

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761065Orig1s000**

**CLINICAL REVIEW(S)**

### CLINICAL REVIEW ADDENDUM

<b>Application Type</b>	Biologic Licensing Application
<b>Application Number(s)</b>	BLA 761065
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	05/03/2017
<b>Received Date(s)</b>	05/03/2017
<b>PDUFA Goal Date</b>	1/03/2018
<b>Division/Office</b>	DAVP/OAP/OND
<b>Reviewer Name(s)</b>	Virginia Sheikh, MD
<b>Addendum Completion Date</b>	11/6/2017
<b>Established Name</b>	Ibalizumab (TNX-355, Hu5A8)
<b>(Proposed) Trade Name</b>	TROGARZO
<b>Applicant</b>	TaiMed Biologics Inc.
<b>Formulation(s)</b>	Intravenous
<b>Dosing Regimen</b>	2000 mg loading dose followed by 800 mg every 2 weeks (IV)
<b>Applicant Proposed Indication(s)/Population(s)</b>	TROGARZO, (b) (4), in combination with other antiretroviral(s), is indicated for the treatment of adults infected with HIV-1 resistant to at least one agent in three different classes
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	TROGARZO, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV infection failing current antiretroviral therapy.

#### 1. Executive Summary

This addendum provides an update of the TMB-301 and TMB-202 analyses of serum phosphate. In addition, it provides results from analyses of laboratory abnormalities that were not available for complete review prior to the initial review due date. Specifically, the applicant provided results of serum creatinine for study TMB-301 and serum creatinine, urine protein, and urine glucose results for study TMB-202.

Regarding abnormalities of serum phosphate, communications with the applicant and further analysis of the issue revealed that the Grade 3 or higher abnormalities reported in the Clinical Review were artefactual. Analysis of the original study data using mg/dL units shows that Grade 3 or higher serum hypophosphatemia did not occur in TMB-301 and was very rare in TMB-202. Therefore, abnormalities of serum phosphate will not be presented in the label.

Analysis of baseline renal abnormalities demonstrate that renal disease was common in participants of both TMB-301 and TMB-202 prior to ibalizumab exposure. After ibalizumab exposure, renal abnormalities were common in participants of both studies; however, abnormalities occurred almost exclusively in participants with underlying renal disease, risk factors for nephrotoxicity, and/or concomitant nephrotoxic medications. These data do not show a causal relationship between ibalizumab administration and renal abnormalities. Because elevations in creatinine were frequent, Grade 3 creatinine events will be labeled.

## 2. Serum Phosphate in TMB-301 and TMB-202

The frequency and severity of serum hypophosphatemia presented in the clinical review submitted on October 3, 2017 was based on serum phosphate and grading data submitted by the applicant. Per that data, the frequency of Grade 3 or higher treatment-emergent serum phosphate was 8% (3/40) in TMB-301 and 19% (22/113) in TMB-202. Communications with the applicant and further analysis of the issue reveal the apparent Grade 3 or higher abnormalities were artefactual. In actuality, Grade 3 or higher hypophosphatemia did not occur in TMB-301 and was very rare (1/113, 1%) in TMB-202. The reasons for the discrepancy are described below.

- A. Error in 2014 DAIDS Toxicity Scale: The serum phosphate data submitted by the applicant was graded using the DAIDS toxicity table Version 2.0 (2014) using millimole/Liter units (mmol/L). Version 2.0 of the toxicity table included a change to the mg/dL criteria for grading serum phosphate; however, in error, no change was made to the mmol/L criteria. In effect, this resulted in two different grading scales depending on the units used. Values graded using mmol/L units were generally assigned higher toxicity grades than values graded using equivalent mg/dL units. For example, 0.5 mmol/L would be Grade 3 using mmol/L, but the equivalent value in mg/dL (1.5 mg/dL) would be Grade 2. This error was corrected in the July 2017 version of the toxicity table (Version 2.1 July 2017 correction). See **Appendix 1**. Reanalysis of the submitted TMB-301 and TMB-202 serum phosphate values using the corrected toxicity criteria (2017) reveals significantly decreased rates of treatment emergent serum phosphate: 0% (0/40) in TMB-301 and 6% (7/113) in TMB-202. See **Table 1**.

**Table 1. TMB-301 and TMB-202 Serum Phosphate Toxicity using submitted values and 2014 (V2.0) verses 2017 (V2.1) DAIDS Toxicity Criteria**

Phosphate, (Hypophosphatemia)	Grade	Toxicity Criteria	TMB-301	TMB-202	
			Ibalizumab 2000 mg x1 then 800mg Q2W N=40	Ibalizumab 2000 mg Q4W N=54	Ibalizumab 800 mg Q2W N=59
<b>V 2.0 (2014)</b>	1	0.81 mmol/L to < LLN	NA	NA	NA
	2	0.65 to < 0.81 mmol/L	7(18%)	7(13%)	12 (20%)
	3	0.32 to < 0.65 mmol/L	3 (8%)	7(13%)	11(19%)
	4	< 0.32 mmol/L	0	2 (4%)	2 (3%)
<b>2017 V2.1 July 2017 Clarification</b>	1	0.65 mmol/L to < LLN	2(5%)	5(9%)	4(7%)
	2	0.45 to < 0.65 mmol/L	3(8%)	5(9%)	10(17%)
	3	0.32 to < 0.45 mmol/L	0	2 (4%)	1(2%)
	4	< 0.32 mmol/L	0	2 (4%)	2 (3%)

B. Standardization of TMB-202 data: In further communication with the Division, TaiMed explained that it standardized units from three different laboratories to integrate the TMB-301 and TMB-202 laboratory results for the submission. Because TMB-301 was the pivotal study, the serum phosphate units and normal ranges were used as the “standard” and values from TMB-202 were adjusted to the respective TMB-301 units and normal ranges. The normal range for serum phosphate was wider for the laboratory used for study TMB-301 than for the laboratories used for TMB-202. Therefore, when the values were integrated, the TMB-202 results were “stretched” through the interpolation. Thus, low TMB-202 serum phosphate values became artefactually lower. On November 2, 2017 TaiMed provided analysis of TMB-202 serum phosphate toxicity using the original data (in mg/dL) compared to the standardized data (in mmol/L); only one participant had a Grade 3 or higher serum phosphate.

These factors demonstrate that the serum phosphate abnormalities noted in the Clinical Review were in fact artefactually low. TaiMed's analysis of the original data using mg/dL units shows that Grade 3 or higher serum hypophosphatemia did not occur in TMB-301 and was very rare in TMB-202. Therefore, abnormalities of serum phosphate will not be presented in the label.

### **3. Analysis of abnormalities of serum creatinine, urine protein, and urine glucose**

This section provides analysis of TMB-301 and TMB-202 serum creatinine, urine protein, and urine glucose results, which were not available for review prior to the initial review due date.

#### **3.1 Baseline renal abnormalities in TMB-301 and TMB-202**

At baseline and/or pre-baseline, four (10%) TMB-301 participants had graded elevations in creatinine. Three participants (301-02-002, 301-09-002, 301-13-001) had Grade 1 elevations and one participant (301-22-001) had a Grade 3 elevation. Although the TMB-301 protocol specified collection of urine protein and urine glucose, these were not collected and therefore will not be discussed for this trial.

Underlying renal disease, as evidenced by pre-ibalizumab abnormalities in creatinine and urine protein was common in TMB-202 participants. At baseline and/or at one of the other two pre-ibalizumab visits (Weeks -4 to -6 or Weeks -2 or -1), fourteen (12%) TMB-202 participants had graded elevations in creatinine, including six participants who had Grade 3 elevations, four who had Grade 2 elevations, and four who had Grade 1 elevations. Urine proteinuria was very common at baseline as well; fifty-four participants (48%) had proteinuria including 12 (11%) who had Grade 3 proteinuria, 22 (19%) who had Grade 2 proteinuria, and 20 (18%) who had Grade 1 proteinuria. Glycosuria, indicative of underlying diabetes mellitus in many cases, was less frequent; twelve (11%) participants had glycosuria including 3 (3%) who had Grade 3 glycosuria, 3 (3%) who had Grade 2 glycosuria, and 6 (5%) who had grade 1 glycosuria.

In conclusion, analysis of the baseline parameters of creatinine, urine protein, and urine glucose demonstrated that renal disease and/or co-morbidities predisposing to renal disease were highly prevalent in TMB-202 participants prior to ibalizumab administration. Data from TMB-301, which is limited due to the missing urine protein and urine glucose data, suggest that renal disease was also present at baseline in at least 10% of TMB-301 participants.

#### **3.2 Emergent renal abnormalities in TMB-301 and TMB-202**

Treatment-emergent Grade 1-4 abnormalities of creatinine, urine glucose, and urine protein are shown in **Table 2**.

**Table 2. TMB-301 and TMB-202 Grade 1-4 Serum Creatinine, Urine Protein, and Urine Glucose Laboratory Abnormalities \***

Parameter	Toxicity Grade	Result Range	TMB-301	TMB-202	
			Ibalizumab 2000 mg x1 then 800mg Q2W N=40	Ibalizumab 2000 mg Q4W N=54	Ibalizumab 800 mg Q2W N=59
<b>Creatinine (Increased)</b>	1	≥ 1.1 x ULN	0	0	1
	2	> 1.3 x ULN or 0.3 mg/dL above baseline	2 (5%)	6 (11%)	7(12%)
	3	> 1.8 x ULN or 1.5 to <2.0 x mg/dL above baseline	4 (10%)	6(11%)	10(17%)
	4	≥ 3.5 x ULN or ≥2.0 x mg/dL above baseline	0	1(3%)	1(2%)
<b>Urine protein (Increased)</b>	1	≥ 30 mg	Data not collected	3(6%)	7(12%)
	2	≥ 100 mg	Data not collected	4 (7%)	3(5%)
	3	≥ 300 mg	Data not collected	5 (7%)	2(3%)
	4	Not applicable (NA)	Data not collected	NA	NA
<b>Urine glucose (Increased)</b>	1	≤250 mg	Data not collected	4(7%)	3(5%)
	2	>250 and ≤500 mg	Data not collected	1(3%)	3(5%)
	3	>500 mg	Data not collected	3(6%)	4(7%)
	4	NA	Data not collected	NA	NA

\*Increased in grade from baseline and, for study TMB-202, occurring with the first 24 weeks (168 days).

### TMB-301

After the initiation of ibalizumab, six TMB-301 participants experienced graded elevations in creatinine (emergent since baseline). Two participants experienced grade 2 elevations and four (10%) TMB-301 participants experienced Grade 3 or higher elevations. All four Grade 3 events were based on a change in the participants' baseline creatinine values, and not due to increases greater than 1.8 x ULN (Grade 3). Descriptive cases for the four TMB-301 participants who experienced a Grade 3 or higher increase in creatinine are provided below.

**301-01-005** was a 54-year-old non-Hispanic black man with a past medical history of CMV gastritis and severe weight loss. His baseline creatinine was 0.8 mg/dL (Grade 0). His optimized background regimen (OBR) included tenofovir (also a component of his failing regimen), emtricitabine, dolutegravir, darunavir, ritonavir, and fostemsavir. Other concomitant medications included Bactrim and ganciclovir (followed by valganciclovir). His creatinine increased slowly during the trial, peaking at 1.5 mg/dL at week 21. Based on the toxicity table, an increase in creatinine of 1.5x over baseline is Grade 3. His creatinine was 1.3 mg/dL (Grade 2) at his end of study visit.

**301-01-006** was a 61-year-old non-Hispanic white man with a past medical history of nephrolithiasis, peripheral arterial disease, hyperglycemia, and hypertension. His baseline creatinine was 0.6 mg/dL. His OBR included tenofovir (also a component of his failing regimen), emtricitabine, dolutegravir, atazanavir, cobicistat, and fostemsavir. At Day 21, he experienced an increase in creatinine to 0.9 mg/dL, which qualified as a Grade 3 toxicity based on the 1.5 x increase from baseline. His creatinine remained at 0.8 mg/dL to 0.9 mg/dL throughout the study.

**301-05-003** was a 53-year-old Hispanic, white man with a past medical history of hyperlipidemia, cerebrovascular disease, Type II diabetes, and erectile dysfunction. He had a baseline creatinine of 0.9 mg/dL. His OBR included dolutegravir, darunavir, and cobicistat. Other concomitant drugs included lisinopril and ibuprofen (PRN for arthritic pain). He experienced a transient elevation in creatinine to 1.4 mg/dL at week 8, which normalized by week 13.

**301-09-002** was a 45-year-old non-Hispanic, black woman with a past medical history of hypertension, renal insufficiency, and toxoplasmosis. Her baseline creatinine was 1.4 mg/dL and her OBR consisted only of dolutegravir (also a component of her failing regimen). Her other concomitant medications included lisinopril, hydrochlorothiazide, and aspirin. She experienced a slow increase in creatinine with a peak value of 2.1 at week 21, which was Grade 3 based on an increase of 1.5x above baseline.

In conclusion, Grade 3 elevations in creatinine occurred only in TMB-301 participants with one or more of the following: underlying renal disease, risk factors for renal disease, concomitant medications known to be nephrotoxic, and/or concomitant medications known to cause modest elevations in creatinine via inhibition of tubular secretion (e.g., cobicistat). These data do not show a causal relationship between ibalizumab administration and elevation in creatinine. However, because this laboratory abnormality was frequent, Grade 3 creatinine events will be included in the label.

### TMB-202

Emergent Grade 3 or higher abnormalities in creatinine were also common in the TMB-202 study. Eighteen (16%) TMB-202 participants experienced Grade 3 or 4 elevations in creatinine in the 24 weeks (168 days) that followed initiation of ibalizumab treatment. Fifteen (15/18, 83%) of these participants experienced Grade 3 or higher events based on changes from their baseline creatinine values rather than due to increases of greater than 1.8 x upper limit of normal (ULN, Grade 3). In several cases, participants' graded abnormalities were not truly treatment emergent because they were present at one of the two pre-baseline visits. In nearly all cases, participants who experienced Grade 3 or higher treatment emergent creatinine elevations had underlying renal disease, risk factors for renal disease, and/or were taking concomitant medications known to be nephrotoxic. In many cases, elevations in creatinine resolved or improved significantly despite continuation of ibalizumab.

Seven (6%) TMB-202 participants experienced Grade 3 or higher proteinuria. Two of these participants experienced transient proteinuria without any other emergent abnormalities consistent with renal toxicity (e.g., elevations in creatinine). The five other participants with Grade 3 proteinuria experienced treatment-emergent elevations in creatinine; two experienced Grade 2 elevations and three experienced Grade 3 elevations. Each of these graded abnormalities of creatinine was based on change in baseline creatinine rather than an increase above ULN. All of these participants had proteinuria prior to ibalizumab (at baseline or pre-baseline) and had underlying renal disease or co-morbidities (e.g. type II diabetes, hypertension) known to cause kidney disease.

Seven (6%) participants, all of whom had diabetes, experienced Grade 3 or higher elevations in urine glucose that were higher in grade than at baseline. Six of participants experienced abnormalities that were not clinically significant for the following reasons:

- The glycosuria events occurred in the context of serum hyperglycemia and/or the participants had Grade 3 pre-baseline glycosuria (and therefore the laboratory abnormality was not truly treatment-emergent *and*

- The participants did not experience other emergent abnormalities consistent with renal toxicity (i.e. elevations in creatinine or proteinuria).

In conclusion, the findings regarding renal abnormalities in TMB-202 are consistent with what was seen in TMB-301. Renal abnormalities were common in TMB-202 participants prior to ibalizumab exposure and, like in TMB-301, nearly all treatment emergent abnormalities occurred in participants with underlying renal disease, risk factors for nephrotoxicity, and/or concomitant nephrotoxic medications.

#### **4. Conclusion**

Communications with the applicant and further analyses revealed that the Grade 3 or higher abnormalities of serum phosphate reported in the Clinical Review were artefactual. Analysis of the original study data using mg/dL units shows that Grade 3 or higher serum hypophosphatemia did not occur in TMB-301 and was very rare in TMB-202. Therefore, abnormalities of serum phosphate will not be presented in the label.

Analysis of baseline renal abnormalities demonstrated that renal disease was common in participants of both TMB-301 and TMB-202 prior to ibalizumab exposure. After ibalizumab exposure, renal abnormalities occurred frequently in participants of both studies; however, abnormalities occurred almost exclusively in participants with underlying renal disease, risk factors for renal impairment, and/or concomitant nephrotoxic medications. In many cases, renal abnormalities resolved despite continuation of ibalizumab. In conclusion, these data do not show a causal relationship between ibalizumab administration and renal abnormalities. Because Grade 3 or higher creatinine elevations were frequent and investigator-based causality assessments for laboratory abnormalities were not performed, these events will be labeled.

**Appendix 1. Serum Phosphate Toxicity Criteria (> 14 years of age) 2004, 2014, and 2017**

DAIDS tox table year	GRADE 1	GRADE 2	GRADE 3	GRADE 4
2004	2.5 mg/dL ≤ LLN  0.81 mmol/L ≤ LLN	2.0 – 2.4 mg/dL  0.65 – 0.80 mmol/L	1.0 – 1.9 mg/dL  0.32 – 0.64 mmol/L	< 1.0 mg/dL  < 0.32 mmol/L
2004 V1.0 August 2009 Clarification	2.5 mg/dL ≤ LLN  0.81 mmol/L ≤ LLN	2.0 – 2.4 mg/dL  0.65 – 0.80 mmol/L	1.0 – 1.9 mg/dL  0.32 – 0.64 mmol/L	< 1.0 mg/dL  < 0.32 mmol/L
2014 V 2.0	<b>*2.0 mg/dL to &lt; LLN</b>  0.81 mmol/L to < LLN	<b>*1.4 mg/dL to &lt; 2.0</b>  0.65 to < 0.81 mmol/L	1.0 mg/dL <b>*to &lt; 1.4</b>  0.32 to < 0.65 mmol/L	< 1.0 mg/dL  < 0.32 mmol/L
2017 V2.1	2.0 mg/dL to < LLN 0.81 mmol/L to < LLN	1.4 to < 2.0 mg/dL 0.65 to < 0.81 mmol/L	1.0 to < 1.4 mg/dL 0.32 to < 0.65 mmol/L	< 1.0 mg/dL < 0.32 mmol/L
2017 V2.1 July 2017 Clarification	2.0 mg/dL to < LLN <b>*0.65 mmol/L to &lt; LLN</b>	1.4 to < 2.0 mg/dL <b>*0.45 to &lt; 0.65 mmol/L</b>	1.0 to < 1.4 mg/dL 0.32 to <b>&lt;* 0.45</b> mmol/L	< 1.0 mg/dL < 0.32 mmol/L

\*Indicates changes made in comparison to the previously published toxicity table.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

VIRGINIA M SHEIKH  
11/06/2017

ADAM I SHERWAT  
11/06/2017

Clinical Review  
 Virginia Sheikh, MD  
 Biologic Licensing Application 761065  
 Ibalizumab/TROGARZO

### CLINICAL REVIEW

<b>Application Type</b>	Biologic Licensing Application
<b>Application Number(s)</b>	BLA 761065
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	05/03/2017
<b>Received Date(s)</b>	05/03/2017
<b>PDUFA Goal Date</b>	1/03/2018
<b>Division/Office</b>	DAVP/OAP/OND
<b>Reviewer Name(s)</b>	Virginia Sheikh, MD
<b>Review Completion Date</b>	10/3/2017
<b>Established Name</b>	Ibalizumab (TNX-355, Hu5A8)
<b>(Proposed) Trade Name</b>	TROGARZO
<b>Applicant</b>	TaiMed Biologics Inc.
<b>Formulation(s)</b>	Intravenous
<b>Dosing Regimen</b>	2000 mg loading dose followed by 800 mg every 2 weeks (IV)
<b>Applicant Proposed Indication(s)/Population(s)</b>	TROGARZO, (b) (4) in combination with other antiretroviral(s), is indicated for the treatment of adults infected with HIV-1 resistant to at least one agent in three different classes
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	TROGARZO, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV infection failing current antiretroviral therapy.

