CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761065Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	761065
Link to EDR	\\CDSESUB1\evsprod\BLA761065\0010
Submission Date	05/03/2017
Submission Type	Priority
Brand Name	Trogarzo®
Generic Name	Ibalizumab
Dosage Form and Strength	IV solution; 200 mg/1.33 mL (150 mg/mL) per vial
Route of Administration	Intravenous infusion
Proposed Indication	Treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing current antiretroviral therapy, in combination with other antiretroviral(s)
Applicant	TaiMed Biologics
Associated INDs	IND 09776, 108904
OCP Review Team	Qin Sun, PhD; Shirley Seo, PhD; Ada Zhuang, PhD; Jeffry Florian, PhD
OCP Final Signatory	Kellie Reynolds, PharmD Division IV Deputy Director Office of Clinical Pharmacology

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1 EXECUTIVE SUMMARY

TaiMed Biologics is seeking the approval of ibalizumab for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing current antiretroviral therapy, in combination with other antiretroviral(s). Ibalizumab is a CD4 domain 2-directed humanized IgG4 monoclonal antibody that interferes with the post-attachment steps required for entry of HIV-1 virus particles into $CD4^+$ T cells.

The efficacy and safety of ibalizumab at the proposed dose regimen (administered intravenously as a single loading dose of 2000 mg, followed by a maintenance dose of 800 mg every 2 weeks) were evaluated in a Phase 3 trial (TMB-301). The results indicated that 83% of patients achieved ≥ 0.5 $\log_{10}$ HIV RNA reduction following 7 days on ibalizumab functional monotherapy (2000 mg ibalizumab loading dose added to a failing regimen), compared to 2.5% following 7 days on a failing regimen alone. Forty-three percent of patients achieved HIV RNA <50 copies/mL at Week 25, suggesting some durability of virologic suppression from the combination of ibalizumab with an optimized background regimen (OBR). There were no significant safety concerns identified in the Phase 3 trial.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information contained in BLA 761065. This BLA is considered approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Pivotal or Supportive evidence of effectiveness	The primary evidence of effectiveness is provided by the Phase 3 trial – TMB-301. The supportive evidence for efficacy comes from the Phase 2b trial – TMB-202.
General dosing instructions	The proposed dose regimen for ibalizumab administered intravenously as a single loading dose of 2000 mg, followed by a maintenance dose of 800 mg every 2 weeks is effective and appears to be safe based on the Phase 2b and 3 trials, and is acceptable from a clinical pharmacology perspective.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments are recommended based on intrinsic and extrinsic factors. Body weight based dosing is not needed.
Labeling	Generally acceptable. The review team has specific content and formatting recommendations (refer to **Section 2.4**).
Bridge between to-be-marketed and clinical trial formulations	Not applicable. To-be-marketed formulation was used in the pivotal Phase 3 trial.

1.2 Post-Marketing Requirements and Commitments

None.

2 Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

Ibalizumab is a CD4 domain 2-directed humanized IgG4 monoclonal antibody. It interferes with post-attachment steps required for entry of HIV-1 virus particles into host cells and prevents the viral transmission that occurs via cell-cell fusion. It is active against R5-tropic, dual-tropic, and X4-tropic HIV-1. Ibalizumab does not impact CD4-mediated immune functions since it does not interfere with domain 1, which is required for CD4 binding of the major histocompatibility complex (MHC) class II molecules. The proposed dose regimen for ibalizumab is a single loading dose of 2000 mg, followed by a maintenance dose of 800 mg every 2 weeks administered as intravenous infusions.

The following is a summary of the clinical pharmacokinetics (PK) of ibalizumab:

The PK of ibalizumab in HIV-1 patients is described by a one compartmental model with parallel linear first-order elimination and nonlinear Michaelis-Menten (MM) elimination (potential target-mediated drug disposition mechanism) after intravenous (IV) infusion (refer to **Appendix 4.3**). Ibalizumab exposure increased in a greater than dose-proportional manner; the AUC increased by 2409-fold when the dose increased 83-fold from 0.3 to 25 mg/kg.

Absorption: Ibalizumab is administered as an IV infusion. No studies were performed with other routes of administration.

Distribution: The estimated volume of distribution is 4.8 L.

Metabolism: Not studied. In general antibodies are degraded into small peptides and amino acids via catabolic pathways.

Elimination: The mean clearance for the linear elimination pathway is 0.0121 L/h with inter-subject variability of 73% and intra-subject variability of 100%. The clearance for the nonlinear elimination pathway is concentration-dependent and is relevant in the studied dose range, based on the population PK analysis.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The Applicant's proposed dose regimen of ibalizumab administered intravenously as a single loading dose of 2000 mg, followed 14 days later by a maintenance dose of 800 mg every 2 weeks is supported by the PK, efficacy and safety data from the clinical trials

submitted in this BLA, and the recommended dose regimen is acceptable (see **Section 3.3.2** for additional discussion).

2.2.2 Therapeutic Individualization

Therapeutic individualization is not recommended based on intrinsic or extrinsic factors. A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates (age, body weight, sex, and baseline $CD4^+$ cell count) on ibalizumab pharmacokinetics. The result suggests that body weight was the only statistically significant covariate and ibalizumab concentrations decreased as body weight increased; however, the effect would not be great enough to produce a significant change in viral suppression and thus, does not warrant dose adjustment.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert (**Table 2.4-1**).

Table 2.4-1 Summary of Labeling Issue Identification and Recommendations

Section/heading	Acceptable to OCP?			Comment
	A	AWE	NA	
Section 7	☐	☒	☐	Delete Section 7 in the absence of drug interactions
Section 8.6	☐	☒	☐	Move renal/hepatic impairment to Section 12.3 under heading of Specific Populations because there is no dose adjustment
Section 12.2	☐	☐	☒	• Delete non-related information (b) (4) • Delete (b) (4) since information is not known. • Add "A clear trend was identified between exposure and response rate for the Phase 2b trial (TMB-202) which studied two different intravenous dose regimens, 2,000 mg every 4 weeks and 800 mg every 2 weeks. The recommended intravenous dose regimen consisting of a 2,000 mg loading dose followed by a maintenance dose of 800 mg every 2 weeks was selected on the basis of these results."
Section 12.3	☐	☐	☒	• Delete (b) (4) due to (b) (4) data verification • Re-summarize the PK results to include all the key PK parameters and delete speculative information • Add population PK and covariates analysis results based on reviewer's analysis

				• Add new heading of specific populations with subheading of pediatric/geriatric patients and renal/hepatic impairment, and new heading of drug interaction studies with related information
Section 12.5	☐	☒	☐	Delete (b) (4)

A = Acceptable; AWE=Acceptable with minor edits; NA=not acceptable/substantive disagreement (must provide comment)

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

Ibalizumab is a CD4 domain 2-directed humanized IgG4 monoclonal antibody with a molecular weight of ~150 KDa, and it interferes with the post-attachment steps required for entry of HIV-1 virus particles into $CD4^+$ T cells. There is no evidence of cross-resistance between ibalizumab and enfuvirtide or maraviroc and it is active against R5-tropic, dual-tropic, and X4-tropic HIV-1. Ibalizumab does not impact CD4-mediated immune functions.

The proposed dose regimen for ibalizumab is intravenous administration of a single loading dose of 2000 mg, followed by a maintenance dose of 800 mg every 2 weeks. Ibalizumab is supplied at a concentration of 150 mg/mL in 200 mg single (b) (4) vials, and it is formulated in 10 mM histidine, 5.2% sucrose, 52 mM sodium chloride, 0.045% polysorbate 80, and (b) (4) with a final pH of 6.0.

INDs 09776 and 108904 are the associated INDs in the Division of Antiviral Products, and ibalizumab was granted Breakthrough Therapy Designation on February 23, 2015, and Orphan Drug Designation on October 20, 2014 (~ 5000 patients in US).

The Applicant has requested a waiver for the use of ibalizumab in the pediatric population for the proposed indication, since pediatric studies are exempted for orphan drugs.

3.2 General Pharmacology and Pharmacokinetic Characteristics

<table>
<tr><th colspan="2">Pharmacology</th></tr>
<tr><td>Mechanism of Action</td><td>Ibalizumab is a CD4 domain 2-directed humanized IgG4 monoclonal antibody that interferes with the post-attachment steps required for entry of HIV-1 virus particles into $CD4^+$ T cells.</td></tr>
<tr><th colspan="2">General Information</th></tr>
<tr><td>Bioanalysis</td><td>Validated sandwich or competitive enzyme-linked immunosorbent assay (ELISA) were used to determine ibalizumab serum concentrations as summarized below (refer to Appendix 4.1 for more details).
<table>
<tr><td>Study #</td><td>TMB-301</td><td>TMB-202</td><td>TNX-355.01</td><td>TNX-355.02</td><td>TNX-355.03</td></tr>
<tr><td>Assay type</td><td>Sandwich ELISA</td><td colspan="4">Competitive ELISA</td></tr>
</table></td></tr>
</table>

Capture antibody	Anti-ibalizumab antibody	Anti-ibalizumab antibody captured by the secondary antibody - goat anti-mouse IgG (Fc specific) antibody		
Detection antibody	HRP-conjugated mouse anti-human IgG4 antibody	NA		
LLOQ (ng/mL)	10	100	100	
Lab	(b) (4)		Tanox	

HRP: horseradish peroxidase; NA: not appicable; LLOQ: Lower limit of detection.

Validated bridging or non-bridging sandwich ELISA with or without acid dissociation were used for ADA detection as summarized below (refer to **Appendix 4.1** for more details).

Study #	TMB-301	TMB-202	TNX-355.01	TNX-355.02	TNX-355.03
Assay type	Bridging with acid dissociation	Bridging	Bridging	Non-bridging	Bridging and non-bridging
Capture antibody	Ibalizumab	Ibalizumab	Ibalizumab	Ibalizumab	Ibalizumab
Detection antibody	SULFO-conjugated ibalizumab	HRP-conjugated ibalizumab	HRP-conjugated ibalizumab	HRP-conjugated anti-human IgG1 antibody	HRP-conjugated ibalizumab or anti-human IgG1 antibody
Sensitivity (ng/mL)	24.8	6.67	10	33	10 or 33
Drug tolerance level (ng/mL)	2500	500	Not determined		
Lab	(b) (4)		Tanox		

HRP: horseradish peroxidase.

Patients *vs.* Healthy Volunteers	No studies were conducted in healthy subjects.
Drug Exposure at Steady State following the Therapeutic Dosing Regimen	Following the recommended dose regimen (2000 mg as a loading dose and 800 mg once every 2 weeks as a maintenance dose), ibalizumab concentrations reached steady-state levels after the first 800 mg maintenance dose with mean C_{trough} > 30 µg/mL throughout the dosing period. The mean C_{trough} and AUC_{tau} (2 weeks) for the loading dose of 2000 mg were 47.8 µg/mL and 64969 h*µg/mL, and the mean C_{trough} and AUC_{tau} (2 weeks) for the maintenance dose of 800 mg were 5.3 µg/mL and 21491 h*µg/mL, respectively, based on population PK analysis.
Minimal Effective Dose or Exposure	Not reached. Only one dose regimen (2000 mg loading dose + 800 mg maintenance dose once every 2 weeks) was evaluated for efficacy and safety in the Phase 3 study. Other doses were evaluated during drug development. (But minimum still may not be known)
Maximal Tolerated Dose	Not tested. Only one dose regimen (2000 mg loading dose + 800 mg maintenance dose once every 2

or Exposure	weeks) was evaluated for efficacy and safety in the Phase 3 study.
Dose Proportionality	Ibalizumab exhibited nonlinear PK profile and exposure increased in a greater than dose-proportional manner; the AUC increased by 2409-fold when the dose increased 83-fold from 0.3 to 25 mg/kg.
ADME	
Absorption	Ibalizumab is administered as an IV infusion. No studies were performed with other routes of administration.
Distribution	The estimated volume of distribution was 4.8 L.
Metabolism	Not studied. In general antibodies are degraded into small peptides and amino acids via catabolic pathways.
Elimination	The mean clearance for the linear elimination pathway was 0.0121 L/h with inter-subject variability of 73% and intra-subject variability of 100%, and the clearance for the nonlinear elimination pathway is concentration-dependent and is relevant in the studied dose range, based on the population PK analysis.
Immunogenicity	
Immunogenicity	For TNX-355.01, 02, 03 studies, the ELISA assay for ADA detection was not carried out using a standard 3-tiered assay approach, and have several limitations. In addition, the bioanalytical report for ADA detection was not submitted for TNX-355.02 study. The ADA assay results were inconclusive for TNX-355.01, 02, and 03 studies (refer to the CMC/OBP immunogenicity review for further details). For study TMB-202, one subject (10008) in the 2000 mg once every 4 weeks treatment group had an ADA positive result at Week 24, and the neutralizing antibody (nAb) assay was positive for that sample. However, the titer was low at 16, thus the ADA did not appear to have a negative impact on the antiviral efficacy of ibalizumab. Subject 10008 completed Week 24 with undetectable HIV-1 RNA and a significant increase in $CD4^+$ T-cell count. The subject had no AEs associated with the positive immunogenicity result (refer to the CMC/OBP review for the final conclusion regarding immunogenicity risk). The effect on PK was inconclusive due to limited ADA positive samples and large variability in ibalizumab concentrations. For study TMB-301, no subjects developed ADAs during 24 weeks of treatment with ibalizumab (refer to the CMC/OBP review for further details and the final conclusion).

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The clinical pharmacology information provided supportive evidence of effectiveness. Dose selection for the Phase 3 trial was based on a dose-response relationship from the Phase 2b trial, where the 800 mg Q2W regimen was associated with a higher Week 24 response (percentage of patients with HIV-1 RNA <50 copies/mL) than the 2000 mg Q4W regimen. In addition, analysis of the Phase 2b data showed a clear trend of an

exposure-response relationship (higher response rate with higher exposures).

Note: different ELISA (sandwich vs. competitive) was used to determine ibalizumab serum concentrations for the Phase 3 vs.Phase 2b and earlier clinical studies. No bridging validation study was performed to ensure consistency and accuracy in the data based on different methods from different laboratories. Thus, the concentration data from Phase 3 study were not pooled in the population PK analyses. The E-R relationship analysis was conducted for the Phase 2b study only. There were not sufficient subject numbers in the Phase 3 trial alone to develop a robust population PK model.

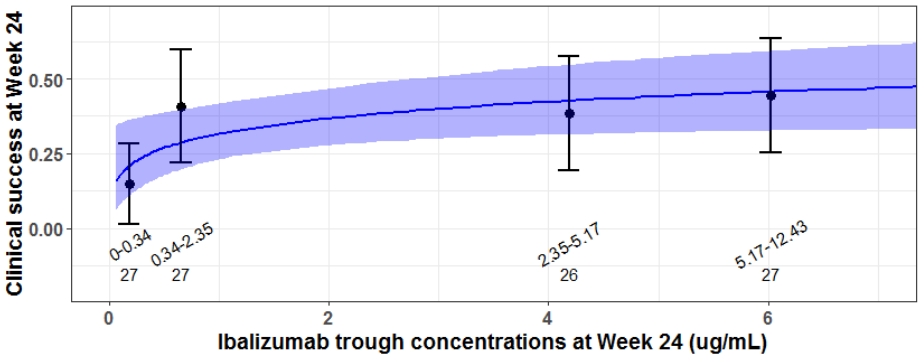
The E-R relationship for efficacy was evaluated in HIV-1 infected patients in the Phase 2b trial (TMB-202) using ibalizumab serum concentrations derived from population PK modeling (N=107) (refer to reviewer's analysis in **Appendix 4.3 and 4.4**). A numerically lower response rate (15%) was observed at Week 24 in those subjects with predicted C_{trough} concentrations in the lowest exposure quartile (ranging between 0.1-0.3 μg/mL) (**Table 3.3.1-1**). The response rate at Week 24 achieved a platuea for subjects in all other quartiles.

Table 3.3.1-1 Relationship between exposure quartile and primary efficacy endpoint for the Phase 2b study (TMB-202)

Quartile	C_{trough} at Week 24 (μg/mL)	No. of Subjects	% patients with HIV-1 RNA levels <50 copies/mL at week 25
Q1	0.1-0.3	27	15%
Q2	0.3-2.3	27	41%
Q3	2.4-5.1	26	38%
Q4	5.2-12.4	27	43%

Based on logistic regression analysis with log-transformed concentrations, there was a clear trend between exposure and the efficacy endpoint (**Figure 3.3.1-1)**, and the slope was statistically significant with p value of 0.026. The E-R relationship was relatively steep, with a substantial drop-off in response rate for concentrations lower than 0.5 μg/mL. The response rate reached plateau at the proposed maintenance dose regimen, with the majority of patients having trough concentrations at Week 24 greater than 0.5 μg/mL (mean: 5.3 μg/mL, 95% CI: 2.3 to 8.6 μg/mL).

Figure 3.3.1-1 Relationship between exposure and efficacy endpoint for Phase 2b study



3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen for ibalizumab administered intravenously as a single loading dose of 2000 mg, followed by a maintenance dose of 800 mg every 2 weeks is acceptable for the general patient population, who are heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing current antiretroviral therapy, in combination with other antiretroviral(s) (final indication wording is still under negotiation at the time of this review).

The proposed dose regimen for ibalizumab was used in the Phase 3 trial (TMB-301), and sufficient effectiveness was demonstrated. The result indicate 83% of patients achieved ≥0.5 $\log_{10}$ HIV RNA reduction on Day 14 following 7 days of ibalizumab functional monotherapy, compared to 2.5% on Day 7 from the failing regimen. About 43% of patients achieved HIV RNA <50 copies/mL at Week 25 (24 weeks of ibalizumab therapy), suggesting the durability of virologic suppression from the combination of ibalizumab with OBR.

Treatment outcomes were found to be influenced by various patient factors including CD4 cell count, viral load, and to a lesser extent OSS (overall sensitivity score; sum of active drugs in OBR based on a net assessment of information from genotypic and phenotypic testing results). The impact of covariates on the response rate was evaluated for the combined data from the Phase 2b and Phase 3 studies. These covariates include viral load at baseline ($\log_{10}$ transformed), CD4 cell count at baseline ($\log_{10}$ transformed), GSS (genotype sensitivity score; sum of active drugs in OBR based only on assessments from genotypic (Geneseq) testing), OSS, and body weight. The CD4 cell count and viral load at baseline had a significant impact on response rate. The results show that higher CD4 cell count at baseline is predictive of a higher response rate (**Table 3.3.2-1**) and higher viral load at baseline was associated with a lower response rate (**Table 3.3.2-2**). This is not unexpected as both higher CD4 cell count and lower viral load at baseline are associated with a less extensive infection and better treatment outcomes across other HIV drug development programs. Although OSS was not identified as a significant covariate

on response rate, there was a trend of higher OSS being associated with higher response rate (**Table 3.3.2-3)**. Body weight and GSS had little impact on response rate.

Table 3.3.2-1 Relationship between CD4 cell count at baseline quartile and efficacy endpoint for Phase 2b and 3 studies

Quartile	CD4 cell count at baseline (log_{10}) (cells/μL)	No. of Subjects	% patients with HIV-1 RNA levels <50 copies/mL at week 25
Q1	0-19 (0-1.3)	37	16%
Q2	19-68 (1.3-1.8)	36	29%
Q3	68-173.5 (1.8-2.2)	37	50%
Q4	173.5-676 (2.2-2.8)	37	54%

Table 3.3.2-2 Relationship between viral load at baseline quartile and efficacy endpoint for Phase 2b and 3 studies

Quartile	Viral load at baseline (log_{10}) (copies/mL)	No. of Subjects	% patients with HIV-1 RNA levels <50 copies/mL at week 25
Q1	71-14000 (1.9-4.2)	39	46%
Q2	14000-43100 (4.2-4.6)	35	49%
Q3	43100-145500 (4.6-5.2)	36	33%
Q4	145500-292000 (5.2-6.5)	37	19%

Table 3.3.2-3 Relationship between OSS at baseline and efficacy endpoint for Phase 2b and 3 studies

OSS	No. of Subjects	% patients with HIV-1 RNA levels <50 copies/mL at week 25
0	21	24%
1	48	33%
2	59	42%
>2	19	42%

The E-R relationship for safety was not evaluated, since there were no significant safety concerns identified in the Phase 3 study. The majority of the reported safety events appear to be secondary to HIV/AIDS (refer to the clinical review for further details). The most common adverse reactions (all Grades) reported in at least 3% of subjects were diarrhea, dizziness, nausea, and rash, and most (90%) of the adverse reactions reported were mild or moderate in severity.

Dose Selection from the Phase 2b Trial

The proposed dose regimen for ibalizumab administered intravenously as a single loading dose of 2000 mg, followed by a maintenance dose of 800 mg every 2 weeks was selected based on a Phase 2b dose-finding trial (Study TMB-202) in HIV-infected patients. Study TMB-202 was a randomized, double-blind, two arm study, conducted in 113 treatment-

experienced HIV infected patients. Two fixed dose regimens of intravenous ibalizumab (800 mg every 2 weeks or 2000 mg every 4 weeks), in combination with OBR, were assessed for safety, antiviral activity and PK. The primary efficacy endpoint was the proportion of patients with HIV-1 RNA levels <50 copies/mL at Week 24.

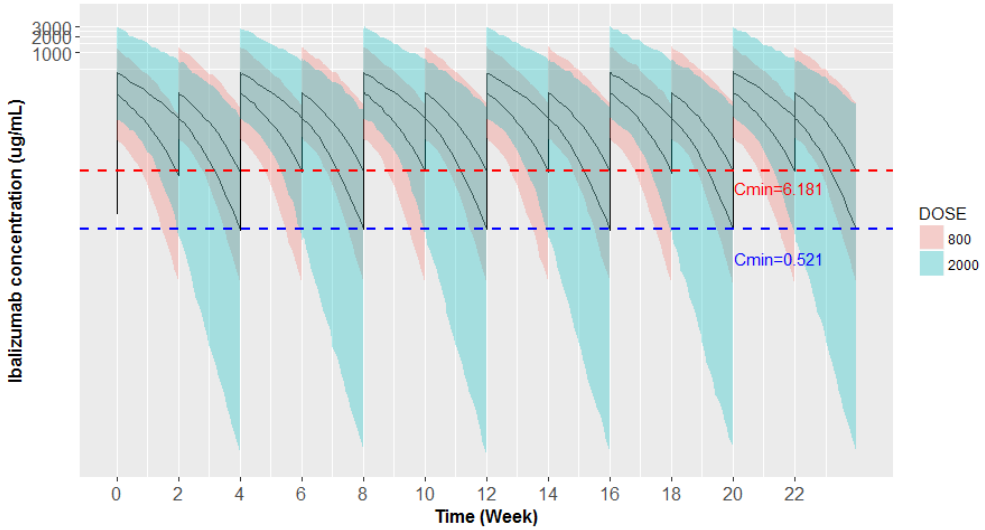
As summarized in **Table 3.3.2-4**, the 2000 mg every 4 weeks arm provided better efficacy at Week 2, likely due to higher exposure achieved by the higher dose at Week 2. However, the 800 mg every 2 weeks demonstrated better efficacy at Week 24, likely due to the higher C_{trough} maintained throughout the trial period as a result of the shorter dosing interval (**Figure 3.3.2-1**). The AE profile was similar for both regimens. Thus, the proposed dosing regimen used in the Phase 3 trial was designed to achieve the following:

1. Attain maximal initial drug exposure from a 2000 mg dose in order to achieve the early efficacy endpoint of proportion of subjects achieving >0.5 log_{10} HIV-1 RNA decrease at Week 2.
2. Maintain a higher C_{trough} throughout the trial to maximize the ability to demonstrate durability through a long-term efficacy endpoint (proportion of subjects achieving <50 copies/mL at Week 25) from the 800 mg every 2 weeks dosing regimen.

