload dose should be 800mg and scheduled for Day 72 (±2 day window). The visit schedule would be adjusted to 800 mg every 2 weeks from the day the drug was actually administered.

No adjustments to dosage or dosing schedules are required for a missed dose that occurs before the dosing window. However, any dose administered before the dosing window is also considered a missed dose.

4.5 Study Drug Description

The Sponsor or designee will provide the Research Pharmacists at the sites with vials containing study drug (active ibalizumab) manufactured under current Good Manufacturing Practices (cGMP). Ibalizumab is provided as a parenteral formulation in a 2 mL, clear-glass vial. The drug product contains ibalizumab 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 either at least 1.2 mL of fluid delivering a total of 180 mg study drug per vial (Lot 201403001) or at least 1.33 mL of fluid delivering a total of 200 mg study drug per vial (Lots 201509019 and 201505012). Labeling will clearly identify the configuration of vials in each carton and of each individual vial.

4.6 Study Drug Packaging, Storage, and Disposal

Study drug is provided as a single-use parenteral formulation in a 2 mL, clear-glass vial containing either at least 1.2 mL (Lot 204103001) or at least 1.33 mL (Lots 201509019 and 201505012) of drug product. The stability of the ibalizumab drug product at 2ºC to 8ºC is evaluated in ongoing studies. Study drug will be shipped under refrigerated conditions with a temperature-monitoring device.

Ibalizumab vials should be stored refrigerated at 2°C to 8°C (but NOT FROZEN) and protected from light. Investigator sites must store the investigational product in a secure location and maintain a temperature log of the storage conditions.

The temperature must be continuously monitored with a continuous-monitoring temperature device. Temperature logs must be available for review at each site-monitoring visit. Temperature excursions outside the required limits should be reported promptly to the Sponsor, and the affected study drug should not be administered to any study patients until further instruction. The Sponsor or designee will investigate temperature excursions and adjudicate the disposition of any affected study drug.

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

4.7 Study Drug Accountability

The investigator will maintain accurate records of receipt of the entire supply of the study drug, including when, how much of, and conditions under which the study drug is received, dispensed, and destroyed by site personnel. In addition, the administration of study drug to each patient should be documented to the vial level for each infusion (i.e., lot number of every vial for that infusion, time of infusion bag preparation, time of administration, and documentation of full infusion received). Reasons for departure from the expected dispensing regimen must also be recorded. Drug accountability will be reviewed and documented at each study visit. Reconciliation and accountability of study drug will be done throughout the study during the monitoring visits. After the completion of the study, the Sponsor or designee may authorize the site to dispose of unused supplies of the investigational drug, provided this alternative disposition does not expose humans to risks from the drug. 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.

5. Patient Enrollment

It is anticipated that approximately 50 patients will be enrolled at approximately 50 sites in North America and Taiwan; however, the numbers of participating patients and sites will not be limited and may exceed 50. Patients will be enrolled only if they meet all of the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

Patients may be enrolled in Cohort 1 if they meet both of the following criteria:

1. Are currently receiving ibalizumab via other TaiMed-sponsored or Investigator-sponsored IND protocol
2. Are capable of understanding and have voluntarily signed the informed consent document

Patients may be enrolled in Cohort 2 if they meet all of the following criteria:

1. Are 18 years of age or older
2. Are capable of understanding and have voluntarily signed the informed consent document
3. Have documented HIV-1 infection by official, signed, written history (e.g., laboratory report); otherwise, an HIV-antibody test will be performed
4. Are able and willing to comply with all protocol requirements and procedures
5. Have a viral load >1,000 copies/mL and documented resistance to at least one antiretroviral medication from each of three classes of antiretroviral medications as measured by previous resistance testing (resistance testing is not provided by the study for qualification purposes)
6. Have a history of at least 6 months on antiretroviral treatment
7. Are receiving a failing antiretroviral regimen OR have failed and are off therapy
8. Have viral sensitivity/susceptibility to at least one antiretroviral agent other than ibalizumab, as determined by previous resistance test performed within 6 months prior to Screening and be willing and able to be treated with at least one agent to which the

patient's viral isolate is fully sensitive/susceptible according to the Screening resistance tests as a component of the OBR

9. If sexually active, are willing to use an effective method of contraception during the study and for 30 days after the last administration of the study drug

5.2 Exclusion Criteria

There are no Exclusion Criteria for patients meeting the Inclusion Criteria for Cohort 1.

For Cohort 2, patients having or meeting any of the following conditions or characteristics will be excluded from the study:

1. Eligible for participation in other TaiMed Biologics-sponsored clinical trials of ibalizumab
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 patient from participating in this study
3. Any significant acute illness within 1 week before the first administration of investigational medication on this study
4. Any active infection secondary to HIV requiring acute therapy; however, patients who 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 4 weeks before Day 0
6. Any prior exposure to ibalizumab (formerly TNX-355 and Hu5A8)
7. Any vaccination within 7 days before Day 0
8. Any female patient who is pregnant, intends to become pregnant, or is currently breastfeeding
9. Any current alcohol or illicit drug use that, in the investigator's opinion, will interfere with the patient's ability to comply with the study schedule and protocol evaluations
10. Any previous clinically significant allergy or hypersensitivity to any excipient in the ibalizumab formulation

11. Any radiation therapy during the 28 days before first administration of investigational medication on this study
12. Any clinically significant Grade 3 or 4 laboratory abnormality according to the DAIDS grading scale, except for the following asymptomatic Grade 3 events:
    - triglyceride elevation
    - total cholesterol elevation

5.3 Patient Withdrawal and Discontinuation

5.3.1 Reasons for Withdrawal

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

- Withdraws consent to participate or requests an early discontinuation at any time during the study
- Is in violation of the protocol
- Becomes pregnant during the study (see Section 8.7 for a description of procedures to be followed in case of pregnancy)
- Experiences virologic failure
- Experiences a treatment-related serious or intolerable AE(s) (according to DAIDS criteria, see Appendix B)
- Experiences toxicity, defined as two consecutive laboratory results, at least 14 days apart, with a $CD4^+$ cell count below 200 cells/mm^3 that also represents a 50% reduction from the baseline $CD4^+$ cell count

The study treatment should be discontinued for all Grade 3 or 4 treatment-related abnormalities, as defined in Appendix B. Treatment-emergent Grade 3 or Grade 4 lab abnormalities should be retested within 72 hours. Any patient with a Grade 3 or Grade 4 lab abnormality that resolves before the next scheduled dose may have the study drug reinstituted. If a patient develops a persistent Grade 3 or Grade 4 treatment-emergent laboratory abnormality, excluding triglycerides and cholesterol, that does not resolve prior to the next scheduled study drug administration, study drug may be discontinued.