## Table of Contents

Glossary .....	8
1 Executive Summary.....	11
1.1. Product Introduction.....	11
1.2. Conclusions on the Substantial Evidence of Effectiveness .....	11
1.3. Benefit-Risk Assessment.....	12
2 Therapeutic Context .....	17
2.1. Analysis of Condition.....	17
2.2. Analysis of Current Treatment Options.....	18
3 Regulatory Background.....	19
3.1. U.S. Regulatory Actions and Marketing History .....	19
3.2. Summary of Presubmission/Submission Regulatory Activity .....	19
3.3. Foreign Regulatory Actions and Marketing History .....	20
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety .....	20
4.1. Office of Scientific Investigations (OSI).....	20
4.2. Product Quality.....	21
4.3. Clinical Microbiology.....	22
4.4. Nonclinical Pharmacology/Toxicology .....	25
4.5. Clinical Pharmacology .....	26
4.5.1. Mechanism of Action.....	26
4.5.2. Pharmacodynamics .....	26
4.5.3. Pharmacokinetics .....	26
4.6. Devices and Companion Diagnostic Issues.....	27
4.7. Consumer Study Reviews.....	27
5 Sources of Clinical Data and Review Strategy.....	28
5.1. Table of Clinical Studies .....	28
5.2. Review Strategy.....	30
6 Review of Relevant Individual Trials.....	30
6.1. TMB-301 .....	30
6.1.1. Study Design.....	30
6.1.2. Study Results .....	34
CDER Clinical Review Template 2015 Edition	2
<i>Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)</i>	

6.2.	TMB-202 .....	46
6.2.1.	Study Design.....	46
6.2.2.	Study Results .....	49
6.3.	TNX-355.03.....	58
6.3.1.	Study Design.....	58
6.3.2.	Study Results .....	61
6.4.	TNX 355.02.....	63
6.4.1.	Study Design.....	64
6.4.2.	Study Results .....	64
6.5.	Hu5A 8.0 .....	64
6.5.1.	Study Design.....	65
6.5.2.	Study Results .....	65
6.6.	TMB-311 .....	65
6.6.1.	Study Design.....	66
6.6.2.	Study Results .....	66
6.7.	Investigator-Sponsored INDs .....	69
6.7.1.	Study Designs .....	69
6.7.2.	Study Results .....	70
7	Integrated Review of Effectiveness.....	71
7.1.	Assessment of Efficacy Across Trials .....	71
7.1.1.	Primary Endpoints .....	71
7.1.2.	Secondary and Other Endpoints.....	71
7.1.3.	Subpopulations Dose and Dose-Response.....	71
7.1.4.	Onset, Duration, and Durability of Efficacy Effects.....	71
7.2.	Additional Efficacy Considerations.....	72
7.2.1.	Considerations on Benefit in the Postmarket Setting .....	72
7.2.2.	Other Relevant Benefits .....	72
7.3.	Integrated Assessment of Effectiveness .....	72
8	Review of Safety .....	73
8.1.	Safety Review Approach .....	73
8.2.	Review of the Safety Database .....	74
8.2.1.	Overall Exposure .....	74
8.2.2.	Relevant characteristics of the safety population: .....	76

8.2.3. Adequacy of the safety database:.....	76
8.3. Adequacy of Applicant’s Clinical Safety Assessments.....	76
8.3.1. Issues Regarding Data Integrity and Submission Quality .....	76
8.3.2. Categorization of Adverse Events .....	76
8.3.3. Routine Clinical Tests.....	77
8.4. Safety Results .....	77
8.4.1. Deaths .....	79
8.4.2. Serious Adverse Events .....	81
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects .....	83
8.4.4. Significant Adverse Events.....	86
8.4.5. Treatment Emergent Adverse Events and Adverse Reactions .....	88
8.4.6. Laboratory Findings.....	92
8.4.7. Vital Signs.....	101
8.4.8. Electrocardiograms (ECGs).....	102
8.4.9. QT .....	102
8.4.10. Immunogenicity.....	103
8.5. Analysis of Submission-Specific Safety Issues.....	103
8.5.1. Infusion Reactions .....	103
8.5.2. Rash.....	104
8.5.3. Infections and Infestations .....	104
8.6. Safety Analyses by Demographic Subgroups .....	105
8.7. Specific Safety Studies/Clinical Trials .....	108
8.8. Additional Safety Explorations .....	108
8.8.1. Human Carcinogenicity or Tumor Development .....	108
8.8.2. Human Reproduction and Pregnancy .....	108
8.8.3. Pediatrics and Assessment of Effects on Growth .....	108
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound .....	108
8.9. Safety in the Postmarket Setting.....	108
8.9.1. Safety Concerns Identified Through Postmarket Experience.....	108
8.9.2. Expectations on Safety in the Postmarket Setting .....	108
8.10. Additional Safety Issues From Other Disciplines .....	108
8.11. Integrated Assessment of Safety.....	109
9 Advisory Committee Meeting and Other External Consultations.....	109

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

10	Labeling Recommendations .....	109
10.1.	Prescribing Information .....	109
10.2.	Patient Labeling .....	110
10.3.	Nonprescription Labeling .....	110
11	Risk Evaluation and Mitigation Strategies (REMS).....	110
11.1.	Safety Issue(s) that Warrant Consideration of a REMS .....	110
11.2.	Conditions of Use to Address Safety Issue(s) .....	110
11.3.	Recommendations on REMS.....	111
12	Postmarketing Requirements and Commitments .....	111
13	Appendices .....	112
13.1.	References .....	112
13.2.	Financial Disclosure .....	114

### Table of Tables

Table 1 Drugs Approved for the Treatment of HIV infection in the United States.....	18
Table 2. Summary Calculations Used to Generate ART susceptibility Scores .....	24
Table 3. Ibalizumab Clinical Trials. ....	28
Table 4. TMB-301 Participant Disposition.....	35
Table 5 TMB-301 Protocol Deviations. ....	36
Table 6 Demographic Characteristics of Participants in Trial TMB-301 .....	37
Table 7 Clinical Characteristics of Participants in Trial TMB-301 .....	38
Table 8 ART History and HIV Viral Resistance of Participants in Trial TMB-301.....	40
Table 9 Primary Efficacy Outcome in TMB-301 .....	43
Table 10 TMB-301 Secondary Efficacy Results (ITT analysis) .....	44
Table 11 TMB-301 Efficacy with and without Fostemsavir as OBR (ITT analysis) .....	45
Table 12 TMB-301 Primary Efficacy Outcome by baseline GSS, PSS, or OSS .....	46
Table 13 TMB-202 Participant Disposition .....	50
Table 14 TMB-202 Protocol Deviations. ....	51
Table 15 Demographic Characteristics of TMB-202 Participants in by Planned Treatment*.....	52
Table 16 Clinical Characteristics of TMB-202 Participants by Planned Treatment* .....	53
Table 17 ART Drug History of TMB-202 Participants by Planned Treatment Group* .....	55
Table 18 Primary and Secondary TMB-202 Efficacy Outcomes by Planned Treatment*(Snapshot Approach) .....	57
Table 19 Trial 353.03 Demographics and Baseline Clinical Characteristics.....	62
Table 20 Trial 353.03 Efficacy Results.....	63
Table 21 TMB-311 Disposition as of February 28, 2017 .....	67
Table 22 TMB-311 Demographic Characteristics .....	68
Table 23 Previous Ibalizumab Exposure in TMB-311 Participants.....	69
Table 24 Disposition of patients enrolled in investigator-sponsored INDs .....	70
Table 25 Ibalizumab Safety Database .....	75
Table 26 Safety Overview: TMB-301 and TMB-202.....	78
Table 27 Adverse Reactions occurring in one or more participants in TMB-301 .....	91
Table 28 TMB-301 and TMB-202 Laboratory Abnormalities * .....	93
Table 29 Vital Signs Pre and Post Ibalizumab infusion in TMB-301(all visits).....	102
Table 30 Changes in QT interval in TMB-301 .....	102
Table 31 ARs occurring in two or more TMB-301 participant by race, ethnicity, and sex.....	107

**Table of Figures**

Figure 1. TMB-301 Trial Design .....	31
Figure 2. ART Drug History in TMB-301 Participants .....	39
Figure 3. TMB-202 Trial Design .....	48
Figure 4. ART Drug History in TMB-202 Participants by Planned Treatment Group* .....	54
Figure 5. TNX-355.03 Study Design .....	60
Figure 6 TEAEs occurring in $\geq 5\%$ (two or more) TMB-301 participants by system organ class (SOC). .....	89

## Glossary

---

AC	advisory committee
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CD4	glycoprotein expressed on the surface of T-helper cells
CD4+	type of white blood cell, also called T-lymphocytes, T-cells, T-helper cells
CDC	Centers for Disease Control and Prevention
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DAIDS	Division of AIDS
DAVP	Division of Antiviral Products
DSMB	data safety monitoring board
DMC	data monitoring committee
DRM(s)	drug resistance mutation
ECG	electrocardiogram
eCTD	electronic common technical document
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
EOS	end of study
ETASU	elements to assure safe use
EAP	expanded access protocol
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HAART	highly active antiretroviral therapy
HIV-1	human immunodeficiency virus type-1
HTE	heterogeneous treatment effect
ICH	International Conference on Harmonization
IND	Investigational New Drug
IQR	Interquartile Range
IRB	institutional review board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LLOQ	lower limit of quantitation
Mab	monoclonal antibody
MDR HIV	multidrug resistant HIV
MedDRA	Medical Dictionary for Regulatory Activities
MEF	missing equals failure
MESF	Molecules of Equivalent Soluble Fluorescence
mITT	modified intent to treat
Mu5A8	murine progenitor of Ibalizumab
OBR	optimized background regimen
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
q2wk	every 2 weeks
q4wk	every 4 weeks
QOL	Quality of Life
RNA	ribonucleic acid

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAF	safety dataset for analysis
SD	Standard Deviation
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TFDA	Taiwan Food and Drug Administration
US	United States
USP	United States Pharmacopoeia
WHODD	WHO Drug Dictionary

## 1 Executive Summary

---

### 1.1. Product Introduction

TaiMed Biologics Incorporated seeks the approval of a new molecular entity (NME) ibalizumab for the treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy. Ibalizumab is a humanized IgG4 monoclonal antibody that recognizes domain 2 of the extracellular portion of the CD4 molecule. Binding to domain 2 causes a conformational change in the CD4 molecule, which prevents entry of HIV into CD4+ cells and prevents viral transmission via cell-cell fusion. Ibalizumab is dosed intravenously with a 2000 mg loading dose followed by 800 mg dose every two weeks.

Established name:	Ibalizumab (TNX-355, Hu5A8)
Trade name:	Trogarzo
Chemical Class:	Humanized IgG4 monoclonal antibody
Pharmacologic class:	CD4 receptor antagonist
Proposed Indication:	Treatment of adults infected with HIV-1 resistant to at least one agent in three different classes
Dosage Form:	Intravenous formulation with 2000 mg loading dose followed by an 800mg dose every two weeks

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

This application contains substantial evidence of potency required by law (21 CFR 314.126) to support approval of ibalizumab for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV infection failing current antiretroviral therapy. The Phase 3 Trial TMB-301, performed in heavily treatment-experienced adults with multidrug resistant HIV infection and persistent viremia despite antiretroviral therapy, demonstrated that ibalizumab treatment led to significant reductions in HIV viral load. The majority (83%) of participants achieved a 0.5 log<sub>10</sub> decrease in HIV RNA after one week of functional ibalizumab monotherapy, compared to only one participant (3%) who achieved the same decrease during the control period. Reductions in HIV-RNA levels are highly predictive of meaningful clinical benefit and analysis of clinical trial data submitted to the FDA demonstrate

that a 0.5 log HIV-RNA reduction in HIV-RNA is associated with a reduction in clinical disease progression. The secondary endpoint results, which provide support for the durability of ibalizumab, demonstrated that ibalizumab, in combination with various OBR drugs, led to sustained decreases in HIV RNA.

### 1.3. **Benefit-Risk Assessment**

#### Benefit-Risk Summary and Assessment

Ibalizumab is a humanized immunoglobulin isotype 4 monoclonal antibody that selectively binds domain 2 of the host CD4 molecule, causing a conformational change that prevents entry of HIV into CD4+ cells and viral transmission via cell-cell fusion. Ibalizumab has been developed for the treatment of HIV-1 infection, in combination with other antiretroviral (ARV) agents, in heavily treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy. Ibalizumab is administered intravenously with a 2000 mg loading dose followed by a maintenance dose of 800 mg every two weeks.

In the United States, more than 1.2 million people are living with HIV. The goal of HIV treatment is to maximally and durably suppress plasma HIV RNA, preserve and restore the immune system, reduce HIV-associated morbidity and improve survival, and prevent HIV transmission<sup>1</sup>. Most patients with limited previous HIV treatment experience can achieve these goals using a combination of two or more commercially available drugs. However, drug resistance can occur during treatment via the development of HIV drug resistance substitutions (DRSs). DRSs can impact a single drug, several drugs within a class, or an entire class of drugs. Some heavily treatment-experienced patients have multiple HIV DRSs, which confer resistance to at least one drug in first three classes of ART drugs (Nucleoside Reverse Transcriptase Inhibitors [NRTI], Non-Nucleoside Reverse Transcriptase Inhibitors [NNRTI], and Protease Inhibitors [PI]). These patients have what will be referred to as multidrug resistant (MDR) HIV. In some cases, patients with MDR have DRSs that confer resistance to most or all available drugs.

Healthcare providers have few, if any, drugs with which they can create an effective combination regimen for patients with MDR HIV infection. The resulting combination regimens are usually burdensome, toxic, and often associated with inadequate HIV viral suppression. As a result, these patients are at high risk of AIDS events and death<sup>2</sup>. The applicant designed the ibalizumab development program for the treatment of heavily treatment-experienced patients with MDR HIV with ongoing HIV viremia despite antiretroviral therapy (ART).

The TMB-301 trial data support the efficacy of ibalizumab in the treatment of heavily-treatment experienced adults with multi-drug resistant HIV. The majority (83%) of participants achieved a 0.5 log<sub>10</sub> decrease in HIV RNA after one week of functional ibalizumab monotherapy, compared to only one participant (3%) who achieved the same decrease during the control period. Reductions in HIV-RNA levels are highly predictive of meaningful clinical benefit and analysis of clinical trial data submitted to the FDA demonstrate that a 0.5 log HIV-RNA reduction in

HIV-RNA is associated with a reduction in clinical disease progression. The secondary endpoints of TMB-301 and the primary and secondary endpoints of supportive trial TMB-202, which reflect ibalizumab durability, were, assessed after 24 weeks of ibalizumab treatment and demonstrated that Ibalizumab, in combination with various OBR drugs, led to sustained decreases in HIV RNA.

The TMB-301 trial design and the complexity of the patient population introduce some uncertainties regarding the longer term efficacy of Ibalizumab. First, because the target patient population is rare, medically complex, and at high risk of disease progression and death in the absence of effective ART, the Division agreed to several TMB-301 design features including lack of a control arm, small sample size, and individualized OBR, that limit our ability to assess ibalizumab's durability. Secondly, the variability in background DRs and OBR adherence among the patient population, further limit the durability assessment. Because ibalizumab has been developed for the rare patient population of heavily-treatment experienced adults with MDR HIV infection with limited treatment options and high risk of disease progression and death in the absence of effective ART, some degree of uncertainty regarding ibalizumab's contribution to durability is acceptable.

The safety data submitted with this BLA demonstrate a favorable safety profile. The adverse events that occurred, regardless of severity, were generally consistent with events expected in patients with advanced HIV. The following adverse reactions occurred in at least five percent of participants in the Phase 3 clinical trial (TMB-301): dizziness, diarrhea, rash, and nausea. One serious adverse reaction, immune reconstitution inflammatory syndrome, occurred in TMB-301. Analysis of the supportive Phase 2b trial TMB-202 and review of safety from early phase trials and expanded access studies show similar safety results.

The small size of the ibalizumab safety database and limited placebo-control data are two limitations of the ibalizumab application. A total of 303 patients were exposed throughout the ibalizumab development program, including 20 patients who received ibalizumab exclusively through expanded access studies. Only 40 patients were exposed to the dosage regimen proposed in the label. An additional 113 patients received the drug at similar doses (2000 mg IV q4 weeks or 800 mg IV q2 hours) in the supportive Phase 2b trial. Only one Phase 2a trial (n=82) included a placebo control and those placebo arm participants were allowed to receive open-label ibalizumab if they experienced virologic failure after trial week 16. The limited use of placebo control in the ibalizumab development program limited the ability to determine if adverse events were the result of drug effect, underlying disease, or chance. The safety database of patients exposed to the intended dosage regimen is small, but sufficient to assess frequent adverse events, and acceptable for this serious disease with great unmet medical need. Post-marketing pharmacovigilance will play an important role in further defining the safety profile of this drug, especially for rare adverse reactions.

In conclusion, approval of ibalizumab, in combination with other antiretroviral(s) for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV infection and viremia despite antiretroviral therapy is fully supported by the available evidence of efficacy and safety.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#"><u>Analysis of Condition</u></a></p>	<p>In the United States, more than 1.2 million people are living with HIV. Without antiretroviral therapy (ART), most HIV-infected patients will develop progressive immunodeficiency leading to AIDS-defining illnesses and premature death. Maximal and durable suppression of HIV viremia preserves the immune system and reduces morbidity and mortality. Most treatment-adherent patients with limited previous HIV treatment experience can maximally and durably suppress plasma HIV RNA using a combination of two or more commercially available drugs.</p> <p>Heavily treatment-experienced patients with HIV replication despite ongoing ART, however, often have evidence of multiple HIV drug resistance substitutions (DRSs). Many DRSs cause resistance to several drugs within a drug class, and several DRSs cause resistance to an entire drug class. In some cases, patients with MDR have DRSs that confer resistance to most or all available drugs. For the purposes of this review, “MDR HIV” infection refers to infection with HIV viruses that contain DRSs conferring resistance to at least one drug in each of the first three classes of ART drugs (Nucleoside Reverse Transcriptase Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors).</p>	<p>With limited treatment options due to HIV viral resistance, heavily treatment-experienced HIV-infected patients with MDR HIV and evidence of ongoing HIV replication despite ART are at high risk of AIDS events and death.</p>
<p><a href="#"><u>Current Treatment Options</u></a></p>	<p>For patients with MDR HIV infection, providers must individually tailor combination treatment regimens based on previous ART exposure, viral resistance testing, pharmacogenomics, drug tolerability, and co-morbid conditions. The resulting antiretroviral regimens are usually burdensome (multiple pills given multiple times per day), more toxic, and often associated with inadequate HIV viral suppression.</p>	<p>Heavily treatment experienced HIV-infected patients need effective antiretroviral products that lack cross-resistance with commercially available products. Ideally, these products would have a good tolerability profile and allow for convenient dosing.</p>
<p><a href="#"><u>Benefit</u></a></p>	<p>The TMB-301 trial data support the efficacy of ibalizumab for the treatment of heavily-treatment experienced adults with multi-drug resistant HIV. The majority (83%) of participants achieved a 0.5 log<sub>10</sub> decrease in HIV RNA after</p>	<p>Data from pivotal trial TMB-301 show that seven days of ibalizumab treatment results in a 0.5 log<sub>10</sub> decrease in HIV RNA in a majority of</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>one week of ibalizumab functional monotherapy (with the failing regimen), compared to only one participant (3%) who achieved the same decrease during the control period(failing regimen alone).</p> <p>The secondary endpoints of TMB-301 and the primary and secondary endpoints of supportive trial TMB-202, which reflect ibalizumab durability, were assessed at 24 weeks and demonstrated that ibalizumab, in combination with various OBR drugs, led to sustained decreases in HIV RNA. Because of the targeted patient population, the Division agreed to several TMB-301 design features that are only appropriate in the context of heavily-treatment experienced adults with multi-drug resistant HIV. These patients are rare, have limited available treatment options, and are at high risk of disease progression and death in the absence of effective ART. Several of these design features, including lack of a control arm, small sample size, and individualized OBR, limit our ability to assess Ibalizumab’s durability. Additionally, characteristics of the patient population, including variability in background DRSs and OBR adherence, further limit the assessment of durability.</p>	<p>heavily treatment experienced patients infected with MDR HIV. Reductions in HIV-RNA levels are highly predictive of meaningful clinical benefit and analysis of clinical trial data submitted to the FDA demonstrate that a 0.5 log HIV-RNA reduction in HIV-RNA is associated with a reduction in clinical disease progression.</p> <p>Secondary outcomes from trial TMB-301 and primary and secondary endpoints of supportive trial TMB2-202 demonstrated that ibalizumab, in combination with various OBR drugs, led to sustained decreases in HIV RNA. The trial design and high variability of the patient population limited the assessment of durability. However, because ibalizumab has been developed for the rare patient population of heavily-treatment experienced adults with MDR HIV infection with limited treatment options and high risk of disease progression and death in the absence of effective ART, some degree of uncertainty regarding ibalizumab’s contribution to durability is acceptable.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk</u>	<p>The safety data submitted with this BLA demonstrate a favorable safety profile. The following adverse reactions occurred in at least five percent of participants in the Phase 3 clinical trial (TMB-301): dizziness, diarrhea, rash, and nausea. One serious adverse reaction, immune reconstitution inflammatory syndrome, occurred in TMB-301. Analysis of the supportive Phase 2b trial TMB-202 and review of safety from early phase trials and expanded access studies show similar safety results.</p> <p>The small size of the ibalizumab safety database and the limited placebo-controlled data are two limitations of the ibalizumab application. Only 40 patients were exposed to the dosage regimen proposed in the label. A total of 303 patients were exposed, including 20 patients who received ibalizumab exclusively through expanded access studies. Only one Phase 2a trial (n=82) included a placebo control and those placebo arm participants were allowed to receive open-label ibalizumab if they experienced virologic failure after trial week 16. The lack of placebo control in the key trials also limited the ability to determine if adverse events were the result of drug effect, underlying disease, or chance. However, the adverse events that occurred, regardless of severity, were generally consistent with events expected in patients with advanced HIV/AIDS.</p>	<p>The safety data submitted with this BLA demonstrate a favorable safety profile.</p> <p>The safety database of patients exposed to the intended dosage regimen is small, but sufficient to assess frequent adverse events, and acceptable for this serious disease with great unmet medical need. Post-marketing pharmacovigilance will play an important role in further defining the safety profile of this drug, especially for rare adverse reactions.</p>
<u>Risk Management</u>	<p>Safety risks have not been identified that would require risk management beyond standard pharmacovigilance.</p>	<p>Safety risks have not been identified that would require risk management beyond standard pharmacovigilance.</p>

## 2 Therapeutic Context

---

### 2.1. Analysis of Condition

In the United States, more than 1.2 million people are living with HIV. In the absence of antiretroviral therapy (ART), HIV infection leads to progressive destruction of the immune system, resulting in AIDS-defining illnesses and premature death in almost all cases. The goal of HIV treatment is to durably suppress plasma HIV RNA, preserve and restore the immune system, reduce HIV-associated morbidity and improve survival, and prevent HIV transmission<sup>1</sup>. Provided they are fully adherent to ART over their lifetimes, most patients with limited previous HIV treatment experience can now achieve these goals using a combination of two or more commercially available drugs.