Table 3.3.2-4 Proportion of patients with viral load <50 copies/mL at each time point in Phase 2b study

	Number (%) of Patients		
	Ibalizumab + OBR		
Time point	800 mg q2wk (N=59)	2000 mg q4wk (N=54)	Total (N=113)
Viral load <50 copies/mL			
Baseline	0	0	0
Week 2	2 (3.4)	7 (13.0)	9 (8.0)
Week 4	10 (16.9)	11 (20.4)	21 (18.6)
Week 8	15 (25.4)	11 (20.4)	26 (23.0)
Week 12	21 (35.6)	13 (24.1)	34 (30.1)
Week 16	22 (37.3)	11 (20.4)	33 (29.2)
Week 20	23 (39.0)	14 (25.9)	37 (32.7)
Week 24	26 (44.1)	15 (27.8)	41 (36.3)

Figure 3.3.2-1 Ibalizumab serum concentrations from 2000 mg every 4 weeks (grey) and 800 mg every 2 weeks (green) in Phase 2b study



The simulated mean ibalizumab serum concentrations with 95% predictive interval were shown in the figure based on population PK modeling and simulation.
The median C_{trough} was 0.521 µg/mL for 2000 mg every 4 weeks, and was 6.181 µg/mL for 800 mg every 2 weeks.

During the review cycle, the possibility of optimizing the dose even further was evaluated. The following section details the two scenarios that were considered and the risk/benefit rationale for rejecting each.

1. The possibility to provide better efficacy with a higher dose of 2000 mg every 2 weeks:

   Although the response rate for proportion of subjects with HIV RNA <50 copies/mL was about 43% using the proposed dose regimen, the potential for further improvement by increasing ibalizumab dosage to 2000 mg every 2 weeks would likely be small due to the following reasons:

   a) No significant trend was identified between exposure and response rate for concentration range at 0.3 to 12.4 µg/mL, and the response rate achieved a platuea when concentration >0.3 µg/mL. In addition, the simulated steady state C_{trough} for the proposed dose regimen was 5.3 µg/mL, which is much higher than the *in vitro* baseline EC_{50} at <0.05 µg/mL.

   b) Ibalizumab resistance was caused by decreased MPI (maximum percent inhibition; the highest level of HIV inhibition acheived by an inhibitor, representing the efficiency with which HIV-1 can infect cells in the presence of the inhibitor versus the absence of the inhibitor), intead of increased EC_{50}, thus higher ibalizumab dose may not improve the efficacy for ibalizumab resistant isolates (refer to clinical virology review for more details).

c) The efficacy comes from the combination of ibalizumab and OBR, and a higher dose of ibalizumab is unlikely to overcome the resistance acquired from OBR-resistant isolates during treatment.

d) Higher dose may carry a greater immunogenicity concern.

In conclusion, 2000 mg every 2 weeks is not recommended based on currently available data, since it may not provide better efficacy, while carrying an unknown ADA risk (plus higher cost).

2. The feasibility to simplify the dose regimen to 800 mg every 2 weeks without the loading dose:

After discussion with the review team, the benefit *vs.* risk evaluation did not favor dropping the loading dose.

The rationale is summarized below, comparing the Phase 3 trial (2000 mg loading dose + 800 mg every 2 weeks, N=40) to the Phase 2b trial (800 mg every 2 weeks arm without the loading dose, N=59):

1) There was no clear AE difference with or without the loading dose.

2) Although the response rate for HIV RNA <50 copies/mL was similar in the clinical trials (43% *vs.* 44%) with limited subject numbers, certain patients may still need the higher ibalizumab loading dose for efficacy if the background regimen is not fully optimized.

In conclusion, the proposed dose regimen with the loading dose is acceptable.

3.3.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic factors?

No. There is no need for alternative dose or dosing regimen for subpopulations based on the intrinsic factors described below. The proposed dose regimen as a single loading dose of 2000 mg, followed by a maintenance dose of 800 mg every 2 weeks is appropriate given the non-clinically relevant effect of covariates on PK and convenience in a clinical setting.

Renal/Hepatic Impairment

There were no dedicated studies conducted in patients with renal or hepatic impairment. Additionally, the large size of ibalizumab (~150 kDa) would suggest that it is not filtered by the kidneys and thus, the pharmacokinetics of ibalizumab is unlikely to be affected by renal impairment. Currently, there is not enough evidence to conclude that hepatic impairment will not affect PK of ibalizumab *(Clin Ther. 2013; 35:1444-51)*.

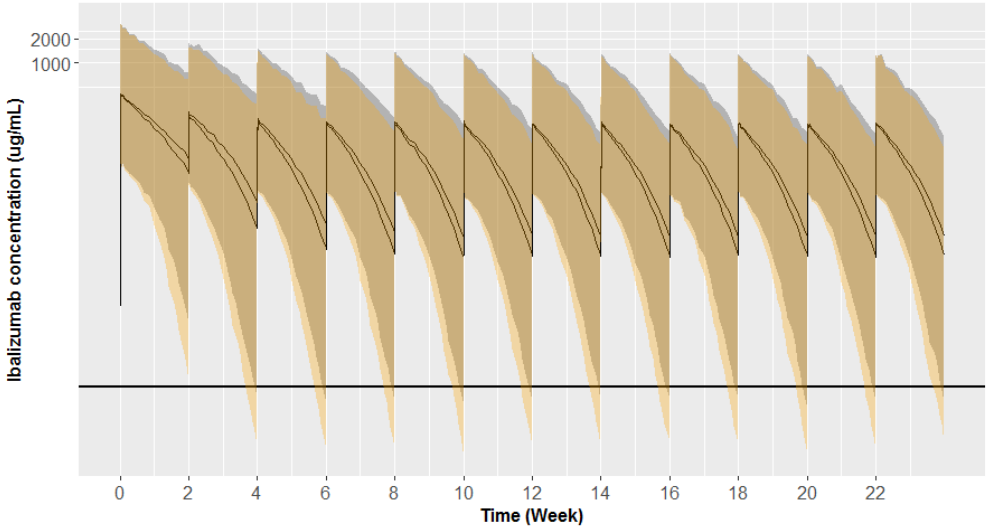
Demographic Factors
No clinically relevant effect has been found for age, body weight, sex, or baseline $CD4^+$ cell count.

Several demographic factors, such as age (22-71 years), body weight (43-152 kg), sex, and baseline $CD4^+$ cell count (0-760 cells/mL) have been evaluated to determine if these factors have an effect on PK of ibalizumab. Although body weight was identified as a statistically significant covariate for ibalizumab PK and ibalizumab concentrations decreased as body weight increased, the effect does not warrant dose adjustment as summaried below.

Body weight:
The PK profiles were simulated based on the final population PK model and demographic information from the Phase 3 trial with a dose of 2000 mg followed by 800 mg every 2 weeks infused over 30 min starting from Week 2. A total of 100 simulations per subject were conducted for 40 subjects with two uniform body weight ranges: 50-90 kg and 90-130 kg. The mean PK profiles and their 95% predictive intervals were plotted in **Figure 3.3.3-1** (refer to **Appendix 4.3**).

No significant difference in trough concentrations was identified between the two body weight ranges (**Table 3.3.3-1**). Both mean trough values are well above 0.3 µg/mL and thus reside on the plateau portion of the E-R curve. Therefore, a fixed dosing regimen appears to be reasonable in HIV-1 infected patients. It is worth noting that the body weight range was very narrow for the subjects included in the population PK model, and that the impact of body weight may not be precisely estimated.

Figure 3.3.3-1 Simulated PK profiles with a dose of 2000 mg followed by 800 mg every 2 weeks by two body weight ranges



Grey shaded area represents the 95% predictive interval for PK profiles in a body weight range of 50-90 kg; Orange shaded area represents the 95% predictive interval for PK profiles in a body weight range of 90-130 kg; solid line at bottom represents the concentration threshold of 0.1 µg/mL (BLQ).

Table 3.3.3-1 Predicted PK parameters for patients by different body weight range

Parameter	Patients with body weight range of 50-90 kg	Patients with body weight range of 90-130 kg
C_{trough} at Week 2 (µg/mL) Median, 95% quartile	68.5 (0.6-751.8)	45.9 (0.1-620.1)
C_{trough} at Week 24 (µg/mL) Median, 95% quartile	7.4 (0.06-124.1)	4.4 (0.02- 88.0)

3.3.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No. Since ibalizumab is administered by IV infusion, food-drug interactions are not applicable. Drug-drug interactions are not expected with CYPs, other metabolizing enzymes, or transporters, since ibalizumab is a monoclonal antibody. Therefore, no drug-drug interaction studies were conducted *in vitro* or *in vivo*.

4 Appendix

4.1 Summary of Bioanalytical Method Validation

Ibalizumab human serum concentrations:
Multiple validated assays from different bioanalytical labs were used for quantification of ibalizumab human serum concentrations in the five clinical studies (TMB-301, TMB-202, TNX-355.01, TNX-355.02, and TNX-355.03), and the validation parameters are summarized in **Table 4.1-1**.

Standards, quality controls, blank matrix, and study samples were prepared according to the validated methods. The standard curve and QC data indicated that the serum assay methods for ibalizumab were precise and accurate. However, cross validation of bioanalytical methods between different labs was not performed. Furthermore, it is unknown if all the samples were analyzed within the time frame supported by the long-term storage stability for TNX-355.01, 02, and 03 studies, since the long-term storage stability was not documented. For TMB-202, the long-term storage stability was demonstrated to be 784 days at - 80°C, and all samples were analyzed within that time frame. For TMB-301, ~ 60% of samples were analyzed beyond the established long-term storage stability of 214 days, and another assay for evaluating long-term storage stability of up to 684 days is planned. The bioanalytical report for ibalizumab concentrations in TNX-355.03 study was not submitted.

For measure of ibalizumab serum concentrations, a sandwich enzyme-linked immunosorbent assay (ELISA) was used for TMB-301 study, and a competitive ELISA was used for TMB-202 and TNX-355.01, 02, 03 studies.

Sandwich ELISA method:
Two monoclonal antibodies (capture antibody and detection antibody) are used to immobilize and detect ibalizumab. Plates are coated with anti-ibalizumab antibody which is used as the capture reagent. After blocking and a subsequent wash step, standards, quality controls and unknown samples are added to the plate at minimum required dilution (MRD) of 1:10. After incubation and a wash step, a horseradish peroxidase (HRP)-conjugated mouse anti-human IgG4 antibody is added as the detection reagent. After another incubation and wash step, 3, 3', 5, 5',-tetramethyl benzidine (TMB) is allowed to react with the bound HRP complex. A regression of the absorbance of the standard curve samples against the concentration is performed and the concentrations of ibalizumab in the samples are determined.

Competitive ELISA method:
The microplate wells are coated with goat anti-mouse IgG (Fc specific). The matrix blank, calibrators, quality controls, and study samples are loaded onto the plate along with solutions containing HRP conjugated ibalizumab and anti-idiotype antibody against ibalizumab. The ibalizumab in the calibrators, quality controls, and samples competes with the ibalizumab-HRP for limited binding sites on the anti-idiotype antibody against ibalizumab, which is subsequently captured by the secondary antibody coated onto the plate. After incubating, any unbound material is removed by washing the plate and TMB substrate solution is added to the wells. TMB acts as the substrate for HRP and produces a colorimetric signal that is inversely proportional to the amount of ibalizumab found in the sample. A high level of bound HRP is an indicator of low levels of ibalizumab in the sample.

Table 4.1-1 Bioanalytical method validation for ibalizumab concentrations in human serum

Study #	TMB-301	TMB-202	TNX-355.01	TNX-355.02	TNX-355.03
Assay type	Sandwich ELISA	Competitive ELISA			
Validation report	TNJS15-039	UNS2 TMB-202	E-1028		
Bioanalytical report	TNJS15-051	TOS TMB-202	E-1007	E-1037	Not submitted
Lab	(b) (4)		Tanox		
Calibration range (ng/mL)	10 to 2000	100 to 2700	100 to 2500		
QC levels (ng/mL)	30, 150, 1400	250, 750, 1500	250, 600, 1800		
Minimum required dilution	10	2	NA		
Dilution linearity (ng/mL)	Up to 160,600,000	Up to 1,000,000	Up to 700,000		
Freeze/Thaw stability	Five cycles	Five cycles	Three cycles		

Storage stability	214 days at -70°C	784 days at -80°C	Not determined
Bench top /refrigerator stability	22 hours 45 minutes	24 hours	4/16 hours
Specificity	Yes	Yes	Yes
Accuracy (%Bias)	± 20% (25% for LLOQ/ULOQ)	< 25%	< 15%
Precision (%CV)	< 20% (25% for LLOQ/ULOQ)	< 20%	< 15%

Anti-drug antibody (ADA):
Multiple validated assays from different bioanalytical labs were used for ADA detection in the five clinical studies, and the validation parameters are summarized in **Table 4.1-2**.

For TNX-355.01, 02, and 03 studies, the ELISA assays for ADA detection were not carried out using a standard 3-tiered assay approach, with some additional limitations as summarized in **Table 4.1-2**. The ADA assay results from these studies were inconclusive (refer to CMC/OBP immunogenicity review for further details).

For TMB-301 study, a bridging sandwich ELISA with acid dissociation was used for ADA detection, while a bridging sandwich ELISA without acid dissociation was used for TMB-202 study.

Bridging sandwich ELISA with acid dissociation method:
The method contains three components: (1) screening assay, which identifies initial putative positive or negative samples, (2) confirmatory assay, which assesses specificity of the positive screen samples, and (3) titration assay which estimates the level of antibody for the confirmed positive samples. In the screening assay, ibalizumab was labelled with Biotin and SULFO-TAG independently. Controls and samples were treated with 600 mM acetic acid first, then neutralized with 1M Trizma base buffer and assay buffer. The neutralized samples were incubated with a mixture of Biotin labeled and SULFO-TAG labeled Ibalizumab. After blocking streptavidin-coated microplates, the sample mixture was added and the plates were then incubated on a plate shaker at room temperature. Next the plates were washed and 1X MSD (Meso Scale Discovery) read buffer was added immediately followed by reading of the plates. The confirmatory assay confirms a positive response from the screening assay is specific by immunodepletion with free drug. The titration assay assesses the amount of antibody present by determining the titer needed to dilute a positive sample to below the sensitivity of the assay.

Bridging sandwich ELISA method:
This assay was carried out using a standard 3-tiered assay approach. Anti-ibalizumab antibodies are captured from human serum samples by a bridging format, taking advantage of the multiple antigen epitopes on each antibody. To capture anti-ibalizumab antibody from human serum samples, the drug, ibalizumab, is bound on a 96-well plate. Diluted human serum (MRD 1:2) is then incubated on plate. This is followed by incubation with HRP conjugated ibalizumab. TMB is used as the HRP substrate in order

to produce a colorimetric signal that is detected a using wavelength of 405nm. Samples are reported as being either negative or potentially positive. This assessment is made by comparing the signal to noise (S/N) value of individual human serum samples to a cutpoint value established during validation. Samples which have a S/N value that is less that the cutpoint value are considered negative, while those that have a S/N greater than or equal to the cutpoint are potentially positive and subjected to further testing. Two levels of PCs, consisting of anti-ibalizumab antibody spiked into human serum, are run on each plate to ensure assay performance. All samples are screened for a +/- response in Tier 1. Tier 2 confirms a positive response is specific by immunodepletion with free drug. Tier 3 assesses the amount of antibody present by determining the titer needed to dilute a positive sample to below the sensitivity of the assay.

Non-bridging sandwich ELISA method:
This assay was developed by using immobilized ibalizumab as capture antibody and HRP labeled anti-human lgG1 as detection antibody. In this assay, rhesus monkey serum containing anti-ibalizumab antibodies from previous preclinical safety study (study No. 575384) was used as reference which was calibrated against mouse anti-idiotype to ibalizumab in the bridging assay (human anti-ibalizumab antibody was not available at that time). The anti-human lgG1 selected as detection antibody have binding capability to both rhesus monkey lgG1 and human lgG1. The concentration of anti-ibalizumab antibodies in patient serum determined by sandwich ELISA is reported in a relative arbitrary unit (eq. ng/ml of monkey anti-ibalizumab). Based on the assay format and calibrator, this assay is intended to be a relative quantitative assay measuring relative amount of anti-ibalizumab antibodies in patient serum if the antibody is present.

Table 4.1-2 Bioanalytical method validation for ADA in human serum

Study #	TMB-301	TMB-202	TNX-355.01	TNX-355.02	TNX-355.03
Assay type	Bridging with acid dissociation	Bridging	Bridging	Non-bridging	Bridging and non-bridging
Validation report	8322-269	VNS2 TMB-202	E-1030	E-1036	E-1030, E-1036
Bioanalytical report	8326-252	UOS TMB-202	E-1008	Not submitted	E-1056
Lab	(b) (4)		Tanox		
Drug tolerance level (ng/mL)	2500	500	Not determined		
Positive control levels (ng/mL)	48 and 4000	50 and 200	50, 250, 750	50, 200, 450, 1000	Same as E-1030/E-1036
Minimum required dilution	10	2	Not determined		
Hook effect (ng/mL)	Up to 8750	Up to 4860	Up to 900	Up to 550	Same as E-1030 /E-1036
Freeze/Thaw stability	Six cycles	Five cycles	Not determined		

Storage stability	566 days at -60 to 80°C	19 days at -70°C	Not determined		
Bench top stability	25 hours 38 minutes	24 hours	Not determined		
Sensitivity (ng/mL)	24.8	6.67	10	33	Same as E-1030/E-1036
Precision (%CV)	< 25%	< 20%	< 20%		

Neutralizing antibody (nAb):
The nAb assay was performed for one ADA positive sample in TMB-202 study (subject 10008 at Week 24 from 2000 mg every 4 weeks arm). This functional ligand binding assay measures neutralizing anti-ibalizumab antibodies in the samples. A streptavidin-coated microplate is first blocked with 1 % BSA/PBST (bovine serum albumin/phosphate buffered saline with Tween-20). Then biotinylated ibalizumab is added to and incubated on the blocked streptavidin-coated plate. After washing step, acid dissociation treated controls and sample are added to the plate and incubated. Next, the incubated plate is washed and ruthenylated CD4 is added to it. After incubation the plate is washed and read within 15 minutes after addition of the MSD read buffer. If nAb is present in the sample, it will competitively block the binding of CD4 to the drug and reduce the assay signal. The assay performance is summarized briefly in **Table 4.1-3** (refer to the CMC/OBP immunogenicity review for further details).

Table 4.1-3 Bioanalytical method validation for nAb in human serum

Study #	TMB-202
Assay type	Functional ligand binding assay
Validation report	(b) (4) RPT04176
Bioanalytical report	(b) (4) RPT04305
Lab	(b) (4)
Drug tolerance level (DTL)	6200 ng/mL for 2000 ng/mL ADA; <160 ng/mL for 100 ng/mL ADA
Positive control levels	100 and 2000 ng/mL
Minimum required dilution	1
Hook effect	Up to 60,000 ng/mL
Freeze/Thaw stability	Five cycles
Storage stability	NA
Bench top stability	~ 24 hours
Sensitivity (ng/mL)	76.29
Precision (%CV)	< 20%

RO/RD:
The bioanalytical reports of clinical samples for RO/RD assays were not submitted, and the validation results are not reviewed.

4.2 Immunogenicity

Immunogenicity was monitored in all the five clinical studies (TMB-301, TMB-202, TNX-355.01, TNX-355.02, and TNX-355.03).

For TNX-355.01, 02, 03 studies, the ELISA assay for ADA detection was not carried out using a standard 3-tiered assay approach, and have several limitations. In addition, the bioanalytical report for ADA detection was not submitted for TNX-355.02 study. The ADA assay results were inconclusive for TNX-355.01, 02, and 03 studies (refer to the CMC/OBP immunogenicity review for further details).

For study TMB-202, one subject (10008) in the 2000 mg once every 4 weeks treatment group had an ADA positive result at Week 24, and the neutralizing antibody (nAb) assay was positive for that sample. However, the titer was low at 16, thus the ADA did not appear to have a negative impact on the antiviral efficacy of ibalizumab. Subject 10008 completed Week 24 with undetectable HIV-1 RNA and a significant increase in $CD4^+$ T-cell count (131 cells/μL). The subject had no AEs associated with the positive immunogenicity result (refer to the CMC/OBP review for the final conclusion regarding immunogenicity risk). The effect on PK was inconclusive due to limited ADA positive samples and large variability in ibalizumab concentrations.

For study TMB-301, no subjects developed ADAs during 24 weeks of treatment with ibalizumab (refer to the CMC/OBP review for further details and the final conclusion).

4.3 Population PK Analysis

4.3.1 Applicant's population PK analysis

Two population PK analyses for ibalizumab were conducted by Applicant. The first one used pooled PK data from a Phase 1a study (Study Hu5A8.01), a Phase 1b study (Study TNX 355.02), and a Phase 2a study (Study TNX 355.03). The second one used PK data from a Phase 2b (Study TMB-202). Different model structures were used in these two population PK analyses and no population PK analysis was conducted based on PK data from the Phase 3 (Study TMB 301).