A patient experiencing one or more treatment-emergent SAEs will receive treatment and follow-up evaluations by the Principal 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 Principal Investigator/Sponsor.

The investigator will also withdraw a patient if the Sponsor or local regulatory agency (e.g., FDA) terminates the study. Upon occurrence of an SAE, the Principal Investigator will notify the Sponsor or designee of these events via the SAE hotline. If a patient is discontinued because of an AE, the

event will be followed until satisfactory resolution or until the Principal Investigator deems the event to be chronic or the patient to be stable.

5.3.2 Handling Withdrawals and Discontinuations

Patients are free to withdraw from the study at any time upon request. Patient 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 patient.

When a patient withdraws or is discontinued from the study, the reason(s) for withdrawal or discontinuation will be recorded by the investigator. Whenever possible, all patients who withdraw, or are discontinued from the study prematurely, will undergo all Early Withdrawal procedures as described in the Schedule of Events in Section 3.4. Patients who fail to return for final assessments will be contacted by the site personnel in an attempt to have the patients 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 patient contact the site regarding their status in the study. If the patient 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 patient 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 patient withdrawn because of an AE or SAE. In such cases, the patient will be followed to satisfactory resolution or until the Principal Investigator deems the event to be chronic or the patient 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, upon commercial availability of ibalizumab, or if

required by the local regulatory authority (e.g., FDA). If the Sponsor discontinues the study, the FDA will be notified promptly.

6. Study Visits

6.1 Cohort 1: 800 mg Every 2 Weeks

Since there are no laboratory parameters required for entry into Cohort 1 of this study, Screening procedures and Day 0 procedures are scheduled for the same day. Patients who qualify for entry into Cohort 1 of this study who are currently receiving 800 mg ibalizumab every 2 weeks will have physical and laboratory measures performed and receive the first on-study dose of ibalizumab at Screening/Day 0 as specified in the Schedule of Events (see Table 3-1). These patients will return to the clinic on Day 14 and every 2 weeks thereafter through the remainder of participation in the study for study drug administration (800 mg) and effectiveness and safety evaluations. Patients who are discontinued or who withdraw from the study prematurely will be asked to return for an Early Withdrawal visit to have all assessments detailed in the Schedule of Events for that visit performed.

6.1.1 Screening/Day 0

Screening and Day 0 (first on-study administration of ibalizumab) are scheduled for the same day. At this visit, study information will be reviewed and discussed, and the informed consent form will be reviewed and signed by the participant. No procedures, other than a preliminary verbal assessment of eligibility by review of inclusion/exclusion criteria, may be done before the informed consent process is complete. Once informed consent has been obtained and documented, the following procedures may be completed (pre-infusion):

- Record demographics, medical history (general and HIV), and the patient's height
- Record all prior ART exposure; record all other medications taken within the last 30 days
- Record results of a complete physical examination
- Record vital sign measurements

- Record the patient's weight
- Record all AEs that begin after the patient has signed the informed consent (see Section 8.1 for definitions)
- Collect blood and urine for the following laboratory samples:
  - Hepatitis serology and C-reactive protein
  - Clinical laboratory assessments (serum chemistry, hematology, and urinalysis; see Section 7.2.2 for a complete list of parameters)
  - Archive sample
  - Serum pregnancy test in females of childbearing potential and a follicle-stimulating hormone (FSH) test in postmenopausal females
  - HIV-1 RNA (viral load)
  - HIV-1 viral resistance sample (will be stored for later use if needed)
  - $CD4^+$ cell count (within 1 hour before the start of the infusion)
  - Immunogenicity of ibalizumab

After the preceding procedures are completed, site personnel will undertake the following (infusion and post-infusion):

- Administer study medication (800 mg)
- Record vital sign measurements after the completion of the infusion and observe the patient for at least 15 minutes
- Record AEs

6.1.2 Events for Day 14 (±1 day) and Weeks 4, 6, 8, 10, 14, 16, 18, 20, 22, 26, 28, 30, 32, 34, 38, 40, 42, 44, 46, 50, 52, 54, 56, 58, 62, 64, 66, 68, 70, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 98, 100, 102, 104, 106, 110, 112, 114, 116, 118, 122, 124, 126, 128, 130, 134, 136, 138, 140, and 142 (±2 days)

The following will be completed before study drug administration:

- Record vital sign measurements
- Record AEs and concomitant medications
- Assess adherence to the OBR (Weeks 4, 8, and 84 only)
- Collect urine sample for the following:

  Urine pregnancy test for females of childbearing potential (Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 84, 88, 92, 100, 104, 112, 116, 124, 128, 136, and 140 only)

Site personnel will undertake the following after administration of study drug (800 mg):

- Record vital sign measurements after completion of infusion and observe patient for at least 15 minutes
- Record AEs

6.1.3 Events for Weeks 12, 24, 36, 48, 60, 72, 96, 108, 120, 132, 144/EOS and 150/Follow-up (±2 days)

The following will be completed before study drug administration:

- Record results of physical examination (complete exam at Weeks 24, 48, 72, 96, 120, 144, and 150; abbreviated exam at Weeks 12, 36, and 60)
- Record the patient's weight (Weeks 12, 24, 36, 48, 60, 72, 96, 120, 144 and 150 only)
- Record vital sign measurements

- Record AEs and concomitant medications
- Assess adherence to the OBR
- Collect blood and/or urine samples for the following:
  - Hepatitis serology and C-reactive protein (Weeks 24, 48, 96, and 150 only)
  - Clinical laboratory assessments (serum chemistry, hematology, and urinalysis; See Section 7.2.2 for a complete list of parameters) (Weeks 12, 24, 36, 48, 60, 72, 96, 120, and 150 only)
  - Archive sample (Weeks 12, 24, 36, 48, 60, 72, 96, 120, 144, and 150 only)
  - Pregnancy test for females of childbearing potential (urine at Weeks 12, 36, 60, 108, 120, 132, 144, and 150 only); serum at Weeks 24, 48, 72, and 96 only)
  - HIV-1 RNA (viral load)
  - HIV-1 viral resistance sample (will be stored for later use if needed)
  - $CD4^+$ cell count (within 1 hour before the start of the infusion)
  - Immunogenicity of ibalizumab (Weeks 24, 48, 72, 96, 120, 144, and 150 only).

Site personnel will undertake the following after administration of study drug (800 mg) (not done at Week 150/Follow-up):

- Record vital sign measurements after completion of infusion and observe patient for at least 15 minutes
- Record AEs

6.2 Cohort 1: 2,000 mg Every 4 Weeks

Since there are no laboratory parameters required for entry into Cohort 1 of this study, Screening procedures and Day 0 procedures are scheduled for the same day. Patients who qualify for entry into Cohort 1 of this study who are currently receiving 2,000 mg ibalizumab every 4 weeks will have physical and laboratory measures performed and will receive the first on-study dose of ibalizumab at Screening/Day 0, as specified in the Schedule of Events (see Table 3-3). These patients will return to the clinic at Week 4 and every 4 weeks thereafter through the remainder of participation in the study

for study drug administration (2,000 mg) and effectiveness and safety evaluations. Patients who are discontinued or who withdraw from the study prematurely will be asked to return for an Early Withdrawal visit to have all assessments detailed in the Schedule of Events for that visit performed.

6.2.1 Screening/Day 0

Screening and Day 0 (first on-study administration of ibalizumab) are scheduled for the same day. At this visit, study information will be reviewed and discussed, and the participant will review and sign the informed consent form. No procedures, other than a preliminary verbal assessment of eligibility by review of inclusion/exclusion criteria, may be done before the informed consent process is complete. Once informed consent has been obtained and documented, the following procedures may be completed (pre-infusion):

- Record demographics, medical history (general and HIV), and the patient's height
- Record all prior ART exposure; record all other medications taken within the last 30 days
- Record results of a complete physical examination
- Record vital sign measurements
- Record the patient's weight
- Record AEs that begin after the patient signs the informed consent (see Section 8.1 for definitions)
- Collect blood and urine for the following laboratory samples:
  - Hepatitis serology and C-reactive protein
  - Clinical laboratory assessments (serum chemistry, hematology, and urinalysis; see Section 7.2.2 for a complete list of parameters)
  - Archive sample
  - Serum pregnancy test in females of childbearing potential and an FSH test in postmenopausal females
  - HIV-1 RNA (viral load)
  - HIV-1 viral resistance sample (will be stored for later use if needed)

- $CD4^+$ cell count (within 1 hour before the start of the infusion)
- Immunogenicity of ibalizumab

After the preceding procedures are completed, site personnel will undertake the following (infusion and post-infusion):

- Administer study medication (2,000 mg)
- Record vital sign measurements after the completion of the infusion and observe the patient for at least 15 minutes
- Record AEs

6.2.2 Events for Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 84, 88, 92, 100, 104, 112, 116, 124, 128, 136, and 140 (±2 days)

The following will be completed before study drug administration:

- Assess adherence to the OBR (Weeks 4, 8, and 84 only)
- Record vital measurements
- Record AEs and concomitant medications
- Collect urine sample for the following:

  Urine pregnancy test for females of childbearing potential

Site personnel will undertake the following after administration of study drug (2,000 mg):

- Record vital sign measurements after completion of infusion and observe patient for at least 15 minutes
- Record AEs

6.2.3 Events for Weeks 12, 24, 36, 48, 60, 72, 96, 108, 120, 132, , 144/EOS, and 150/Follow-up (±2 days)

The following will be completed before study drug administration:

- Record results of physical examination (complete exam at Weeks 24, 48, 72, 96, 120, 144, and 150 only; abbreviated exam at Weeks 12, 36, and 60 only)
- Record the patient's weight (Weeks 12, 24, 36, 48, 60, 72, 96, 120, 144, and 150 only)
- Record vital sign measurements
- Record AEs and concomitant medications
- Assess adherence to the OBR
- Collect blood and/or urine samples for the following:
  - Hepatitis serology and C-reactive protein (Weeks 24, 48, 7296, and 150 only)

- Clinical laboratory assessments (serum chemistry, hematology, and urinalysis; See Section 7.2.2 for a complete list of parameters) (Weeks 12, 24, 36, 48, 60, 72, 96, 120, and 150 only)
- Archive sample (Weeks 12, 24, 36, 48, 60, 72, 96, 120, 144, and 150 only)
- Pregnancy test for females of childbearing potential (urine at Weeks 12, 36, 60, 108, 120, 132, 140, 144, and 150 only; serum at Weeks 24, 48, 72, and 96 only)
- HIV-1 RNA (viral load)
- HIV-1 viral resistance sample (will be stored for later use if needed)
- $CD4^+$ cell count (within 1 hour before the start of the infusion)
- Immunogenicity of ibalizumab (Weeks 24, 48, 72, 96, 120, 144, and 150 only)