Despite the potential of currently available ART drugs, however, more than eighty thousand HIV-infected Americans who are prescribed ART are unable to achieve durable HIV viral suppression<sup>3</sup>. This phenomenon is called “virologic failure”. Suboptimal ART regimens, poor medication adherence, inadequate drug absorption, and drug-drug interactions are the primary causes of virologic failure. Mental illness, substance abuse, and unstable housing or food security are important risk factors.<sup>4</sup> Patients with sustained viremia while on ART are at high risk of developing drug resistance substitutions (DRSs).<sup>5</sup> DRSs, which are detected using genotypic and/or phenotypic laboratory assays, can confer resistance to an entire class of drugs, persist for the life of the patient, and be transmitted to at-risk contacts.<sup>6,7</sup>

For the purposes of this review, “MDR HIV” infection refers to ART-experienced, HIV-infected patients with multiple DRSs that confer resistance to at least one drug in each of the first three classes of ART (Nucleoside Reverse Transcriptase Inhibitors [NRTI], Non-Nucleoside Reverse Transcriptase Inhibitors [NNRTI], and Protease Inhibitors [PI]). In some cases, patients with MDR have DRSs that confer resistance to most or all available drugs. Although the precise definitions for these terms may vary somewhat in the medical literature and over time, terms such as “triple drug class resistance”, “extensive drug resistance”, “heavily-treatment experienced”, “extensive drug resistance”, and “extensive deep salvage” describe the same or a similar patient population. For these patients, providers have few, if any, drugs with which they can create an effective combination ART regimen. Without effective ART regimens, patients with MDR HIV cannot achieve virologic suppression and are therefore at high risk of AIDS events<sup>8-10</sup> and death.<sup>2,11,12</sup>

MDR HIV infection is relatively rare in the U.S. today. Although there are no comprehensive population-based data available, analyses of large cohorts in Europe and the US demonstrate that the prevalence of MDR HIV has decreased in the recent decades, most likely because of the availability of effective, convenient, and well-tolerated HIV drugs.<sup>13-15</sup> Data collected between 1999 and 2008 in a large, multi-cohort European study showed that approximately one percent of

ART-exposed HIV-infected patients had MDR HIV<sup>15</sup>. Results of a 2011 informal survey of HIV physicians suggest that the number of U.S. patients in care with MDR HIV is now closer to five thousand<sup>16</sup>.

In summary, although most patients with HIV infection in the U.S. today have numerous safe, well-tolerated, and convenient ART treatment options, a rare subgroup of patients, those with MDR HIV, have DRSs that confer resistance to many of the available first and second-line drugs. In the absence of effective ART regimens consisting of at least two fully active drugs, these patients are at high risk of AIDS events and death.

## 2.2. Analysis of Current Treatment Options

Twenty-nine agents in seven drug classes are approved for the treatment of HIV in the U.S. (**Table 1**). Patients with MDR HIV have DRSs that confer resistance to at least one drug in the NRTI, NNRTI, and PI drug classes. Many DRSs cause resistance to several drugs within a drug class, and several DRSs cause resistance to an entire drug class. In some cases, patients with MDR have DRSs that confer resistance to most or all available drugs.

The goal of a new ART regimen in a patient with MDR HIV and virologic failure is to achieve virologic suppression with at least two fully active agents in order improve the patient’s immune system, thereby decreasing the risk of AIDS-related events including death, and to prevent the development of new DRSs<sup>17</sup>. Healthcare providers must individually tailor these new ART regimens based on numerous factors including cumulative genotypic and/or phenotypic testing, previous ART exposure, pharmacogenomics, drug-drug interactions, drug tolerability, and co-morbid conditions. Often, the resulting combination ART regimens are more burdensome and toxic than first or second-line ART drugs, and associated with greater risk of virologic failure.

**Table 1 Drugs Approved for the Treatment of HIV infection in the United States**

Drug Class	Generic Name	Trade Name
<b>Nucleoside Reverse Transcriptase Inhibitor (NRTI)</b>	Zidovudine (AZT)	Retrovir®
	Didanosine (ddI)	Videx®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir (ABC)	Ziagen®
	Tenofovir (TDF)	Viread®
	Emtricitabine (FTC)	Emtriva®
<b>Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)</b>	Delavirdine *	Rescriptor®
	Nevirapine, Immediate Release (NVP)	Viramune®
	Nevirapine, Extended Release,(NVP)	Viramune XR®

Drug Class	Generic Name	Trade Name
	Efavirenz (EFV)	Sustiva®
	Etravirine (ETR)	Intelence®
	Rilpivirine (RPV)	Edurant®
<b>Protease Inhibitor (PI)</b>	Indinavir (IDV)	Crixivan®
	Ritonavir (RTV)	Norvir®
	Saquinavir, hard gel (SQV)	Invirase®
	Saquinavir, soft gel (SQV)	Fortavase®
	Nelfinavir	Viracept®
	Amprenavir	Agenerase®
	Fosamprenavir (FPV)	Lexiva®
	Atazanavir (ATV)	Reyataz ®
	Lopinavir/ritonavir (LPV/r)	Kaletra®
	Tipranavir (TPV)	Aptivus®
	Darunavir (DRV)	Prezista®
<b>Fusion Inhibitor</b>	Enfuvirtide (ENF)	Fuzeon ®
<b>CCR5 co-receptor antagonist</b>	Maraviroc (MVC)	Selzentry®
<b>Integrase Strand Inhibitors</b>	Raltegravir (RAL)	Isentress®
	Elvitegravir (EVG)	Vitekta ®
	Dolutegravir (DTG)	Tivicay ®
<b>Pharmacokinetic Enhancers</b>	Cobicistat (COBI)	Tybost®

### 3 Regulatory Background

---

#### 3.1. U.S. Regulatory Actions and Marketing History

Ibalizumab is a new molecular entity (NME) and is not currently marketed in the U.S.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

Tanox, the original sponsor of IND 9776, submitted an initial IND application for ibalizumab on April 16, 2001. FDA granted Tanox Fast Track designation on October 6, 2003. In 2007, Tanox transferred sponsorship of IND 9776 to TaiMed Biologics, Inc. (TaiMed). FDA granted Ibalizumab orphan drug designation on October 20, 2014 and breakthrough therapy designation on February 23, 2015. Over the course of the ibalizumab clinical development program, DAVP and TaiMed held several meetings, including two Type C meetings and two Pre-BLA meetings, which are described below.

On January 22, 2015, TaiMed and DAVP conducted a Type C meeting to discuss ibalizumab chemistry, manufacturing, and controls (CMC) issues relevant to clinical development and a

future BLA submission. Of note, ibalizumab was initially manufactured by Tanox; however, in 2014, TaiMed contracted WuXi AppTecm Wuxi, China, to be the new ibalizumab drug substance (DS) and drug product (DP) manufacturer. During the meeting, DAVP and TaiMed agreed on plans for satisfying CMC requirements for both the IND and the future BLA.

On March 2, 2015, TaiMed and DAVP held a Type C meeting to discuss the design of the Phase 3 registrational trial in heavily treatment-experienced HIV-infected participants with evidence of HIV viral replication despite ongoing antiretroviral therapy. Major issues discussed included the primary efficacy endpoint, the dosing schedule, and the size of efficacy and safety datasets required for the registration of ibalizumab for this patient population. DAVP's thinking on appropriate endpoints for this patient population ("Group 2") are described in an FDA guidance document<sup>17</sup>. DAVP recommended that the primary efficacy endpoint be defined as the proportion of patients with HIV RNA decreases from baseline exceeding 0.5 log<sub>10</sub> after 7 days of functional monotherapy and that all participants should undergo HIV RNA testing at week 24 to allow for an assessment of treatment durability. DAVP accepted TaiMed's proposal to have each participant serve as his/her own control for the primary endpoint as this would help to address concerns both related to inter-participant variability (e.g. variably in terms of DRSSs, medical adherence, co-morbid conditions, and optimized background regimens [OBR]), and the feasibility of enrolling sufficient patients in the target population. Because the target population is rare, DAVP further concluded that the efficacy dataset from the Phase 2b trial in combination with approximately 30 – 50 subjects from a Phase 3 trial would be adequate to support a BLA submission. TaiMed incorporated each of these recommendations into their Phase 3 trial design.

A pre-BLA CMC meeting was held February 3, 2016. TaiMed requested Rolling Review which the DAVP granted July 19, 2016. On the same date TaiMed submitted Module 3 (CMC) to new BLA 761065. DAVP and TaiMed conducted a pre-BLA meeting on September 26, 2016 to discuss all aspects of the BLA application including additional concerns related to CMC.

### 3.3. Foreign Regulatory Actions and Marketing History

This product is not marketed and is not currently undergoing regulatory evaluation overseas.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

---

### 4.1. Office of Scientific Investigations (OSI)

Inspection sites were selected from the pivotal trial TMB-301 as well as the supportive Phase 2b trial TMB-202. Four U.S. sites were selected, two of the sites enrolled participants in both trials, one site enrolled participants in TMB-301 only, and one site enrolled participants in TMB-202 only. These sites were chosen based on enrollment, protocol violations, and previous inspection

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

history. For the two sites that enrolled participants into both trials, OSI was asked to focus primarily on investigating TMB-301 records and include TMB-202 records if irregularities were identified in the TMB-301 records.

The following information comes from preliminary OSI reports. The final reports from the clinical site inspections are pending at the time of this review.

At three of the inspected sites, OSI identified only minor deficiencies, none of which appeared to have a significant effect on safety or efficacy considerations. OSI's preliminary conclusions for these three sites are that inspectional findings support the validity of the data as reported by the sponsor under this BLA.

OSI's investigation into the fourth site is ongoing at the time of this review. Dr. Shannon Schrader's TMB-301 records were inspected and OSI found poor record keeping and discrepancies not in keeping with the signed investigational plan. These identified discrepancies with TMB-301 did not appear to significantly impact safety or efficacy considerations. However, OSI was not able to investigate Dr. Schrader's TMB-202 records because the records were thought to have been "accidentally destroyed" at the time of the inspection. Five (4%) participants took part in TMB-202 through Dr. Schrader's site. Dr. Schrader subsequently located the records but, because OSI has not reviewed them, OSI considers the records to be unverified at this time. OSI's final determination and recommendations are pending at the time of this review. This review includes data from Dr. Schrader's TMB-202 site.

#### 4.2. **Product Quality**

The review of product quality is ongoing at the time of this review and this section reflects preliminary conclusions presented by the CMC reviewers.

Ibalizumab is a humanized anti-CD4 monoclonal IgG4 antibody produced in NS0 cells and is comprised of two gamma 4 heavy chains (449a amino acids) and two kappa light chains (219 amino acids). There is a single N-linked oligosaccharide chain on N299 of each heavy chain constant region.

The ibalizumab manufacturing process was originally developed by Tanox Inc. (San Diego, CA). WuXi Biologics (Wuxi, China) is the current CMO for the manufacture of drug substance and drug product, and analytical testing of ibalizumab. (b) (4)

An expiratory period of 36 months was proposed by the Applicant for ibalizumab drug product when stored at 2 -8°C.

The multidisciplinary product quality review team identified a number of deficiencies related to the CMC data submitted in support of the BLA. Additionally, the inspection of the manufacturing facility, WuXi Biologics, identified manufacturing deficiencies leading to the issuance of FDA Form 483 on August 2, 2017. At the time of finalization of this review, the

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

assessment of the Sponsor's responses to the identified CMC data deficiencies as well as the deficiencies identified during the inspection of the WuXi Biologics manufacturing facility is currently ongoing.

For further details related to CMC, please see Dr. Steve Bowen's review. For details regarding Microbial Quality of drug substance, please see Dr. Bo Chi's review. For details regarding Microbial Quality of drug product, see Dr. Virginia Carroll's review. For the Facilities and Compliance Evaluation, please see Dr. Michael Shank's review.

#### 4.3. **Clinical Microbiology**

##### **Mechanism of Action**

Ibalizumab blocks HIV-1 from infecting CD4<sup>+</sup> T cells by binding to domain 2 of CD4 and interfering 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 function**

Epitope mapping studies indicate that ibalizumab binds to a conformational epitope located primarily in domain 2 of the extracellular portion of the CD4 receptor. This epitope is positioned on the surface of CD4 opposite to the site in domain 1 that is required for CD4 binding of the MHC class II molecules and therefore does not interfere with CD4-mediated immune functions. There were no adverse effects on immune responsiveness of lymphocytes isolated from monkeys treated with ibalizumab or on antigen-specific T cell responses in normal human peripheral blood mononuclear cells (PBMCs). Weekly administration of ibalizumab to monkeys was not associated with any suppression of humoral immune responses. Additionally, ibalizumab does not interfere with gp120 attachment to CD4. This unique binding specificity of ibalizumab to domain 2 of CD4 allows ibalizumab to block viral entry into host cell without causing immunosuppression.

##### **Antiviral Activity**

Cell culture: In a single-cycle infection assay, ibalizumab inhibited 17 clinical isolates of subtype B with a median EC<sub>50</sub> value of 12 ng/mL (range 8.8 to 16.9 ng/ml; mean value of 12 ± 3 ng/mL) and a median maximum percentage inhibition (MPI) of 97% (range 89 to 99%; mean value of 97 ± 3%). Ibalizumab inhibits C-C chemokine receptor type 5 (CCR5)-tropic, C-X-C chemokine receptor type 4 (CXCR4)-tropic, and dual-tropic HIV-1. Three CCR5-tropic clinical isolates from clades B, C, and D, were inhibited with EC<sub>50</sub> values ranging from 59-66 ng/mL and 3 CXCR4- tropic clinical isolates from clades B, C, and D, with EC<sub>50</sub> values ranging from 44-59 ng/mL.

##### **Antiviral Activity in Combination with Other Antiviral Agents**

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

No antagonism was observed when PBMCs or MAGI-CCR5 cells infected with the subtype B Ba-L or ADA variants of HIV-1 were incubated with ibalizumab in combination with the CCR5 co-receptor antagonist maraviroc or when PBMCs infected with the subtype B HT/92/599 variant of HIV-1 were incubated with ibalizumab in combination with the gp41 fusion inhibitor enfuvirtide; a nonnucleoside reverse transcriptase inhibitor (efavirenz); nucleoside analog reverse transcriptase inhibitors (abacavir, didanosine, emtricitabine, tenofovir, or zidovudine); or a protease inhibitor (atazanavir).

### **Antiviral Activity in Antiretroviral-Resistant Virus**

Subjects enrolled in TMB-202 and TMB-301 had HIV-1 with documented triple-class resistance. Ibalizumab inhibited baseline isolates at a median EC<sub>50</sub> value of 25 ng/mL (range of 9 to 218 ng/mL, n=104; mean value of 33 ± 32 ng/mL) with a median MPI of 97% (range of 64 to 100%; n=105; mean value of 95 ± 7%) in TMB-202, and at a median EC<sub>50</sub> value of 31 ng/mL (range of 13 to 212 ng/mL, n=38; mean value of 39 ± 35 ng/mL) with a median MPI of 97% (range of 41-100%, n=38; mean value of 91 ± 14%) in TMB-301.

### **Decreased Susceptibility**

Decreased susceptibility to ibalizumab, as defined by a decrease in MPI, has been observed in subjects experiencing virologic failure and may be associated with genotypic changes in the HIV-1 envelope coding sequence that result in the loss of a potential N-linked glycosylation site (PNGS) in the V5 loop of gp120.

The clinical significance of decreased susceptibility to ibalizumab has not been established.

### **Cross-Resistance**

Phenotypic and genotypic test results revealed no evidence of cross-resistance between ibalizumab and all approved classes of ART (CCR5 co-receptor antagonists, a gp41 fusion inhibitor, INSTI, NNRTI, NRTI, and PI).

Ibalizumab is active against HIV-1 that is resistant to other approved antiretroviral agents and is not impacted by coreceptor tropism.

Decreased susceptibility to ibalizumab following multiple doses of ibalizumab has been observed in some subjects. Cell culture studies performed with HIV-1 variants with reduced susceptibility to ibalizumab indicate that phenotypic changes associated with resistance to ibalizumab do not alter susceptibility to other approved agents and do not result in the selection of CD4-independent viral isolates.

### **ART susceptibility Scores used in Trials TMB-301 and TMB-202**

ART susceptibility testing was performed by (b) (4) for all enrolled TMB-301 participants except for seven participants who were co-enrolled in the AI438047 clinical trial sponsored by Bristol-Myers-Squibb (BMS). For those participants,

results of resistance testing performed through BMS were used for analysis. The PhenoSense GT (PSGT) assay was used to measure in vitro sensitivity to PIs, NRTIs, and NNRTIs and also genotypic changes associated with resistance to these agents. The PhenoSense Integrase assay was used to measure in vitro sensitivities to integrase inhibitors and GeneSeq Integrase assay was used to identify genotypic changes associated with integrase inhibitor resistance. The Trophile assay was used for phenotypic assessment of co-receptor tropism and to determine the susceptibility to CCR5 co-receptor antagonist maraviroc. The PhenoSense HIV Entry assay was used to measure phenotypic sensitivity to inhibitors of viral entry including ibalizumab, enfuvirtide, and maraviroc.

The results of susceptibility tests performed at screening combined with patients’ historical resistance tests, when available, were used to calculate baseline Genotypic Sensitivity Scores (GSS), Phenotypic Scores (PSS), and Overall Susceptibility Scores (OSS); see Table 2 for details. (b) (4) has determined biological or clinical cut-offs of drug susceptibility for most approved ARV drugs by proprietary methods based on analysis of large panels of viruses with matched Genotypic and Phenotypic test results. Phenotypic test results and most genotypic test results were reported by (b) (4). In some instances genotypic results were generated by other assays including TruGene HIV-1, vircoTYPE HIV-1, and ARUP/ViroSeq HIV-1 assays.

**Table 2. Summary Calculations Used to Generate ART susceptibility Scores**

<b>Score</b>	<b>Description</b>	<b>Calculation</b>
<b>GSS</b>	Sum of active drugs in OBR based only on assessments from genotypic (GeneSeq) testing	<u>Protease inhibitors, reverse transcriptase inhibitors, and integrase inhibitors</u> Score “1” if virus from patient is “Susceptible” to drug in GeneSeq assessment, and no or low probability of resistance in similar assessments. Score “0” if virus from patient has “Partial” or “No” Susceptibility in GeneSeq assessment, or intermediate to high probability of resistance in similar assessments. <u>Entry inhibitors</u> No score was assigned for either enfuvirtide or maraviroc as genotypic assessments are not reported for these agents. <u>Investigational agent - fostemsavir</u> No score was assigned for fostemsavir as genotypic assessments were not available for this agent.
<b>PSS</b>	Sum of active drugs in OBR based only on assessments from phenotypic (Phenosense) testing.	<u>Protease inhibitors, reverse transcriptase inhibitors, and integrase inhibitors</u> Score “1” if virus from patient is “Sensitive” to drug in Phenosense assessments. Score “0” if virus from patient is “Partially Sensitive” or “Resistant” in Phenosense assessment. <u>Entry inhibitors</u> Score “1” for enfuvirtide if virus from patient is “Sensitive” in HIV Entry report Enfuvirtide Assessment; score “0” for

		<p>enfuvirtide if virus from patient has “Reduced Susceptibility” in HIV Entry report Enfuvirtide Assessment. Score “1” for maraviroc if virus from patient is CCR5-tropic (“R5”) in HIV Trofile report; score “0” for maraviroc if virus from patient is CXCR4-tropic or dual-mixed tropic (R5 and X4) in Trofile report.  <u>Investigational agent - fostemsavir</u>          Score “1” for fostemsavir if no prior experience. Score “0” for fostemsavir if historical resistance testing reveals an IC50 ≥10 nM (partially sensitive) or &gt;100 nM (resistant) in HIV Entry report from (b) (4)</p>
<b>OSS</b>	<p>Sum of active drugs in OBR based on combined information, or assessments, from genotypic and phenotypic testing.</p>	<p><u>Protease inhibitors, reverse transcriptase inhibitors, and integrase inhibitors</u>          Score “1” if virus from patient is “Sensitive” to drug in both Phenosense and Geneseq assessments. Score “0” if virus from patient is “Partially Sensitive” or ‘Resistant’ in either Phenosense or Geneseq assessment.  <u>Entry inhibitors</u>          Score “1” for enfuvirtide if virus from patient is “Sensitive” in HIV Entry report Enfuvirtide Assessment; score “0” for enfuvirtide if virus from patient has “Reduced Susceptibility” in HIV Entry report Enfuvirtide Assessment. Score “1” for maraviroc if virus from patient is CCR5-tropic (“R5”) in HIV Trofile report; score “0” for maraviroc if virus from patient is CXCR4-tropic or dual-mixed tropic (R5 and X4) in Trofile report.  <u>Investigational agent - fostemsavir</u>          Score “1” for fostemsavir if no prior experience. Score “0” for fostemsavir if historical resistance testing reveals an IC50 ≥10 nM (partially sensitive) or &gt;100 nM (resistant) in HIV Entry report from (b) (4)</p>

For TMB-202, prior exposure to integrase inhibitors, chemokine coreceptor 5 (CCR5) inhibitors, or investigational antiretroviral agents not captured by resistance testing resulted in the patient’s viral isolates being considered ‘resistant’ to those agents; if the patient had no prior exposure to these agents, the isolates were considered sensitive/susceptible. Note that CXCR4-tropic and dual/mixed virus, as indicated in the results of the Trofile™ assay, were considered “resistant” CCR5 inhibitors, regardless of prior exposure.