4.3.1.1 Population PK analysis based on PK data from Phase 1a, 1b and 2a

A population PK model for ibalizumab was developed by the Applicant using pooled PK data from studies Hu5A8.01, TNX 355.02, and TNX 355.03 in HIV-infected patients. Study Hu5A8.01: The study was an open-label, dose-escalation study to assess safety and PK of ibalizumab in HAART-experienced HIV-infected patients. A total of 30 patients were enrolled and randomized to receive a single intravenous (IV) infusion of ibalizumab at escalating dose levels of 0.3, 1, 3, 10 or 25 mg/kg. Each dose group had six patients. IV infusion duration was between 30 to 60 minutes. In addition to pre-dose samples, PK sample were collected at the following times: 0.5 h (for dose cohorts 0.3, 1, and 3 mg/kg), 1 h (for dose cohorts 0.3, 1, 3, and 10 mg/kg), and at 3, 6, 12, 24, 48, 72, and 96

h after the start of treatment. PK samples were also collected on days 7, 14, 21 (only for the cohort 25 mg/kg), 28 and 90 after the start of the treatment. The ibalizumab serum concentrations were determined using a validated ELISA.

Study TNX 355.02: The study was an open-label, multiple-dose study to assess safety and PK of ibalizumab in HIV-infected patients. A total of 22 treatment-experienced and treatment-naïve patients were enrolled and randomized to one of three arms. Patients in Arm A received 10 mg/kg ibalizumab IV infusions every 7 days for a total of 10 doses (N=9). Patients randomized to Arm B received a single loading dose of 10 mg/kg on Day 1 followed by 5 maintenance doses of 6 mg/kg administered every 2 weeks beginning at week 1 by IV infusion (N=10). Only three patients were randomized to Arm C to receive 25 mg/kg every 2 weeks for a dose of 5 doses by IV infusion (infused over 30 to 75 min). Serial serum samples were collected at Day 1 and Week 1, 2, 3, 5, 7, 9, 10, 10+3 days, 11, 11+3 days, 12, 13, 14, 15, and 16 visits for all subjects, and at the Week 24 and 32 visits for subjects in the 25 mg/kg dose cohort. At each visit when ibalizumab was administered, two samples were collected, one an hour or less before the start of infusion and one after the end of the infusion. The ibalizumab serum concentrations were determined using a validated ELISA.

Study TNX 355.03: The study was a randomized, double-blinded, placebo-controlled study with optimized background therapy in treatment-experienced HIV-infected patients. A total of 82 patients (including patients in placebo arm) were randomized to one of three arms. Arm A received IV infusions of 15 mg/kg every two weeks for 48 weeks, with placebo administered on the off weeks during the first nine weeks (N=28). Arm B received 10 mg/kg weekly for nine weeks followed by 10 mg/kg every two weeks until week 48 (N=27). Serum samples were collected prior to dose administration and immediately after the end of the infusion for 48 weeks post dose and when possible during the extended treatment period. The ibalizumab serum concentrations were determined using a validated ELISA.

A one-compartment model with saturable and non-saturable clearance pathways was used to model the PK data. The following modeling equations were used:

$$C_p = \frac{A}{V}$$

$$CL_{Total} = CL_{min} + (CL_{max} - CL_{\min}) \times C_{50}/(C_p + C_{50})$$

$$\frac{dA}{dt} = - CL_{Total} \times C_p + Endg$$

where A is the drug amount (mg) in the compartment, V is the volume of distribution (L), CL_{Total} is the total elimination clearance (L/hr), CL_{min} is the minimum possible clearance (L/hr) occurring at large values of C_p, CL_{max} is the maximum possible clearance occurring as Cp approaches zero, C_{50} is the concentration (mg/L) at which total clearance decreases halfway from its maximum to minimum value, and Endg is a secondary input rate (mg/hr). If the assay does not distinguish between endogenous and therapeutic antibody, then it is possible that endogenous antibody is being included in the concentration measurements, and including the term Endg accounts for this possibility.

Log-normal inter-individual variability was included on V, CL_{min}, and Endg terms. CL_{max} was fixed to 1.5 L/hr in the modeling, based on an extrapolation of non-compartmental estimated clearance vs. dose back to a dose of 0. Intra-individual variability was modeled using both additive and proportional errors.

The parameter estimates are shown below. The goodness of fit is shown in Figure 1.

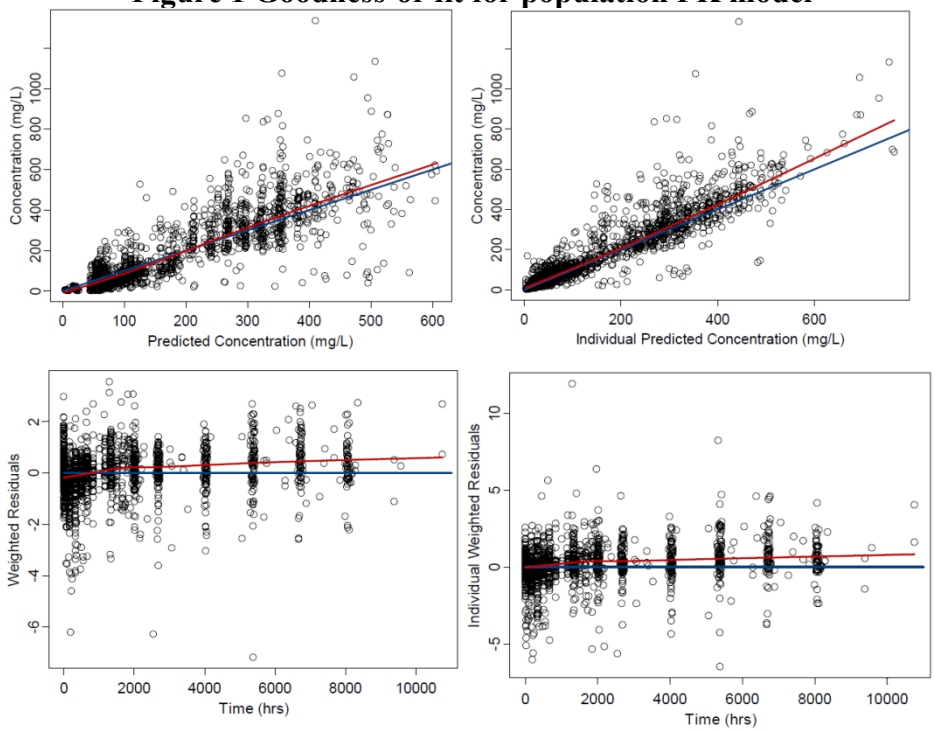
Table 1 Parameter estimates from population PK model

Parameter	Units	Estimate (%SEE)	Between-subject variability (%SEE)
CL_{min}	L/hr	0.032 (8.2%)	43% (28%)
V	L	3.8 (3.7%)	26% (24%)
C_{50}	mg/L	0.010 (230%)	–
CL_{max}	L/hr	1.5 (fixed)	–
Endg	mg/hr	1.5 (18%)	120% (23%)
σ_{prop}	–	0.40 (7.0%)	–
σ_{add}	–	0.0020 (51%)	–

σ_{prop} = proportional error component of intra-individual variability; σ_{add} = additive error component of intra-individual variability.

Source: Applicant's population PK report for TNX 355, Page 7, Table 3

Figure 1 Goodness-of-fit for population PK model



Source: Applicant's population PK report for TNX 355, Page 12-15, Figure 3-6

The estimated volume of distribution (V) was 3.8 L (with 3.7% SEE), indicating that ibalizumab is primarily confined to plasma volume. The clearance model used here is

similar to a first-order clearance plus a Michaelis-Menten clearance term model, and was used because monoclonal antibodies usually demonstrate saturable and non-saturable clearance pathways. The lower limit of quantitation (LLOQ) for the assay was 0.1 μg/mL. For model fitting, concentrations less than or equal to 1 μg/mL were excluded.

Reviewer's comment: The reviewer verified the population PK model based on Phase 1a, 1b and 2a studies. The model can reasonably describe the data. The Applicant did not conduct covariate analysis. The demographics of Phase 1a, 1b, 2a studies are summarized in Table 2.

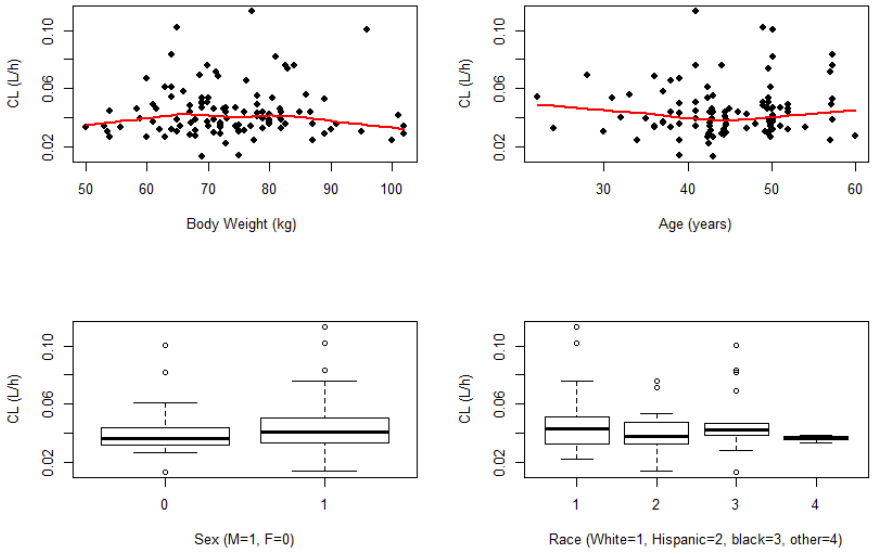
Table 2 Demographics of Phase 1a, 1b, and 2a studies

	Phase 1a	*Phase 1b*	*Phase 2a*	*Total*
No. of subjects	*30*	*22*	*55*	*107*
Age (mean±SD), year	*42.3±7.0*	*40.5±9.3*	*48.1±4.7*	*45.1±7.2*
Gender				
Male (%)	*26 (87%)*	*18 (82%)*	*41(75%)*	*85 (79%)*
Female (%)	*4 (23%)*	*4 (18%)*	*14 (25%)*	*22 (21%)*
Race				
Caucasian (%)	*24 (80%)*	*17 (77%)*	*26 (47%)*	*67 (63%)*
Hispanic (%)	*3 (10%)*	*2 (9%)*	*15 (27%)*	*20 (19%)*
Black (%)	*2 (7%)*	*3 (14%)*	*12 (22%)*	*17 (16%)*
Other (%)	*1 (3%)*	*0*	*2 (4%)*	*3 (3%)*
Weight (mean±SD), kg	*72.0±8.6*	*75.6±11.7*	*74.0±11.6*	*73.9±11.0*

Source: Reviewer's analysis

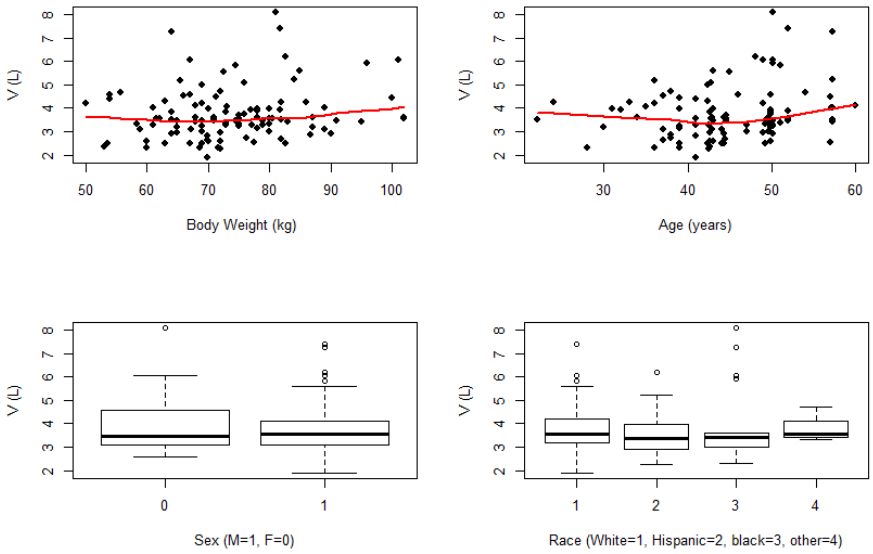
The Reviewer did exploratory graphical analysis to identify potential covariates (body weight, age, sex and race) on CL_{min}, V, and Endg as shown in Figures 2, 3 and 4. No significant covariate relationships were identified for CL_{min}, V, and Endg based on these assessments. This population model structure with maximum and minimum CL would result in a limited use of simulations as the prediction would only be qualified for the dose range included in the population PK dataset (0.3 mg/kg to 25 mg/kg). As such, it would not be suitable for exploration of different doses and dosing intervals.
In addition, the Applicant excluded all the concentrations below 1 μg/mL. As most of the concentrations lower than 1 μg/mL were trough concentrations that are important for CL_{max} estimation, it is not reasonable to exclude these data. In addition, it is highly recommended to use M3 method to deal with the LLOQ data (concentration lower than 0.1 μg/mL) in the population PK model as these measurements are informative regarding model parameters. Likewise, the outright exclusion of these samples can lead to biased parameter estimates. The Reviewer conducted an independent population PK analysis with all the data including concentrations lower than 1 μg/mL and LLOQ data. Details on this analysis are provided in section 4.3.2.

Figure 2 Relationship between potential covariates and CL_{min}



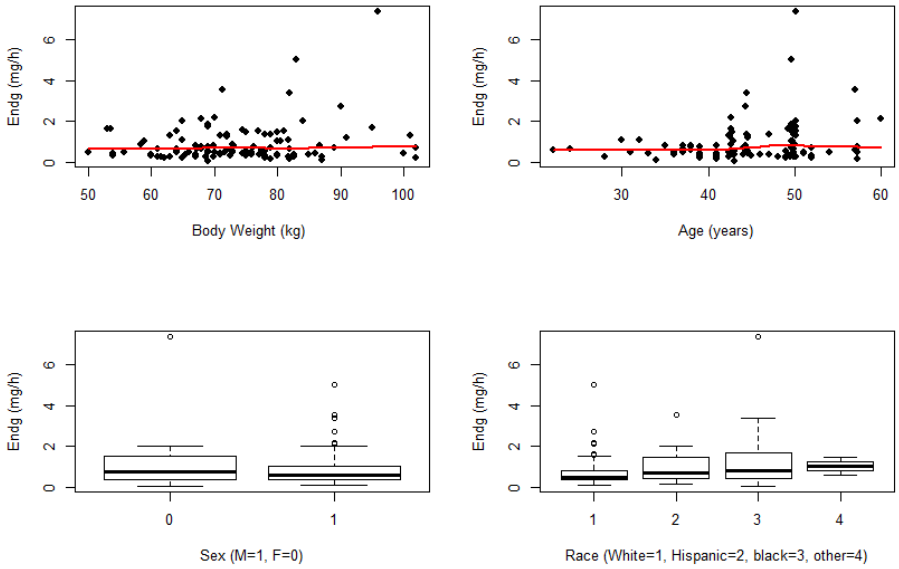
Source: Reviewer's analysis

Figure 3 ***Relationship between potential covariates and volume of distribution (V)***



Source: Reviewer's analysis

Figure 4 ***Relationship between potential covariates and endogenous antibody (Endg)***



Source: Reviewer's analysis

4.3.1.2 Population PK analysis based on PK data from Phase 2b

A population PK model with parallel Michaelis-Menten (MM) and first order elimination was developed by the Applicant using PK data from Study TMB-202 (Phase 2b) in HIV-infected patients.

Study TMB-202: The study was a randomized, double-blinded study. A total of 113 patients infected with HIV-1 who had been treated with HAART for at least 6 months and were failing, or had recently failed (i.e., in the last 8 weeks) therapy were enrolled. Patients were 1:1 randomly assigned to receive one of the following two dose regimens: 1) 800 mg of ibalizumab every 2 weeks plus OBR; 2) 2000 mg of ibalizumab every 4 weeks and placebo on the intervening 2-week period visit plus OBR. All patients had blood samples collected before and immediately after administration of study drug for the duration of the study. Sixteen patients were enrolled in the PK substudy in the 800 mg every 2 week arm and 11 patients were enrolled in the 2000 mg every 4 weeks arm. Beginning at Week 8, patients in the PK substudy had an additional series of 23 blood samples collected over 28 days. These additional samples were drawn immediately following the Week 8 study drug administration and on the following days, ± 3 hours, after the Week 8 study drug administration: 7, 8, 9, 10, 11, 14 (coincides with Week 10 Visit: 2 PK samples), 21, 22, 23, 24, 25, and 28 (coincides with Week 12 Visit: 2 PK samples). Serum concentrations were measured using a validated ELISA assay.

A summary of demographic and baseline characteristics of the patients is shown in Table 3.

Table 3 Summary of demographic characteristics

Parameter (units)	Subjects N = 108
Mean Age, years (± SD)	48.9 (± 7.4)
Sex	
Female (%)	12 (11.1%)
Male (%)	96 (88.9%)
Race	
Caucasian (%)	69 (63.9%)
Hispanic	13 (12.0%)
Asian	0 (0.0%)
Black (%)	27 (25.0%)
Mean Weight, lbs. (± SD)	
Female	178.1 (± 34.4)
Male	178.4 (± 35.4)

Source: Applicant's population PK report for Study TMB-202, Page 29, Table 1

As information of receptor concentrations was not available in this study, a population PK model with zero order input and parallel first order and saturable output was developed. Age was identified as a significant covariate on Kss.

$$V2 = \theta_1$$
$$K = \theta_2$$
$$Kss = \theta_3 + \theta_5 * Age$$
$$Vm = \theta_4 * e^{-\eta 1}$$
$$\frac{dC}{dt} = \frac{Dose}{V2} - K * C - \frac{Vm * C}{Kss + C * V2}$$

The parameter estimates of final model are listed in Table 4.

Table 4 Estimates for final model parameters

Parameter	V_2	K	K_{ss}	V_m	THETA (AGE)	η (V_m)	ε
Model Value	5.83	0.00244	1.83	0.0435	0.0779	0.281	0.491
SE%*	3.3	16.9	70.5	53.1	72.5	18.7	9.5
Bootstrap Mean	5.68	0.00214	34.42	0.539	0.926	0.326	0.448
Mean SE%	3.8	132.0	167.8	138.6	164.2	45.8	10.5
Bootstrap Median	5.74	0.00225	3.96	0.068	0.116	0.315	0.467
Bootstrap 95% Confidence Interval	5.0-6.1	0.00003-0.00368	4.0-165.6	0.021-3.42	0.006-7.48	0.130-0.593	0.252-0.560

*Standard Error %

Source: Applicant's population PK report for Study TMB-202, Page 41, Table 5

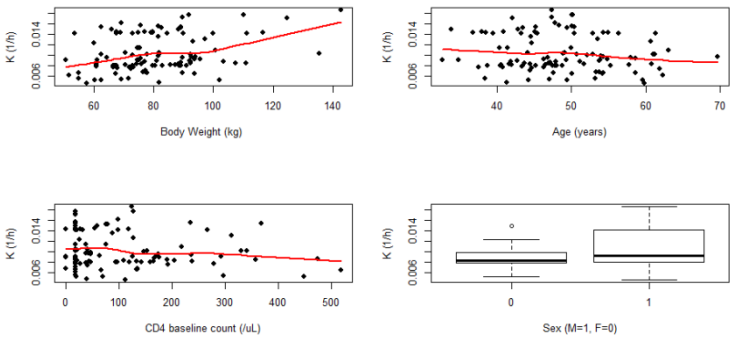
The parameters associated with the nonlinear process were not well estimated, although still reasonable. The SE% for the bootstrap parameter estimates was substantially greater

than those of the final model with associated SE% bigger than 100%. The final model tended to under predict the high concentrations while over predicting lower concentrations. Applicant did not provide any diagnostic plots that would suitably permit evaluation of model performance.

Reviewer's comments: The Reviewer repeated the population PK analysis submitted by Applicant. The Reviewer identified a significant flaw in the population PK dataset in that 2000 mg ibalizumab was supposed to be given every 4 weeks with placebo on the intervening 2-week period visit to match the dosing interval of 800 mg treatment arm. However, the dose of 2000 mg was coded as being given every 2 weeks in the population PK dataset. The Reviewer corrected the dosing error and conducted an independent population PK analysis on the updated dataset.

A one compartment model with parallel Michaelis-Menten (MM) and first order elimination was used as a base model. The unit for concentration in Applicant's population PK analysis was µmol/L. The Reviewer used concentration units of µg/mL. The PK data was log-transformed to improve the fitting. The reviewer excluded concentrations lower than 1 µg/mL and did not use M3 method to handle the BLQ as the reviewer was trying to follow Applicant's analysis. Inter-subject variability was added to K (clearance divided by volume of distribution using more traditional parameterization). Body weight was identified as a significant covariate on K as shown in Figure 5.

Figure 5 Covariate analyses for K



Source: Reviewer's analysis

As only Study 202 with sparse PK sampling was used to develop the population PK model, the parameters were poorly estimated with large variability. The model successfully converged but standard errors cannot be generated until the values of kss and Vm were fixed. The parameter estimates are shown in Table 5.

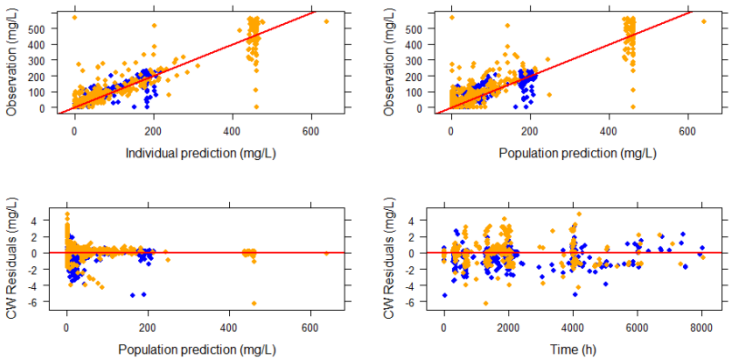
Table 5 Parameter estimates for population PK model using concentrations of µg/mL

Parameter	*V2 (L)*	*K (h^{-1})*	*Kss (mg)*	*Vm (mg/h)*	*BW*	*ETA(K)*	*Residual*
Model value	*3.24*	*0.0084*	*1.2 FIX*	*0.472 FIX*	*0.629*	*0.223*	*1.32*
SE%	*3%*	*0.4%*	*-*	*-*	*0.4%*	*1591.9%*	*6.4%*

Source: Reviewer's analysis

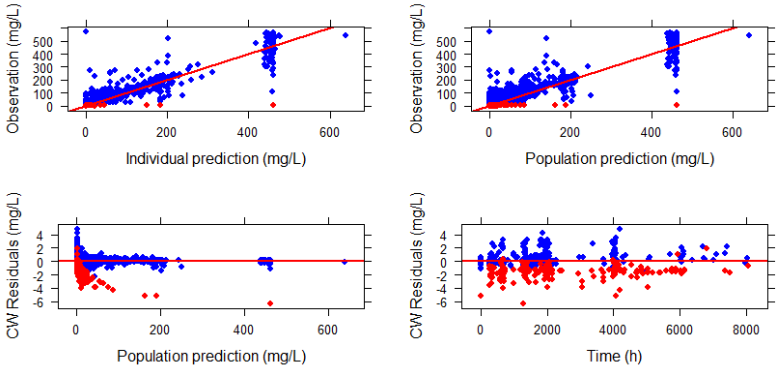
The goodness of fit by dosing regimen showed the PK of ibalizumab appeared to reasonably predict the PK data for both dosing regimens (Figure 6). The goodness of fit by concentrations less than 1 µg/mL/greater than 1 µg/mL showed the concentrations less than 1 µg/mL were over-predicted and the concentrations greater than 1 µg/mL were under-predicted by the population PK model (Figure 7).