Site personnel will undertake the following after administration of study drug (2,000 mg) (not done at Week 150/Follow-up):

- Record vital sign measurements after completion of infusion and observe patient for at least 15 minutes
- Record AEs

6.3 Cohort 2

Patients will complete all Screening procedures during the 6 weeks before Day 0/Baseline. Successful Screening results will allow the patients to proceed to the Day 0/Baseline visit, where they will initiate the selected OBR in addition to undergoing physical and laboratory measures as specified in the Schedule of Events (see Table 3-5). At this visit, patients will also receive the loading dose of the study medication (2,000 mg). Patients will return to the clinic on Day 7 for effectiveness and safety evaluations and on Day 14 and every 2 weeks thereafter through the remainder of participation in the study for study drug administration (800 mg) and effectiveness and safety evaluations. Patients who are discontinued or who withdraw from the study prematurely will be asked to return for an Early Withdrawal visit to complete all assessments for that visit, as detailed in the Schedule of Events.

6.3.1 Screening (Weeks -6 to -1)

Screening will begin up to 6 weeks before Day 0. During Screening, study information will be reviewed and discussed, and the participant will review and sign the informed consent form. No procedures, other than a preliminary verbal assessment of eligibility by review of inclusion/exclusion criteria, may be done before the informed consent process is complete. Once informed consent has been obtained and documented, the following Screening procedures may be completed:

- Record demographics, medical history (general and HIV), and the patient's height
- Record all prior ART exposure; record all other medications taken within the last 30 days
- Obtain documentation of HIV-1 infection; if official, signed, written documentation is unavailable, then collect a sample for HIV antibody testing as indicated below:
  - Obtain documentation of viral resistance, if available (within 6 months of Screening), and select an OBR
  - Record results of a complete physical examination
  - Record vital sign measurements
  - Record the patient's weight
  - Record only study-related AEs, which begin once the patient signs the informed consent (see Section 8.1 for definitions)
- Collect blood and urine for the following laboratory samples:
  - Hepatitis serology and C-reactive protein
  - Clinical laboratory assessments (serum chemistry, hematology, and urinalysis; see Section 7.2.2 for a complete list of parameters)
  - Serum pregnancy test in females of childbearing potential and an FSH test in postmenopausal females
  - HIV-1 RNA (viral load)
  - HIV-1 antibody level, if documentation of HIV-1 infection is not provided as indicated above
  - HIV-1 viral resistance sample (will be stored for later use if needed)

- $CD4^+$ cell count

If a patient fails Screening, they may be re-screened one time.

6.3.2 Day 0/Baseline

The Day 0/Baseline visit may take place at any point during the 4 weeks following the Screening Visit. At this visit, patients will receive the first study drug infusion: a loading dose of 2,000 mg. All patients must be observed for 1 hour after completion of study drug administration at Baseline. If the patient does not experience an AE(s) related to the infusion (local or systemic) through and including the second infusion on Day 14, then the observation time can be reduced to 15 minutes thereafter. Patients will return to the site every 2 weeks (±2 days) for the remainder of the study to receive additional study drug and for effectiveness and safety evaluations. At this visit, the following will be completed before study drug administration:

- Record any changes to ART; record all other medications taken within the 30 days before the baseline visit
- Record results of a complete physical examination
- Record vital sign measurements
- Record the patient's weight
- Record only study-related AEs
- Collect blood and urine samples for the following:
  - Clinical laboratory assessments (serum chemistry, hematology, and urinalysis; see Section 7.2.2 for a complete list of parameters)
  - Archive sample
  - Urine pregnancy test for females of childbearing potential
  - HIV-1 RNA (viral load)
  - HIV-1 viral resistance sample (will be stored for later use if needed)
  - $CD4^+$ cell count (within 1 hour before the start of the infusion)

- Immunogenicity of ibalizumab

The patient will also initiate the selected OBR on this day, either at home or in the clinic with site personnel supervision.

After the preceding procedures are completed, site personnel will undertake the following (infusion and post-infusion):

- Administer loading dose of study medication (2,000 mg)
- Record vital sign measurements after the completion of the infusion and observe the patient for at least 1 hour
- Record all AEs

6.3.3 Events for Day 7 (±1 day)

Day 7 serves as the time point at which the antiviral activity of ibalizumab will be assessed to address the primary effectiveness objective of the study.

Site personnel will undertake the following:

- Assess adherence to the OBR
- Record results of abbreviated physical examination
- Record vital sign measurements, AEs, and concomitant medications
- Collect blood and urine samples for the following:
  - Clinical laboratory assessments (serum chemistry, hematology, and urinalysis; see Section 7.2.2 for a complete list of parameters)
  - Archive sample
  - HIV-1 RNA (viral load)
  - HIV-1 viral resistance sample (will be stored for later use if needed)
  - $CD4^+$ cell count

6.3.4 Events for Day 14 (±1 day), and Weeks 4, 6, 8, 10, 14, 16, 18, 20, 22, 26, 30, 32, 34, 38, 40, 42, 44, 46, 50, 52, 54, 56, 58, 62, 64, 66, 68, 70, 74, 76, 78, 80, 82, 86, 88, 90, 92, 94, 98, 100, 102, 104, 106, 110, 112, 114, 116, 118, 122, 124, 126, 128, 130, 134, 136, 138, 140, and 142 (±2 days)

The following will be completed before study drug administration:

- Record results of physical examination (complete exam at Week 4 only, abbreviated exam at Weeks 20, 32, and 40 only)
- Record the patient's weight (Weeks 4, 20, 32, and 40 only)
- Record vital sign measurements
- Record AEs and concomitant medications
- Assess adherence to the OBR (Weeks 4, 8, 20, 32, and 40 only)
- Collect urine and perform pregnancy test for females of childbearing potential (Weeks 4, 8, 16, 20, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92, 100, 104, 112, 116, 124, 128, 136, and 140 only)
- Collect blood samples for the following:
  - HIV-1 RNA (viral load) (Day 14, and Weeks 4, 6, 8, 16, and 20 only)
  - HIV-1 viral resistance sample (will be stored for later use if needed) (Day 14, and Weeks 4, 6, 8, 16, and 20 only)
  - $CD4^+$ cell count (Day 14, and Weeks 4, 6, 8, 16, and 20 only)