Please see Dr. Eric Donaldson’s clinical microbiology (virology) review for complete details.

#### 4.4. Nonclinical Pharmacology/Toxicology

Preclinical safety assessments have been performed with ibalizumab in *in vitro* cross-reactivity studies of human and rhesus monkey tissues and four *in vivo* GLP single and repeated dose

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

studies of intravenous administration to rhesus and cynomolgus monkeys, including a 9 month chronic dosing study. No unexpected toxicities or tissue reactivity were observed.

The carcinogenesis and mutagenesis potential of TROGARZO has not been studied.

Please refer to the Pharmacology/Toxicology Review by Dr. David McMillan for additional details.

#### 4.5. **Clinical Pharmacology**

This section summarizes the key outcomes of the clinical pharmacology discipline review, including highlights of pharmacokinetics (PK), pharmacodynamics (PD), and dose-response relationships that support dose selection. Please see the Clinical Pharmacology review by Dr. Qin Sun for full details.

##### 4.5.1. **Mechanism of Action**

Ibalizumab blocks HIV-1 from infecting CD4<sup>+</sup> T cells by binding to domain 2 of CD4 and interfering 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. Ibalizumab does not interact with CD4 domain 1 which binds with MHC (*major histocompatibility complex*) class II complex for immune function

##### 4.5.2. **Pharmacodynamics**

No significant exposure-response relationship for efficacy was identified in the Phase 2b trial, TMB-202, in which two different dose regimens were evaluated.

Due to an absence of bio-analytical reports to support the use of the receptor-occupancy assay, the submitted receptor-occupancy data could not be used in support of this BLA.

##### 4.5.3. **Pharmacokinetics**

Ibalizumab administered as a single agent exhibits nonlinear pharmacokinetics. Following single-dose administrations of ibalizumab as 0.5 to 1.5-hour infusions, the area under the concentration-time curve increased in a greater than dose-proportional manner, clearance decreased from 9.54 to 0.36 mL/h/kg and elimination half-life increased from 2.7 to 64 hours as the dose increased from 0.3 to 25 mg/kg. The volume of distribution of ibalizumab was approximately that of serum volume, at 4.8 L.

Following the recommended dose regimen (2,000 mg as a loading dose and 800 mg once every 2 weeks as maintenance doses), ibalizumab concentrations reached steady-state levels after the

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

first 800 mg maintenance dose with mean concentrations over 30 mcg/mL throughout the dosing period.

### **Specific Populations**

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates (age, body weight, sex, baseline CD4<sup>+</sup> cell counts) 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 is unlikely to impact virologic outcome and does not warrant dose adjustment.

Ibalizumab PK has not been evaluated in pediatric or geriatric patients. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of ibalizumab. However, renal impairment is not anticipated to impact the PK of a monoclonal antibody.

### **Drug Interaction studies**

No drug interaction studies have been conducted with ibalizumab. Based on ibalizumab's mechanism of action and target-mediated drug disposition, drug-drug interactions are not expected.

#### **4.6. Devices and Companion Diagnostic Issues**

No companion device or diagnostic is included in this application.

#### **4.7. Consumer Study Reviews**

None performed.

## 5 Sources of Clinical Data and Review Strategy

### 5.1. Table of Clinical Studies

In total, this application includes results from two phase 1 trials, two phase 2 trials, one Phase 3 trial and one expanded access protocol (EAP), all of which are summarized below.

**Table 3. Ibalizumab Clinical Trials.**

Type of Trial	Study ID	Objectives	Study Design	Dosing	Number of participants	Patient population	Duration
Phase 3	TMB-301	Safety, efficacy	Single arm, open-label	2000 mg IV x1 (loading dose), then 800 mg q 2 wks with OBR	40	MDR HIV	24 wks
Phase 2b	TMB-202	Safety, efficacy, PK	Double-blind, two arm	IV, 800 mg q 2 wks with OBR, or 2000 mg q 4 wks with OBR	113: 800q2: 59 2000q4: 54	MDR HIV	24 wks,
Phase 2a	TNX-355.03	Safety, efficacy, PK	Double blind, placebo controlled, cross over	<u>Arm A</u> : 15 mg/kg q 2 wk for 48 wks; <u>Arm B</u> : 10 mg/kg q wk for 9 wks, then 10 mg q 2 wks for 39 wks; <u>Arm C</u> : placebo, cross over to 15 mg/kg when viral load failed	82: Arm A: 28; Arm B: 27; Arm C: 27 (23 X-over)	HIV	48 wks, up to 216 wks
Phase 1b	TNX 355.02	Safety, tolerability,	Open label, 3 dose arms	<u>Arm A</u> : 10 mg/kg q wk for 10 doses; <u>Arm B</u> : 10 mg/kg single dose, then 6 mg/kg q 2 wks for 5 doses; <u>Arm C</u> : 25 mg/kg q 2 wks for 5 doses	22: Arm A: 9; Arm B: 10; Arm C: 3	HIV	10 weeks
Phase 1a, 1 <sup>st</sup> in human	Hu5A 8.01	Safety, tolerability,	SAD	Single dose IV, 0.3, 1.0, 3.0, 10, 25 mg/kg	30: 5/group	HIV	Single dose

Clinical Review  
 Virginia Sheikh, MD  
 Biologic Licensing Application 761065  
 Ibalizumab/TROGARZO

Type of Trial	Study ID	Objectives	Study Design	Dosing	Number of participants	Patient population	Duration
<b>Expanded Access Protocol (EAP)</b>	TMB-311	Long term efficacy, durability, safety	Expanded access	<u>Cohort 1:</u> 800mg IV q2 wks or 2000mg IV q4 wks <u>Cohort 2:</u> 2000 mg IV LD, then 800mg q2 wks	51: 800q2:31 2000q4: 8 2000 then 800q2wks: 13	MDR HIV	NA
<b>Investigator-Sponsored INDs</b>		Expanded access		<u>2000 mg IV q4 weeks</u> or <u>800mg IV q2 weeks</u>	2000 q4: 6 800q2:1	MDR HIV	NA

## 5.2. Review Strategy

The clinical review of efficacy relies primarily on the pivotal Phase 3 registration trial (TMB-301) with support from the Phase 2b trial (TMB-202). The clinical review of safety primarily relies on TMB-301 because TMB-301 is the only trial which used the dosing regimen anticipated for approval (2000mg IV loading dose followed by 800mg IV every two weeks). Data from TMB-202, which used two different dosing regimens (800mg IV q2 weeks or 2000mg IV q4 weeks) provides support for the safety of ibalizumab. Phase 1 & 2a trials (TNX 355.03, TNX 355.02, and Hu5A 8.01) provide additional support for the safety. The expanded access program, including TMB-311 (the expanded access protocol) and investigator-sponsored INDs, provide additional support for the safety and durability of ibalizumab.

## 6 Review of Relevant Individual Trials

---

### 6.1. TMB-301

TMB-301 was a pivotal, 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. Eligible subjects had been treated with ART for at least six months and were failing or had recently failed therapy. Each participant was administered a loading IV dose of 2000mg of ibalizumab on study day 7 followed by 800 mg IV every two weeks. The primary endpoint was the assessment of antiviral activity at Day 14 (functional monotherapy, i.e., Day 7 of ibalizumab and continued failing regimen). The secondary endpoints included antiviral activity and change in CD4 T cells at week 25. Screening began on August 4, 2015 and enrollment was completed on April 27, 2016. All tables and graphs were prepared by the clinical reviewer using data provided by the sponsor unless otherwise noted.

#### 6.1.1. Study Design

##### Overview and Objective

TMB-301 sought to evaluate the safety and effectiveness of ibalizumab in treatment-experienced patients infected with MDR HIV-1. To be eligible for the trial, participants had to be ART-experienced with virologic failure despite ongoing ART, and have DRSs conferring resistance to at least one drug in each of following drug classes: NRTI, NNRTI, and PI. In addition, participants had to have a life-expectancy of at least six months and could not have an opportunistic infection (OI) diagnosis in the previous three months. Because patients with MDR HIV are at high risk of developing additional DRSs when only one fully active ART drug is used, participants had to have at least one other ART drug that could be combined with Ibalizumab as part of an optimized background regimen (OBR).

### Trial Design

Taimed designed the TMB-301 trial with three distinct trial periods: a control period, the functional monotherapy period, and the maintenance period. The control period took place on Days 0 through 6; participants continued their current failing ART regimens (or no ART, if the participant had failed and discontinued ART within the 8 weeks preceding screening). HIV-RNA and CD4 T cell testing performed on Day 7 was considered the participant’s baseline. The functional monotherapy period took place on Days 7 through 14. On Day 7, participants were given a 2000 mg ibalizumab loading dose intravenously. Participants were instructed to continue their failing ART regimens. On Day 14 (primary endpoint), HIV RNA testing was performed and subsequently the OBR was started. The maintenance period took place between Day 15 through Week 25. Beginning on Day 21, 800 mg of ibalizumab was administered every 2 weeks through Week 23 and OBR was continued. The secondary endpoints were evaluated at the Week 25/ End-of-Study (EOS) Visit time points. (Figure 1)

**Figure 1. TMB-301 Trial Design**

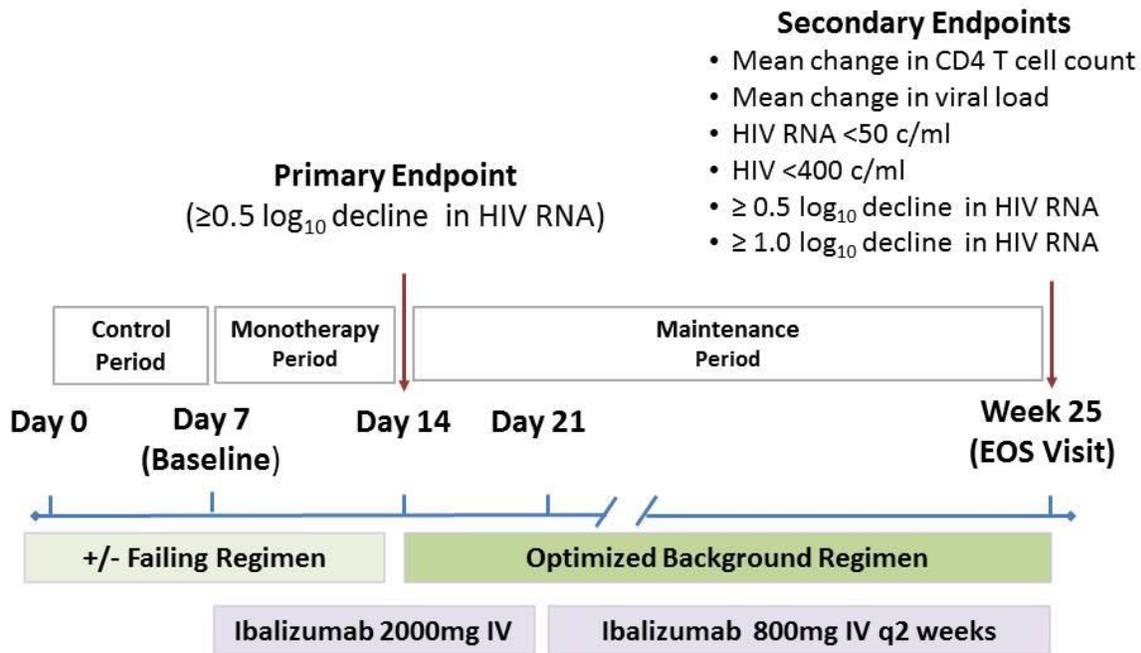


Figure created by reviewer using study design elements and planned procedures described in the TMB-301 protocol.

## Study Endpoints

The primary efficacy endpoint was the proportion of participants achieving a  $\geq 0.5 \log_{10}$  decline in HIV-1 RNA level on Day 14 compared to Day 7/Baseline.

The secondary efficacy endpoints included the following:

- Proportion of participants with HIV-1 RNA levels  $< 50$  copies/ $\mu\text{L}$  and  $< 400$  copies/ $\mu\text{L}$  at week 25/End of Study (EOS).
- Proportion of participants with  $\geq 0.5 \log_{10}$  and  $\geq 1.0 \log_{10}$  decline in HIV RNA at week 25/EOS.
- Mean change from Day 7/Baseline in HIV-RNA
- $\geq 0.5 \log_{10}$  decrease in HIV RNA at week 24 (vs. Week 0/Day 1)
- Mean change in CD4 T cell count at week 24 (vs. Week 0/Day 1)

## Statistical Analysis Plan

TaiMed defined the primary efficacy endpoint as the proportion of subjects achieving a  $\geq 0.5 \log_{10}$  decrease from baseline (i.e., Day 7) in viral load at Day 14. TaiMed used McNemar's test to make a paired comparison between the proportion of subjects achieving a  $\geq 0.5 \log_{10}$  decrease in viral load from Day 0 to Day 7 and the proportion of subjects achieving a  $\geq 0.5 \log_{10}$  decrease in viral load from Day 7 to Day 14. A paired t-test was employed to make a similar comparison between the mean change in viral load from Day 0 to Day 7 and the mean change in viral load from Day 7 to Day 14. Subgroup analyses by gender, age ( $< 50$  vs.  $\geq 50$  years), race, geographic location (US vs. Taiwan) were also conducted.

For the following secondary efficacy endpoint parameters, the frequency, proportion and 95% confidence intervals were calculated. The secondary efficacy endpoints assessed the following parameters:

- proportion of subjects achieving HIV RNA level  $< 50$  copies/mL and  $< 400$  copies/mL at Week 25/EOS
- proportion of subjects achieving a  $\geq 0.5 \log_{10}$  and  $\geq 1.0 \log_{10}$  decrease from the baseline in viral load at EOS/Week 25
- CD4 cell count and change from baseline in CD4 cell count at 25/EOS.

The efficacy analysis was performed in the intent-to-treat (ITT) population defined as all subjects enrolled into the study. The modified ITT (mITT) population included all ITT subjects who received at least one dose of study drug and was the same as the ITT population.

The primary method for imputation of missing data was "missing equals failure" (MEF). A sensitivity analysis was also conducted using "last observation carried forward" (LOCF). Specifically, TaiMed planned to handle missing data with the following approaches:

- Subjects with missing viral load data at Day 14 or Week 24/EOS will have their result set to failure for all dichotomous efficacy variables.

- If a viral load measurement is missing at any visit, the value will be replaced with the baseline viral load measurement.
- All visits after a confirmed virologic failure will be imputed as failures through Week 25 even if the subject discontinued early.
- Any subject who has a change in OBR between Day 14 and Week 25/EOS will have their efficacy set to failure if their HIV-1 RNA is  $\geq 50$  copies/mL at the specified visit. A change in OBR is defined as any replacement or addition of an OBR medication, regardless of medication class, but does not include removal of an OBR medication

*Reviewer comment: The applicant designed the SAP using the HIV guidance recommendations for the snapshot approach to efficacy analysis (Appendix A)<sup>17</sup>. In the snapshot approach, which has been used primarily in trials in treatment-naïve patients (Group 1) and in patients with some drug resistance but still able to construct a suppressive regimen (Group 3), participants who change optimized background therapy later in the trial are treated as failures. The Division of Antiviral Products has determined that the SAP methodology is not appropriate for this trial for the following reasons:*

- *The optimized background therapy section of the guidance was designed for trials with primary endpoints at 24 or 48 weeks. The primary endpoint for this trial is assessed at Day 14, prior to the initiation of the OBR, with each participant serving as his/her own control.*
- *The optimized background therapy section of the guidance was designed for randomized trials with fixed optimized background treatment. Because TMB-301 was designed to assess efficacy in heavily treatment-experienced patients (Group 2), each participant's OBR is tailored to that participant's viral resistance testing results.*
- *The snapshot guidance allowed for substitutions in optimized background treatment for toxicity reasons, but emphasized that these changes would typically occur early in the trial, on or before the first trial visit. The TMB-301 trial design includes a visit on Day 21, just seven days after OBR is initiated on Day 14. This may not be an adequate period of time to develop or assess drug toxicities. In addition, patients with MDR HIV have limited HIV drug options and therefore may, on their own or with consultation from their treating physicians, opt to continue poorly tolerated drugs longer before substituting HIV drugs as compared to patients with more treatment options.*
- *For this rare patient population with MDR HIV and advanced HIV disease, changes in OBR may be clinically necessary over a twenty-four week period. Therefore, the data generated under these conditions may be a better reflection of real-world outcomes.*

*Therefore, for the purposes of this trial, we did not automatically treat all participants who changed OBR after Day 14 as failures with respect to the Week 25 durability endpoint. Instead week 25 durability determinations were based on the presence or absence of HIV virologic suppression at the Week 25 window. However, a sensitivity analysis excluding participants who changed OBR for reasons other than side-effects will also be performed.*

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

The safety analysis was to include all subjects who receive at least one partial dose of study drug. The following are key aspects of the pre-specified safety analysis:

- All AEs will be coded using MedDRA dictionary version 17.0. All summary tables will be based on coded preferred terms instead of verbatim terms.
- Treatment-emergent AE (TEAE) were defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency following exposure to study drug. AEs with missing start dates, but with stop dates either overlapping into the dosing period or missing, will be considered TEAEs. A TEAE with missing severity or relationship will be considered severe or related, respectively.
- Summary statistics will be presented for laboratory measurements (hematology and chemistry), vital signs, and weight for all patients in the safety analysis population

Please refer to Dr. Karen Qi's review for a detailed evaluation of TaiMed's planned statistical analysis.

### **Protocol Amendments**

The TMB-301 protocol was amended once and administrative changes were made three times. Version 1.0 was submitted to the Division for review in March 2015 and Version 2.0 (April 2015) integrated the Division's recommendations. Version 2.1 administrative change 1, made in June 2015, clarified that investigational agent BMS- 663068 (fostemsavir) could be used as part of the OBR. Version 2.1 Administrative change 2, made in May 2016, clarified that the protocol would enroll between 30 and 50 participants. With Version 2.1 administrative change 3, which was approved on October 4, 2016, the protocol wash-out period between weeks 25 and 29 was eliminated because all participants who wanted to continue on Ibalizumab in TMB-301 were enrolled in the expanded access protocol TMB-311 and therefore would not participate in the wash-out period.

### **Data Quality and Integrity:**

TaiMed Biologics reports that the study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council (ICH) Good Clinical Practice (GCP) guidelines. In addition, each of the investigators provided testimony to their lack of financial conflicts of interest.

In collaboration with the Office of Computational Science (OCS), data fitness assessment was performed on June 1, 2017. No major concerns were identified.

### **6.1.2. Study Results**

#### **Compliance with Good Clinical Practices**

TaiMed Biologics reports that the study was conducted in compliance with the ethical principles

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

originating in or derived from the Declaration of Helsinki and in compliance with all International Council (ICH) Good Clinical Practice (GCP) guidelines

### Financial Disclosure

Each of the investigators provided testimony to their lack of financial conflicts of interest. Refer to section 13.2.

### Patient Disposition

Forty patients with MDR HIV in the US (n=36) and Taiwan (n=4) were enrolled and were included in the full analysis set. Eight (20.0%) participants discontinued study drug early. The most common reason for treatment discontinuation was adverse event (4 participants, 10%). One participant discontinued treatment for each of the following reasons: lost-to-follow-up, withdrawal by subject, subject non-adherence, and physician decision. One participant completed study drug but died from Kaposi's sarcoma before week 25. **Table 4** shows participant disposition, which matches the Applicant's analysis.

**Table 4. TMB-301 Participant Disposition**

Patient Disposition	Number of Participants
<b>Full Analysis Set (Received <math>\geq</math> 1 dose)</b>	40
<b>Discontinued Study Drug before Day 14 (Primary Efficacy Endpoint)</b>	0
<b>Taking Study Drug at Day 14 (Primary Efficacy Endpoint)</b>	40
<b>Discontinued Study Drug before Week 25</b>	8
Adverse Event	4
Lost To Follow-up	1
Withdrawal by participant	1
Participant non-adherence	1
Physician Decision	1
<b>Completed Week 25/End-of-Study Visit (Secondary Efficacy Endpoints)</b>	9
<b>Taking Study Drug at Week 25 (Secondary Efficacy Endpoint)</b>	31

### Protocol Violations/Deviations

The applicant reported 202 protocol deviations involving 32 (75%) participants over the course of trial TMB-301 (**Table 5**). The majority of the deviations were related to the timing or performance of assessments, informed consent (e.g. blood sample drawn inadvertently), changes to ibalizumab dosing or administration (e.g. IV placed in vein other than protocol-mandated cephalic vein) and were unlikely to affect the efficacy results. Four protocol deviations were related to participants receiving Ibalizumab on week 25 (EOS) because they were to

subsequently continue ibalizumab in expanded access studies. Because the secondary endpoints are assessed at week 25, these four deviations do not have any impact on the efficacy results of the trial.

The protocol did not prohibit changes to the OBR; however, the applicant reported six protocol deviations related to changes in OBR for clinical reasons after Day 14. Changes to the OBR and the potential impact on the efficacy results of the trial are discussed below in the section titled “**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**”.