Figure 6 Goodness of fit by dosing regimen



Blue dots represent the concentrations with a dose of 2000 mg Q4W and orange dots represent the concentrations with a dose of 800 mg Q2W.
Source: Reviewer's analysis

Figure 7 Goodness of fit by concentrations lower than 1 µg/mL or not



Blue dots represent the concentrations not lower than 1 µg/mL and red dots represent the concentrations lower than 1 µg/mL
Source: Reviewer's analysis

In summary, the two population PK models developed by Applicant had limitations and may not be able to provide information for informing dose adjustments in subpopulations or for conducting exposure-response analysis. To address this limitation, independent population PK analyses were conducted by the reviewer.

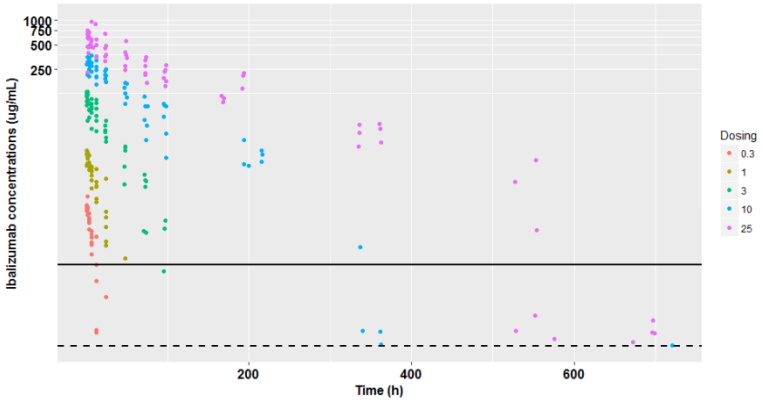
4.3.2 Reviewer's population PK model

The Reviewer conducted an independent population PK analysis using pooled PK data from the Phase 1a study (Study Hu5A8.01), Phase 1b study (Study TNX 355.02), Phase 2a study (Study TNX 355.03), and Phase 2b study (Study TMB-202). The population PK analysis did not included Phase 3 study (Study TMB-301) as a different bioanalytical method was used in this study.

The dataset was created by the Reviewer based on two submitted population PK dataset (m101906.xpt and f12_5_4.xpt). The concentrations lower than 1 µg/mL was not included in dataset of m101906.xpt. The Reviewer added these PK data back for Phase 1a and 1b studies based on the provided population PK datasets of ph1apk.xpt and ph1bpk.xpt. As discrepancies in dosing and PK sampling time were identified for Phase 2a study based on the population PK dataset (m101906.xpt) and three clinical study datasets (PKTIME.xpt, serum.xpt, and exposure.xpt), an IR letter was sent on July 21, 2017 to the Applicant requesting inclusion of concentrations lower than 1 µg/mL in dataset m101906.xpt. The Applicant responded on July 31, 2017 with an updated dataset including these concentrations (m101906r.xpt).

The observed PK data for Phase 1a study is listed in Figure 8. A faster elimination was observed for low doses (0.3, 1 and 3 mg/kg), and a slower elimination was observed for high doses (10 and 25 mg/kg). This observation is consistent with target-mediated drug disposition, which is hypothesized to play a role in the elimination of ibalizumab.

Figure 8 Observed PK data for Phase 1a study by dose



The red, yellow, green, blue and pink dots represent the PK data for doses of 0.3, 1, 3, 10, and 25 mg/kg, respectively; the horizontal solid line and dashed line represent the concentration of 1 µg/mL and 0.1 µg/mL, respectively.
Source: Reviewer's analysis

A one-compartment model with parallel Michaelis-Menten (MM) and first-order elimination was used to describe the PK. The equation for this compartmental structure is displayed below. PK data was log-transformed in the population PK analysis. As more than 10% observations are lower than LLOQ, defined as concentrations lower than 0.1

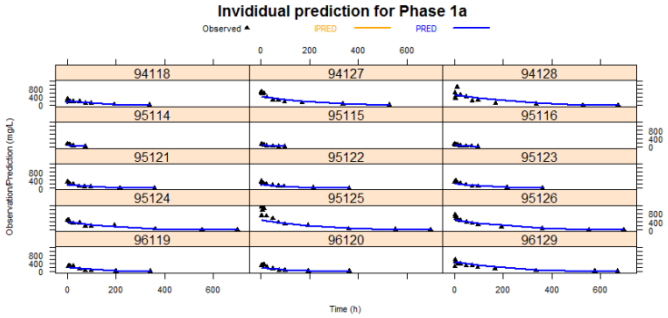
μg/mL, the M3 method was used to deal with the LLOQ data (Bergstrand, Karlsson, AAPS J, 2009).

$$\frac{dC}{dt} = \frac{Dose}{V2} - \frac{CL}{V2} * C - \frac{Vm * C}{Kss + C}$$

The model was initially applied to the PK data in Phase 1a study, which included a wide range of single doses. The partial results of individual prediction and goodness of fit by dose are listed in Figures 9 and 10.

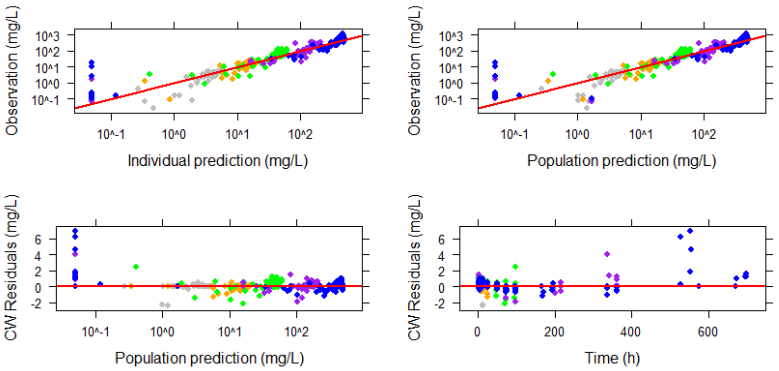
As no inter-subject variability was introduced initially, the individual and population predictions were identical. In general, the model can reasonably describe the PK data across all five doses, though there is some bias at low concentrations.

Figure 9 Individual predictions for Phase 1a (partial results)



Source: Reviewer's analysis

Figure 10 Goodness of fit for Phase 1a by dose (log scale)



Grey, orange, green, purple, and blue dots represent the PK data with dose of 0.3, 1, 3, 10, 25 mg/kg.
Source: Reviewer's analysis

The parameter estimates for the Phase 1a study data are summarized in Table 6.

Table 6 Parameter estimates for Phase 1a study

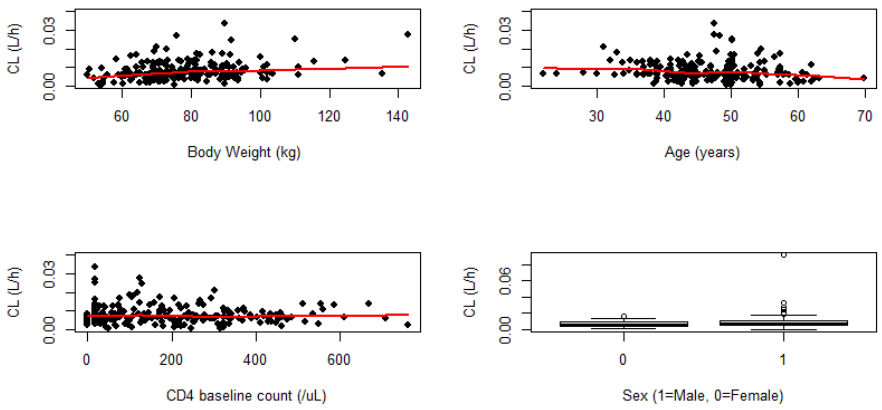
Parameter	Model value	RSE%
CL (L/h)	0.0094	0.1%

V2 (L)	4.1	6.0%
Vm (mg/L/h)	0.547	2.8%
Kss (mg/L)	3.06	23.3%
Residual	0.861	11.6%

Source: Reviewer's analysis

The PK data from Phase 1b, 2a, and 2b studies were added afterwards. As sparse PK data were collected in these studies, it would be difficult to precisely estimate all the parameters. The value of Vm was fixed to 0.547 as the doses evaluated in these studies did not reliably permit estimation of the nonlinear elimination term. The estimate of Kss was dramatically increased after adding PK data from Phase 1b, 2a, and 2b studies. Inter-subject variability was added to CL based on an improvement in the objective function value (OFV). The covariate analysis tested several potential demographic parameters (e.g. body weight, age, CD4 count at baseline, sex) on CL. The results are shown in Figure 11. A shallow relationship between CL and body weight was visualized suggesting that higher body weight patients would have a higher CL. A reverse trend was found for age and it is because the body weight and age are well correlated. OFV was used to evaluate the potential covariate candidate, and a reduction in the OFV of 3.8 units or more is considered as a statistically significant improvement in model fitting.

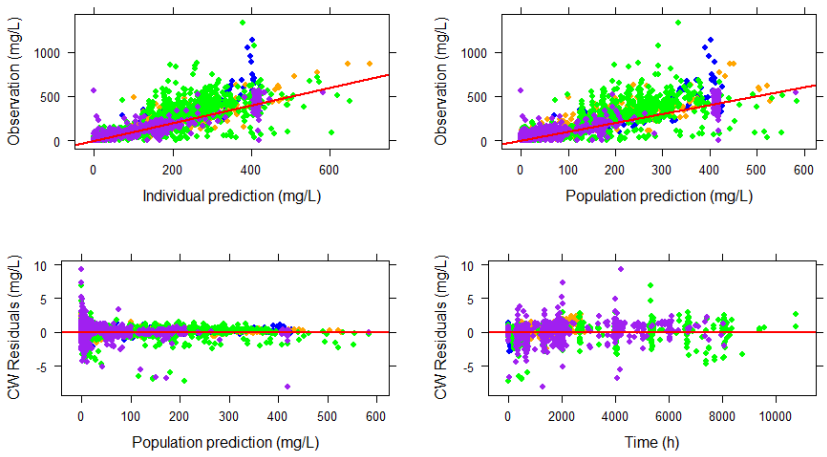
Figure 11 Covariate analyses for CL



Source: Reviewer's analysis

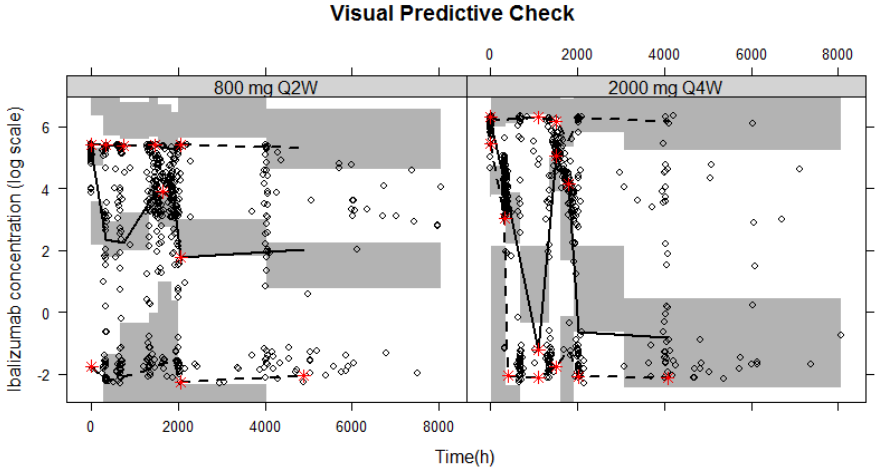
The final model included body weight as significant covariate on CL. No additional covariates were identified. Due to sparse PK sampling, the standard error in model parameters could not be generated until the Kss was fixed to the final estimates of 31.7. The goodness of fit by study is shown in Figure 12. The VPC plot with log scale for Phase 2b is shown in Figure 13. The big spike in VPC plot is because that sparse PK samples were taken at other time points while relative intensive PK samples were taken at that time (Week 8 to 14). Overall, the VPC plots show the model can reasonably describe the available PK data.

Figure 12 Goodness of fit for the population PK model by Phase 1a, 1b, 2a, and 2b studies



Blue dots represent PK from Phase 1a study; orange dots represent PK from Phase 1b study; green dots represent PK from Phase 2a study; purple dots represent PK form Phase 2b study.
Source: Reviewer's analysis

Figure 13 VPC plot for Population PK model based on Phase 2b study (log scale)



Source: Reviewer's analysis

The final parameter estimates are listed in Table 8.

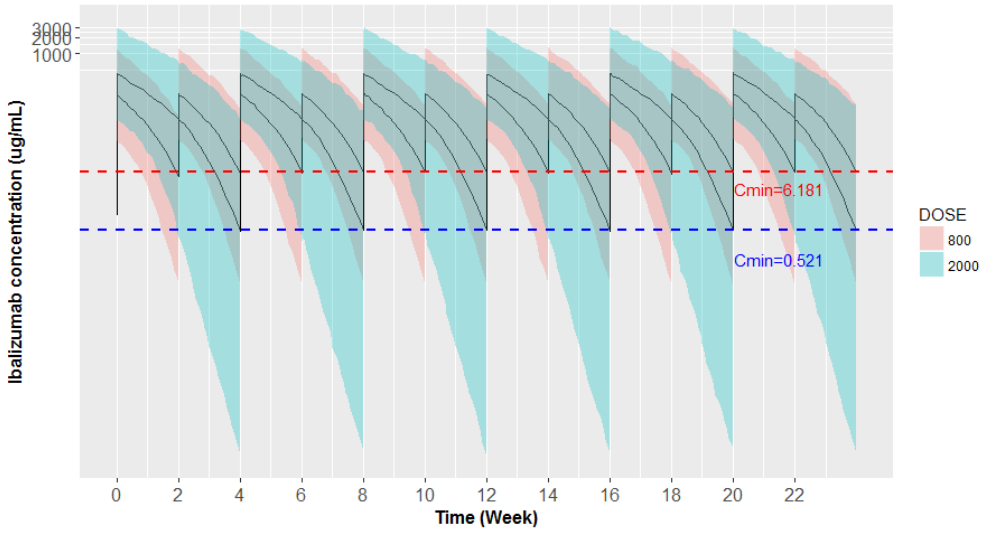
Table 8 Final Parameter estimates for population PK model based on 4 clinical studies

Parameter	Model value (CV%)	RSE%
CL (L/h)	0.0121	<0.01%
V2 (L)	4.77	0.01%
Vm (mg/L/h)	0.547 FIX	-
Kss (mg/L)	35.3 FIX	-
Body Weight on CL	0.608	<0.01%
ETA on CL	0.536 (73.2%)	0.01%
Residual	1.01 (100%)	0.01%

Source: Reviewer's analysis

The PK profiles of patients in Phase 2b were simulated based on the final population PK model. A total of 100 simulations were conducted. The mean (and 95% predictive interval) of the simulated PK profiles for the two dosing regimens are plotted in Figure 14. The summary of trough concentrations at week 24 was listed in Table 9.

Figure 14 Simulated mean (±95% predictive interval) PK profiles with doses of 2000 mg Q4W and 800 mg Q2W



Red represents the predicted PK profile with a dose of 800 mg Q2W and blue represents the predicted PK profile with a dose of 2000 mg Q4W.
Source: Reviewer's analysis

Table 9 Predicted PK parameters for patients in Phase 2b study

Parameter	Dose	No. of Subject	Median	95% Predictive interval
C_{trough} at Week 24 (µg/mL)	800 mg	5600	6.181	0.047-111.153
C_{trough} at Week 24 (µg/mL)	2000 mg	5100	0.521	<0.001-111.992

Source: Reviewer's analysis

PK profiles for the Phase 3 dosing regimen (2000 mg followed by 800 mg Q2W infused over 30 min starting from Week 2) were simulated based on the final population PK model with 4 clinical studies and demographic information from Phase 3 study. A total of 100 simulations were conducted. The mean of PK profile based on 100 simulations was generated for each subject. The predicted C_{trough}, AUC values for patients in Phase 3 study are listed in Table 10.

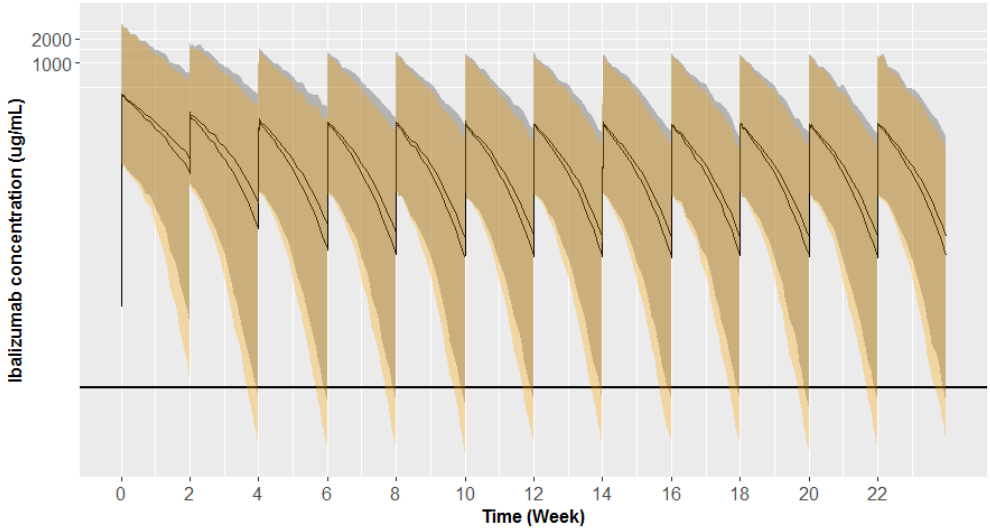
Table 10 Predicted PK parameters for patients in Phase 3 study

Parameter	Last Dose	No. of Subject	Mean	95% Predictive interval	Max
C_{trough} at Week 2 (µg/mL)	2000 mg	40	47.8	22.9-73.5	87.9
C_{trough} at Week 24 (µg/mL)	800 mg	40	5.3	2.3-8.6	9.2
$AUC_{0\text{-}2weeks}$ (µg*hr/mL)	2000 mg	40	64969	55873-75538	76809
$AUC_{22\text{-}24weeks}$ (µg*hr/mL)	800 mg	40	21491	18210-24964	26991

Source: Reviewer's analysis

A similar simulation was conducted for 40 subjects with two uniform body weight ranges: one was 50-90 kg and the other was 90-130 kg. The mean PK profiles and their 95% predictive intervals are plotted in Figure 15. Comparable trough concentrations were identified between the two body weight ranges (Table 11). As such, a fixed dosing regimen appears to be reasonable in HIV-1 infected patients. It is worth noting that the body weight range was very narrow in the population PK model, and that the impact of body weight may not be precisely estimated.

Figure 15 Simulated PK profiles with a dose of 2000 mg followed by 800 mg Q2W starting from Week 2 by two body weight ranges



Grey shaded area represents the 95% predictive interval for PK profiles in a body weight range of 50-90 kg; Orange shaded area represents the 95% predictive interval for PK profiles in a body weight range of 90-130 kg; solid line at bottom represents the concentration threshold of 0.1 µg/mL (BLQ).
Source: Reviewer's analysis

Table 11 Predicted PK parameters for patients by different body weight range

Parameter	Patients with body weight range of 50-90 kg	Patients with body weight range of 90-130 kg
C_{trough} at Week 2 (µg/mL) Median, 95% predictive interval	68.5 (0.6-751.8)	45.9 (0.1-620.1)
C_{trough} at Week 24 (µg/mL) Median, 95% predictive interval	7.4 (0.06-124.1)	4.4 (0.02- 88.0)

Source: Reviewer's analysis

4.4 Exposure-response Analysis

The exposure-response relationship for efficacy was evaluated in HIV-1 infected patients from the Phase 2b study. The trough concentrations at week 24 were generated based on the reviewer's population PK model (Section 4.3.2) with doses of 2000 mg Q4W or 800 mg Q2W infused over 30 min. The evaluated efficacy endpoint was the percent of patients with HIV-1 RNA levels <50 copies/mL at week 24. A numerically lower response rate was observed at Week 24 (15%) in those subjects with predicted C_{trough} concentrations in the lowest exposure quartile (ranging between 0.1-0.3 µg/mL) (Table 12). The response rate at Week 24 achieved a platuea for subjects in all other quartiles.

Table 12 Relationship between exposure quartile and efficacy endpoint for Phase 2b study

Quartile	Ctrough at Week 24 (µg/mL)	No. of Subjects	% patients with HIV-1 RNA levels < 50 copies/mL at week 24
Q1	0.1-0.3	27	15%
Q2	0.3-2.3	27	41%
Q3	2.4-5.1	26	38%
Q4	5.2-12.4	27	43%

Source: Reviewer's analysis

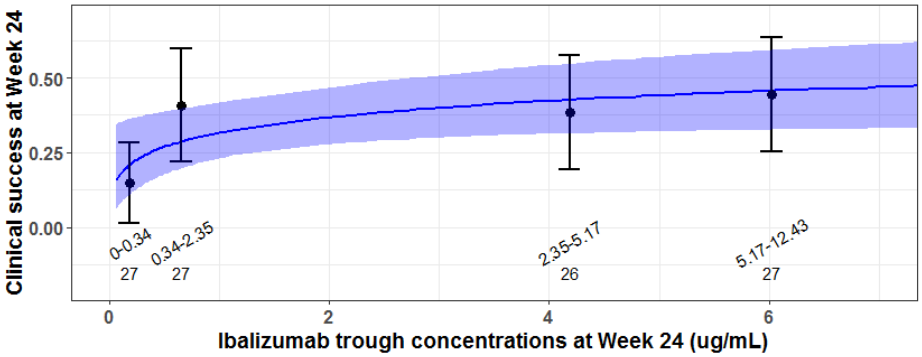
A logistic regression with log-transformed concentrations was used to predict the relationship between trough concentrations and response rate at Week 24. The equation is as follows:

$$Logit\ (y) = \alpha + \beta \times \log\ (x) + \varepsilon$$

Where y represents the response rate (binary); α represents the intercept; β represents the slope; χ represents the individual trough concentration at Week 24; ε represents the residual variability.