Site personnel will undertake the following after administration of study drug (800 mg):

- Record vital sign measurements after completion of infusion and observe patient for at least 1 hour; if the patient did not experience an AE(s) related to the infusion (local or systemic) through and including the infusion on Day 14, then the observation time can be reduced to 15 minutes
- Record AEs

6.3.5 Events for Weeks 12, 24, 48, 60, 72, 84, 96, 108, 120, 132, and 144/EOS (±2 days)

Site personnel will undertake the following before administration of study drug:

- Record results of physical examination (complete exam at Week 24, 48, 72, 96, 120, and 144 only ; abbreviated exam at Weeks 12, 60, and 84 only)
- Record the patient's weight (Weeks 12, 24, 48, 60, 72, 84, 96, 120, and 144 only)
- Record vital sign measurements
- Record AEs and concomitant medications
- Assess adherence to the OBR
- Collect blood and/or urine samples for the following:
  - Hepatitis serology and C-reactive protein (Weeks 24, 48, and 96, only)
  - Clinical laboratory assessments (serum chemistry, hematology, and urinalysis; see Section 7.2.2 for a complete list of parameters) (Weeks 12, 24, 48, 60, 72, 84, 96, and 120 only)
  - Archive sample (Weeks 12, 24, 48, 60, 72, 84, 96, 120, and 144 only)
  - Pregnancy test for females of childbearing potential (serum at Weeks 24, 48, 72, and 96 only; urine at all other listed weeks)
  - HIV-1 RNA (viral load)
  - HIV-1 viral resistance sample (will be stored for later use if needed)
  -
  - $CD4^+$ cell count (within 1 hour before the start of the infusion)
  - Immunogenicity of ibalizumab (Weeks 24, 48, 72, 96, , 120, and 144 only)

Site personnel will undertake the following after administration of study drug (800 mg):

- Record vital sign measurements after completion of infusion and observe patient for at least 1 hour; if the patient did not experience an AE(s) related to the infusion (local or systemic) through and including the second infusion on Day 14, then the observation time can be reduced to 15 minutes

- Record AEs

6.3.6 Events for Weeks 28 and 36 (±2 days)

The following will be completed before study drug administration:

- Record the patient's weight (Week 36 only)
- Record vital sign measurements
- Record AEs and concomitant medications
- Collect blood and/or urine samples for the following:
  - Clinical laboratory assessments (serum chemistry, hematology, and urinalysis; see Section 7.2.2 for a complete list of parameters)
  - Archive sample
  - Urine pregnancy test for females of childbearing potential
  - HIV-1 RNA (viral load)
  - HIV-1 viral resistance sample (will be stored for later use if needed)
  - $CD4^+$ cell count (within 1 hour before the start of the infusion)

Site personnel will undertake the following after administration of study drug (800 mg):

- Record vital sign measurements after completion of infusion and observe patient for at least 1 hour; if the patient did not experience an AE(s) related to the infusion (local or systemic) through and including the infusion on Day 14, then the observation time can be reduced to 15 minutes
- Record AEs

6.3.7 Events for Week 150/Follow-up Visit (±2 days) (Study drug is not administered at this visit)

The following procedures will be completed at the Week 102/Follow-up visit:

- Record results of a complete physical examination
- Record the patient's weight
- Record vital sign measurements;
- Record AEs and concomitant medications
- Assess adherence to the OBR
- Collect blood and/or urine samples for the following:
  - Hepatitis serology and C-reactive protein
  - Clinical laboratory assessments (serum chemistry, hematology, and urinalysis; see Section 7.2.2 for a complete list of parameters)
  - Archive sample
  - Urine pregnancy test for females of childbearing potential
  - HIV-1 RNA (viral load)
  - HIV-1 viral resistance sample (will be stored for later use if needed)
  - $CD4^+$ cell count
  - Immunogenicity of ibalizumab

6.4 Early Withdrawal Procedures

Patients who withdraw from the study at any time before Week 96/EOS will be asked to complete all Early Withdrawal procedures to ensure safety and collect as much effectiveness data as possible.

The following procedures will be completed at the Early Withdrawal visit (study drug is not administered at Early Withdrawal):

- Record results of a complete physical examination
- Record the patient's weight
- Record vital sign measurements

- Record AEs and concomitant medications
- Assess adherence to the OBR
- Collect blood and/or urine samples for the following:
  - Hepatitis serology and C-reactive protein
  - Clinical laboratory assessments (serum chemistry, hematology, and urinalysis; see Section 7.2.2 for a complete list of parameters)
  - Archive sample
  - Serum pregnancy test for females of childbearing potential
  - HIV-1 RNA (viral load)
  - HIV-1 viral resistance sample (will be stored for later use if needed)
  - $CD4^+$ cell count
  - Immunogenicity of ibalizumab

6.5 Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

- To perform a confirmatory plasma viral load determination
- To perform confirmatory laboratory testing for clinically abnormal values
- Any time the investigator feels that they are clinically required for safety reasons related to the patient'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 and immunogenicity testing, which will be undertaken by appropriate specialty contract laboratories. Urine samples will be analyzed at the site; if abnormal results are obtained for a patient, 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 Schedule of Events (Tables 3-1 through 3-6).

7.1 Activities to Be Completed

7.1.1 Demographic Data, Medical History, and Concomitant Medications

Demographic data, a complete medical history (per patient report), and documentation of prior medications will be collected at Screening; information about recent or concomitant medications will be obtained at each visit. If the patient is enrolling into Cohort 2, the patient will supply official written documentation of HIV-1 infection at Screening, if possible. Otherwise, a sample for an HIV-1 antibody test must be collected as part of the Screening procedures.