**Table 5 TMB-301 Protocol Deviations.**

<b>Protocol Deviation Type</b>	<b>Number of Violations</b>
Assessment not done in required timeframe	138 (68.7%)
Required assessment not done	41 (20.3%)
Informed consent	5 (2.5%)
Change in dose or administration of Ibalizumab	2 (1.0%)
Inclusion/Exclusion Criteria	2 (1.0%)
Study drug given at week 25 (EOS)with Expanded Access	4 (2.0%)
Change or missed doses of OBR	6 (3.0%)
Early OBR	2 (1.0%)
Contraindicated Medications (foscarnet)	2 (1.0%)
Other	1 (0.5%)
<b>Total</b>	<b>202 (100%)</b>

Two protocol deviations were reported for use of the antiviral drug foscarnet, which was prohibited from the protocol due to its inherent antiviral activity. The two participants who received Foscarnet (301-01-001 and 301-01-002) were treated with these drugs after Day 14 (primary efficacy endpoint) and died before week 25 (secondary efficacy endpoints). Thus, these deviations are unlikely to affect the trial results.

Two of the reported protocol deviations had the potential to affect the primary efficacy endpoint.

Participant 301-27-001 was given one dose of OBR component DTG in error on Day 6, one day prior to his Day 7 baseline labs and starting ibalizumab. Although 301-27-001 had been exposed to RAL, 301-27-001 had never been exposed to DTG and baseline genotypic/phenotypic testing demonstrated no evidence of viral resistance. He formally started OBR (DRV, DTG, fostemsavir, TDF, FTC) on Day 14. HIV RNA results were as follows:

- Day 0: 21,700c/ml (4.3 log<sub>10</sub> copies/ml)
- Day 7: 6290 c/ml (3.8 log<sub>10</sub> copies/ml)
- Day 14: 7690 c/ml, (3.9 log<sub>10</sub> copies/ml)

*Reviewer comment: Participant 301-27-001’s HIV RNA decreased significantly at day 7 and*

*some of that decrease is likely attributable to the single dose of DTG on day 6. As a result, the difference in HIV RNA level between the Day 7 and Day 14 RNA values reflects both the addition of Ibalizumab and the withdrawal of DTG and is essentially uninterpretable.*

Participant 301-04-002 started ibalizumab on Day 7 and was scheduled to start OBR (DRV, DTG, fostemsavir, TDF, FTC) on Day 14. According to TaiMed, genotypic/phenotypic testing revealed resistance to DTG, TDF, and FTC (GSS score was 0, PSS was 3, and OSS was 1). On the morning of Day 13, the participant started components of his OBR (dolutegravir 50mg and emtricitabine/tenofovir) in error, before being reminded that OBR should not start until Day 14. He did not take the evening dose of DTG and he did not take fostemsavir. DRV was part of the participant’s failing regimen as well as the OBR. The HIV RNA for the Day 14 timepoint (primary endpoint) was collected in the morning of Day14. The participant then formally started OBR same day. His HIV RNA results were as follows;

- Day 0: 117,000 c/ml (5.1 log<sub>10</sub> copies/ml)
- Day 7: 88,600 c/ml (4.9 log<sub>10</sub> copies/ml)
- Day 14: 15,000 c/ml, (4.2 log<sub>10</sub> copies/ml)

Because the participant’s virus was resistant to DTG, TDF, and FTC and because clinical trials data from DTG monotherapy trials demonstrated only a 0.1 log<sub>10</sub> mean viral load reduction after 50mg of DTG (Min 2011) in integrase-naïve participants, Taimed concludes that the viral load reduction as a result of these three drugs would not significantly impact on the primary endpoint.

*Reviewer comment: The applicant’s conclusion is reasonable.*

### Demographic Characteristics

The median age was 53 years, 15% of participants were female. The majority (55.0%) of participants were white, 13 (32.5%) were black or African American, and 4 (10%) were Asian. Eleven (27.5%) participants were Hispanic/Latino. Thirty-six (90.0%) participants were enrolled in the U.S. and four (10%) of participants were enrolled in Taiwan. See **Table 6** for additional details.

**Table 6 Demographic Characteristics of Participants in Trial TMB-301**

Demographic Parameter		Number (%) of participants (Total n=40)
Sex	Male	34 (85.0%)
	Female	6 (15.0%)
Age (years)	Mean (SD)	50.45 (10.99)
	Median (IQR)	53.00 (46.25-57.75)
	Min, max	23.0-65.0

<b>Age group</b>	≥18 - 39 years	5 (12.5%)
	≥ 39 - < 65 years	33 (82.5%)
	≥ 65 years	2 (5.0%)
<b>Race</b>	White	22 (55.0%)
	Black or African American	13 (32.5%)
	Asian	4 (10.0%)
	American Indian or Alaska Native	0
	Native Hawaiian or other Pacific Islander	0
	Not reported	1 (2.5%)
<b>Ethnicity</b>	Hispanic or Latino	11 (27.5%)
	Not Hispanic or Latino	27 (67.5%)
	Not reported	2 (5.0%)
<b>Region</b>	United States	36 (90.0%)
	Taiwan	4(10.0%)

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

The majority of participants of TMB-301 had advanced AIDS: the median CD4 T cell count was 73 cells/μL and the majority (22 participants, 55%) had baseline CD4 T cell counts less than 100 cells/ μL. The median number of years since HIV diagnosis was 23.1 years. The median HIV RNA level was 4.5 log<sub>10</sub> copies/ml. Co-infection with HBV or HCV was rare (one and two participants, respectively). See **Table 7** for additional details.

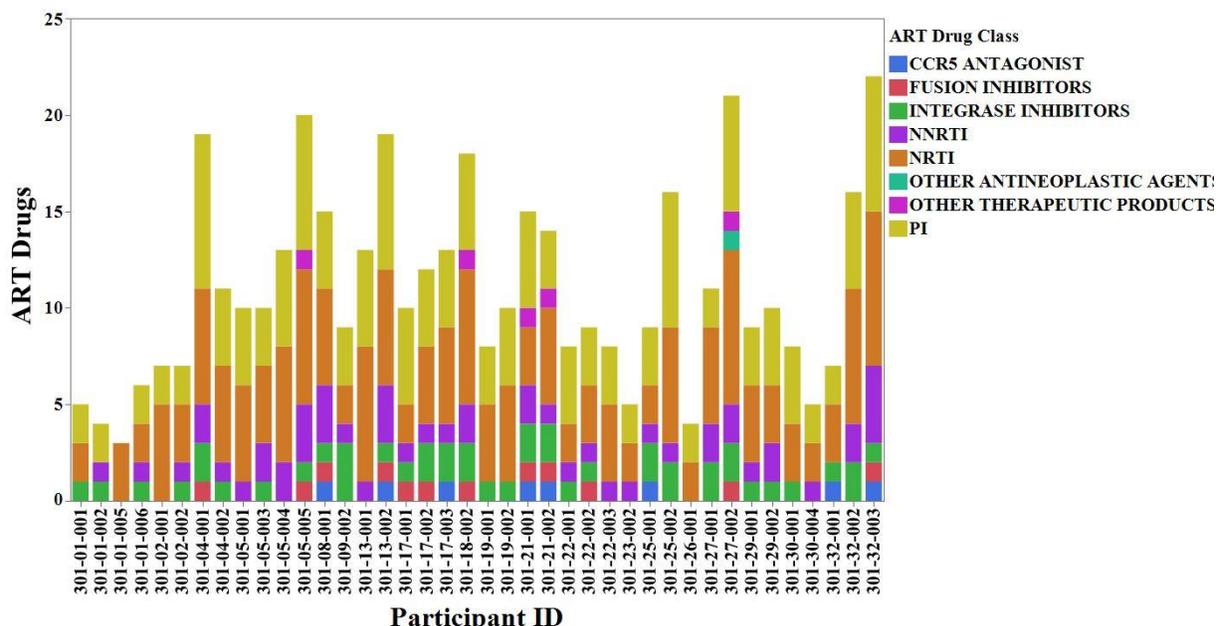
**Table 7 Clinical Characteristics of Participants in Trial TMB-301**

Clinical Characteristic	Variable or Statistic	Number (%) of participants (unless noted otherwise)
<b>Years since HIV diagnosis</b>	Mean	20.6
	Median (IQR)	23.1(16.3-23.1)
	Min, max	2.1-31.1
<b>Baseline CD4 T cell count (cells/μL)</b>	Mean	150.2
	Median (IQR)	73(5.5-226.3)
	Min, max	0-676
<b>Baseline CD4 T cell group (n, %)</b>	CD4 <200 cells/μL	27 (67.5%)
	CD4<100 cells/μL	22 (55%)
	CD4 <50 cells/μL	17 (42.5%)
	CD4 <10 cells/μL	12 (30%)
<b>HIV Status</b>	Asymptomatic AIDS	11 (27.5%)
	Asymptomatic HIV	11(27.5%)
	Symptomatic AIDS	9 (22.5%)

Clinical Characteristic	Variable or Statistic	Number (%) of participants (unless noted otherwise)
	Symptomatic HIV	9 (22.5%)
<b>Baseline HIV RNA</b> (log <sub>10</sub> copies/ml)	Mean	4.46
	Median (IQR)	4.5(3.90-4.86)
	Min, max	2.4-5.87
<b>Co-infections</b>	HBV	1 (2.5%)
	HCV	2 (5%)

The participants in TMB-301 were heavily treatment-experienced; 28% of participants were treated with 10 or more antiretroviral drugs prior to study enrollment (**Figure 2**). Most participants had been previously exposed to NRTIs, NNRTIs, PIs, and Integrase Inhibitors (**Table 8**). Twelve participants (30%) had been exposed to Fusion Inhibitors and eight (20%) had been exposed to CCR5 antagonists. Of note, tropism testing performed as part of the TMB-301 trial demonstrated that only five (13.2%) participants had CCR5-tropic virus at the time of study entry (**Table 8**).

**Figure 2. ART Drug History in TMB-301 Participants**



The “antineoplastic agent” was hydroxyurea. The “Other therapeutic products” included various investigational drugs.

As discussed in Section 4.3 (Clinical Microbiology), Taimed used (b) (4) for calculation of baseline GSS, PSS, and OSS scores for each of the TMB-301 participants. TMB-

301 participants had MDR HIV and were highly resistant to available HIV therapy; the median GSS, PSS, and OSS scores (Interquartile Range, IQR) were 1 (IQR 0-2), 2 (IQR 1-3), and 2 (IQR 1-2), respectively (**Table 8**).

**Table 8 ART History and HIV Viral Resistance of Participants in Trial TMB-301**

ART History or Resistance Characteristic	Variable or Statistic	Number (%) of participants or statistical result (Total n=40)
<b>Previous ART drug exposure</b>	NRTI	39(97.5)
	NNRTI	32 (80.0%)
	PI	39 (97.5%)
	Integrase Inhibitor	31 (77.5%)
	Fusion Inhibitor	12(30.0%)
	CCR5 Antagonist	8(20.0%)
<b>Co-Receptor Tropism</b>	CXCR4	5 (13.2%)
	CCR5	5 (13.2%)
	Dual	28 (74.7%)
	Not known	2 (5.0%)
<b>Genotypic Sensitivity Score (GSS)</b>	Mean	1.13
	Median (IQR)	1 (0-2)
	Min, max	0-4
<b>GSS group</b>	0	14 (35.0%)
	1	13 (32.5%)
	2	9 (22.5%)
	3	2 (5.0%)
	4	2 (5.0%)
<b>Phenotypic Sensitivity Score (PSS)</b>	Mean	1.62
	Median (IQR)	2(1-3)
	Min, max	0-5
<b>PSS group</b>	0	5 (12.5%)
	1	10 (25.0%)
	2	9 (22.5%)
	3	10 (25%)
	4	4 (10.0%)
	5	1 (2.5%)
<b>OSS (Overall Sensitivity Score)</b>	Mean	1.62
	Median (IQR)	2(1-2)
	Min, max	0-4
<b>OSS group</b>	0	5 (12.5%)
	1	12 (30.0%)

ART History or Resistance Characteristic	Variable or Statistic	Number (%) of participants or statistical result (Total n=40)
	2	18 (45.0%)
	3	3(7.5%)
	4	2(5.0%)
	5	0

### Treatment Compliance

The TMB-301 protocol specified that participants should receive a total of 12 doses of ibalizumab: a loading dose (2000 mg) of ibalizumab administered intravenously on Day 7 followed by 11 maintenance doses of 800 mg every-other-week beginning on Day 21 and ending on week 23. Participants who missed maintenance doses by 3-7 days were to receive a 2000mg dose at the next opportunity and that dose would substitute for the maintenance dose that was missed. Participants who missed maintenance doses by more than 7 days but less than 14 days were also to receive a loading dose of 2000 mg; however, that dose would not substitute for the missed dose but instead substitute for the following dose.

Thirty-one of the forty TMB-301 participants received all twelve doses of ibalizumab, including seven participants who received at least one additional loading dose because their visits were delayed. Participant 03-001-001, who completed ibalizumab treatment but died prior to EOS, missed his week 17 and 21 doses due to hospitalization and therefore received 2000mg loading doses at week 19 and 23. The remaining nine participants who missed one or more doses of Ibalizumab withdrew from the trial as described in **Patient Disposition** above.

### Investigational drug as part of Optimized Background Regimen

As is discussed in **Section 2.3 (Analysis of Current Treatment Options)**, a new ART regimen in a patient with MDR HIV and virologic failure should include at least two fully active ART drugs, and preferably three. Patients with only one fully active ART drug are unlikely to achieve virologic suppression and are highly likely to develop new DRs. Therefore, the inclusion criteria for TMB-301 stipulated that participants had to have at least one other ART OBR drug to which the participant's HIV virus was susceptible. The TMB-301 protocol stipulated that investigational agent Fostemsavir was an acceptable OBR agent.

Eighteen participants (45.0%) received investigational product fostemsavir (FOST) as part of OBR. Fourteen of these participants started FOST on study Day 14 as planned; however three participants started FOST later than planned (Days 16, 22, 25, and 40) because of logistical problems obtaining the investigational drug. Of note, participant 301-01-001 received FOST with his initial OBR, however this drug was mistakenly omitted from the datasets.

Participants who received FOST as part of their OBR had more advanced HIV and had more

resistant MDR HIV as compared to participants who did not. Participants who received FOST had lower median baseline CD4 T cell counts (27 cells/ $\mu$ l verses 103.5 cells/ $\mu$ l), higher median baseline HIV RNA (36,350 c/ml verses 31,850 c/ml), and had been diagnosed with HIV a median of six years earlier (26 verses 20 years). Baseline GSS scores (which did not include sensitivity to FOST were lower in participants who received FOST (GSS 0 vs GSS 2). Both PSS and OSS scores, both of which included FOST sensitivity, were also lower in the participants who received FOST (PSS 1 vs PSS 2 and OSS 1.5 verses OSS 2.0).

### **Changes in Optimized Background Regimen after Day 14**

As is discussed in **Statistical Analysis Plan** section above, changes in OBR may be clinically necessary over a twenty-four week period for patients with MDR HIV and advanced HIV disease. Several participants changed OBR drugs over the course of the TMB-301. Because the primary endpoint for this trial is assessed at Day 14 prior to the initiation of OBR, these changes have no impact on the primary efficacy endpoint. Each of the OBR changes is discussed below along with a discussion of the potential for that change to impact the secondary efficacy endpoints assessed at week 25.

For three participants, in-class OBR drug substitutions were made in the first several weeks of the trial for reasons of safety. Two participants (301-01-006 and 301-01-004) switched from TDF/FTC to TAF/FTC because of the better safety profile of TAF/FTC. 301-13-001 stopped DRV on Day 28 because of a side-effect and started lopinavir.

*Reviewer comment: Because the two forms of tenofovir have equivalent efficacy, changing from TDF to TAF does not impact the efficacy results of the trial. Clinical trials have demonstrated that darunavir and lopinavir are similar with regard to efficacy in treatment-naïve and treatment-experienced patients. In the absence of DRs conferring resistance to darunavir but not lopinavir, which are uncommon, this change in OBR is unlikely to impact the efficacy results of the trial.*

One participant had an out-of-class OBR drug substitution in the first several weeks of the trial. Because of a side-effect, 301-19-001 stopped all of this OBR drugs (MVC, etravirine, and TDF) on Day 20 and, after 9 days off ART, restarted etravirine and tenofovir with two new OBR drugs ABC and lamivudine. By the time of these changes to OBR, this participant had already achieved adequate viral suppression (Day 21 HIV RNA 33 c/ml).

*Reviewer comment: For this participant, a second and third NRTI was substituted for MRV in his OBR for reasons of safety. This occurred early in the protocol-defined treatment period and after the participant had achieved viral suppression. This change is unlikely to impact the secondary efficacy endpoints of TMB-301.*

One participant made an in-class OBR drug substitution later in the protocol-defined treatment period for reasons of safety. 301-13-002 stopped DTG on Day 86 due to a side-effect and started raltegravir.

*Reviewer comment: Dolutegravir treatment was associated with higher rates of virologic suppression in treatment-experienced patients at week 48 in comparison to raltegravir in the clinical trial SAILING. Therefore, this OBR change is not likely to increase the likelihood that this participant could achieve the secondary efficacy endpoints of TMB-301.*

Participant 301-01-001, who later died due to complications of Kaposi’s sarcoma, had many changes to in his OBR through the course of the trial. This participant added etravirine to his OBR on Day 60, stopped OBR component darunavir and started atazanavir on Day 102, and finally added enfurvidide and investigational drug cabotegravir on Days 129 and 156 respectively.

*Reviewer comment: Because this change was made after Day 14 and the participant died before the secondary endpoints were reached, these changes in OBR do not affect the efficacy results of the trial.*

### **Efficacy Results – Primary Endpoint**

Thirty-three of forty (82.5%) participants achieved a  $\geq 0.5 \log_{10}$  decline in HIV-1 RNA level on Day 14 compared to Day 7/Baseline (essential monotherapy period). In contrast, only one (2.5%) of forty participants achieved a  $\geq 0.5 \log_{10}$  decline in HIV-1 RNA level on Day 7 compared to Day 0 (Control Period). This reviewer’s analysis produced results (**Table 9**) that agreed with the sponsor’s results.

**Table 9 Primary Efficacy Outcome in TMB-301**

<b>Endpoint Type</b>	<b>Trial period</b>	<b>Endpoint</b>	<b># Participants (n=40)</b>
<b>Control</b>	Control Period (Failing regimen)	$\geq 0.5\% \log_{10} \downarrow$ in HIV RNA at Day 7	1 (2.5%)
<b>Primary</b>	Functional Monotherapy (ibalizumab plus Failing Regimen)	$\geq 0.5\% \log_{10} \downarrow$ in HIV RNA at Day 14	33 (82.5%)

### **Data Quality and Integrity – Reviewers’ Assessment**

Please see the “Data quality and integrity” section above for the Reviewer’s assessment of Data Quality and Integrity.

### **Efficacy Results – Secondary and other relevant endpoints**

All of the secondary endpoints for TMB-301 were evaluated at week 25, which was 24 weeks after initiation of ibalizumab. These endpoints provided information about the durability of ibalizumab over this period. A total of 17 (42.5%) participants achieved HIV RNA <50 copies/ml. Twenty-one (52.5%) participants achieved HIV RNA <200 copies/ml. Twenty-five (62.5%) participants achieved a  $\geq 0.5\%$   $\log_{10}$  decrease in HIV RNA. The median change from baseline in HIV RNA was  $-2.5 \log_{10}$  copies/mL and the median change from baseline in CD4 T cell count was 42 cells/ $\mu$ l. (**Table 10**)

**Table 10 TMB-301 Secondary Efficacy Results (ITT analysis)**

Endpoint Type	Trial period	Endpoint	# Participants (n=40)
Secondary	Maintenance (ibalizumab plus OBR)	HIV-1 RNA <50 copies/ml at Week 25	17 (42.5%)
		HIV-RNA <400 copies/ml at Week 25	21 (52.5%)
		$\geq 0.5\% \log_{10}$ ↓ in HIV RNA at Week 25	25 (62.5%)
		$\geq 1.0\% \log_{10}$ ↓ in HIV RNA at Week 25	23(58%)
		Median change from Day 7/Baseline in HIV-RNA	$-2.5 \log_{10}$ c/ml (-4.3-0.1)
		Median change in CD4 T cell count at week 24 (vs. Week 0/Day 1), observed analysis	42 cells/mcl (-119-341 cells/mcl)
		Mean change in CD4 T cell count at week 24 (vs. Week 0/Day 1), last observation carried forward	17 cells/mcl (-119-341 cells/mcl)

### Dose/Dose Response

All participants in TMB-301 received the same ibalizumab dosing regimen (2000 mg IV once followed by 800mg IV every two weeks); therefore dose response cannot be evaluated using results from this trial. For data supporting the dosing regimen used in TMB-301 and proposed in the BLA application, see sections 6.2 and 6.3, which describe the results from Trials TMB-202 and TNX-355.03. Both TMB-202 and TNX-355.03 had more than one dosing arm.

### Durability of Response

The secondary endpoints covered a 24 week period. Please see “Efficacy Results” above.

**Persistence of Effect**

The secondary endpoints covered a 24 week period. Please see “Efficacy Results” above.