The result is shown in Figure 16. The parameter esimates are listed in Table 13. The slope was statistically significant with p value of 0.026, suggesting that there was a clear trend between exposure and response rate. The E-R relationship was relative sharp with a substantial drop-off in response rate for concentrations lower than 0.5 µg/mL.

Figure 16 Relationship between exposure and efficacy endpoint for Phase 2b study



Source: Reviewer's analysis

Table 13 Parameter estimates for the logistic regression with log-transformed concentrations

	Estimates	*Standard Error*	*P value*
Intercept (α)	*-0.77*	*0.22*	*<0.01*
Slope (β)	*0.33*	*0.15*	*0.026*

Source: Reviewer's analysis

The impacts of covariates including viral load at baseline (log_{10} transformed), CD4 cell count at baseline (log_{10} transformed), genotype sensitivity score (GSS), overall sensitivity score (OSS), and body weight were tested. There was no relationship between body weight and GSS with response rate. CD4 cell count at baseline and viral load at baseline had a significant impact on response rate with p values of 0.005 and 0.0287, respectively. The relationship between CD4 cell count or viral load at baseline and response rate is summarized in Tables 14 and 15. The results show that the higher CD4 cell count at baseline is predictive of a higher response rate. Likewise, higher viral load at baseline was associated with a lower response rate. This is not unexpected as both higher CD4 cell count and lower viral load at baseline are associated with a less extensive infection and better treatment outcomes across other HIV drug development programs. Although OSS was not identified as a significant covariate on response rate, Table 16 summarizes the response rate at different OSS levels. There was a trend that higher OSS is associated with higher response rate.

Table 14 Relationship between CD4 cell count at baseline quartile and efficacy endpoint for Phase 2b study

Quartile	CD4 cell count at baseline (log10) (/μL)	No. of Subjects	% patients with HIV-1 RNA levels < 50 copies/mL at week 24
Q1	19 (1.3)	30	13%
Q2	20-65 (1.3-1.8)	24	29%
Q3	68-147(1.8-2.2)	26	54%
Q4	154-518 (2.2-2.7)	27	44%

Source: Reviewer's analysis

Table 15 Relationship between viral load at baseline quartile and efficacy endpoint for Phase 2b study

Quartile	Viral load at baseline (log10) (copies/mL)	No. of Subjects	% patients with HIV-1 RNA levels < 50 copies/mL at week 24
Q1	71-14000 (1.9-4.2)	28	43%
Q2	14100-51300 (4.2-4.7)	26	46%
Q3	51600-153000 (4.7-5.2)	26	31%
Q4	154000-292000 (5.2-6.5)	27	19%

Source: Reviewer's analysis

Table 16 Relationship between OSS at baseline and efficacy endpoint for Phase 2b study

OSS	No. of Subjects	% patients with HIV-1 RNA levels < 50 copies/mL at week 24
0	16	25%
1	36	31%
2	41	39%
>2	14	43%

Source: Reviewer's analysis

A similar covariate analysis was conducted in patients from Phase 2b and 3 studies. The results are consistent with those in patients from Phase 2b study only (Table 17, 18 and 19).

Table 17 Relationship between CD4 cell count at baseline quartile and efficacy endpoint for Phase 2b and 3

Quartile	CD4 cell count at baseline (log10) (/μL)	No. of Subjects	% patients with HIV-1 RNA levels < 50 copies/mL at week 25
Q1	0-19 (0-1.3)	37	16%
Q2	19-68 (1.3-1.8)	36	29%
Q3	68-173.5 (1.8-2.2)	37	50%
Q4	173.5-676 (2.2-2.8)	37	54%

Source: Reviewer's analysis

Table 18 Relationship between viral load at baseline quartile and efficacy endpoint for Phase 2b and 3

Quartile	Viral load at baseline (log10) (copies/mL)	No. of Subjects	% patients with HIV-1 RNA levels < 50 copies/mL at week 25
Q1	71-14000 (1.9-4.2)	39	46%
Q2	14000-43100 (4.2-4.6)	35	49%
Q3	43100-145500 (4.6-5.2)	36	33%
Q4	145500-292000 (5.2-6.5)	37	19%

Source: Reviewer's analysis

Table 19 Relationship between OSS at baseline and efficacy endpoint for Phase 2b and 3

OSS	No. of Subjects	% patients with HIV-1 RNA levels < 50 copies/mL at week 25
0	21	24%
1	48	33%
2	59	42%
>2	19	42%

Source: Reviewer's analysis

In conclusion, lower response rates were observed in patients with predicted C_{trough} in the lowest quartile (C_{trough} range of 0.1-0.3 μg/mL). There was a clear trend between

exposure and the efficacy endpoint using logistic regression with log-transformed cocentrations. This result suggests that exposures (Week 24 trough concentrations) exceeding a certain threshold would not provide further benefit. Based on Table 9, the dose of 800 mg Q2W would result in more patients having trough concentrations at Week 24 higher than the threshold while the dose of 2000 mg Q4W would result in around half of the patients having trough concentrations at Week 24 lower than the threshold. Therefor, the E-R analysis supports the selection of 800 mg Q2W to avoid the potential loss of efficacy.

On the other hand, based on Table 11, body weight, which is the only covariate on CL, did not have a relevant impact on exposure. Therefore, a need for dose adjustment based on patient covariates or the exposure-response relationship was not identified for any subpopulation. The Applicant's proposed fixed dosing appears appropriate, and mg/kg dosing as was utilized earlier in development does not appear to be necessary. Treatment outcomes were influenced by various patient factors included CD4 cell count, viral load, and to a lesser extent OSS. These findings are not unexpected and a similar role of these patient factors on HIV-treatment outcomes has been observed in other development programs and described in labeling, reviews, literature, and treatment guidelines.

The E-R relationship for safety was not performed, since there were no significant safety concerns identified in the Phase 3 study. The majority of the reported safety events appear to be secondary to HIV/AIDS (refer to the clinical review for further details). The most common adverse reactions (all Grades) reported in at least 3% of subjects were diarrhea, dizziness, nausea, and rash, and most (90%) of the adverse reactions reported were mild or moderate in severity.

4.5 Individual Clinical Pharmacology Report Reviews

4.5.1 TNX-355.01 Phase 1a Study

1. Title

A Phase 1, Multicenter, Open-Label, Dose-Escalation, Safety, and Pharmacokinetic Study of the Anti-CD4 Monoclonal Antibody Hu5A8 or TNX-355 in Patients Infected with the Human Immunodeficiency Virus

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at 6 US clinical sites from October 24, 2001 to September 09, 2002, with the final report date of February 26, 2004.

3. Objectives

Primary objective:

- To assess the safety of single intravenous infusions of 0.3, 1.0, 3.0, 10.0 and 25 mg/kg of the anti-CD4 monoclonal antibody (mAb) TNX-355 in patients infected with

human immunodeficiency virus (HIV).

Secondary objectives:

- To determine the pharmacokinetics (PK) of TNX-355 after single-dose administration
- To determine the effects of a single dose of TNX-355 on HIV load
- To determine the effects of a single dose of TNX-355 on the number of $CD4^+$ T lymphocytes ($CD4^+$ cells)

4. Trial Design

This was a phase 1, multicenter, open-label, dose-escalation, safety, and pharmacokinetics study of the anti-CD4 mAb, TNX-355, in patients infected with HIV. The initial cohort of 6 patients who satisfied inclusion criteria received a single dose by intravenous infusion of 0.3-mg/kg TNX-355; successive cohorts received increasing dose levels of 1.0, 3.0, 10.0, or 25 mg/kg TNX-355. The safety and tolerability of an individual dose level of TNX-355 were determined before enrollment of patients for infusion at the next higher dose.

The duration of infusion was 0.5 hour for 0.3, 1.0, and 3 mg/kg, 1 hour for 10 mg/kg, and 1.5 hours for 25 mg/kg.

Eligible subjects were HIV-1 infected patients meeting the following criteria:

- 18 years of age or older
- Weight ≤ 100 kg
- Had a $CD4^+$ cell count > 200 cells/μL (however, 50% of enrolled subjects in the study may have had a $CD4^+$ cell count of > 100 cells/μL and ≤ 200 cells/μL).
- Had a viral load > 5,000 copies/mL and had a stable plasma HIV RNA level
- Patients who discontinued any antiviral regimen were to have been off-therapy for ≥ 8 weeks prior to enrollment.
- Patients who were failing their current antiviral regimen at the time of enrollment were to continue that same regimen for the duration of the study.

5. Excluded Medications and Restrictions

- Received immunomodulating therapy, systemic chemotherapy, or had participated in a trial of an experimental immunomodulating drug or antiretroviral therapy within 12 weeks of enrollment.
- Participated in an HIV vaccine study at any time

6. Rationale for Doses Used in the Trial

Ibalizumab: single IV infusion doses at 0.3, 1.0, 3.0, 10.0 and 25 mg/kg

These single ascending IV infusion doses were chosen based on pre-clinical efficacy model and toxicity studies. The dose at 3.0 mg/kg, given intravenously every 3 days to rhesus monkeys that were chronically infected with SIV_{mac}, resulted in a significant decrease in SIV proviral load. The chosen dose levels permitted analysis of the safety and tolerability of TNX-355 doses that bracket the 3 mg/kg dose and differ in TNX-355 dose levels relative to the 3-mg/kg dose by 3- to 10-fold, according to the sponsor.

7. Drugs Used in the Trial

Ibalizumab: injection solution, ~ 5.3 mg/mL in phosphate-buffered saline containing 0.02% polysorbate 80, pH 7.0.
Lot number: 801736A or 801736AA
Manufacturer: Tanox

8. Sample Collection, Bioanalysis, and Pharmacokinetic/Pharmacodynamic Assessments

Sample Collection
Ibalizumab serum concentrations:
Serum concentrations of TNX-355 were determined prior to the start of infusion and on Day 0: 30 minutes (only for doses of 0.3, 1.0, and 3.0 mg/kg; end of infusion), 1, 3, 6, and 12 hours after the start of infusion. Serum concentrations were also measured on Days 1 through 4, 7, 14, 21 (only for the 25.0 mg/kg), 28, and 90 after the start of infusion.

Receptor occupancy (RO):
Blood samples were collected for RO assay on Day 0 within 1 hour before the start of infusion, at 3 hours after the start of the infusion, and on Days 1, 2, 3, 4, 7, 14, 21 (only for the 25.0 mg/kg), and 28.

ADA:
Blood samples were collected for immunogenicity on Day 0 within 1 hour prior to the start of infusion, and at 14, 28, and 90 days after study drug administration.

Bioanalytical method
Ibalizumab serum concentration:
Ibalizumab serum concentrations were determined using fully validated competitive enzyme-linked immunosorbent assay (ELISA). Standard curve and quality control data indicated the bioanalytical assays for ibalizumab serum concentrations were precise and accurate. The details for the assay performance are listed below:

Analyte	Ibalizumab
Matrix	Human serum
Assay type	Competitive ELISA

Validation report	E-1028
Bioanalytical report	E-1007
Lab	Tanox
Calibration range	100 to 2500 ng/mL
QC levels	140, 732, 2471 ng/mL
Minimum required dilution	Not determined
Dilution linearity	Up to 700,000 ng/mL
Freeze/Thaw stability	Three cycles
Storage stability	Not determined
Bench top/refrigerator stability	4/16 hours
Accuracy	< 15%
Precision (%CV)	< 15% (20% for LLOQ)

Reviewer's comment*: Based on the sponsor's response to an information request, the long-term stability was* ***not*** *documented for TNX-355.01, 02, and 03. In TMB-202 study, the long-term storage stability has been established for 784 days at -80 ± 10°C, which may provide some supportive evidence for the long-term storage stability. Therefore, this has no impact on essential assessments for BLA review.*

RO:
According to the sponsor's response to an information request, the bioanalytical reports for clinical samples were not written for RO assays, thus RO results cannot be verified, although the assay method validation report was submitted (TNX-355.01 RO validation report: (b) (4) HU5A8).

ADA:
Anti-ibalizumab antibody was determined by a bridging sandwich ELISA immunoassay for TNX-355.01 study. The ELISA assay was **not** carried out using a standard 3-tiered assay approach, and has several limitations, such as: 1. Drug tolerance level was not established; 2. Minimum required dilution was not evaluated; 3. Matrix could lead to false positive results; 4. Stability was not checked. The ADA assay results for TNX-355.01 study were inconclusive (refer to the CMC/OBP immunogenicity review for further details).

Pharmacokinetic Assessments
The following pharmacokinetic parameters were determined: C_{max}, AUC_{0-t}, $t_{1/2}$, CL, and V_d.

9. Results

9.1 Subject Demographics and Disposition
A total of 30 subjects were enrolled, and 6 received each of the following ibalizumab doses at 0.3, 1, 3, 10, and 25 mg/kg dose, respectively. Demographic characteristics (gender, age, race, and weight) were similar among dosing groups. The majority of

subjects were white (80%, 24 subjects), with more males than females (90% male, 27 subjects). Subjects had a mean (SD) age of 42.3 (7.0) years and a mean (SD) weight of 72.0 (8.6) kg.

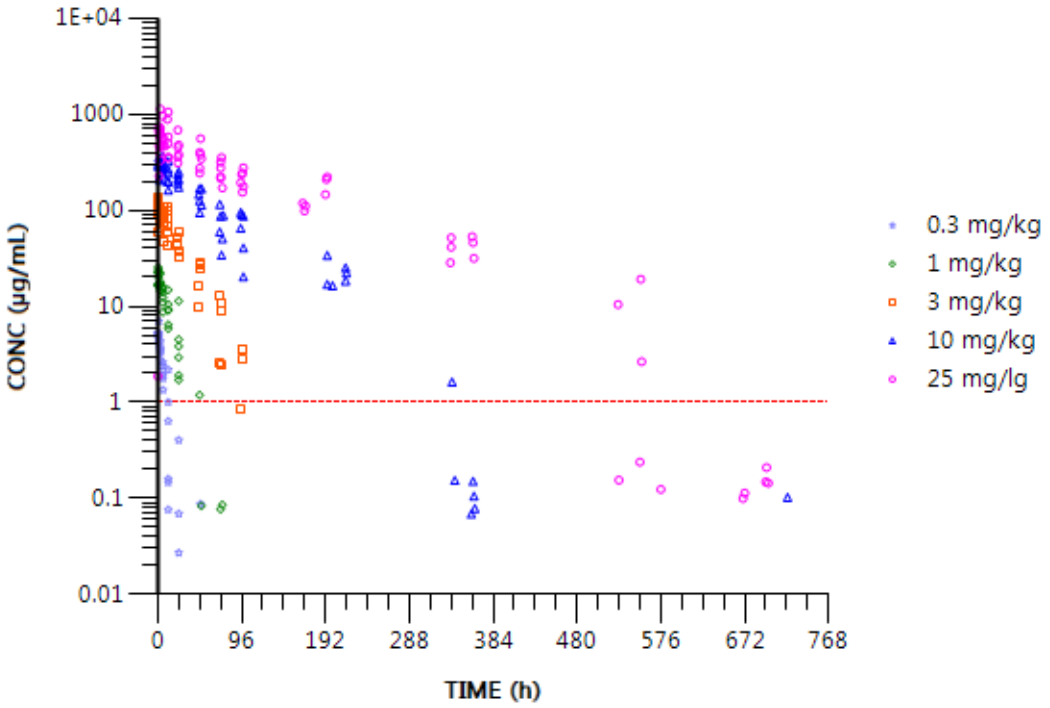
9.2 Pharmacokinetic Analysis
Following single IV dose of ibalizumab at 0.3, 1, 3, 10, and 25 mg/kg, the PK parameters were summarized in **Table 1**, and the PK profile was shown in **Figure 1**.

Ibalizumab exhibited a nonlinear PK profile and exposure increased in a greater than dose-proportional manner; the AUC increased by 2409-fold when the dose increased 83-fold from 0.3 to 25 mg/kg. The half-life increased from 2.7 to 64 hours, and the CL decreased from 10.3 to 0.36 mL/h/kg as dose increased from 0.3 to 25 mg/kg, suggesting capacity-limited elimination (potential target-mediated drug disposition mechanism). The V_d was approximately the volume of human serum, suggesting limited extravascular distribution.

Table 1: PK parameters from single IV dose of ibalizumab in TNX-355.01 study

Dose (mg/kg)	C_{max} (µg/mL)	$AUC_{(0-t)}$ (µg*h/mL)	Dose ratio	C_{max} ratio	AUC ratio	$t_{1/2}$ (h)	V_d (mL/kg)	CL (mL/h/kg)
0.3	5.4	30	1	1	1	2.7	40	10.3
1	21	277	3.3	3.9	9.2	8.2	43	3.62
3	123	2944	10	23	97	14	25	1.05
10	306	20637	33	57	682	38 (1.6 d)	34	0.50
25	750	72947	83	140	2409	64 (2.7 d)	43	0.36

Figure 1: PK profile from single IV dose of ibalizumab in TNX-355.01 study



Note: Assay interference at lower level (< 1 µg/mL); Assay BLQ: 0.1 µg/mL

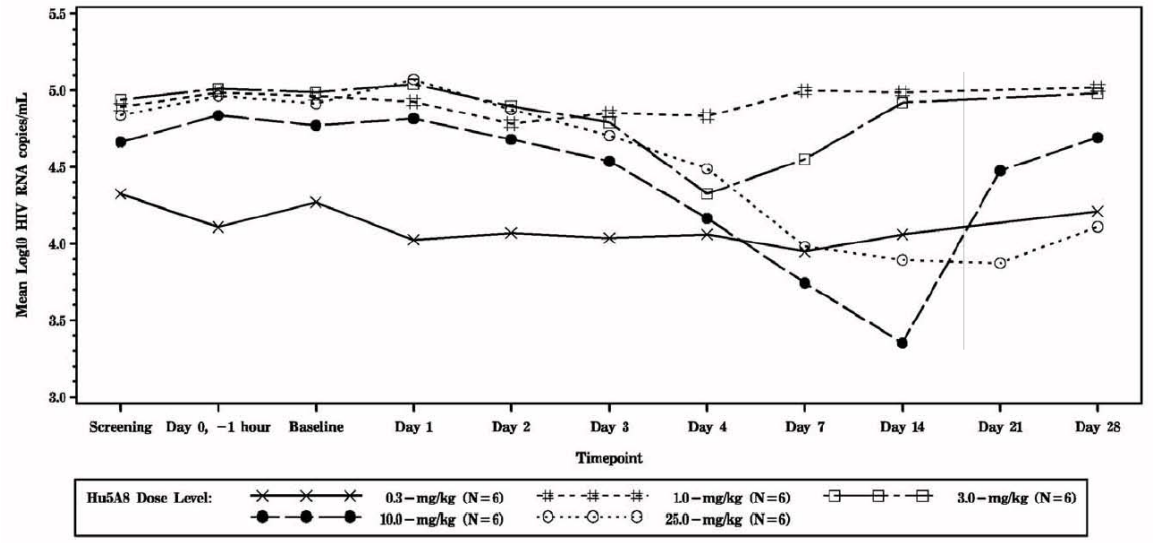
9.3 PK-PD relationship Analysis
RO *vs.* ibalizumab conc.

Reviewer's comment*: Bioanalytical reports were not written for RO assays, thus the RO results cannot be verified. Sponsor's analysis cannot provide supportive evidence for efficacy/dose strategy.*

9.4 Immunogenicity
The ELISA assay was not carried out using a standard 3-tiered assay approach, and have several limitations. The ADA assay results for TNX-355.01 study were inconclusive (refer to the CMC/OBP immunogenicity review for further details).

9.5 Efficacy
As shown in **Figure 2**, single doses of 3.0, 10.0, and 25.0 mg/kg of ibalizumab were effective in reducing viral load in patients infected with HIV. Reductions in plasma HIV RNA levels were greater after 3.0, 10.0, and 25 mg/kg than after 0.3 and 1.0 mg/kg doses. The viral load bounced back to baseline due to the single dose monotherapy of ibalizumab.

Figure 2: Summary of viral load (log_{10} values) over time in TNX-355.01 study



9.6 Safety

According to the sponsor, single doses of up to 25.0 mg/kg of TNX-355 were safe and well tolerated in patients infected with HIV. No patients experienced SAEs during this study and no patients experienced AEs that led to discontinuation of study drug infusion. No dose-dependent effect of TNX-355 on clinical laboratory variables was observed.

10. Conclusions

- Ibalizumab exhibited a nonlinear PK profile and exposure increased in a greater than dose-proportional manner.

- The half-life increased and the CL decreased as dose increased, consistent with a potential target-mediated drug disposition mechanism. The V_d was approximately the volume of human serum.

- Single doses of TNX-355 were effective in reducing viral load. The extent of reductions in viral load was dose dependent.

11. Reviewer's Assessment

- The study design is reasonable and the PK conclusions are acceptable.

- Upon consultation with the OCP BOB (Biologics Oversight Board), the RO-related analysis by the sponsor cannot provide supportive evidence for efficacy/dose strategy, due to lack of bioanalytical reports for data validation. (b) (4)

(b) (4)

- Refer to the CMC/OBP review for the final conclusion regarding immunogenicity risk.

4.5.2 TNX-355.02 Phase 1b Study

1. Title

An Open Label Study to Evaluate the Safety, Pharmacokinetic, and Pharmacodynamic Profile of Multiple Administrations of the Anti-CD4 Monoclonal Antibody TNX-355 in Subjects Infected with HIV-1

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at 6 US clinical sites from January 21, 2003 to November 13, 2003, with the final report date of May 18, 2007.

3. Objectives

Primary objective:

- To assess the safety of multiple administrations of the anti-CD4 monoclonal antibody TNX-355 when given as intravenous (IV) infusions, either as 10 mg/kg every 7 days, as a 10 mg/kg single loading dose followed 1 week later by maintenance doses of 6 mg/kg every 14 days, or as 25 mg/kg given every 14 days, in subjects infected with HIV-1

Secondary objectives:

- To assess the PK behavior of TNX-355 after multiple administrations
- To assess the effect of multiple administrations of 10 mg/kg of TNX-355 given every 7 days, versus 6 mg/kg every 14 days following a single loading dose of 10 mg/kg, versus 25 mg/kg every 14 days, on HIV-1 RNA load and coating of CD4 receptors on $CD4^+$ cells in peripheral blood

4. Trial Design

This Phase 1, multi-center, open-label, partially randomized, multi-dose, parallel group clinical study was designed to evaluate the safety, systemic exposure, and PD/efficacy of TNX-355 in subjects infected with HIV-1. The first 20 subjects were to be randomized between 2 treatment arms (Arm A and Arm B), and an additional 4 subjects were to be assigned (non-randomized) to Arm C:

Arm A: 10 mg/kg every 7 days for a total of 10 doses;
Arm B: 10 mg/kg infusion (loading dose) on Day 1 (Week 0) followed by 5 maintenance doses of 6 mg/kg every 14 days;
Arms C: 25 mg/kg every 14 days for a total of 5 doses

The IV infusion rate was 100 mL/30 minutes for all three arms.