7.1.2 Complete Physical Examination

A complete physical examination will include the following organ or body system assessments: head, eyes, ears, nose, throat, musculoskeletal, cardiovascular, lymphatic, respiratory, gastrointestinal, skin, neurological, and other findings of note. Height and weight will be measured at Screening, and weight only will be measured at other times specified.

7.1.3 Abbreviated Physical Examination

An abbreviated physical examination will be limited to lymph nodes, respiratory and cardiovascular systems, abdomen, extremities, and nervous system and assessment of any specific signs and symptoms that the patient reports.

7.1.4 Vital Sign Measurements

Vital sign measurements will include the patient's heart rate (beats/minute taken for 1 full minute), blood pressure (mm Hg), respiratory rate (breaths/minute taken for 1 full minute), and oral temperature (°C). Measurements will be taken within 1 hour before the start of the infusion and 15 minutes after the end of the infusion. Blood pressure and heart rate measurements will be obtained after the patient has been seated for at least 5 minutes. Ideally, each patient's blood pressure should be measured using the same arm and the same size cuff at each visit.

7.2 Blood and Urine Samples

7.2.1 Hepatitis Serology and C-Reactive Protein

Patients will be screened for hepatitis B (surface antigen) and hepatitis C to determine their hepatitis status.

Blood samples will be taken for the analysis of C-reactive protein, which is an inflammatory marker whose concentration increases with acute or chronic inflammation.

7.2.2 Clinical Laboratory Parameters

Collection of blood and urine samples for clinical laboratory assessments will be part of a normal safety profile assessment for the study patients. Patients need not 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
- **Serum chemistry profile:** albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), blood urea nitrogen, calcium, chloride, creatine phosphokinase, creatinine, direct bilirubin, gamma glutamyl transferase, glucose, lactate dehydrogenase, lipase, lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides), 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). See Appendix B for details and definitions of toxicities. The Principal Investigator should discuss any Grade 3 or 4 abnormal laboratory results with the medical monitor/Sponsor for appropriate patient disposition, including potential withdrawal from the study (see Section 5.3.1 for additional information). Per Section 5.3.1, the study treatment should be stopped for all Grade 3 or 4 treatment-related laboratory abnormalities, as defined in Appendix B. Any patient with a Grade 3 or Grade 4 laboratory abnormality that resolves before the next scheduled dose may have the study drug reinstituted. If a patient develops a persistent Grade 3 or Grade 4 treatment-emergent laboratory abnormality, excluding triglycerides and cholesterol, that does not resolve prior to the next scheduled study drug administration, study drug may be discontinued. Patients with Grade 3 or 4 triglyceride and/or cholesterol elevations are allowed to continue to receive study drug.

7.2.3 Archive Sample

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

7.2.4 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 35 IU/L for the patient to be considered postmenopausal. If the patient 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 Schedule of Events.

7.2.5 Pregnancy Testing

A serum pregnancy test will be performed at Screening, EOS, Early Withdrawal and other defined visits for all females of childbearing potential. A urine pregnancy test will be performed at other defined study visits to confirm that a female has not become pregnant during the study. These tests are performed for the protection and safety of the fetus, as the risk to the fetus is unknown. Any patient 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.

7.2.6 HIV-1 RNA Level

Blood samples for viral load will be used to determine the effectiveness of the study regimens and should be drawn before infusion during visits that include an infusion.

7.2.7 HIV-1 Viral Resistance Testing

Blood samples for HIV-1 viral resistance testing should be collected before the start of the infusion at the indicated visits. Viral resistance testing will include assessments of reverse transcriptase, protease, integrase and envelope genes, and chemokine coreceptor utilization; the samples will be collected and stored, and testing will only be performed for patients who experience virologic failure while on the study.

Collected and stored samples may also be used for the Trofile™ Assay, a blood test that identifies the tropism of a patient's HIV strain (i.e., R5, X4, or a combination). The results show whether the patient is infected with the virus that enters cells using the R5 co-receptor, the X4 co-receptor, or both.

7.2.8 $CD4^+$ Cell Count

Blood samples for $CD4^+$ cell count will be collected over the course of the study to determine how well the immune system is functioning. In most patients infected with HIV, an increase in the number of $CD4^+$ cells is an indicator of the effectiveness of antiretroviral medication.

If a patient experiences toxicity, defined as two consecutive laboratory results, at least 14 days apart, with a $CD4^+$ cell count below 200 cells/mm^3 that also represents a 50% reduction from the baseline $CD4^+$ cell count, the patient will be discontinued from the study.

7.2.9 Immunogenicity of Ibalizumab

Blood samples will be collected to test for the development of antibodies against ibalizumab at Day 0, EOS, Early Withdrawal, and other defined visits. Samples will be collected prior to ibalizumab infusion if an infusion is scheduled for that visit. The incidence of anti-ibalizumab antibody production will be determined using a validated enzyme-linked immunosorbent assay (ELISA) that has been validated for the detection of anti-ibalizumab antibodies in human serum even if circulating drug is present. Additional samples may be collected when clinical observations suggest the possibility of a clinically significant anti-ibalizumab immune response (e.g., allergic response, serum sickness, low drug levels, and/or loss of virologic response).

8. Adverse Events

8.1 Definitions

Per the FDA regulations in 21 CFR 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 AE caused by a drug.

Treatment-Emergent AEs. A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency following exposure to test medication.

Serious Adverse Event or Serious Suspected Adverse Reaction. An AE 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 AE, 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 patient 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 caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.

Unexpected Adverse Event or Unexpected Adverse Reaction. This term refers to 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.