**Additional Analyses Conducted on the Individual Trial**

Participants who received FOST as part of their OBR were less likely to achieve secondary efficacy outcomes compared to those who did not, however, this difference is likely attributable to the significant imbalances in HIV disease severity and baseline HIV resistance between these subgroups (**Table 11**). Please see Dr. Karen Qi’s Statistics Review for full details of this comparison.

**Table 11 TMB-301 Efficacy with and without Fostemsavir as OBR (ITT analysis)**

Endpoint	With Fostemsavir (n=18)	Without Fostemsavir (n=22)
HIV RNA < 50 copies/mL	6 (33%)	11 (50%)
HIV RNA < 400 copies/mL	8 (44%)	13 (59%)
Achieving HIV RNA $\geq 0.5 \log_{10}$ decrease from baseline (Day 7) at week 25	10 (56%)	16 (73%)
Achieving HIV RNA $\geq 1 \log_{10}$ decrease from baseline (Day 7) at week 25	9 (50%)	14 (64%)
Change from baseline in CD4 T cell count (Last observation carried forward) Median (min, max)	15 (-59-154)	17 (-119-341)

Table created by Statistics Reviewer using data provided by the sponsor.

Additional analyses were performed by the clinical reviewer to assess for differences on the primary endpoint based on baseline GSS, PSS, and OSS scores. Because the TMB-301 protocol was not powered to detect differences based on these scores, the analyses are exploratory. Participants with baseline GSS scores of three or higher or OSS scores of three or higher were more likely to achieve the primary endpoint compared to participants with lower GSS and OSS scores (**Table 12**). Baseline PSS score did not appear to influence primary efficacy outcome. Please see Dr. Eric Donaldson’s Virology Review for full details of this comparison.

**Table 12 TMB-301 Primary Efficacy Outcome by baseline GSS, PSS, or OSS**

	Baseline score	$\geq 0.5 \log_{10}$ reduction in HIV RNA (percent)	$< 0.5 \log_{10}$ reduction in HIV RNA (percent)
GSS	0	12 (86%)	2 (14%)
	1	10 (77%)	3 (23%)
	2	7(78%)	2 (14%)
	3	2 (100%)	0
	4	2 (100%)	0
PSS	0	5 (100%)	0
	1	8 (80%)	2 (20%)
	2	8 (89%)	1 (11%)
	3)	8 (80%)	2 (20%)
	4	3 (75%)	1 (25%)
	5	0	1
OSS	0	4(80%)	1(20%)
	1	11(92%)	1(8%)
	2	13(72%)	5(28%)
	3	3(100%)	0
	4	2(100%)	0

## 6.2. TMB-202

TMB-202 was a Phase 2b trial that compared two dosing regimens of ibalizumab (2000 mg q4 weeks versus 800 mg q2 weeks). Although neither of the dosing regimens used in TMB-202 is the same as the dosing regimen proposed in the label, the results of the trial provide support for both the efficacy and safety of ibalizumab. All tables and graphs were prepared by the clinical reviewer using data provided by the sponsor unless otherwise noted.

### 6.2.1. Study Design

#### Overview and Objective

The primary objectives of TMB-202 follow:

- 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

The secondary objectives of this study follow:

- Evaluate changes from Baseline in viral load, CD4+ T-cell counts, and time to loss of virologic response (TLOVR).
- Characterize HIV-1 sensitivity/susceptibility changes associated with ibalizumab administration in combination with OBR.
- Determine the presence and significance of anti- ibalizumab antibodies, if any (immunogenicity of ibalizumab)
- Assess CD4 receptor density and occupancy
- Determine the impact of ibalizumab on quality of life as assessed by patient-reported outcomes on questionnaires.
- Evaluate the pharmacokinetic profile of two dose regimens of ibalizumab at steady state

### **Trial Design**

TMB-202 was a Phase 2b, multicenter, randomized, double-blind study, which evaluated the effectiveness and safety of ibalizumab in patients infected with HIV-1. To be considered for participation in the study, patients had to have been receiving treatment with highly active antiretroviral therapy (HAART) for at least 6 months and were to be failing, or were to have recently failed (i.e., in the last 8 weeks) therapy. 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, and (b) use or non-use of an integrase inhibitor in OBR.

Participants 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

The selection of the OBR was aided by results of a screening resistance test and review of the patient's prior antiretroviral therapy. Once the screening resistance data became available and before randomization, the investigator selected an OBR including at least one agent to which the patient's viral isolate demonstrates viral sensitivity/susceptibility and which the patient was willing and able to take. After randomization, the OBR was not to be changed until the last infusion of study drug (up to 24 weeks of treatment) except for tolerability reasons. In that event, one OBR substitution, regardless of drug class, could be made provided the participant continued to meet inclusion criteria for the trial by having at least one OBR drug to which the participant's HIV virus was susceptible.

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

The primary and secondary endpoints were assessed at Week 24/End of Study (EOS). The study period was between October 14, 2008 and January 26, 2011.

**Figure 3. TMB-202 Trial Design**

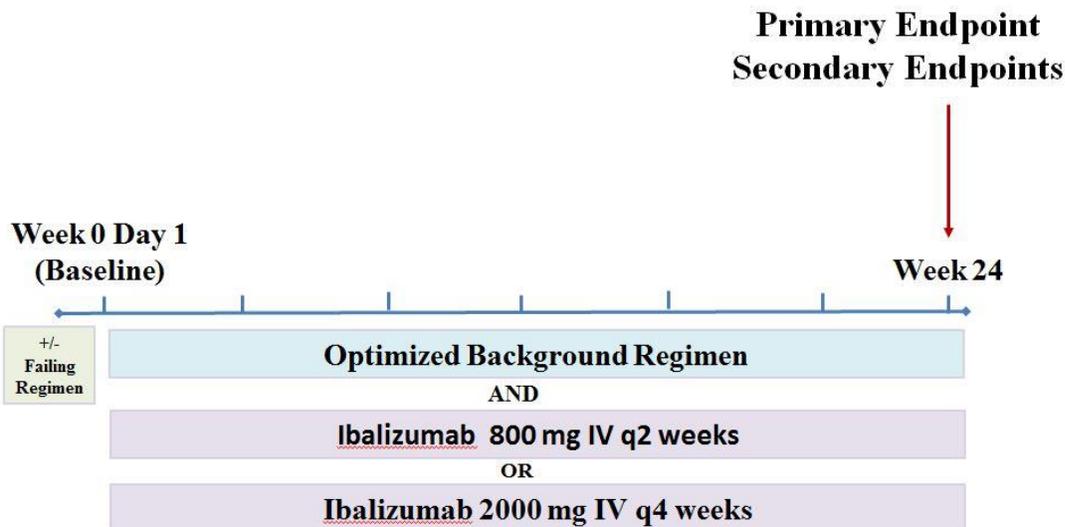


Figure created by reviewer using study design elements and planned procedures described in the TMB-202 protocol.

Beginning at Week 8, blood samples were collected to further define the pharmacokinetic profile of ibalizumab.

### Study Endpoints

The primary efficacy endpoint is the proportion of patients with HIV-1 RNA below the assay limit (<50 copies/mL) at Week 24.

Secondary efficacy endpoints include the following:

- Mean change from Baseline in HIV-1 RNA levels at Week 24/EOS.
- Proportion of patients achieving a  $\geq 1.0$  log<sub>10</sub> decrease from Baseline in HIV-1 RNA level at Week 24
- Time to loss of virologic response (TLOVR) through Week 24
- Mean change from Baseline in CD4+ T-cell count at Week 24/EOS
- Changes in HIV-1 sensitivity/susceptibility associated with ibalizumab administration in combination with selected OBR
- CD4 receptor occupancy and mean percentage change from Baseline in CD4 receptor density

### Statistical Analysis Plan

CDER Clinical Review Template 2015 Edition  
Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

TaiMed compared the key efficacy endpoints between the two treatment groups using the Fisher exact test. The primary efficacy analysis was performed at Week 24 using two different methods of handling missing data, with missing data equals failure (MEF) and with the last observation carried forward (LOCF). The primary analysis was based on the ITT population (LOCF and MEF) and supported with the PP population.

## **8.1. Primary Efficacy Endpoints and Analyses**

### **Protocol Amendments**

The TMB-202 protocol was amended twice; the first amendment (V2.0 Jul 8, 2008) incorporated administrative changes and the second amendment (V3.0, May 15, 2009) shortened the duration of the trial from 48 weeks to 24 weeks.

### **Data Quality and Integrity: Sponsor's Assurance**

TaiMed Biologics reports that the study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Counsel (ICH) Good Clinical Practice (GCP) guidelines.

#### **6.2.2. Study Results**

### **Compliance with Good Clinical Practices**

TaiMed Biologics reports that the study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Counsel (ICH) Good Clinical Practice (GCP) guidelines.

### **Financial Disclosure**

One hundred and fifty-two of one hundred and fifty-seven TMB-202 investigators provided testimony to their lack of financial conflicts of interest. TaiMed was unable to obtain some or all of the financial information as required for the remaining five investigators, despite reasonable efforts to obtain such information. For those five investigators, TaiMed provided a financial due diligence statement.

### **Patient Disposition**

A total of 133 participants enrolled in TMB-202, including 54 participants who were randomized to receive 2000 mg q 4 weeks and 59 participants who were randomized to receive 800mg IV q 2 weeks. Nine participants in each arm (17% and 15%, respectively) discontinued study drug before week 24, including one participant in each arm who discontinued drug due to AE, two participants in the 800 mg q2 week arm who died, and six and seven participants in each arm, respectively who discontinued due to virologic failure (**Table 13**).

**Table 13 TMB-202 Participant Disposition**

<b>Patient Disposition</b>	<b>Ibalizumab 2000mg Q4W N=54</b>	<b>Ibalizumab 800mg Q2W N=59</b>	<b>All TMB-202 N=113</b>
<b>Full Analysis Set</b> (Received $\geq$ 1 dose)	54 (100%)	59 (100%)	113 (100%)
<b>Discontinued Study Drug before Week 24</b>	9 (17%)	9 (15%)	18 (16%)
Adverse Event *	1 (2%)	1 (2%)	2 (2%)
Death	0	2 (3%)	2 (2%)
Virologic Failure	6 (11%)	7 (12%)	13 (12%)
Suboptimal Response	1 (2%)	1 (2%)	2 (2%)
Lost To Follow-up	4 (7%)	2 (3%)	6 (5%)
Withdrawal by participant*	2 (4%)	0	2 (2%)
Protocol Deviation	1 (2%)	1 (2%)	2 (2%)
Physician Decision	0	0	0
<b>Completed Week 24/End-of-Study Visit</b> (Primary and secondary Efficacy Endpoints)	45 (83%)	50 (85%)	95 (84%)
<b>Taking Study Drug at Week 24</b>	38 (70%)	43 (73%)	81 (72%)

\* TaiMed provided narrative reports for two participants who discontinued Ibalizumab due to AE (202-13-003 and 202-25-001). In the disposition dataset, however, these two participants were listed as “withdrawal by participant”. Because the participants discontinued Ibalizumab because of the AE, this reviewer has re-categorized those two participants as discontinued due to AE.

### **Protocol Violations/Deviations**

TaiMed reported 54 protocol deviations involving 24 TMB-202 participants. The most frequent deviations were changes in dose or administration of ibalizumab, required assessment not done, and assessment not done in the required timeframe. The majority of the deviations were minor and would not affect the efficacy outcome of the study. TaiMed identified nine deviations that were major.

The major deviations included four deviations of inclusion/exclusion criteria. One participant (202-13-003) was enrolled in the 800mg q2 week arm despite having an HIV RNA <1000 copies/ml. This participant was removed from study (see section 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects) after two doses of ibalizumab and therefore is considered a treatment failure with regard to primary and secondary endpoints. Two participants in the 2000mg q4 week arm (202-34-001, 202-48-007) and one participant in the 800 mg q2 week arm (202-39-001) were enrolled despite having OSS scores of 0 (no other susceptible ART drug). 202-39-001 and 202-34-001 both experienced virologic failure. 202-48-007 completed the trial but did not achieve success on the virologic endpoints.

*Reviewer comment: Overall, these major protocol deviations related to violations of inclusion and exclusion criteria reduced the likelihood that the trial participants would achieve success on the primary and secondary endpoints. As expected, the three participants without other ART*

*drugs to which their viruses were susceptible did not achieve success on these endpoints. The participant who was enrolled despite having baseline HIV RNA below the required threshold was removed from study for various reasons including AE (see section 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects) and ineligibility.*

The five other deviations that TaiMed deemed major were related to errors in ibalizumab dosing. Three of the dosing violations occurred in participants in the 2000mg q4 group (202-14-006, 202-21-001, and 202-28-003) and three occurred in participants in the 800mg IV q2 week group (202-28-01 and 202-28-002). Only 202-14-006 completed study and achieved virologic suppression. 202-28-003 and 202-28-003 experienced virologic failure and 202-21-001 and 202-28-001 were removed from study due to protocol violations.

*Reviewer comment: Although it is not possible to determine what the outcome for each of these participants would have been had these deviations not occurred, four of the five participants did not complete the trial for reasons related to either virologic failure or the protocol violations. Therefore, these major protocol deviations related to ibalizumab dosing errors failed to bias the overall trials results toward success.*

**Table 14 TMB-202 Protocol Deviations.**

Protocol Deviation Type	Number of Deviations	Number of Major Deviations
Assessment not done in required timeframe	7	0
Required assessment not done	16	0
Informed consent	5	0
Change in dose or administration of Ibalizumab	19	5
Inclusion/Exclusion Criteria	5	4
Good Clinical Practice Deviations	3	0
Change or missed doses of OBR	1	0
Other	3	0
Total	59	9

Table created by the Clinical Reviewer using data provided by the sponsor.

### Demographic Characteristics

The TMB-202 protocol enrolled participants whose racial and ethnic make-up approximate that of the U.S. population<sup>18</sup>. Sixty-nine (61.0%) participants were white, 27 (23.9%) were black or African American, and 4 (5.2%) were Asian. Forty (35.4%) participants were Hispanic/Latino (**Table 15**). Distribution of race and ethnicity was similar in the two arms of the trial. Thirty-six (90.0%) participants were enrolled in the U.S. and four (10%) of participants were enrolled in Taiwan. The median age was 47.0 (IQR 43.0-53.0) years and was similar between the two dose groups (**Table 15**). The majority of participants were male; only twelve (10.6%) participants overall were female. Slightly more female participants were in the 800 mg q2 week dosing arm

compared to the 2000 mg q4 week arm (eight, 15.6% participants verses four, 7.4% participants respectively).

**Table 15 Demographic Characteristics of TMB-202 Participants in by Planned Treatment\***

Demographic Parameter		Ibalizumab 2000 mg Q4W N=54	Ibalizumab 800 mg Q4W N=59	All TMB-202 participants N=113
<b>Sex</b>	Male	50 (93%)	51 (86%)	101 (89%)
	Female	4 (7%)	8 (16%)	12 (11%)
<b>Age</b>	Mean years (SD)	47.5 (6)	47.9 (8.2)	47.7 (7.4)
	Median (years)	47.0	48.0	47.0
	Min, max (years)	32-62	29-69	29-69
	IQR (years)	43.8-53.0	42.0-53.0	43.0-53.0
<b>Age Group</b>	≥18 - 39 years	4 (8%)	7 (12%)	11(6%)
	≥ 39 - < 64 years	50 (93%)	51 (86%)	101 (51%)
	≥ 65 years	0 (0%)	1 (2%)	1 (1%)
<b>Race</b>	White	27 (50%)	42(71%)	69 (61%)
	Black or African American	15 (28%)	12 (20%)	27 (24%)
	Asian	3 (6%)	1(2%)	4(5%)
	Multiple (American Indian or Alaska Native and Spanish)	1(2%)	0	1(1%)
	Other	8 (15%)	4(7%)	12 (11%)
<b>Ethnicity</b>	Hispanic or Latino	20 (37%)	20 (34%)	40 (35%)
	Not Hispanic or Latino	34 (63%)	39 (66%)	73 (65%)
<b>Region</b>	United States	51 (94%)	58 (98%)	109 (97%)
	Taiwan	3 (6%)	1 (2%)	4 (4%)

\*Participant 202-21-001 was randomized to receive 2000 mg q4 weeks; the participant received the correct dose on Day 1 but, in error, was given 800 mg at week 2. He was then removed from protocol due to this protocol deviation.

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

The majority of participants of TMB-202 had advanced AIDS: the median CD4 T cell count was 47.5 cells/μL and the majority of participants (33, 61.1%) had baseline CD4 T cell counts less than 100 cells/ μL. The participants in the 2000mg q4 week dosing group had slightly lower CD4 T cell counts compared to the 800 mg q2 week group. The median number of years since HIV

diagnosis was 14.8 years overall and was similar between both dose groups. The median HIV RNA level was 4.7 log<sub>10</sub> copies/ml and was similar in both dosing groups. Nine (8.0%) and two (1.8%) participants were co-infected with HBV and HCV. HBV/HCV co-infection rates were similar in the two dosing arms (**Table 16**).

**Table 16 Clinical Characteristics of TMB-202 Participants by Planned Treatment\***

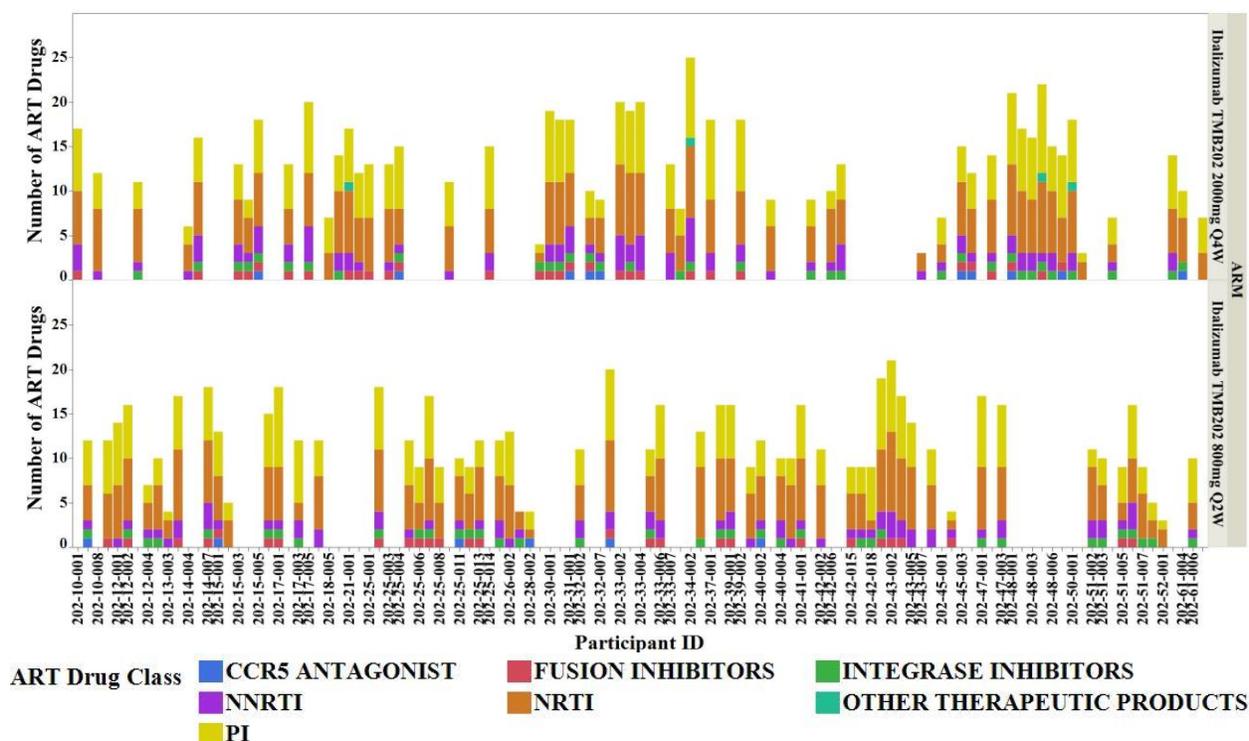
Clinical Characteristic	Variable or Statistic	Ibalizumab 2000mg q4 weeks n=54	Ibalizumab 800 mg q2 weeks n=59	All TMB-202 participants n=113
<b>Years since HIV diagnosis</b>	Participants with data available	40	45	85
	Mean	15.5	13.9	14.7
	Median (IQR)	16.2 (10.8-20.3)	14.3 (11.2-19.3)	14.8 (11.0-19.9)
	Min, max	0.3-26.3	0.2-25.9	0.2-26.3
<b>Baseline CD4 T cell count (cells/μL)</b>	Mean	110.5	102.3	106.2
	Median (IQR)	47.5 (19.0-165.5)	76.0 (22.0-136.0)	68.0 (19.0-146.0)
	Min, max	6-518	19-368	6-518
<b>Baseline CD4 T cell group (n, %)</b>	CD4 <200 cells/μL	45 (83.3%)	50(84.7%)	95(84.1%)
	CD4<100 cells/μL	33 (61.1%)	35(59.3%)	68(60.2%)
	CD4 <50 cells/μL	29(53.7%)	24(40.7%)	53(46.9%)
	CD4 <10 cells/μL	1(1.9%)	0	1(0.9%)
<b>Baseline HIV RNA (log<sub>10</sub> copies/ml)</b>	Mean	4.7	4.5	4.6
	Median (IQR)	4.7(4.1-5.2)	4.6(4.1-5.2)	4.7(4.1-5.2)
	Min, max	2.2-6.5	1.9-6.2	1.9-6.5
<b>Baseline HIV RNA (copies/ml)</b>	Mean	130,190	169,380	148,918
	Median (IQR)	39,500	52,300	51,300
	Min, max	71-1,500,000	145-2,920,000	71-2,920,000
<b>Co-infections</b>	HBV	5(9%)	4(7%)	9(8%)
	HCV	1(2%)	1(2%)	2(2%)

\*Participant 202-21-001 was randomized to receive 2000 mg q4 weeks; the participant received the correct dose on Day 1 but, in error, was given 800 mg at week 2. He was then removed from protocol due to this protocol deviation.