Eligible subjects were HIV-1 infected patients meeting the following criteria:

- 18 years of age or older
- Weight < 100 kg
- $CD4^+$ cell count between 100 and 500 cells/μL
- Stable HIV-1 RNA plasma level of ≥5,000 copies/mL
- If antiretroviral regimens had been discontinued, the subject should not have received therapy for ≥12 weeks prior to enrollment.
- If still receiving antiretroviral therapy, the subject should have been receiving the same regimen for ≥12 weeks prior to enrollment and be willing to continue that regimen for the duration of the study.

5. Excluded Medications and Restrictions

- Received immunomodulating therapy, systemic chemotherapy, or had participated in a trial of an experimental immunomodulating drug or antiretroviral therapy within 12 weeks of enrollment.
- Participated in an HIV vaccine study at any time
- Vaccination within 21 days prior to screening
- Prior treatment with Hu5A8 (TNX-355)
- Treatment with any experimental therapy for any indication within 30 days prior to study drug initiation

6. Rationale for Doses Used in the Trial

Arm A: 10 mg/kg every 7 days for a total of 10 doses;
Arm B: 10 mg/kg infusion (loading dose) on Day 1 (Week 0) followed by 5 maintenance doses of 6 mg/kg every 14 days;
Arms C: 25 mg/kg every 14 days for a total of 5 doses

The choice of the dose levels and administration intervals for this study was based on the results of Hu5A8.01 or TNX-355.01 (Phase 1a) study. Arm A and C were predicted to provide significant viral load reduction at the proposed dose intervals, while Arm B was predicted to provide less efficacy.

7. Drugs Used in the Trial

Ibalizumab: injection solution, ~ 5.3 mg/mL in phosphate buffered saline containing 0.02% polysorbate 80, pH 7.

Lot number: 801736A
Manufacturer: Tanox

8. Sample Collection, Bioanalysis, and Pharmacokinetic/Pharmacodynamic Assessments

Sample Collection

Ibalizumab serum concentrations:

Samples for determination of TNX-355 concentrations in serum were collected on Day 1 and at Weeks 1, 2, 3, 5, 7, 9, 10, 10.5, 11, 11.5, 12, 13, 14, 15, and 16 for subjects in Arms A and B; and on Day 1 and at Weeks 1, 2, 4, 6, 8, 9, 10, 10.5, 11, 11.5, 12, 13, 14, 15, 16, 24, and 32 for subjects in Arm C. At each visit when TNX-355 was administered, 2 samples were collected, one within 1 hour before the start of infusion and one after the end of the infusion. Samples from Weeks 14 through Week 32 were analyzed for any subject who had measurable serum concentrations of TNX-355 at the preceding visit.

Receptor occupancy (RO):

Blood samples were collected for RO assay on Day 1 (pre- and post-infusion) and at weekly intervals thereafter up to Week 9. Blood samples for RO were also collected at Weeks 10, 10.5, 11, 11.5, 12, 13, 14, 15, and 16.

ADA:

Blood samples were collected for immunogenicity prior to administration of the initial dose and at Weeks 3, 8, 11, 13, 16, 24 (Arm C only), and 32 (Arm C only).

Bioanalytical method

Ibalizumab serum concentration:

Ibalizumab serum concentrations were determined using fully validated competitive enzyme-linked immunosorbent assay (ELISA). Standard curve and quality control data indicated the bioanalytical assays for ibalizumab serum concentrations were precise and accurate. The details for the assay performance are listed below:

Analyte	Ibalizumab
Matrix	Human serum
Assay type	Competitive ELISA
Validation report	E-1028
Bioanalytical report	E-1037
Lab	Tanox
Calibration range	100 to 2500 ng/mL
QC levels	250, 600, 1800 ng/mL
Minimum required dilution	NA
Dilution linearity	Up to 700,000 ng/mL
Freeze/Thaw stability	Three cycles
Storage stability	Not determined

Bench top/refrigerator stability	4/16 hours
Accuracy	< 20%
Precision (%CV)	< 15%

Reviewer's comment: *Based on sponsor's response, the long-term stability was* ***not*** *documented for TNX-355.01, 02, and 03. In TMB-202 study, the long-term storage stability has been established for 784 days at -80 ± 10°C, which may provide some supportive evidence for the long-term storage stability. Therefore, this has no impact on essential assessments for BLA review.*

RO:
According to sponsor's response, the bioanalytical reports for clinical samples were not written for RO assays, thus RO results cannot be verified, although the assay validation report was submitted (TNX-355.02 RO validation report: (b) (4) HU5A8).

ADA:
Anti-ibalizumab antibody was determined by a non-bridging sandwich ELISA immunoassay for TNX-355.02 study. The ELISA assay was **not** carried out using a standard 3-tiered assay approach, and the bioanalytical report for the clinical samples was not submitted, thus the ADA assay results for TNX-355.02 study were inconclusive (refer to the CMC/OBP immunogenicity review for further details).

Pharmacokinetic Assessments
The pre- and post-infusion concentrations were summarized over time. For the final dose, the following pharmacokinetic parameters were determined for Arms A and C: C_{max}, AUC_{all}, $t_{1/2}$, V_{ss}, and CL_{ss}.

9. Results

9.1 Subject Demographics and Disposition
A total of 22 subjects were enrolled, with 9, 10, and 3 subjects in Arms A, B, and C, respectively. Demographic characteristics for each arm were summarized in **Table 1**.

Table 1: Baseline subject demographics in TNX-355.02 study

	TNX-355 Treatment Group		
Demographics	**Arm A 10 mg/kg N = 9**	**Arm B 10 mg/kg + 6 mg/kg N = 10**	**Arm C 25 mg/kg N = 3**
Age (years)			
N	9	10	3
Mean (SD)	39.0 (9.97)	41.7 (10.45)	41.0 (2.00)
Median	39.0	45.0	41.0
Min, Max	24, 60	22, 52	39, 43
Gender [n (%)]			
Male	8 (88.9)	9 (90.0)	2 (66.7)
Female	1 (11.1)	1 (10.0)	1 (33.3)
Race [n (%)]			
White	7 (77.8)	8 (80.0)	2 (66.7)
Black	1 (11.1)	0 (0.0)	1 (33.3)
Hispanic	1 (11.1)	2 (20.0)	0 (0.0)
Height (cm)			
N	9	10	3
Mean (SD)	175.4 (10.99)	177.0 (9.64)	172.7 (6.72)
Median	179.0	179.1	175.3
Min, Max	158, 193	160, 188	165, 178
Weight (kg)			
N	9	10	3
Mean (SD)	80.42 (13.62)	74.93 (7.60)	69.00 (11.00)
Median	80.50	76.0	69.0
Min, Max	60.0, 100.0	64.5, 86.8	58.0, 80.0
Weight [n (%)]			
≤60 kg	1 (11.1)	0 (0.0)	1 (33.3)
>60 kg	8 (88.9)	10 (100.0)	2 (66.7)

9.2 Pharmacokinetic Analysis

Mean serum concentrations of ibalizumab calculated for each study arm at each time point are presented in **Table 2**. For Arm A, steady state trough concentration was reached between Week 3 and Week 7, and the mean C_{trough} accumulation ratio was 3.27 ± 1.06 (Week 10/Week 1). For Arm B, no accumulation was observed. For Arm C, due to the limited number (n=3) and large variability observed, the accumulation was inconclusive.

Table 2: Mean serum concentrations over time in TNX-355.02 study

Visit	Mean serum concentration ± standard deviation of TNX-355 (µg/mL) for subjects in:		
	ARM A 10 mg/kg weekly Day 1 and Weeks 1, 2, 3, 4, 5, 6, 7, 8, and 9	ARM B 10 mg/kg loading dose on Day 1 followed by 6 mg/kg every 2 weeks at Weeks 1, 3, 5, 7, and 9	ARM C 25 mg/kg every 2 weeks Day 1 and Weeks 2, 4, 6, and 8
Day 1 (Pre-infusion)	0.1 ± 0.2	0.0 ± 0.1	0
Day 1 (Post-infusion)	280 ± 69	215 ± 51	429 ± 195
Week 1 (Pre-infusion)	48 ± 14	31 ± 12	96 ± 31
Week 1 (Post-infusion)	309 ± 58	156 ± 44	NA
Week 2 (Pre-infusion)	73 ± 25	33 ± 14	51 ± 52
Week 2 (Post-infusion)	350 ± 73	NA	535 ± 225
Week 3 (Pre-infusion)	102 ± 29	2.1 ± 3.6	295
Week 3 (Post-infusion)	344 ± 81	118 ± 35	NA
Week 4 (Pre-infusion)	NA	NA	70 ± 64
Week 4 (Post-infusion)	NA	NA	542 ± 250
Week 5 (Pre-infusion)	114 ± 57	0.2 ± 0.1	NA
Week 5 (Post-infusion)	367 ± 78	153 ± 129	NA
Week 6 (Pre-infusion)	NA	NA	99 ± 98
Week 6 (Post-infusion)	NA	NA	584 ± 308
Week 7 (Pre-infusion)	148 ± 69	0.2 ± 0.1	106
Week 7 (Post-infusion)	401 ± 97	125 ± 24	NA
Week 8 (Pre-infusion)	NA	NA	96 ± 106
Week 8 (Post-infusion)	NA	NA	564 ± 267
Week 9 (Pre-infusion)	138 ± 58	0.2 ± 0.1	112 ± 8
Week 9 (Post-infusion)	411 ± 122	108 ± 33	NA
Week 10	171 ± 89	9.3 ± 6.7	81 ± 65
Week 10.5	141 ± 83	2.0 ± 2.7	80 ± 83
Week 11	113 ± 81	0.2 ± 0.1	47 ± 77
Week 11.5	71 ± 58	0.2 ± 0.1	43 ± 74
Week 12	40 ± 39	0.1 ± 0.1	39 ± 67
Week 13	19 ± 28	0.1 ± 0.1	28 ± 40
Week 14	0.4 ± 0.2	0.1 ± 0.1	6.9 ± 11.7
Week 15	0.4 ± 0.2	0.1 ± 0.1	0.5 ± 0.8
Week 16	0.3 ± 0.2	0.1 ± 0.1	0.3 ± 0.3
Week 24	NA	NA	0.1 ± 0.1
Week 32	NA	NA	0.0

NA-not assayed (no visit at this time) for this Arm or there was no infusion (hence, no post-infusion sample)

The serum concentrations of ibalizumab in subjects in Arm A and Arm C were sufficient to provide an estimate of the pharmacokinetics of TNX-355 following the final dose of drug. For subjects in Arm B, the rapid drop in serum concentrations of ibalizumab and the lack of multiple collection points in the first week following the final dose precluded any estimation of terminal elimination pharmacokinetics. The PK parameters following the final dose in Arms A and C are summarized in **Table 3**. The half-life values need to be interpreted with caution due to non-linear PK (potential target-mediated drug disposition mechanism), which were concentration dependent. The C_{max} and AUC were higher, and the $t_{1/2}$ was longer in Arm A, compared to results observed from a single dose of 10 mg/kg in TNX-355.01 study, most likely due to accumulation after repeated dosing.

The PK parameters in Arm C were similar as results observed from a single dose of 25 mg/kg in TNX-355.01 study.

Table 3: PK parameters of ibalizumab following the final dose in Arms A and C in TNX-355.02 study

Arm	Dose regimen	C_{max} (µg/mL)	AUC_{all} (µg*day/mL)	Effective $t_{1/2}$ (day)	V_{ss} (mL/kg)	CL (mL/day/kg)
A	10 mg/kg (~ 700 mg) weekly	402	3604	3 27	44	5.74
C	25 mg/kg (~ 1750 mg) every 2 weeks	564	4941	3 11	50	8.83

9.3 PK-PD relationship Analysis
RO *vs.* ibalizumab conc.

Reviewer's comment*: Bioanalytical reports were not written for RO assays, thus the RO results cannot be verified. Sponsor's analysis cannot provide supportive evidence for efficacy/dose strategy.*

9.4 Immunogenicity
The ELISA assay was not carried out using a standard 3-tiered assay approach, and the bioanalytical report for clinical samples was not submitted, thus the ADA assay results for TNX-355.02 study were inconclusive (refer to the CMC/OBP immunogenicity review for further details).

9.5 Safety
According to the sponsor, ibalizumab was well tolerated in HIV-1 patients in all three arms. None of the SAEs were considered treatment-related, and no subjects died in the study.

10. Conclusions

- Accumulation was observed for Arm A, no accumulation was observed for Arm B, and the result was inconclusive for Arm C.
- The PK results aligned with results from TNX-355.01 study.
- There was a return to baseline viral RNA levels in most patients despite continued administration of ibalizumab monotherapy, although viral suppression was observed at the earlier stage (nadir within first two weeks).

11. Reviewer's Assessment

- The study design is reasonable and the PK conclusions are acceptable.

- Although the average mg dose was 1750 mg for mean body weight at 70 kg in Arm C (25 mg/kg), there was no durability in response with ibalizumab monotherapy, since there was no OBR administered in combination.

- Upon consultation with the OCP BOB (Biologics Oversight Board), the RO-related analysis by the sponsor cannot provide supportive evidence for efficacy/dose strategy, due to lack of bioanalytical reports for data validation. (b) (4)

- Refer to the CMC/OBP review for the final conclusion regarding immunogenicity risk.

4.5.3 TNX-355.03 Phase 2a Study

1. Title

A Phase 2, Multicenter, Randomized, Double-Blinded, Placebo-Controlled, Three-Arm Study of the Anti-CD4 Monoclonal Antibody Ibalizumab (TNX-355) with Optimized Background Therapy in Treatment-Experienced Subjects Infected with HIV-1

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at 20 US clinical sites from March 09, 2004 to March 02, 2006, with the final report date of February 24, 2009.

3. Objectives

Primary objectives:

- To compare the safety and efficacy, as assessed by viral load reduction at Week 24, of 2 dosages of ibalizumab added to optimized background therapy (OBT) versus OBT plus placebo in treatment-experienced, human immunodeficiency virus (HIV)-1-infected subjects who were failing or had recently failed a highly active antiretroviral therapy (HAART) regimen
- To determine if 1 of the ibalizumab treatment arms differs from the placebo-containing arm in terms of HIV RNA levels after 24 weeks of study drug administration

Secondary objectives:

- To compare the safety and efficacy, as assessed at Week 48, of 2 dosages of ibalizumab added to OBT versus OBT plus placebo
- To characterize HIV-1 phenotypes/genotypes associated with ibalizumab treatment susceptibility and failure
- To determine the relation, if any, between cell coating of circulating $CD4^+$ cells and virologic response and treatment failure
- To determine the relation, if any, between serum concentrations of ibalizumab and cell coating of $CD4^+$ cells
- To determine the difference, if any, in delayed-type hypersensitivity (DTH) responses between treatment groups

4. Trial Design

This multicenter, randomized, double-blind, placebo-controlled, multi-dose, 3-arm safety and efficacy study of approximately 80 subjects compared 2 dosage regimens of ibalizumab plus OBT with placebo plus OBT in adult subjects infected with HIV-1. Subjects were randomized to 1 of the following 3 treatment arms; all received OBT plus 1 of the following regimens:

Arm A: Alternating intravenous (IV) infusions of 15 mg/kg ibalizumab and placebo, weekly for the first 9 doses, then IV infusions of 15 mg/kg ibalizumab every 2 weeks
Arm B: 10 mg/kg ibalizumab IV infusions weekly for the first 9 doses, then IV infusions of 10 mg/kg ibalizumab every 2 weeks
Placebo Arm: Placebo, weekly IV infusions for the first 9 doses, then IV infusions of placebo every 2 weeks

Eligible subjects were HIV-1 infected patients meeting the following criteria:

- 18 years of age or older
- Be treatment-naïve for any virus fusion/entry inhibitors for entry into the study
- $CD4^+$ cell count $\geq$ 50 cells/μL
- Stable plasma HIV-1 RNA levels of >10,000 copies/mL within 8 weeks prior to randomization
- Cumulative HAART experience for a minimum of 6 months
- Failing their current HAART regimen or have discontinued a failing HAART regimen within 8 weeks prior to Screening

5. Excluded Medications and Restrictions

- Immunomodulating therapy or systemic chemotherapy within 12 weeks prior to randomization

- Any investigational drug within 30 days prior to randomization, except for treatment of HIV-1 under expanded access
- Any prior participation in an HIV vaccine study
- Vaccination within 21 days prior to screening
- Prior treatment with Hu5A8 (TNX-355)
- Any previous exposure to any virus fusion/entry inhibitors
- Any previous exposure to a mAb (prior treatment with hepatitis B immune globulin or IV immune globulin was acceptable)

6. Rationale for Doses Used in the Trial

Arm A: 15 mg/kg every 2 weeks + OBT until Week 48;
Arm B: 10 mg/kg every week for 9 weeks, followed by every 2 weeks until Week 48 + OBT

The choice of the dose levels and administration intervals for this study was based on the results from TNX-355.01 (Phase 1a) and TNX-355.02 (Phase 1b) studies. The dose regimens of 10 mg/kg weekly and 25 mg/kg every 2 weeks in TNX-355.02 showed viral suppression at the earlier stage, and the 2-week dosing interval in Arm A and B should reduce inconvenience and improve compliance, while have the chance to provide viral suppression for longer duration in combination with OBT.

7. Drugs Used in the Trial

Ibalizumab: injection solution, 25 mg/mL in a histidine-buffered aqueous solution containing 5.6% sucrose and 0.02% polysorbate 80, pH 6.
Placebo: the same histidine-buffered aqueous solution containing the same amounts of sucrose and polysorbate 80 at pH 6, but without drug substance
Lot number: TNX-355-504001-5, TNX-355-505002-4
Manufacturer: Tanox

8. Sample Collection, Bioanalysis, and Pharmacokinetic/Pharmacodynamic Assessments

Sample Collection
Ibalizumab serum concentrations:
Samples for determination of ibalizumab concentrations in serum were collected on Day 1 (prior to and after infusion), and at Weeks 1, 2, 3, 4, 8, 12, and 16, then every 8 weeks through Week 48.

Receptor occupancy (RO):
Blood samples were collected for RO assay on Day 1 and at Weeks 1, 2, 3, 4, and every 4 weeks thereafter to Week 48.

ADA:
Blood samples were collected for immunogenicity on Day 1 (prior to infusion), at Weeks 16, 24, and 48, and at 1-month follow-up visit.

Bioanalytical method

Ibalizumab serum concentration:

Reviewer's comment*: The bioanalytical report for ibalizumab serum concentrations was* ***not*** *submitted for TNX-355.03 study, thus the results cannot be validated. The PK results aligned with results from other clinical studies, thus this has no impact on essential assessments for BLA review.*

RO:
According to sponsor's response, the bioanalytical reports for clinical samples were not written for RO assays, thus RO results cannot be validated, although the validation report was submitted (TNX-355.03 RO validation report: (b) (4) HU5A8).

ADA:
Anti-ibalizumab antibody was determined by both a bridging and a non-bridging sandwich ELISA immunoassays for TNX-355.03 study. The ELISA assays were **not** carried out using a standard 3-tiered assay approach, thus the ADA assay results for TNX-355.03 study were inconclusive (refer to the CMC/OBP immunogenicity review for further details).

Pharmacokinetic Assessments
The pre- and post-infusion concentrations were summarized.

9. Results

9.1 Subject Demographics and Disposition
A total of 28, 27, and 27 subjects were randomized in Arms A, B, and Placebo, respectively. Overall, demographic characteristics were similar between the treatment arms. Demographic characteristics for each arm were summarized in **Table 1**.

Table 1: Baseline subject demographics in TNX-355.03 study

Demographics	Treatment Group Arm A Ibalizumab 15 mg/kg (N=28)	Arm B Ibalizumab 10 mg/kg (N=27)	Placebo Arm (N=27)
Age (years)			
N	28	27	27
Mean (SD)	44.4 (8.39)	47.1 (11.17)	45.5 (8.34)
Median	44.0	46.0	44.0
Min, Max	28, 59	18, 75	31, 66
Gender [n (%)]			
Male	26 (92.9)	21 (77.8)	24 (88.9)
Female	2 (7.1)	6 (22.2)	3 (11.1)
Race [n (%)]			
White	12 (42.9)	14 (51.9)	12 (44.4)
Black	8 (28.6)	4 (14.8)	3 (11.1)
Hispanic	7 (25.0)	8 (29.6)	12 (44.4)
Other	1 (3.6)	1 (3.7)	0 (0.0)
Height (cm)			
N	28	27	27
Mean (SD)	176.5 (6.81)	173.4 (8.95)	173.7 (8.32)
Median	175.0	175.3	172.7
Min, Max	165, 193	155, 185	152, 188
Weight (kg)			
N	28	27	27
Mean (SD)	74.3 (11.79)	73.4 (11.43)	77.8 (15.23)
Median	71.7	73.0	73.0
Min, Max	51, 101	54, 101	61, 124
Weight [n (%)]			
≤60 kg	2 (7.1)	3 (11.1)	0 (0.0)
>60 kg	26 (92.9)	24 (88.9)	27 (100.0)

9.2 Pharmacokinetic Analysis

Mean trough and post-infusion serum concentrations of ibalizumab were summarized for Day 1 (C_{min_init}, C_{max_init}) and Week 48 (C_{min_SS}, C_{max_SS}) in **Table 2**. There was no clear accumulation for C_{max} for both arms, while there was accumulation for C_{min} for Arm A at 15 mg/kg every 2 weeks.

Table 2: Mean (± SD) pre- and post-infusion concentrations of ibalizumab on Day 1 and at Week 48 in TNX-355.03 study

Arm	Dose regimen	Cmax_init (µg/mL)	Cmax_SS (µg/mL)	Cmin_init (µg/mL)	Cmin_SS (µg/mL)
A	15 mg/kg every 2 weeks	340 ± 90	448 ± 110	23 ± 9.2	85 ± 38
B	10 mg/kg weekly for 9 weeks, followed by 10 mg/kg every 2 weeks	242 ± 72	330 ± 113	ND	ND

ND: not determined due to change of dose regimen after Week 9.