8.2 Eliciting Adverse Event Information

At every study visit, patients 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 patient self-report, AEs will be documented from clinically significant findings resulting from abnormal laboratory test values, physical examination findings, or other documents that are relevant to patient 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 patient during the study (from the time the patient signs informed consent until 30 days after the last dose of study medication is given), regardless of their relationship to study drug or their clinical significance. Patients will be instructed to contact study site personnel at any time after informed consent if any symptoms develop.

To ensure compliance with FDA regulations (21 CR 312.64), site investigators must immediately report to the Sponsor all AEs that meet the SAE criteria, regardless of presumed relationship to the investigational agent. The Sponsor will carefully review the SAE information to monitor the investigational drug's toxicity profile and patient 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).

Recording of AEs will begin after study drug is first administered. Any untoward medical condition that occurs after the informed consent is signed but before the first administration of the study drug will be recorded as medical history, unless it is related to a study procedure. AEs will be recorded from the first dose of study medication and until 30 days after the last dose of study medication, regardless of its relationship to study drug. AEs will be documented in the patient's source documents and recorded in the AE section of the EDC system.

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 Principal Investigator deems the event to be chronic or the patient 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, 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 it 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 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 pre-existing condition, the worsening of the condition should be captured as an AE. Elective procedures performed where there is no change in the patient's medical condition should not be recorded as AEs, but should be documented in the patient's source documents.

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

All AEs, whether serious or not, should be followed to a satisfactory resolution or until the Principal Investigator deems the event to be chronic or the patient 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 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 in causing or contributing to the AE will be characterized by the investigator using the following classifications and criteria:

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

Possible. This relationship suggests that treatment with the study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the study drug, but could also have been produced by other factors.

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

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

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.

Details for grading severity are given in Appendix B. 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 Principal Investigator according to the previously described criteria must be reported using the Westat SAE Report Form and submitted to the Westat Regulatory Affairs 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. Key information that must be supported by source documents includes:

- Event term
- Onset date
- Event management
- Relatedness of the event to the study drug
- Changes in study drug dosage, including suspension or discontinuation
- If judged not study drug-related, an alternate etiology
- Resolution date

When reporting an SAE to Westat, a thorough summary of the event should be provided, including copies of related documentation. Before submission of these documents to Westat, all patient identifiers must be obliterated; the documents must be labeled only with the patient's identification number to safeguard the patient'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 ECGs, 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, a copy of the hospital admission and discharge summaries and any pertinent laboratory or diagnostic reports should be faxed to Westat as soon as they become available. Similarly, 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.

The Sponsor or designee will notify the FDA and all participating Principal 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 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 investigator's brochure must also be reported

The Sponsor or designee will notify the FDA and all participating Principal 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 (EC) 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 30 days after the last dose of study drug is administered.

Childbearing Potential. Females of childbearing potential are female patients 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 patients 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 Principal Investigator discuss all options with these female patients and instruct that if the patient 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 35 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 patients will be instructed to contact the investigator if a sexual partner suspects she may be pregnant.

If a patient or investigator suspects that the patient may be pregnant before study drug administration, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the patient must not receive the study drug and must be withdrawn from the study. The investigator must immediately notify the medical monitor of a pregnancy associated with study drug exposure and record the event on the Pregnancy Surveillance Form that will be provided to each site. Protocol-required procedures for study discontinuation must be performed on the patient 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 patient or the pregnant partner of any sexually active male patient 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 who result from such pregnancies should be followed for a minimum of 8 weeks for safety assurances.

Pregnancy Surveillance Forms will be submitted to the Westat Regulatory Affairs Department via the SAE fax line. HHS 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).

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 patients (n), mean, standard deviation, median, minimum, and maximum. For categorical data, the frequency and percentage of patients 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 9.3 or later (SAS Institute Inc., Cary, NC, SAS System). Individual patient data will be presented in patient data listings.

9.2 Populations for Analysis

9.2.1 Efficacy Populations

9.2.1.1 Intent-to-Treat Population

The ITT population is defined as all patients enrolled into the study. Patient disposition will be based on the ITT population. The ITT Analysis Population will be used for the primary analysis at Day 7. Patients with missing effectiveness data at Day 7 will have their effectiveness set to failure for all dichotomous effectiveness variables. This will be referred to as the MEF analysis.

9.2.1.2 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population is defined as all ITT patients who received at least one dose of study drug. The mITT Analysis Population will be used for a supportive effectiveness analysis and will include all data without imputing values for missing data.

9.2.2 Safety Population

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

9.3 Patient Disposition

Study completion data will be summarized for all enrolled patients. The number and percentage of patients who complete treatment, discontinue study medication prematurely, or discontinue the study prematurely, will be tabulated. The primary reason for premature discontinuation of study medication and/or discontinuation from study participation will be tabulated. Any additional reason(s) for premature discontinuation of study medication will also be tabulated. A listing of all enrolled patients will be provided.

9.4 Definition of Baseline

For patients in Cohort 1 who were enrolled in the TMB-202 or TMB-301 studies, Baseline values for TMB-311 are defined as the values recorded for the Baseline visit in the previous study. For patients in Cohort 1 who were not enrolled in the TMB-202 or TMB-301 studies, Baseline values for TMB-311 are defined as the last values recorded prior to receiving the first dose of ibalizumab. For patients in Cohort 2, Baseline is defined as the Day 0 visit of TMB-311 (this study).

9.5 Demographics and Baseline Characteristics

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

9.6 Exposure to Study Medication

Duration of treatment will be presented for the mITT population.

9.7 Safety Analyses

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

9.7.1 Adverse Events

The incidence (n and %) of AEs, SAEs, and early termination of study medication 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 System Organ Class. Each patient will be counted only once for each AE reporting level.

9.7.2 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 patient data listings. Non-numeric data will be presented in patient data listings, but will not be tabulated.

9.8 Efficacy

The primary efficacy endpoint (Cohort 2 only) is the proportion of patients achieving a ≥0.5 log_{10} decrease in viral load from Baseline to Day 7 along with a 95% confidence interval around the observed rate.