The participants in TMB-202 were heavily treatment-experienced; eighty (73.4%) participants were treated with 10 or more antiretroviral drugs prior to study enrollment (**Figure 4**). All participants in both treatment arms had been previously exposed to NRTIs and PIs and most participants had been previously exposed to NNRTIs and integrase inhibitors (**Table 17**). Sixty-seven participants (59.3%) had been exposed to fusion inhibitors and 38 (33.6%) had been exposed to CCR5 antagonists. Tropism testing performed as part of the TMB-202 trial

demonstrated that 26.5% of participants had R5-tropic virus and that tropism was similar in both groups (27.8% in 2000 mg q4 week group versus 25.4% in the 800mg q2 week group (**Table 17**).

**Figure 4. ART Drug History in TMB-202 Participants by Planned Treatment Group\***



Graph produced by the clinical reviewer using data provided by the sponsor. “Other therapeutic products” included various investigational drugs. \*Participant 202-21-001 was randomized to receive 2000 mg q4 weeks; the participant received the correct dose on Day 1 but, in error, was given 800 mg at week 2. He was then removed from protocol due to this protocol deviation.

Taimed used (b) (4) for calculation of baseline GSS, PSS, and OSS scores for each of the TMB-202 participants using the logarithm described in **Section 4.3** (Clinical Microbiology). TMB-202 participants had MDR HIV and were highly resistant to available HIV therapy; the median GSS, PSS, and OSS scores (IQR) were 1 (IQR 0-2), 2 (IQR 1-2), and 2 (IQR 1-2), respectively (**Table 17**). Scores were similar between dosing groups.

**Table 17 ART Drug History of TMB-202 Participants by Planned Treatment Group\***

<b>ART History or Resistance Characteristic</b>	<b>Variable or Statistic</b>	<b>Ibalizumab 2000mg q4 weeks n=54</b>	<b>Ibalizumab 800 mg q2 weeks n=59</b>	<b>All TMB-202 participants n=113</b>
<b>Number of previous ART drugs &gt;10 ART Drugs</b>	Mean	13.6	12.0	12.8
	Median (IQR)	13.5(9.8-18.0)	12.0(9.0-16.0)	12.0(9.0-16.0)
	Min, max	3-25	3-21	3-26
	>10 ART Drugs	41(75.9%)	42(71.2%)	83(73.4%)
<b>Previous ART drug class exposure (Number/Percent of participants)</b>	NRTI	54(100%)	59(100%)	113(100%)
	NNRTI	50(84.7%)	55(93.2%)	105(92.9%)
	PI	54(100%)	59(100%)	113(100%)
	Integrase Inhibitor	50 (84.7%)	51(86.4%)	101(89.4%)
	Fusion Inhibitor	33(61.1%)	34(57.6%)	67(59.3%)
	CCR5 Antagonist	20(37.0%)	18(30.5%)	38(33.6%)
	Other agents	4(7.4%)	0	4(3.5%)
<b>Co-Receptor Tropism (Number/Percent of participants)</b>	CXCR4	4(7.4%)	6(10.2%)	10(8.8%)
	CCR5	15(27.8%)	15(25.4%)	30(26.5%)
	Dual	33(61.1%)	33(55.9%)	66(58.4%)
	Not known	2(3.7%)	5(8.5%)	7(6.2%)
<b>Genotypic Sensitivity Score (GSS)</b>	Mean	0.9	1.1	1.0
	Median (IQR)	1(0-1)	1(0-2)	1(0-2)
	Min, max	0-2	0-4	0-4
<b>GSS group (Number/Percent of participants)</b>	0	16(29.6%)	22(37.3%)	38(33.6%)
	1	26(48.1%)	16(27.1%)	42(37.2%)
	2	12(22.2%)	18(30.5%)	30(26.5%)
	3	0	1(1.7%)	1(0.9%)
	4	0	2(3.4%)	2(1.8%)
<b>Phenotypic Sensitivity Score (PSS)</b>	Mean	1.6	1.7	1.6
	Median (IQR)	2(1-2)	2(1-2)	2(1-2)
	Min, max	0-3	0-5	0-5
<b>PSS group (Number/Percent of participants)</b>	0	4(7.4%)	4(6.8%)	8(7.1%)
	1	20(37.4%)	24(40.7%)	44(38.9%)
	2	26(48.1%)	21(35.6%)	47(41.6%)
	3	4(7.4%)	7(11.9%)	11(9.7%)
	4	0	2(3.4%)	2(1.8%)
	5	0	1(1.7%)	1(0.9%)
<b>OSS (Overall Sensitivity Score)</b>	Mean	1.6	1.7	1.6
	Median (IQR)	2(1-2)	2(1-2)	2(1-2)
	Min, max	0-3	0-5	0-5
<b>OSS group</b>	0	9(17%)	9(15%)	18(16%)

ART History or Resistance Characteristic	Variable or Statistic	Ibalizumab 2000mg q4 weeks n=54	Ibalizumab 800 mg q2 weeks n=59	All TMB-202 participants n=113
(Number/Percent of participants)	1	20(37%)	17(29%)	37(33%)
	2	19(35%)	24(41%)	43(38%)
	3	4(7%)	5(8%)	9(8%)
	4	1(2%)	3(5%)	4(4%)

\*Participant 202-21-001 was randomized to receive 2000 mg q4 weeks; the participant received the correct dose on Day 1 but, in error, was given 800 mg at week 2. He was then removed from protocol due to this protocol deviation.

### Treatment Compliance

As is mentioned above in the Protocol Amendments Section, protocol TMB-202 was amended to shorten the duration of the trial from 48 to 24 weeks. Seventy-eight participants were enrolled prior to the amendment and were supposed to receive 24 doses of either ibalizumab or placebo; the remaining thirty-five participants were enrolled after amendment and were supposed to receive 12 doses of either ibalizumab or placebo.

### Efficacy Results – Primary and Secondary Endpoint

Efficacy outcomes using the snapshot approach are presented here and in the table below. The results produced by this reviewer’s analysis and the statistical reviewer’s analysis are similar to those produced by the applicant. Please see Dr. Karen Qi’s review for results using the “missing equals failure” (MEF) approach, which differed from the applicant’s results.

Fifteen (27.8%) participants who received ibalizumab 2000 mg q4 weeks and twenty-six (44.1%) participants who received 800 mg q2 weeks achieved HIV RNA <50 copies/ml at week 24. Twenty-three (24.6%) participants who received ibalizumab 2000 mg q4 weeks and thirty (50.8%) participants who received 800 mg q2 weeks achieved HIV RNA <200 copies/ml at week 24. Thirty-five (64.8%) participants who received ibalizumab 2000 mg q4 weeks and forty-three (72.9%) participants who received 800 mg q2 weeks achieved a HIV RNA reduction of 0.5 log<sub>10</sub> or greater (**Table 18**).

**Table 18 Primary and Secondary TMB-202 Efficacy Outcomes by Planned Treatment\*(Snapshot Approach)**

Endpoint	Variable (assessed at week 24)	Ibalizumab 2000mg q4 weeks  n=54	Ibalizumab 800 mg q2 weeks  n=59
Primary	HIV RNA < 50 copies/mL	15 (27.8%)	26 (44.1%)
Secondary	HIV RNA < 200 copies/mL	23 (42.6%)	30 (50.8%)
	HIV RNA < 400 copies/mL	25 (46.3%)	33 (55.9%)
	HIV RNA $\geq 0.5 \log_{10}$ decrease from baseline	35 (64.8%)	43 (72.9%)
	HIV RNA $\geq 1 \log_{10}$ decrease from baseline	32 (59.3%)	37 (62.7%)
	CD4 T cell count increase from baseline (median, IQR)	43.5 (4.8-101.0)	36.5 (6.3-95.0)

\*All variables assessed at week 24. All results are number and proportion of participants except increase in CD4 T cell count. \*Participant 202-21-001 was randomized to receive 2000 mg q4 weeks; the participant received the correct dose on Day 1 but, in error, was given 800 mg at week 2. He was then removed from protocol due to this protocol deviation.

*Clinical Reviewer: The results of this Phase 2b trial provide support for efficacy of ibalizumab. Given the highly treatment experienced, MDR patient population enrolled in the trial, the primary and secondary endpoint results are clinically meaningful. The differences between the applicant and the reviewers' snapshot results were minor (one or two participants) and would not have changed this reviewer's overall interpretation of the efficacy results. For details regarding the results of the MEF analysis and differences between the applicant and the statistical reviewer's results, please see Dr. Karen Qi's review.*

**Data Quality and Integrity - Reviewers' Assessment**

In collaboration with the Office of Computational Science (OCS), data fitness assessment was performed on June 1, 2017. No major concerns were identified.

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

### **Dose/Dose Response**

Two dosing regimens were evaluated in the TMB-202 trial; 2000 mg IV every 4 weeks and the 800 mg IV every 2 weeks. According to TaiMed, TMB-202 results demonstrated that higher serum concentrations and maximum receptor occupancy were achieved more rapidly with the 2000 mg dose. Conversely, more patients on the 800 mg dose administered every 2 weeks achieved and maintained HIV-RNA levels below 50 copies at Week 24 than patients on the 2000 mg dose administered every 4 weeks. TaiMed hypothesized that the differences in this primary efficacy outcome may have been related to a trend toward higher trough concentrations observed with the 800 mg dose. The AE profile of both regimens was similar. Based on the results of the TMB-202 trial, TaiMed designed a new dosing regimen (2000 mg loading dose followed by 800 mg maintenance doses administered every 2 weeks) for use in the Phase 3 trial, TMB-301.

### **Durability of Response**

Please see efficacy results above. The primary and secondary endpoints were evaluated at 24 weeks, which was the duration of the trial.

### **Persistence of Effect**

Please see efficacy results above. The primary and secondary endpoints were evaluated at 24 weeks, which was the duration of the trial.

### **Additional Analyses Conducted on the Individual Trial**

No additional analyses were performed.

## **6.3. TNX-355.03**

TNX-355.03 was a Phase 2a trial that compared two dose regimens of ibalizumab with placebo in population of treatment-experienced patients with HIV-1 infection. Although neither of the dosing regimens used in TNX-355.04 is the same as the dosing regimen proposed in the label, the results of the trial provide additional support for the safety of ibalizumab. TaiMed submitted legacy datasets for TNX-355.03 and therefore the summary data presented below is primarily derived from the clinical study report provided by the applicant. Tables are modified versions of the tables provided by TaiMed.

### **6.3.1. Study Design**

#### **Objectives**

The primary objectives of the trial were as follows;

- 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 one of the ibalizumab treatment arms differs from the placebo-containing arm in terms of HIV RNA levels after 24 weeks of study drug administration.

The secondary objectives of the TNX-355.03 were as follows:

- Compare the safety and efficacy, as assessed at Week 48, of 2 dosages of ibalizumab added to OBT versus OBT plus placebo.
- Characterize HIV-1 phenotypes/genotypes associated with ibalizumab treatment susceptibility and failure.
- Determine the relation, if any, between cell coating of circulating CD4+ cells and virologic response and treatment failure.
- Determine the relation, if any, between serum concentrations of ibalizumab and cell coating of CD4+ cells.
- Determine the difference, if any, in delayed-type hypersensitivity response between treatment groups

## Endpoints

The primary efficacy endpoint was the mean change from Baseline in HIV-1 RNA levels at Week 24.

The following secondary efficacy endpoints were evaluated:

- Proportion of subjects who achieved a reduction of  $\geq 0.5$  log<sub>10</sub> HIV-1 RNA copies/mL at and by Weeks 24 and 48
- Proportion of subjects who achieved a reduction of  $\geq 1.0$  log<sub>10</sub> HIV-1 RNA copies/mL at and by Weeks 24 and 48
- Mean change from Baseline in CD4+ cell count (number of cells and percentage) at each time point, including the last available data point

## Inclusion/Exclusion Criteria

Patients were eligible for TNX-355.03 if they were treatment-experienced adults infected with HIV-1 with a stable HIV-1 RNA load of at least 10,000 copies/mL and a CD4+ cell count of  $>50$  cells/ $\mu$ L. In addition, eligible participants must have met the following criteria:

- Cumulative ART experience of a minimum of 6 months
- Triple-class experience (NNRTI, NRTI, and PI)
- Failing their current HAART regimen or had discontinued a failing HAART regimen within 8 weeks prior to screening.
- Virus susceptibility to one or more ART drug (excluding enfurvirtide) in addition to ibalizumab.

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

Patients were excluded from the trial if they had an active opportunistic infection or any significant disease or clinically significant finding that would, in the investigator's opinion, interfere with participation in the trial.

### **Trial Design**

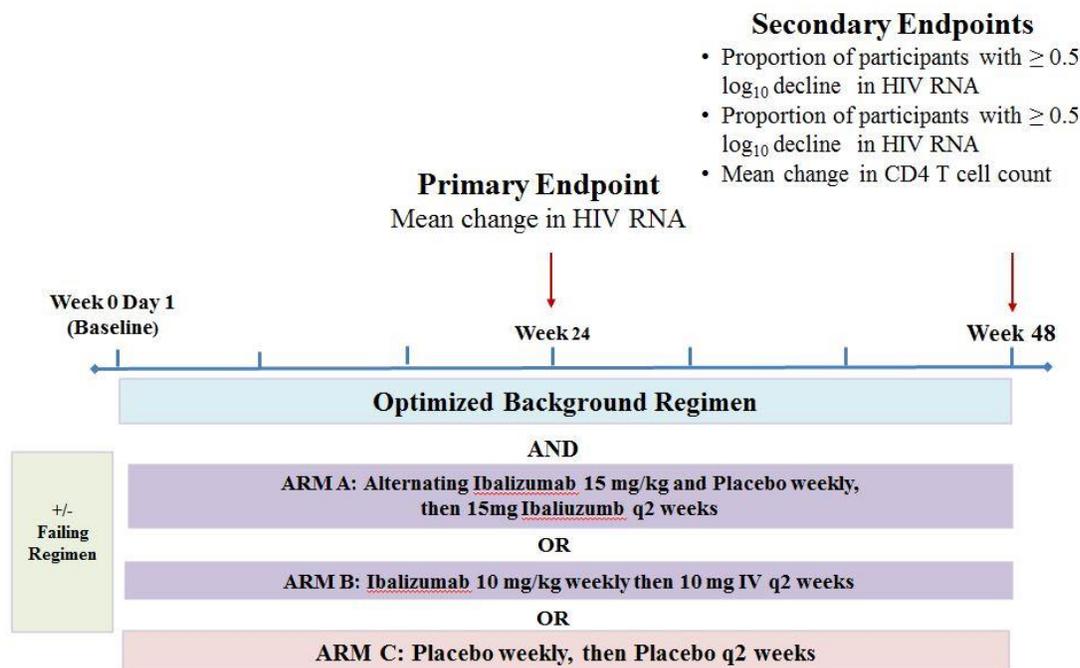
TNX-355.03 was a double-blind, placebo-controlled, randomized three-arm Phase 2a study designed to evaluate the safety, efficacy and PK activity of two ibalizumab dose regimens in combination with OBR versus placebo plus OBR in treatment experienced patients. Eligible participants were randomized to three Arms that are described below:

- Arm A: 15mg/kg ibalizumab or placebo weekly for the first 9 doses followed by 15mg/kg every 2 weeks
- Arm B: TNX-355 10mg/kg q week for 9 doses followed by 10mg/kg q 2weeks
- Arm C: weekly infusions of placebo for 9 doses and then placebo q 2 weeks

All participants received intravenous infusion weekly (ibalizumab or placebo) for the first 8 weeks (9 infusions) and every two weeks for the remaining duration of the study. The maximum duration of the study was 226 weeks (8 weeks of screening, 214 weeks of study treatment (ibalizumab or placebo) and four weeks of follow-up.

Virologic failure was defined as follows; failure to achieve or maintain a decrease from baseline HIV-1 RNA level of  $\geq 0.5$  log<sub>10</sub> copies/ml on two consecutive viral load measurements after week 12. After week 16, participants with virologic failure were reassigned a new OBR (based on additional resistance testing) AND open label ibalizumab at 15mg/kg.

### **Figure 5. TNX-355.03 Study Design**



### 6.3.2. Study Results

#### Enrollment and Disposition

Enrollment began on March 9, 2004 and the trial was completed on March 2, 2009. Twenty sites, all within the U.S., enrolled a total of 82 participants. A total of 28, 27, and 27 participants were randomized in Arms A, B, and Placebo, respectively.

#### Demographics and Baseline Clinical Characteristics

The baseline demographic characteristics of participants in the TNX 355.03 were similar in the three trial arms. Thirty-eight (44.4%) participants were white and fifteen (18.3%) were black. Twenty-seven (32.9%) participants were Hispanic/Latino. Distribution of race and ethnicity was similar in the three arms of the trial. The median ages were 44, 46, and 44 in Arm A, Arm B, and Placebo, respectively. The majority of participants were male; only eleven (13.4%) participants overall were female. More female participants were in Arm B (6 participants, 22.2%) compared to Arm A (2 participants, 7.1%) or the placebo Arm (3 participants, 11.1%) See **Table 19**.

Overall, the clinical characteristics of participants in TNX-355.03 were similar among the three trial arms. The median number of prior ART drugs was 10.5, 11.0, and 12 in Arm A, Arm B, and Placebo, respectively. Participants in Arm A had lower baseline CD4 T cell counts (178 cells/ $\mu$ L) and lower numbers of susceptible ART drugs in the OBR (1.0 ART drug) compared to

Arm B (263 CD4 T cells cells/ $\mu$ L and 2.0 ART drugs) and placebo (240.5 CD4 T cells cells/ $\mu$ L and 2.0 ART drugs) (**Table 19**).

**Table 19 Trial 353.03 Demographics and Baseline Clinical Characteristics**

	Arm A Ibalizumab 15mg/kg (n=28)	Arm B Ibalizumab 10mg/kg (n=27)	Placebo Arm (n=28)
Age (median, range)	44 (28-59)	46 (18-75)	27 (31-66)
Male sex (number of participants and percent)	26 (93%)	21 (78%)	24 (89%)
Race & Ethnicity (number of participants and percent)	White	12 (43%)	14 (52%)
	Black	8 (29%)	4 (15%)
	Hispanic	7 (25%)	8 (30%)
	Other	1 (4%)	1 (4%)
Time since HIV diagnosis (median, range)	11.6 (2.1-22.7)	12.9 (1.2-19.3)	12.7 (3.8-24.4)
HIV RNA , log <sub>10</sub> copies/ml (median, range)	5.2 (1.2-5.6)	4.8 (4.0-5.5)	4.8 (3.9-5.8)
CD4 T cell count, cells/ $\mu$ L (median, range)	178 (37-532)	263 (47-721)	240 (48-715)
CD4 T cell count <200 cells/ $\mu$ L (number of participants and percent)	17 (60.7%)	7 (25.9%)	13 (48.1%)
Number of Previous ART drugs (number of drugs and range)	10.5 (3-19)	11.0 (3-17)	12 (4-16)
Number of Susceptible Baseline ART drugs in OBT (median, range)	1 (1-3)	2 (0-4)	2 (0-4)

### Trial Results

At the 24 week assessment, the mean change in viral load was - 0.75 log<sub>10</sub> for the 15 mg/kg q 2 week + OBT, -1.19 log<sub>10</sub> for the 10 mg/kg q week + OBT, and -0.32 log<sub>10</sub> for placebo plus OBT with the change from baseline set to zero for all those who discontinued prior to week 24 (**Table 20**). The 10 mg/kg q week compared to placebo appeared to be statistically significant but the 15 mg/kg did not. At week 48, the mean change in viral load was -0.58 log<sub>10</sub> for the 15 mg q2week, -0.79 log<sub>10</sub> for the 10 mg/kg q week and -0.22 log<sub>10</sub> for placebo.

**Table 20 Trial 353.03 Efficacy Results**

		<b>Arm A IBALIZUMAB 15mg/kg (n=28)</b>	<b>Arm B IBALIZUMA B 10mg/kg (n=27)</b>	<b>Placebo Arm (n=27)</b>
<b>Week 24</b>	Completed 24 weeks in the study, N (%)	26 (92.9%)	25 (92.6%)	25 (92.6%)
	Participants on open-label medication prior to week 24, N (%)	9 (32.1%)	6 (22.2%)	16 (48.1%)
	Change in HIV-1 RNA at Week 24*, log <sub>10</sub> copies/ml (mean, median, range)	-0.78 -0.53 (-2.87-0.31)	-1.19 -0.97 (-3.08-0.0)	-0.32 0.00 (-1.92-0.30)
	Number (%) of participants who achieved ≥0.5 log <sub>10</sub> reduction in HIV RNA at week 24	14 (50.0%)	15 (55.6%)	6 (22.2%)
	Number (%) of participants who achieved ≥1.0 log <sub>10</sub> reduction in HIV RNA at week 24	10 (35.7%)	12 (44.4%)	6 (22.2%)
<b>Week 48</b>	Completed 48 weeks in the study, N (%)	16 (57.1%)	17 (63.0%)	13 (48.1%)
	Participants on open-label medication prior to week 48, N (%)	12 (42.9%)	11 (40.7%)	19 (70.4%)
	Change in HIV-1 RNA at Week 48, log <sub>10</sub> copies/ml (median, range)**	0 (-2.63-0.0)	0 (-2.93-0.0)	0 (-2.2-0.1)
	Number (%) of participants who achieved ≥0.5 log <sub>10</sub> reduction in HIV RNA at week 48	10 (35.7%)	12 (44.4%)	3 (11.1%)
	Number (%) of participants who achieved ≥1.0 log <sub>10</sub> reduction in HIV RNA at week 48	8 (28.6%)	10 (37.0%)	3 (11.1%)

\*Primary endpoint. For all participants who discontinued Ibalizumab prior to week 24, the change from baseline set to zero.