Reviewer's comment*: The bioanalytical report for ibalizumab serum concentrations was* ***not*** *submitted for TNX-355.03 study, thus the results cannot be validated. The PK results*

aligned with results from other clinical studies, thus this has no impact on essential assessments for BLA review.

9.3 PK-PD relationship Analysis
RO *vs.* ibalizumab conc. or viral load reduction

***Reviewer's comment**: Bioanalytical reports were not written for RO assays, thus the RO results cannot be verified. Sponsor's analysis cannot provide supportive evidence for efficacy/dose strategy.*

9.4 Immunogenicity Analysis
The ELISA assays were not carried out using a standard 3-tiered assay approach, thus the ADA assay results for TNX-355.03 study were inconclusive (refer to the CMC/OBP immunogenicity review for further details).

9.5 Results for Primary Efficacy Endpoint
The primary efficacy endpoint for TNX-355.03 study was mean change from baseline in HIV-1 RNA levels at Week 24. The results calculated using the zero change imputation method for missing values in Arms A, B, and Placebo were -0.767, -1.186, and -0.323 log_{10} copies/mL, respectively. From the sensitivity analysis (mean of the last 2 values method), the differences between either active arm and the Placebo Arm were statistically significant (Dunnett's test: p=0.006 for Arm A *vs* Placebo, and p<0.001 for Arm B *vs* Placebo) (**Table 3**).

Table 3: Summary of HIV-1 RNA levels at Week 24 (log_{10} copies/mL) in TNX-355.03 study

	Treatment Group				
	Arm A Ibalizumab 15 mg/kg	Arm B Ibalizumab 10 mg/kg	Placebo Arm	p-values	
Parameter	(N=28)	(N=27)	(N=27)	Arm A & Placebo	Arm B & Placebo
Baseline					
N	28	27	27		
Mean (SD)	5.005 (0.509)	4.780 (0.367)	4.828 (0.447)		
Median	5.157	4.763	4.807		
Min, Max	4.16, 5.85	3.96, 5.54	3.91, 5.83		
Change from Baseline to Week 24 (Zero Change Imputation)					
N	28	27	27		
Mean (SD)	-0.767 (0.878)	-1.186 (1.129)	-0.323 (0.614)	p=0.126* p=0.114**	p=0.001* p=0.002**
Median	-0.527	-0.970	0.000		
Min, Max	-2.87, 0.31	-3.08, 0.00	-1.92, 0.30		
Change from Baseline to Week 24 (Mean of Last 2 Values)					
N	28	27	27		
Mean (SD)	-0.915 (0.707)	-1.164 (1.033)	-0.222 (0.736)	p=0.006* p=0.001**	p<0.001* p<0.001**
Median	-0.828	-0.832	-0.114		
Min, Max	-2.72, 0.15	-3.07, 0.27	-2.01, 0.80		

**p-values calculated using a Dunnett's 2-sided multiple comparison procedure to contrast mean differences.*
***p-values calculated using a Steele's Test to contrast mean differences.*

9.6 Safety
Overall, there was no dose-related difference in the tolerability profile between the active treatment arms; furthermore, the tolerability profile for subjects in the active treatment arms was similar to placebo with the exception of skin events. Please refer to the Medical Officer's review for additional details.

10. Conclusions

- No clear accumulation for C_{max} was observed for Arms A and B, while there was accumulation for C_{min} in Arm A at 15 mg/kg every 2 weeks, with the ratio at 4.
- The PK results aligned with results from other clinical studies.
- Ibalizumab demonstrated antiviral activity at both doses tested, in terms of mean change from Baseline to Week 24 in HIV-1 RNA, and this antiviral activity was statistically significantly greater than placebo.

11. Reviewer's Assessment

- The study design is reasonable and the PK conclusions are acceptable (*the bioanalytical report for ibalizumab serum concentrations was not submitted for TNX-355.03 study, but the PK results aligned with results from other clinical studies*).
- Upon consultation with the OCP BOB (Biologics Oversight Board), the RO related analysis by the sponsor cannot provide supportive evidence for efficacy/dose strategy, due to the lack of bioanalytical reports for data validation. (b) (4)
- Refer to the CMC/OBP review for the final conclusion regarding immunogenicity risk.

4.5.4 TMB-202 Phase 2b Study

1. Title

A Phase 2b, Randomized, Double-Blinded, 48-Week (Amended to 24-Week Study), Multicenter, Dose-Response Study of Ibalizumab Plus an Optimized Background Regimen in Treatment-Experienced Patients Infected With HIV-1

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at 33 clinical sites (29 in US, 2 in Puerto Rico, and 2 in Taiwan) from October 14, 2008 to January 26, 2011, with the final report date of September 30, 2011.

3. Objectives

Primary objectives:

- To evaluate the dose-response effectiveness of antiviral activity of the ibalizumab dose regimens at Week 24 in order to determine the optimal dose and regimen. The primary evaluation of effectiveness was based on the proportion of patients achieving undetectable viral loads at Week 24.
- Evaluate the safety and tolerability of two dose regimens of ibalizumab for dose selection.

Secondary objectives:

- To evaluate changes from Baseline in viral load, $CD4_+$ T-cell counts, and time to loss of virologic response
- To characterize HIV-1 sensitivity/susceptibility changes associated with ibalizumab administration in combination with an optimized background regimen (OBR)
- To determine the presence and significance of anti-ibalizumab antibodies, if any (immunogenicity of ibalizumab)
- To assess CD4 receptor density and occupancy
- To determine the impact of ibalizumab on quality of life as assessed by patient-reported outcomes on questionnaires
- To evaluate the pharmacokinetic profile of two dose regimens of ibalizumab at steady state

4. Trial Design

This Phase 2b, multicenter, randomized, double-blind study evaluated the effectiveness and safety of two dose regimens of ibalizumab in patients infected with HIV-1. The two dose regimens of ibalizumab were randomly assigned in a 1:1 ratio to approximately 120 patients. The random assignment was stratified by (a) use or non-use of a viral entry inhibitor (EI), and (b) use or non-use of an integrase inhibitor (INI) in OBR.

Patients received one of the following two dose regimens:

- 800 mg of ibalizumab every 2 weeks (q2wk) plus OBR
- 2000 mg of ibalizumab every 4 weeks (q4wk) and placebo on the intervening 2-week

period visit, plus OBR

Beginning at the visit for Week 8, additional blood samples were collected over the following 4 weeks from patients participating in the Pharmacokinetic Substudy, to further define the pharmacokinetic profile of ibalizumab.

The duration of infusion should have lasted no less than 30 minutes during the first three administrations. If no infusion-associated AEs occurred between Baseline and Week 4, the duration of infusion could have been decreased to no less than 15 minutes.

Eligible subjects were HIV-1 infected patients meeting the following criteria:

- 18 years of age or older
- Had a life expectancy > 6 months
- Had a viral load >1,000 copies/mL and documented decreased susceptibility to at least one nucleoside reverse transcriptase inhibitor (NRTI), one non-nucleoside reverse transcriptase inhibitor (NNRTI), and one protease inhibitor (PI), as measured by resistance testing
- Had a history of at least 6 months on ARV treatment
- Were receiving a stable HAART for at least 8 weeks before Screening and were willing to continue that regimen until the Baseline Visit, or (in the past 8 weeks) had failed and were off therapy and were willing to stay off therapy until the Baseline Visit
- Had viral sensitivity/susceptibility to at least one agent as determined by the Screening resistance test and were willing and able to be treated with at least one agent to which the patient's viral isolate was sensitive/susceptible according to the Screening resistance test

5. Excluded Medications and Restrictions

- Any immunomodulating therapy (including interferon), systemic steroids, or systemic chemotherapy within 12 weeks before randomization.
- Any prior exposure to ibalizumab (formerly TNX-355 and Hu5A8)
- Therapeutic HIV vaccines from Screening until the End-of-Study Visit
- Any vaccination within 21 days before randomization
- Any investigational therapy within 30 days before randomization and throughout the study, except for those HIV-agents available in expanded-access programs
- Drugs that can potentiate the activity of ARV drugs or have intrinsic ARV activity (but not indicated for treatment of HIV infection), such as, but not limited to, mycophenolic acid, hydroxyurea, or foscarnet from 30 days before Day 7 (Baseline) and throughout participation in the study
- Immunomodulator compounds (e.g., interleukins and interferons)
- Bone marrow suppressants used in oncology treatment
- Any radiation therapy during the 28 days before the first administration of study medication

6. Rationale for Doses Used in the Trial

Ibalizumab: 1. 800 mg Q2W; 2. 2000 mg Q4W

According to the sponsor, data from the Phase 1a, 1b and 2a studies suggest that doses of ibalizumab producing mean serum trough concentrations greater than 5 µg/mL were generally correlated with significant viral RNA suppression. Additionally, intra-patient and inter-patient biological variations can contribute to the variability in the available data. Given the observed variability, maintaining a range in drug trough levels of between 5 and 50 µg/mL was judged to be desirable in any further clinical study. A number of doses and dose regimens were simulated to find those that could achieve and maintain these trough levels. The doses in this study, 800 mg Q2W, and 2000 mg Q4W, achieve the desired trough level of > 5 µg/mL in simulations, and both dose regimens were expected to provide viral suppression, given the earlier clinical data. Since body weight is not known to correlate well with the number of $CD4^+$ T-cells, CD4 receptors, or the rate of $CD4^+$ T-cell turnover, weight based regimens have been replaced in this study with fixed-dose regimens, which have been selected to approximate the previously tested dosages.

7. Drugs Used in the Trial

Ibalizumab: injection solution, 200 mg/vial (8 mL), 25 mg/mL in histidine USP (1.55 mg/mL), sucrose USP (56.7 mg/mL), polysorbate 80 (0.02 mg/mL), pH 6.0.
Lot number: 24260.2 (800 mg kits), 24260.3 (2000 mg kits), and 24260.1 (placebo)
Manufacturer: Tanox

All patients received an investigator-selected OBR consisting of two to four ARVs, within all the available classes, including NRTI, NNRTI, PI, integrase inhibitor, and entry inhibitor. No patients took investigational drugs as part of the OBR.

8. Sample Collection, Bioanalysis, and Pharmacokinetic/Pharmacodynamic Assessments

Sample Collection
Ibalizumab serum concentrations:
All patients had blood samples collected before and immediately after administration of study drug on Weeks 1, 2, 4, 8, 10, 12 and 24 (additional time points for Day 1 at 1 and 6 hours post-dose). Beginning at Week 8, patients in the PK Substudy had an additional series of 23 blood samples collected over 28 days. These additional samples were drawn immediately following the Week 8 study drug administration and on the following days, ± 3 hours, after the Week 8 study drug administration: 7, 8, 9, 10, 11, 14 (Week 10 Visit), 21, 22, 23, 24, 25, and 28 (Week 12 Visit). The PK specimens collected at Weeks 8, 10 and 12, required two samples; one sample drawn within 1 hour before study drug administration and the second sample drawn immediately (within 10 minutes) after the end of the infusion.

RO and RD (receptor density):
Blood samples for RO and RD were collected at the same time points as for ibalizumab serum concentrations listed above.

Immunogenicity or ADA:
Blood samples were collected to test for the development of antibodies against ibalizumab periodically throughout the study including Baseline, Week 12, and Week 28/Follow-up. Samples were collected prior to ibalizumab infusion if an infusion was scheduled for that visit. Samples were tested at routine intervals, but could also have been obtained when clinical observations suggested 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). Please refer to the CMC/OBP review for additional details.

Bioanalytical method

Ibalizumab serum concentration:
Ibalizumab serum concentrations were determined using fully validated competitive enzyme-linked immunosorbent assay (ELISA). All samples were analyzed within the timeframe supported by storage stability data. Standard curve and quality control data indicated the bioanalytical assays for ibalizumab serum concentrations were precise and accurate. The details for the assay performance are listed below:

Analyte	Ibalizumab
Matrix	Human serum
Assay type	Competitive ELISA
Validation report	UNS2 TMB-202
Bioanalytical report	TOS TMB-202
Lab	(b) (4)
Calibration range	100 to 2700 ng/mL
QC levels	250, 750, 1500 ng/mL
Minimum required dilution	2
Dilution linearity	Up to 1,000,000 ng/mL
Freeze/Thaw stability	Five cycles
Storage stability	784 days at -80°C
Bench top stability	24 hours
Accuracy	< 25%
Precision (%CV)	< 20%

Reviewer note: the method validation and bioanalysis data for ibalizumab serum concentration were reviewed and found to be acceptable by the secondary reviewer, Dr. Shirley Seo.

RO/RD:
According to the sponsor's response to an information request, the bioanalytical reports for clinical samples were not written for RO/RD assays, thus RO/RD results cannot be

verified, although the assay method validation report was submitted (TMB-202 RO/RD validation report: (b) (4) -cd3-cd4).

ADA and neutralizing antibody (nAb):
Anti-ibalizumab antibody was determined by a validated bridging sandwich ELISA immunoassay. The ELISA assay was carried out using a typical 3-tiered assay approach: 1. Tier 1 ADA screening assay: to identify initial putative positive samples; 2. Tier 2 confirmatory assay: to assess specificity of the positive screen samples; 3. Tier 3 titer assay: to estimate the level of antibody for the confirmed positive samples. The assay performance is summarized briefly below (refer to the CMC/OBP immunogenicity review for further details on the assay).

Analyte	ADA
Matrix	Human serum
Assay type	Bridging sandwich ELISA
Validation report	VNS2 TMB-202
Bioanalytical report	UOS TMB-202
Lab	(b) (4)
Drug tolerance level	500 ng/mL
Positive control levels	50 and 200 ng/mL
Minimum required dilution	2
Hook effect	Up to 4860 ng/mL
Freeze/Thaw stability	Five cycles
Storage stability	19 days at -70°C
Bench top stability	24 hours
Precision (%CV)	< 20%

The nAb assay was performed for one ADA positive sample in TMB-202 study (subject 10008 at W24 from 2000 mg Q4W). The assay was determined using a validated functional ligand binding assay by (b) (4). If nAb is present in the sample, it will competitively block the binding of CD4 to the drug and reduce the assay signal. The assay performance is summarized briefly below (refer to the CMC/OBP immunogenicity review for further details).

Analyte	nAb
Matrix	Human serum
Assay type	Functional ligand binding assay
Validation report	(b) (4) RPT04176
Bioanalytical report	(b) (4) RPT04305
Lab	(b) (4)
Drug tolerance level (DTL)	6200 ng/mL for 2000 ng/mL ADA; < 160 ng/mL for 100 ng/mL ADA

Positive control levels	100 and 2000 ng/mL
Minimum required dilution	1
Hook effect	Up to 60,000 ng/mL
Freeze/Thaw stability	Five cycles
Storage stability	NA
Bench top stability	~ 24 hours
Precision (%CV)	< 20%

Pharmacokinetic Assessments

Blood samples from all patients were used to summarize the observed pre-infusion and post-infusion ibalizumab concentrations. For PK Substudy, non-compartmental analysis was performed to calculate C_{max} and $AUC_{0\text{-}tau}$.

Pharmacokinetic –Pharmacodynamics (PK-PD) relationship Assessments

The relationships between receptor occupancy and ibalizumab serum concentration, receptor density and viral load reduction were evaluated by the sponsor, respectively.

Reviewer's comment*: Sponsor's analysis cannot provide supportive evidence for efficacy/dose strategy due to lack of bioanalytical reports for RO/RD.*

9. Results

9.1 Subject Demographics and Disposition

A total of 113 subjects were enrolled, and 59 received ibalizumab 800 mg q2wk and 54 received ibalizumab 2000 mg q4wk along with an OBR selected by the investigator. The majority of subjects were white (61.9%, 70 subjects) or black or African-American (23.9%, 27 subjects) and Non-Hispanic or Latino (64.6%, 73 subjects), with more males than females (89.4% male, 101 subjects). Subjects had a mean (SD) age of 48.1 (7.4) years (range: 30 to 70 years) and a mean (SD) weight of 80.7 (17.2) kg (range: 47.8 to 146.7 kg).

9.2 Pharmacokinetic Analysis

The post-infusion concentrations were high and relatively consistent over time (**Table 1**), while the pre-infusion concentrations were not. The median pre-infusion concentration was 0.3 to 26 µg/mL, and the CV% was 107 to 321% for 800 mg Q2W. The median pre-infusion concentration was 0.2 to 1.2 µg/mL, and the CV% was high, at 320 to 405% for 2000 mg Q4W (**Table 2**).

Reviewer's analysis:

Table 1: Ibalizumab post-infusion concentrations (µg/mL) over time in TMB-202 study

Regimen	Stats	Week 2	Week 4	Week 8	Week 10	Week 12	Week 24
800 mg Q2W	N	53	53	52	13	52	31
	Mean (µg/mL)	**285**	**289**	**318**	**267**	**284**	**293**
	Min (µg/mL)	0.23	105	31	77	129	0.19
	Median (µg/mL)	266	263	262	246	267	286
	Max (µg/mL)	756	735	1610	524	652	620
	CV%	**47**	**41**	**68**	**41**	**36**	**48**
2000 mg Q4W	N		47	45		40	26
	Mean (µg/mL)		**688**	**706**		**641**	**709**
	Min (µg/mL)		253	0.12		0.10	93
	Median (µg/mL)		630	664		634	749
	Max (µg/mL)		2690	1390		1400	1040
	CV%		**52**	**39**		**39**	**27**

Table 2: Ibalizumab pre-infusion concentrations (µg/mL) over time in TMB-202 study

Regimen	Stats	Week 2	Week 4	Week 8	Week 10	Week 12	Week 24
800 mg Q2W	N	46	45	48	13	51	33
	Mean (µg/mL)	**35**	**42**	**28**	**32**	**25**	**39**
	Min (µg/mL)	0.11	0.10	0.12	0.16	0.10	0.11
	Median (µg/mL)	**3.7**	**0.30**	**0.41**	**26**	**2.2**	**9.0**
	Max (µg/mL)	341	783	513	90	280	277
	CV%	**234**	**321**	**291**	**107**	**206**	**174**
2000 mg Q4W	N		45	45		40	31
	Mean (µg/mL)		**45**	**37**		**35**	**61**
	Min (µg/mL)		0.10	0.12		0.12	0.13
	Median (µg/mL)		**0.21**	**0.25**		**0.29**	**1.2**
	Max (µg/mL)		777	722		902	1080
	CV%		**350**	**338**		**405**	**320**

Serum concentrations from the PK Substudy were used for the non-compartmental analysis by the sponsor, and the selected parameters are summarized in **Table 3**.

Sponsor's analysis:

Table 3: Selected parameters from non-compartmental analysis in TMB-202 PK Substudy

Ibalizumab Dose (IV)	N in PK substudy	C_{max} (µg/mL)	AUC_{tau} (h*µg/mL)
800 mg Q2W	16	154	20508
2000 mg Q4W	11	306	68784

9.3 PK-PD relationship Analysis
RO *vs.* ibalizumab conc. or RD or viral load reduction

Reviewer's comment*: Bioanalytical reports were not written for RO/RD assays, thus the RO/RD results cannot be verified. Sponsor's analysis cannot provide supportive evidence for efficacy/dose strategy.*

9.4 Immunogenicity
One patient (10008) in the 2000 mg Q4W treatment group had ADA positive result at Week 24, and the nAb assay was positive for that sample. However, the titer was low at 16, thus the ADA did not appear to have a negative impact on the antiviral efficacy of ibalizumab. Patient 10008 completed Week 24 with undetectable HIV-1 RNA and a significant increase in $CD4^+$ T-cell count (131 cells/µL). The patient had no AEs associated with the positive immunogenicity result (refer to the CMC/OBP review for the final conclusion regarding immunogenicity risk). The effect on PK was inconclusive due to limited ADA positive samples and large variation of ibalizumab concentrations.

9.5 Results for Primary Efficacy Endpoint
The primary effectiveness endpoint was the proportion of patients with HIV-1 RNA levels < 50 copies/mL at Week 24.

As summarized in **Table 4**, the 2000 mg every 4 weeks arm provided better efficacy at Week 2, probably due to the higher exposure by Week 2 from the higher dose. However, the 800 mg every 2 weeks showed better efficacy at Week 24, probably due to the higher C_{trough} from the shorter dose interval. The AE profile was similar for both dosages.

Table 4: Proportion of patients with viral load <50 copies/mL at each time point in Phase 2b study

Time point	Number (%) of Patients		
	Ibalizumab + OBR		
	800 mg q2wk (N=59)	2000 mg q4wk (N=54)	Total (N=113)
Viral load <50 copies/mL			
Baseline	0	0	0
Week 2	2 (3.4)	7 (13.0)	9 (8.0)
Week 4	10 (16.9)	11 (20.4)	21 (18.6)
Week 8	15 (25.4)	11 (20.4)	26 (23.0)
Week 12	21 (35.6)	13 (24.1)	34 (30.1)
Week 16	22 (37.3)	11 (20.4)	33 (29.2)
Week 20	23 (39.0)	14 (25.9)	37 (32.7)
Week 24	26 (44.1)	15 (27.8)	41 (36.3)

9.6 Safety

According to the sponsor, both dosages of ibalizumab in the current study in combination with OBR were well-tolerated in patients with HIV. No differences were observed in dose-related toxicities. Treatment-emergent adverse events were generally mild to moderate and similar in number across treatment arms. Likewise, laboratory test results suggest that the dosages tested were generally well tolerated in the study population with no apparent short-term toxicity. Immunogenicity was not seen in this study nor were injection site reactions observed in relation to ibalizumab administration, according to the sponsor. Please refer to the Medical Officer's review for additional details.

10. Conclusions

- Ibalizumab concentrations reached steady-state levels after the first dose for both 800 mg Q2W and 2000 mg Q4W dose regimens.
- The median trough concentration of ibalizumab was 0.3 to 26 µg/mL with CV% at 107 to 321% for 800 mg Q2W; the median trough concentration was 0.2 to 1.2 µg/mL with CV% at 320 to 405% for 2000 mg Q4W.
- One patient from 2000 mg Q4W was ADA positive at Week 24; however, the ADA did not appear to affect the efficacy due to low titer at 16.

11. Reviewer's Assessment

- The study design is reasonable and the PK conclusions are acceptable.

- The proposed dose regimen used in the Phase 3 study was designed to combine the maximal initial drug exposure of a 2000 mg dose with the more durable efficacy from 800 mg every 2 weeks dose regimen.

- Upon consultation with the OCP BOB (Biologics Oversight Board), the RO/RD related analysis by the sponsor cannot provide supportive evidence for efficacy/dose strategy, due to lack of bioanalytical reports for data validation. (b) (4)

- Refer to the CMC/OBP review for the final conclusion regarding immunogenicity risk.