Secondary effectiveness endpoints (Cohort 2) include:

- Proportion of patients with HIV-1 RNA levels <50 copies/mL and <400 copies/mL at assessment time points
- Mean change from Baseline in viral load at Day 7 and all assessment time points
- Proportion of patients achieving a ≥0.5 log_{10} and ≥1.0 log_{10} decrease from Baseline in viral load at all assessment time points

Exploratory statistical analyses will explore changes in HIV-1 drug sensitivity/susceptibility to determine relationships with protocol-defined virologic failure after ibalizumab administration in combination with the OBR.

10. Data Handling and Quality Assurance

10.1 Electronic Case Report Forms

An EDC 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 patient 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 patients participating in the trial. Therefore, the data are to be entered into the EDC as soon as possible during or after the patient'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 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, and the time and date of the change 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 and the 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., US FDA, Taiwan Food and Drug Administration [TFDA]), the ICH E6(R1): Guidelines for Good Clinical Practice, local IRB policies, and current standard operating procedures at the sites), and the 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 Principal 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 Principal 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

Principal 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 Principal Investigator agrees to allow the Sponsor, representatives of the Sponsor, the US FDA, or other relevant regulatory authorities access to all study records.

The Principal Investigator should immediately notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward, to the Sponsor or designee, copies of any audit reports received.

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). 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 investigational product. However, if required by the applicable regulatory requirements or by an agreement with the Sponsor, these documents should be retained for a longer period. It is the responsibility of the Sponsor or designee to inform the Principal 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 Principal 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 patient 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 patient (or the patient's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the US FDA or applicable regulatory authorities, or the IRB.

The Principal Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose, other than performance of the study, any data, 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/EC before participation of human patients in research studies. Before the study onset, the protocol, informed consent, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient'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(R1), US FDA, TFDA, and other applicable regulatory authorities will be maintained by the site and available for review by the Sponsor or designee.

The Principal Investigator is responsible for obtaining continued review of the clinical research at intervals specified by the IRB, but not exceeding 1 year. The Principal 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 patient. 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 Code of Federal Regulations (CFR) Part 50 and in accordance with other regulations for non-US sites, will be obtained from each patient before any study-related procedures are performed and any personal information is collected. An informed consent template may be provided to investigative sites by the Sponsor or designee. The consent must be reviewed by the Sponsor or designee before IRB submission if the site proposes or makes any institution-specific modifications to study-related procedures, the risk language, or any other significant changes that would alter the information relayed. Once reviewed, the consent will be submitted by the Principal Investigator to his/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 patients must sign the revised IRB-approved consent form.

Before enrollment, each prospective patient will be given a full explanation of the study and allowed to read the approved informed consent form. The information given should be in a language or manner that is easily understandable to the participant or legal guardian. Once the Principal Investigator is assured that the patient/legal guardian understands the implications of participating in the study and has been given the proper time to consider whether to participate or not, the

patient/legal guardian will be asked to give consent to participate in the study by signing the informed consent form. The Principal Investigator will also sign the form at that time.

The Principal Investigator will provide a copy of the signed informed consent form to the patient and/or legal guardian. The original form will be maintained in the patient'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 that were agreed to by the Principal Investigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria. A protocol violation occurs when (1) there is non-adherence to the protocol that results in significant additional risk to the patient, (2) the patient or Principal Investigator has failed to adhere to significant protocol requirements (e.g., inclusion/exclusion criteria), or (3) there is non-adherence to FDA regulations and/or ICH E6(R1) guidelines.

For this protocol, violations will be defined as exceptions to the inclusion or exclusion criteria, situations where a patient is required to withdraw but the investigator believes the patient 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 Principal Investigator or designee must document and explain any protocol deviation or violation in the patient's source documentation. The investigator should notify the IRB of all protocol violations and deviations per local institutional policy. 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 Principal Investigator may implement a change from the protocol without prior Sponsor and IRB approval only to eliminate an immediate hazard to a patient. 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 patient, the investigator may present the facts and rationale to the medical monitor and request a one-time

exception. This request will be submitted in writing on a protocol inquiry form, which will be faxed to the medical monitor for review and disposition. The medical monitor will then fax 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 patient should receive an excluded concomitant medication and remain in the study, or if the investigator believes that a patient should remain in the study when the protocol dictates that the patient 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 Principal Investigator agrees to submit reports of AEs according to the timeline and method outlined in the protocol. In addition, the Principal Investigator agrees to submit periodic reports to his/her IRB as appropriate.

11.7 Financial Disclosure and Obligations

Principal Investigators and subinvestigators 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 Principal Investigator and subinvestigators 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 patient's disease.

11.8 Investigator Documentation

Before beginning the study, the Principal Investigator will be asked to comply with ICH E6(R1) 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 patient or legal guardians.
- A Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
- Curricula vitae for the Principal Investigator and each subinvestigator listed on Form FDA 1572. A copy of the current license must be provided. The curricula vitae must be signed and dated by the Principal Investigators and subinvestigators within 1 year before study start-up to indicate that 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 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 (Section 11.7).
- 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 Principal Investigator agrees that the study will be conducted according to the principles of ICH E6(R1), the principles of the World Medical Association Declaration of Helsinki, and regulatory requirements of the US FDA and TFDA. The Principal 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.

References

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4 Schwartzberg, L.S., Stepanski, E.J., Fortner, B.V., and Houts, A.C. (2008). Retrospective chart review of severe infusion reactions with rituximab, cetuximab, and bevacizumab in community oncology practices: Assessment of clinical consequences. *Supportive Cancer Care*, 16:393-398.

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6 Dalakas, M.C. (2004). The use of intravenous immunoglobulin in the treatment of autoimmune neuromuscular disease: Evidence-based indications and safety profile. *Pharmacology and Therapeutics*, 102:177-193.

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