4.5.5 TMB-301 Phase 3 Study

1. Title

A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab Plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected With Multi-Drug Resistant HIV-1

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at 19 clinical sites (17 in US and 2 in Taiwan) from July 6, 2015 to October 20, 2016, with the final report date of April 18, 2017.

3. Objectives

Primary objective:

- To demonstrate the antiviral activity of ibalizumab at Day 14 and at Week 25 (end of study [EOS]).

Secondary objectives:

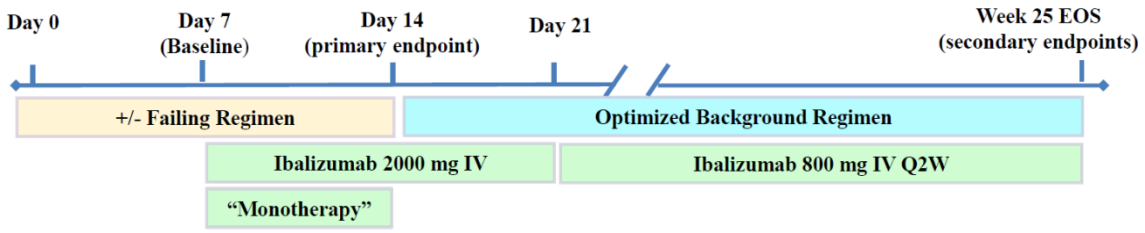
- To assess the safety and tolerability of ibalizumab assessed through Week 25 (EOS)
- To assess the mean change from Day 7 (Baseline) in $CD4^+$ cell count at Week 25 (EOS)
- To characterize HIV-1 sensitivity/susceptibility changes associated with protocol-defined virologic failure (VF) after ibalizumab administration in combination with OBR
- To determine the presence and significance of anti-ibalizumab antibodies (ADA), if any (immunogenicity of ibalizumab)
- To assess CD4 receptor density and occupancy
- To determine the impact of ibalizumab on quality of life (QoL) as assessed by patient-reported outcomes (PROs)

4. Trial Design

This study was a Phase 3, single-arm, multicenter study designed to assess the antiviral activity, efficacy, safety, and tolerability of an IV ibalizumab dose regimen in treatment-experienced patients infected with multi-drug resistant HIV-1.

The study consisted of three periods: a control period (Days 0−6), an essential monotherapy period (Days 7−13), and a maintenance period (Day 14−Week 25) (**Figure 1**).

Figure 1: TMB-301 study scheme



During the control period (Days 0−6) patients were monitored on current failing therapy (or no therapy, if the patient had failed and discontinued treatment within the 8 weeks preceding Screening). During the essential monotherapy period (Days 7−13) patients continued on current failing therapy, receiving one 2000-mg dose (loading dose) of ibalizumab on Day 7. Day 7 was considered Baseline for the treatment period (Day 7−Week 25). Day 14 through Week 25 of the study represented the maintenance period. On Day 14 (primary endpoint), the OBR was initiated and must have included at least one agent to which the patient's virus was fully susceptible (as determined at Screening, in combination with historical resistance testing). Beginning at Day 21, 800 mg of ibalizumab was administered Q2W through Week 23. All patients were to complete the Week 25/EOS Visit and the Week 29/Follow-up Visit procedures.

The duration of the infusion was no less than 30 minutes during the first 2 study drug administrations. If no infusion-associated AEs occurred after 2 administrations, the infusion duration could be decreased to no less than 15 minutes.

Throughout the study, patients were not required to fast before collection of blood samples for safety, efficacy, or PK evaluations. However, patients were to adhere to dietary recommendations as suggested for the components of their OBR or other concomitant medications.

Eligible subjects were HIV-1 infected patients meeting the following criteria:

- 18 years of age or older
- Had a life expectancy > 6 months
- Had a viral load > 1000 copies/mL and documented resistance to at least one ARV medication from each of three classes of ARV medications as measured by resistance

testing
- Had a history of at least 6 months on ARV treatment
- Had been receiving a stable highly active ARV regimen for at least 8 weeks before Screening and were willing to continue that regimen until Day 14, OR (in the past 8 weeks) had failed and was off therapy and willing to stay off therapy until Day 14
- Had full viral sensitivity/susceptibility to at least one ARV agent, other than ibalizumab, as determined by the Screening resistance tests and willing and able to be treated with at least one agent to which the patient's viral isolate was fully sensitive/susceptible according to the Screening resistance tests as a component of OBR

5. Excluded Medications and Restrictions

- Any immunomodulating therapy (including interferon), systemic steroids, or systemic chemotherapy within 12 weeks before enrollment.
- Any prior exposure to ibalizumab (formerly TNX-355 and Hu5A8)
- Therapeutic HIV vaccines from Screening until the Week 25 (EOS) visit
- Any vaccines during the 7 days before Day 0/enrollment through Day 14 of the study
- All investigational drugs from 30 days before Day 0/enrollment and throughout the study (except investigational ARV medications as a component of OBR)
- Drugs that can potentiate the activity of ARV drugs or have intrinsic ARV activity (but not indicated for treatment of HIV infection), such as, but not limited to, mycophenolic acid, hydroxyurea, or foscarnet from 30 days before Day 7 (Baseline) and throughout participation in the study
- Immunomodulator compounds (e.g., interleukins and interferons)
- Bone marrow suppressants used in oncology treatment
- Radiation therapy from 28 days before first to the last administration of study drug

6. Rationale for Doses Used in the Trial

Ibalizumab: 2000 mg IV as loading dose (Day 7) followed 2 weeks later (Day 21) by 800 mg IV Q2W as maintenance dose through Week 23.

The dose selection was based on TMB-202 (Phase 2b) study results which evaluated 800 mg Q2W versus 2000 mg Q4W for 24 weeks. TMB-202 study indicated that higher serum concentrations were achieved more rapidly with the 2000 mg dose, while more patients achieved HIV RNA levels < 50 copies at Week 24 with 800 mg Q2W. In addition, the AE profile was similar for both dosages. This dose regimen was designed to combine the maximal initial drug exposure of a 2000 mg dose with the more durable efficacy of the 800 mg Q2W dose.

7. Drugs Used in the Trial

Ibalizumab: injection solution, 200 mg/vial (~ 1.33 mL), 150 mg/mL in histidine USP (1.55 mg/mL), sucrose USP (52 mg/mL), sodium chloride (3.04 mg/mL), polysorbate 80 (0.45 mg/mL), pH 6.0.

Lot number: [redacted]236, 201505012
Manufacturer: [redacted]

The most frequently prescribed OBR agents were tenofovir (78%), emtricitabine (70%), dolutegravir (65%), and darunavir (60%). Seventeen patients (42.5%) required the addition of a second investigational agent (fostemsavir) to construct an OBR. The entry inhibitor maraviroc was used by 4 patients (10%) in their OBR and 1 patient (2.5%) used enfuvirtide.

8. Sample Collection, Bioanalysis, and Pharmacokinetic/Pharmacodynamic

Assessments

Sample Collection

Ibalizumab serum concentrations:

Blood samples for ibalizumab serum concentrations were collected within 1 hour before the start of infusion (Weeks 1 [Day 7], 2, 3, 5, 9, 13, 17, 21, and 25) and within 10 minutes after the end of infusion (Weeks 1 [Day 7], 3, 13 and 21).

RO and RD (receptor density):

Blood samples for RO and RD were collected at the same time points before and after the infusion as for ibalizumab serum concentrations listed above.

ADA:

Blood samples were collected to test for the development of antibodies against ibalizumab periodically throughout the study including Baseline, Week 13, and Week 29/Follow-up. For patients completing Study TMB-301 who then immediately enrolled in Study TMB-311 - the expanded access program - Week 25 samples were tested instead of Week 29/Follow-up due to the absence of a washout period. Samples were collected prior to ibalizumab infusion if an infusion was scheduled for that visit. Please refer to the CMC/OBP review for additional details.

Bioanalytical method

Ibalizumab serum concentration:

Ibalizumab serum concentrations were determined using fully validated sandwich enzyme-linked immunosorbent assay (ELISA). Standard curve and quality control data indicated the bioanalytical assays for ibalizumab serum concentrations were precise and accurate. The details for the assay performance are listed below:

Analyte	Ibalizumab
Matrix	Human serum
Assay type	Sandwich ELISA
Validation report	TNJS15-039
Bioanalytical report	TNJS15-051
Lab	[redacted]
Calibration range	10 to 2000 ng/mL

QC levels	30, 150, 1400 ng/mL
Minimum required dilution	10
Dilution linearity	Up to 160,600,000 ng/mL
Freeze/Thaw stability	Five cycles
Storage stability	214 days at -70°C
Bench top/refrigerator stability	22 hours 45 minutes
Accuracy (% Bias)	± 20% (25% for LLOQ/ULOQ)
Precision (%CV)	< 20% (25% for LLOQ/ULOQ)

Reviewer's comment: *The long-term storage stability has been established for 214 days at -70°C; however, the maximum time from collection to analysis is 683 days. Based on the sponsor's response to an information request, 60% (276/458) of samples were analyzed beyond the demonstrated long-term stability range of 214 days, and additional interim testing is no longer feasible due to a minimal inventory of frozen quantitative control (QC) samples. The next time point for demonstrating long-term stability is scheduled to be at 684 days and this will occur during the last week of February, 2018.*

In study TMB-202, the long-term storage stability has been established for 784 days at -80 ± 10°C, which may provide some supportive evidence for the long-term storage stability.

RO/RD:
According to the sponsor's response to an information request, the bioanalytical reports for clinical samples were not written for RO/RD assays, thus RO/RD results cannot be verified, although the assay method validation report was submitted (TMB-301 RO/RD validation report: (b) (4) 10039-VR01-01).

ADA and neutralizing antibody (nAb):
Anti-ibalizumab antibody was determined by a validated bridging sandwich ELISA with acid dissociation immunoassay. The ELISA assay was carried out using a typical 3-tiered assay approach: 1. Tier 1 ADA screening assay: to identify initial putative positive samples; 2. Tier 2 confirmatory assay: to assess specificity of the positive screen samples; 3. Tier 3 titer assay: to estimate the level of antibody for the confirmed positive samples. The assay performance is summarized briefly below (refer to the CMC/OBP immunogenicity review for further details on the assay).

The nAb assay was not performed in TMB-301 study, since there was no ADA positive sample.

Analyte	ADA
Matrix	Human serum
Assay type	Bridging sandwich ELISA with acid dissociation
Validation report	8322-269
Bioanalytical report	8326-252

Lab	(b) (4)
Drug tolerance level	2500 ng/mL
Positive control levels	42.2 and 3440 ng/mL
Minimum required dilution	10
Hook effect	Up to 8750 ng/mL
Freeze/Thaw stability	Six cycles
Storage stability	566 days at -60 to 80°C
Bench top stability	25 hours 38 minutes
Precision (%CV)	< 20%

Pharmacokinetic Assessments
Non-compartmental analysis for PK parameter estimation was not performed due to sparse sampling before and after infusion only. The mean ibalizumab serum concentrations were calculated at each time point. The effects of body weight on the peak (Day 7) and trough (Week 25) concentrations were evaluated.

Pharmacokinetic –Pharmacodynamics (PK-PD) relationship Assessments
The relationships between ibalizumab serum concentration and receptor occupancy, receptor density and viral load reduction were evaluated by the sponsor, respectively.

Reviewer's comment*: Sponsor's analysis cannot provide supportive evidence for efficacy/dose strategy due to lack of bioanalytical reports for RO/RD.*

9. Results

9.1 Subject Demographics and Disposition
A total of 40 subjects enrolled in the study. All subjects were included in the pharmacokinetic analysis. The majority of subjects were white (55%, 22 subjects) or black or African-American (32.5%, 13 subjects) and Non-Hispanic or Latino (67.5%, 27 subjects), with more males than females (85% male, 34 subjects). Subjects had a mean (SD) age of 50.5 (11.0) years (range: 26 to 65 years) and a mean (SD) weight of 77.7 (16.5) kg (range: 50 to 118 kg).

9.2 Pharmacokinetic Analysis
The mean post-infusion concentration was high at > 200 µg/mL, and the CV% was 39 to 56%. The mean pre-infusion concentrations were > 30 µg/mL, and the CV% was higher compared to post dose, at 57% for Week 3 (C_{trough} from loading dose), and at 90 to 116% for Weeks 5 to 25 (C_{trough} from maintenance dose) (**Tables 1 and 2**).

The mean pre-infusion concentrations (C_{trough}) in TMB-301 (2000 mg + 800 mg Q2W) were higher than those in TMB-202 (800 mg Q2W) before Week 8 and were comparable after Week 8 (**Figure 1**). The higher concentrations at the earlier stage from the loading dose may contribute to the better efficacy regarding to proportion of patients achieving < 50 copies/mL in HIV-1 RNA at 2 weeks after the first dose **(Table 3)**. However, the efficacy was comparable at 24 weeks after the first dose, with the limited subjects evaluated, with or without the loading dose **(Table 4).**

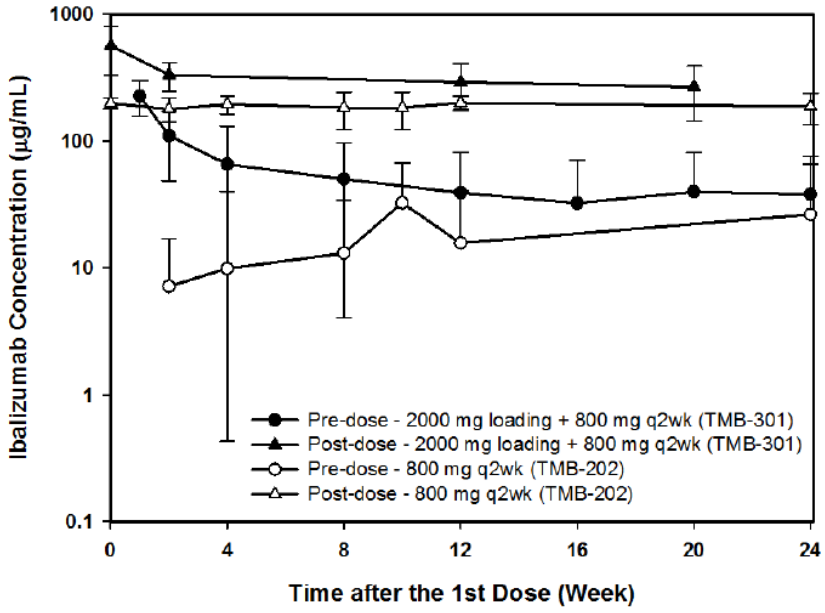
The effect of body weight on ibalizumab serum concentrations was evaluated for post-infusion concentrations on Day 7 (C_{max} from the loading dose) and for trough concentrations on Week 25 (EOS, last maintenance dose on Week 23). It was found that ibalizumab concentrations decreased with increased body weight, especially for body weight ≥ 85 kg, based on the sponsor's analysis (refer to Appendix 4.3 for the pharmacometric reviewer's population PK analyses).

Sponsor's analysis:

Table 1: Ibalizumab serum concentrations (µg/mL) over time (mean ± SD)

Visit	Time after the first dose	Ibalizumab serum concentrations (µg/mL)	
		Pre-dose	Post-dose
Day 7	Day 0	0.00 ± 0.00	566.87 ± 234.67
Day 14	Day 7		227.19 ± 71.58
Day 21	Day 14	110.04 ± 61.86	331.50 ± 85.45
Week 5	Week 4	65.43 ± 65.00	
Week 9	Week 8	49.97 ± 45.91	
Week 13	Week 12	38.97 ± 41.67	291.41 ± 115.60
Week 17	Week 16	32.29 ± 38.05	
Week 21	Week 20	39.63 ± 41.08	266.94 ± 123.92
Week 25/EOS	Week 24/EOS	37.93 ± 38.31	

Figure 1: Comparison of mean (± SD) ibalizumab pre- and post-infusion concentrations in TMB-301 and TMB-202



Reviewer's analysis:

Table 2: Summary of ibalizumab pre-infusion concentrations in study TMB-301

	Week						
	3	**5**	**9**	**13**	**17**	**21**	**25**
N	40	36	30	33	32	31	31
Mean (µg/mL)	**107**	**63**	**50**	**72**	**35**	**48**	**41**
Min (µg/mL)	6.7	0.018	0.021	0.013	0.033	0.018	0.014
Median (µg/mL)	110	54	40	49	29	39	40
Max (µg/mL)	311	252	175	315	142	250	153
CV%	**57**	**100**	**91**	**115**	**107**	**116**	**95**

Table 3: Efficacy comparison between TMB-301 and TMB-202 at 2 weeks after the first dose

Study	Dose regimen	N	Time	> 0.5 $\log_{10}$ reduction	> 1.0 $\log_{10}$ reduction	**< 50 c/mL HIV RNA**	< 400 c/mL HIV RNA
				%	%	**%**	%
TMB-301	2000 mg+800 mg Q2W	40	W2*	88	78	**15**	48
TMB-202	800 mg Q2W	59	W2	90	85	**3**	44

** 2 weeks from the loading dose on Day 7.*

Table 4: Efficacy comparison between TMB-301 and TMB-202 at 24 weeks after the first dose

Study	Dose regimen	N	Time	> 0.5 $\log_{10}$ reduction	> 1.0 $\log_{10}$ reduction	**< 50 c/mL HIV RNA**	< 400 c/mL HIV RNA
				%	%	**%**	%
TMB-301	2000 mg+800 mg Q2W	40	W24*	63	55	**43**	53
TMB-202	800 mg Q2W	59	W24	68	63	**44**	58

** 24 weeks from the loading dose on Day 7.*

9.3 PK-PD relationship Analysis
Ibalizumab serum conc. *vs.* RO/RD

Reviewer's comment*: Bioanalytical reports were not written for RO/RD assays, thus the RO/RD results cannot be verified. Sponsor's analysis cannot provide supportive evidence for efficacy/dose strategy.*

Ibalizumab serum conc. *vs.* viral load reduction
There was no apparent association between ibalizumab serum concentration and viral load reduction due to the underlying effect of different OBR's, according to the sponsor (refer to Appendix 4.4 for reviewer's exposure-response relationship analyses).

9.4 Immunogenicity
No patients developed ADAs during 24 weeks of treatment with ibalizumab (refer to the CMC/OBP review for further details and the final conclusion).

9.5 Safety
A loading dose of 2000 mg ibalizumab with maintenance dosing of 800 mg Q2W was safe and well-tolerated in heavily treatment-experienced HIV-1 patients. The majority of the reported safety events appear to be secondary to HIV/AIDS (refer to Medical Officer's review for further details).

10. Conclusions

- Following the recommended dose regimen (2000 mg as a loading dose and 800 mg once every 2 weeks as maintenance doses), ibalizumab concentrations reached steady-state levels after the first 800 mg maintenance dose with mean concentrations over 30 µg/mL throughout the dosing period.

- The concentrations with a regimen that includes a loading dose (regimen used in this study) were higher before Week 8 and were comparable after Week 8, compared to 800 mg Q2W without the loading dose in TMB-202 study.

- Ibalizumab concentrations decreased with increased body weight, especially for body weight ≥ 85 kg.

- No subjects developed ADAs during 24 weeks of treatment with ibalizumab.

11. Reviewer's Assessment

- The study design is reasonable and the PK conclusions are acceptable.

- Upon consultation with the OCP BOB (Biologics Oversight Board), the RO/RD related analysis by the sponsor cannot provide supportive evidence for efficacy/dose strategy, due to lack of bioanalytical reports for data validation. (b) (4)

- Refer to the CMC/OBP review for the final conclusion regarding immunogenicity risk.

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/s/

QIN SUN
10/02/2017

LUNING ZHUANG
10/02/2017

JEFFRY FLORIAN
10/02/2017

SHIRLEY K SEO
10/02/2017

KELLIE S REYNOLDS
10/02/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

BLA Number	761065	**SDN**	12
Applicant	TaiMed Biologics	**Submission Date**	05/03/2017
Generic Name	Ibalizumab	**Brand Name**	Proposed: Trogarzo
Drug Class	A CD4 domain 2-directed humanized monoclonal antibody (mAb)		
Indication	Treatment of adults infected with HIV-1 resistant to at least one agent in three different classes.		
Dosage Regimen	A single loading dose of 2000 mg followed by a maintenance dose of 800 mg every 2 weeks after dilution in 250 mL of sterile physiological saline.		
Dosage Form	200 mg in solution per vial (~ 1.33 mL at 150 mg/mL)	**Route of Administration**	Intravenously (IV)
OCP Division	DCP4	**OND Division**	DAVP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Qin Sun	Shirley Seo
Pharmacometrics	Ada Zhuang	Jeffry Florian
Genomics	NA	

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	7/2/2017	**74-Day Letter Date**	7/16/2017
Review Due Date	10/3/2017	**PDUFA Goal Date**	1/3/2018

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

IRs have been sent to the sponsor on May 31, 2017 and June 20, 2017 to request the submission of PK datasets, Pop PK datasets, formulation information, and bioanalytical reports.

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**

In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☑ Single Dose	1	Hu5A8.01 or TNX-355.01 (Phase 1a) (with efficacy evaluation)
	☑ Multiple Dose	1	TNX-355.02 (Phase 1b) (with efficacy evaluation)
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients		3	Study TNX-355.03 (Phase 2a), TMB-202 (Phase 2b), and TMB-301 (Phase 3) with OBR
☐ QT			
Pharmacometrics			
☑ Population Pharmacokinetics			Pop PK was submitted only for Study TNX-355.03 (Phase 2a), and IR has been sent to the sponsor on May 31, 2017 to request Pop PK analysis for TMB-202 and TMB-301, if available.

☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	5
Total Number of Studies to be Reviewed				5

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	To-be-marketed formulation has been used in the pivotal phase 3 studies.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑N/A	Although it is not agreed upon at the pre-BLA meeting, the submission of PK datasets and Pop PK datasets is requested through IR on May 31, 2017.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for	☐Yes ☐No ☑N/A	Although it is not agreed upon at the pre-BLA meeting, the submission of PK datasets and Pop

not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		PK datasets is requested through IR on May 31, 2017.
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☑No ☐N/A	IR has been sent to the sponsor on May 31, 2017 to request the submission of PK datasets and Pop PK datasets (in CDISC format, if available)
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☑No ☐N/A	E-R relationship for efficacy and safety has not been submitted, and IR has been sent to the sponsor on May 31, 2017 to request submission, if available.
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☑No ☐N/A	E-R relationship for efficacy and safety has not been submitted, and IR has been sent to the sponsor on May 31, 2017 to request submission, if available.
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

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/s/

QIN SUN
06/28/2017

SHIRLEY K SEO
06/29/2017