\*\*Exploratory endpoint. For all participants who discontinued Ibalizumab prior to week 48, the change from baseline set to zero.

#### 6.4. **TNX 355.02**

TNX 355.02 was a phase 1, multicenter, open-label, dose-escalation, safety, and pharmacokinetics study of ibalizumab (TNX-355) in patients infected with HIV. Results from

this trial provide additional support for the safety of ibalizumab. Data presented are derived from summary information provided by the applicant.

#### 6.4.1. Study Design

Eligible participants had stable HIV RNA levels > 5000 copies/mL. The initial cohort of 6 patients received a single dose by intravenous infusion of 0.3 mg/kg; successive cohorts received increasing dose levels of 1.0, 3.0, 10.0, or 25 mg/kg. 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. Patients were evaluated at 2 weeks, 4 weeks, and 90 days after infusion. If none of the stopping criteria were observed in any patient in a 6 patient cohort during the 2 week safety evaluation period, the next cohort of 6 patients was to be enrolled at a higher dose level. All patients were administered a single dose of TNX-355.

Safety was assessed from the incidence of AEs, clinical laboratory data (hematology, chemistry, and urinalysis), physical examination findings, and vital signs. The total study duration was up to 7 weeks (a 3-week period before study drug administration and a 4-week evaluation period after study drug administration). An additional safety endpoint was TNX-355 immunogenicity.

#### 6.4.2. Study Results

The study took place between October 24, 2001 and September 9, 2002. Thirty patients participated. The majority of participants (27, 90%) were male sex and the median age was 41 years. The median CD4 T cell count was 290 cell/ $\mu$ L and the median baseline HIV RNA ( $\log_{10}$ ) was 4.8 copies/ml. The majority of participants (26, 86.7%) had a history of HIV-related diseases and secondary infections.

The applicant concluded that single doses of 3.0, 10.0, and 25.0 mg/kg of TNX-355 were effective in reducing viral load in patients infected with HIV. They found that 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 of TNX-355. They also found that reductions of >1  $\log_{10}$  in plasma HIV RNA levels were observed after 10 mg/kg and after 25 mg/kg of TNX-355, and mean reductions of >0.6  $\log_{10}$  were observed after 3.0 mg/kg of TNX-355.

### 6.5. **Hu5A 8.0**

Study Hu5A 8.0 was a phase 1, multicenter, open-label, partially-randomized, multi-dose, parallel-group study. Results from this trial provide additional support for the safety of ibalizumab. Data presented are derived from summary information provided by the applicant.

### 6.5.1. Study Design

Eligible participants were treatment-naïve or treatment-experienced patients infected with HIV-1 with a stable HIV-1 RNA load of at least 5,000 copies/mL, and a CD4+ cell count of 100 to 500 cells/ $\mu$ L. The first 20 subjects were to be randomized between 2 treatment arms (Arm A and Arm B) with equal assignment probability. Subjects in Arm A received a 10 mg/kg infusion of TNX-355 every 7 days for a total of 10 doses; subjects in Arm B received a 10 mg/kg loading dose infusion of TNX-355 on Day 1 followed by 5 maintenance doses of 6 mg/kg TNX-355 infused every 14 days, starting at Week 1. Upon completion of subject treatment in Arms A and B, additional subjects were assigned (nonrandomized) to Arm C and received infusions of 25 mg/kg TNX-355 every 14 days for a total of 5 doses. Subjects randomized to Arms A and B received study drug over a 9-week period; subjects in Arm C received their study treatment over an 8-week period.

The study consisted of a screening period, a treatment phase, and a follow-up period. Safety was monitored throughout the conduct of the study. Study medication was to be discontinued for any subject who had a sustained decrease from the baseline value in CD4+ cell counts of  $\geq 50\%$  at 2 consecutive weekly visits, a confirmed  $>0.7$  log<sub>10</sub> increase in HIV-1 RNA from baseline at 2 consecutive weekly visits, or adverse events (AEs) of dose-limiting toxicity (DLT).

### 6.5.2. Study Results

The study took place between January 21, 2003 and November 13, 2003. Hu5A 8.0 enrolled a total of 22 participants including 9, 10, and 3 subjects in Arms A, B, and C, respectively. Mean ages ranged from 39 to 42 years; most of the subjects (19/22) were male and most (17/22) were white. Mean time from HIV diagnosis to initial infusion of TNX-355 was 7.3 years in Arm A, 8.8 years in Arm B, and 12.6 years in Arm C. Mean baseline HIV-1 RNA loads were approximately 5 log<sub>10</sub> copies/mL in each treatment group. Mean baseline CD4+ cell counts ranged from 294 cells/ $\mu$ L in Arm A to 338 cells/ $\mu$ L in Arm C.

The applicant concluded that ibalizumab (TNX-355), at all 3 doses, exhibited anti-HIV-1 RNA activity as demonstrated by decreased HIV-1 RNA viral loads, near-consistent CD4+ cell coating, increased CD4+ cell counts (absolute and as a percent of total T-lymphocytes), and a positive correlation between CD4+ cell coating and decreases from baseline values in HIV-1 RNA viral loads. PK evaluation of the serum concentrations of subjects in Arms A and C revealed a behavior consistent with capacity-limited elimination of TNX-355, with elimination driven by binding to the CD4 antigen, as opposed to normal IgG elimination.

## 6.6. TMB-311

TMB-311 is an ongoing, multicenter, open-label expanded access study of ibalizumab. The main goal of the TMB-311 study is to allow patients with limited HIV treatment options access to ibalizumab prior to drug approval. The majority of the patients in TMB-311 participated in

ibalizumab clinical trials (TMB-202, TMB-301, or investigator-sponsored INDs); these participants continued ibalizumab at the same dose they had received on their respective trials (2000 mg IV q4 or 800mg IV q2 weeks for TMB-202 participants and 800mg q2 weeks for TMB-301 participants). Ibalizumab-naïve, but otherwise heavily ART treatment-experienced patients with MDR HIV are also eligible; these participants are to receive the dose proposed in the ibalizumab label (2000 mg IV loading dose followed by 800mg IV q2 weeks). The study started on January 22, 2016 and is ongoing. The summary data presented below is derived from the 60 day Safety Update (covering January 22, 2016 through 60-day safety cut-off date February 28, 2017).

From a review perspective, results from the TMB-311 provide additional support for the long-term safety and durability of ibalizumab.

#### 6.6.1. Study Design

TMB-311 is a phase 3, multicenter, expanded access study to evaluate the safety and tolerability of ibalizumab plus an Optimized Background Regimen (OBR) in treatment-experienced patients infected with multi-drug resistant (MDR) HIV-1. Eligible patients included those receiving ibalizumab under a TaiMed-sponsored or Investigator-IND protocol, and heavily treatment-experienced patients with no history of ibalizumab treatment who are on a failing regimen, or had failed and are off treatment. Ibalizumab was administered as delineated above with an OBR, which was selected by the site investigator and included at least one drug to which the participant's virus was susceptible. Safety was assessed in all patients by tabulation of AEs and SAEs. Virologic activity was assessed at Day 7 after initiation of ibalizumab in the cohort of ibalizumab-naïve patients.

#### 6.6.2. Study Results

A total of 53 patients had enrolled in TMB-311 as of February 28, 2017. A total of thirteen patients had previously participated in TMB-202, twenty-seven had participated in TMB-301, and thirteen were ibalizumab naïve. Forty-five (84.9%) enrolled patients continued to receive ibalizumab through the trial at the time of data cutoff. **Table 21** describes the participant disposition through February 28, 2017.

**Table 21 TMB-311 Disposition as of February 28, 2017**

	Cohort 1			Cohort 2
	TMB-301 Rollovers	TMB-202 Rollovers		Ibalizumab Naïve
	800 mg IV q2 weeks n=27	800 mg IV q2 weeks n=5	2000 mg IV q4 weeks n=8	2000mg IV LD then 800mg IV q2 weeks n=13
<b>Completed treatment</b>	0	0	0	0
<b>Number continuing Treatment</b>	24(89%)	4(80%)	7(88%)	10(77%)
<b>Discontinued Treatment prematurely</b>	3(11%)	1(20%)	1(13%)	3(23%)
<b>AE</b>	0	0	0	1(8%)
<b>Death</b>	0	1(20%)		0
<b>Consent withdrawn or voluntary withdrawal</b>	2	0	0	1(8%)
<b>Investigator decision</b>	1(33%)	0	0	1(8%)

Table is modified version of Table 1 from 60-Day Safety Summary Update (October 21, 2016-February 28, 2017).

Similar to the other trials in the ibalizumab development program, the majority (48, 90.6%) of enrolled TMB-311 patients are men. Also similar to other trials in the program, most of the patients are white (33, 62.3%), although black patients (16, 30.2%) and Hispanic/Latino patients (17, 32.0%) also participated. **Table 22** describes the participant demographics in TMB-311.

**Table 22 TMB-311 Demographic Characteristics**

		Cohort 1			Cohort 2
		TMB-301 Rollovers	TMB-202 Rollovers		Ibalizumab Naïve
		800 mg IV q2 weeks n=27	800 mg IV q2 weeks n=5	2000 mg IV q4 weeks n=8	2000mg IV LD then 800mg IV q2 weeks n=13
Age (median, range)		54(23-65)	56.6(47-70)	54.5(52-66)	51.0(26-59)
Male sex		23(85.2%)	5(100%)	8(100%)	12(92.3%)
Race	White	16(59.3%)	5(100%)	6(75.0%)	6(46.2%)
	Black	10(37.0%)	0	0	6(46.2%)
	Unknown	1(3.7%)	0	1(12.5%)	1(7.7%)
Ethnicity	Hispanic/Latino	8(29.6%)	2(40.0%)	3(37.5%)	4(30.8%)
	Not Hispanic/Latino	19(70.4%)	3(60.0%)	5(62.5%)	9(69.2%)

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Twenty TMB-311 patients had less than one year of cumulative ibalizumab exposure, seven had between one and five years cumulative ibalizumab exposure and twelve had between five and ten years of cumulative ibalizumab exposure (**Table 23**).

**Table 23 Previous Ibalizumab Exposure in TMB-311 Participants**

Duration	Cohort 1			Cohort 2
	TMB-301 Rollovers	TMB-202 Rollovers		Ibalizumab Naïve
	800 mg IV q2 weeks n=27	800 mg IV q2 weeks n=5	2000 mg IV q4 weeks n=8	2000mg IV LD then 800mg IV q2 weeks n=13
< 1 year	20(74%)	0	0	0
1 year to <5 years	7(26%)	0	0	0
5 year to <10 years	0	5(100%)	7(88%)	0
≥ 10 years	0	0	0	0

TMB-311 is ongoing and efficacy results have not been reported.

### 6.7. Investigator-Sponsored INDs

The ibalizumab Investigator-Sponsored IND program served to permit heavily-treatment experienced patients with MDR HIV access to ibalizumab, but also sought to demonstrate longer term safety of the study drug. The INDs were initiated between 2009 and 2015. In 2016, investigators were encouraged to close the investigator-sponsored INDs and to enroll their patients in the expanded access trial TMB-311(Section 6.6). Data presented are derived from summary information provided by the applicant.

#### 6.7.1. Study Designs

Participants who had received ibalizumab in TMB-202 continued the dose they were receiving in that trial. Ibalizumab-naïve participants were treated with 800 mg IV ibalizumab every two weeks in combination with viral resistance test-guided OBR. Participants were encouraged to discontinue ibalizumab if they experienced virologic failure. Safety assessments were performed per local standard-of-care for the patient population and laboratory assessments were required every 2-3 months. Investigators were responsible for collecting safety data and reporting an annual summary.

### 6.7.2. Study Results

A total of 64 patients were enrolled at 23 sites in North America. The majority (57, 90.4%) of participants had previously participated in TMB-202; 31 received 800mg IV q2 weeks and 26 received 2000 mg IV q4 weeks. Seven patients had not previously been enrolled in ibalizumab trials and were ibalizumab naïve.

Fourteen patients went on to enroll in TMB-311. Of the 50 patients who did not enroll in TMB-311, six died, one stopped ibalizumab because of an AE, and fifteen stopped ibalizumab because of virologic failure. Virologic failure was defined as a  $<0.8 \log_{10}$  decrease from baseline in viral load at two consecutive measurements. For complete listing of reasons for discontinuation by treatment group, see **Table 24**.

**Table 24 Disposition of patients enrolled in investigator-sponsored INDs**

	Ibalizumab -Experienced		Ibalizumab Naïve	
	800 mg IV q2 weeks n=31	2000 mg IV q4 weeks n=26	2000mg IV LD then 800mg IV	
			800 mg IV q2 weeks n=6	2000 mg IV q4 weeks n=1
<b>Discontinued</b>	31(100%)	26(100%)	6(100%)	1(100%)
<b>Enrolled in TMB-311</b>	5(16%)	7(27%)	1(17%)	1(100%)
<b>Death</b>	0	5(19%)	1(17%)	0
<b>AE</b>	0	0	1(17%)	0
<b>Virologic Failure</b>	7(23%)	5(19%)	3(50%)	0
<b>Switched to Alternative Regimen</b>	2(7%)	3(12%)	0	0
<b>Investigator decision</b>	3(9%)	0	0	0
<b>Patient decision/withdrew</b>	3(10%)	2(8%)	0	0
<b>Noncompliance</b>	2(7%)	0	0	0
<b>Unknown</b>	7(23%)	2(8%)	0	
<b>Protocol violation/Not eligible</b>	0	2(8%)	0	0
<b>Other reasons*</b>	2(7%)	0	0	0

\*Other reasons include patient relocations, liver cancer requiring chemotherapy.

The median age was 49.3 years among the patients who had been previously exposed to ibalizumab. The age range (median statistic not provided) of ibalizumab naïve patients was 34 to 61 years. The majority of both groups were men (27, 87.1% of ibalizumab-experienced patients, and 5, 71.4% ibalizumab-naïve patients). Most ibalizumab-experienced patients were white (41, 71.9%); eight (14.0%) were black and eight (14.0%) were Hispanic/Latino. Race data were available for only two ibalizumab-naïve patients; one was white and one was Hispanic/Latino.

Efficacy data was not formally collected or evaluated in investigator-sponsored INDs.

## **7 Integrated Review of Effectiveness**

---

### **7.1. Assessment of Efficacy Across Trials**

Because of the differences in primary endpoints, trial designs, and dosing regimens between trials TMB-301 and TMB-202, pooling for analysis of primary and secondary endpoints is not appropriate. For efficacy results of the pivotal trial, TMB-301, see Sections 6.1.2. For efficacy results of the supportive trial, TMB-202, see Section 6.2.2.

#### **7.1.1. Primary Endpoints**

For primary efficacy endpoint results of trials TMB-301 and TMB-202, see Sections 6.1.2. and 6.2.2.

#### **7.1.2. Secondary and Other Endpoints**

For secondary efficacy endpoint results of trials TMB-301 and TMB-202, see Sections 6.1.2. and 6.2.2.

#### **7.1.3. Subpopulations Dose and Dose-Response**

As discussed in Section 7.1, the differences in trial design between TMB-301 and TMB-202 make pooling results inappropriate. For a discussion of dose response in TMB-202 and its impact on the dosing regimen selected in TMB-301, see Section 6.2.2, subsection “Dose/Dose Response”.

#### **7.1.4. Onset, Duration, and Durability of Efficacy Effects**

The TMB-301 durability endpoints, which are the Phase 3 trial’s secondary endpoints, were assessed at 24 weeks after the initiation of ibalizumab and are presented in the TMB-301 Study Results section (Section 6.1.2). As is discussed in the Therapeutic Context (**Section 2**) and Regulatory History (Section 3), the Division agreed to several TMB-301 design features that are only appropriate in the context of heavily-treatment experienced adults with multi-drug resistant

HIV; these patients are rare, have limited available treatment options, and are at high risk of disease progression and death in the absence of effective ART. Several of these design features, including lack of a control arm, small sample size, and individualized OBR, limit our ability to assess the contribution of ibalizumab to durability. Additionally, characteristics of the patient population, including variability in background DRSS and OBR adherence, further limit the assessment of durability.

Both primary and secondary endpoints in TMB-202 were assessed after 24 weeks of ibalizumab treatment and are durability endpoints. Similar to TMB-301, the TMB-202 study design and patient population limit the assessment of ibalizumab's contribution to durability. Results are presented in TMB-202 Study Results (Section 6.2.2.). Results from expanded access trial TMB-311 (Section 6.6.2) and investigator sponsored INDs (Section 6.7.2) may provide additional, limited support for longer-term ibalizumab durability in some patients.

*Reviewer comment: Because ibalizumab has been developed for the rare patient population of heavily-treatment experienced adults with MDR HIV infection with limited treatment options and high risk of disease progression and death in the absence of effective ART, some degree of uncertainty regarding the contribution of ibalizumab to durability is acceptable.*

## 7.2. Additional Efficacy Considerations

### 7.2.1. Considerations on Benefit in the Postmarket Setting

As is discussed in Section 7.1.4, the TMB-301 trial design and the heterogeneity of the patient population significantly limit our ability to assess the durability of ibalizumab. Therefore, the ibalizumab label should include an indication that is consistent with the rare population studied. However, because the administration of ibalizumab is relatively inconvenient (intravenous administration every two weeks); it is unlikely that clinicians will prescribe ibalizumab off-label.

### 7.2.2. Other Relevant Benefits

See Section 7.3.

## 7.3. Integrated Assessment of Effectiveness

The efficacy of ibalizumab was established in pivotal trial TMB-301, which included 40 highly treatment-experienced patients with advanced HIV infection with MDR virus. The Phase 2B Trial, TMB-202, provides additional support for the efficacy of ibalizumab in this patient population.

The TMB-301 trial data demonstrate the efficacy of ibalizumab in heavily-treatment experienced adults with MDR HIV. The majority (83%) of participants achieved a 0.5 log<sub>10</sub> decrease in HIV RNA after one week of essential ibalizumab monotherapy, compared to only one participant

(3%) who achieved the same decrease during the control period. Reductions in HIV-RNA levels are highly predictive of meaningful clinical benefit and analysis of clinical trial data submitted to the FDA demonstrate that a 0.5 log HIV-RNA reduction in HIV-RNA is associated with a reduction in clinical disease progression.

The secondary endpoints of TMB-301 and primary and secondary endpoints of TMB-202, assessed at 24 weeks, demonstrate that ibalizumab, in combination with various OBR drugs, led to sustained decreases in HIV RNA. Both study designs limit the assessment of ibalizumab's contribution to these durability endpoints. Because ibalizumab has been developed for the rare patient population of heavily-treatment experienced adults with MDR HIV infection with limited treatment options and high risk of disease progression and death in the absence of effective ART, some degree of uncertainty regarding the contribution of ibalizumab to durability is acceptable.

## 8 Review of Safety

---

The safety data submitted with this BLA demonstrate that ibalizumab treatment is associated with a favorable safety profile. The following adverse reactions occurred in at least five percent of participants in the Phase 3 clinical trial (TMB-301): dizziness, diarrhea, rash, and nausea. One serious adverse reaction, immune reconstitution inflammatory syndrome, occurred in TMB-301. Analysis of the supportive Phase 2b trial TMB-202 and review of safety from early phase trials and expanded access studies show similar safety results.

The small size of the ibalizumab safety database is one limitation of the ibalizumab application. A total of 303 patients were exposed across the entire development program, including 20 patients who received ibalizumab exclusively through expanded access studies. Forty patients were exposed to the dosage regimen proposed in the label. An additional 113 patients received the drug at similar doses (2000 mg IV q4 weeks or 800 mg IV q2 hours) in the supportive Phase 2b trial. The safety database of patients exposed to the intended dosage regimen is small, but sufficient to assess frequent adverse events, and acceptable for this serious disease with great unmet medical need.

The Phase 3 (TMB-301) and Phase 2 (TMB-202) ibalizumab trials did not include control arms, which limited the ability to determine if adverse events were the result of drug effect, underlying disease, or chance. Only one trial (Phase 2a, n=82) included a placebo control and those placebo arm participants were allowed to receive open-label ibalizumab if they experienced virologic failure after trial week 16. However, the adverse events that occurred, regardless of severity, were generally consistent with events expected in patients with advanced HIV/AIDS.

### 8.1. Safety Review Approach

This review of safety primarily relies on TMB-301 because TMB-301 was the only trial that used the ibalizumab dosing regimen anticipated for approval (2000mg IV loading dose followed

by 800mg IV every two weeks). Safety data from TMB-202, which compared two different ibalizumab dosing regimens (800mg IV q2 weeks versus 2000 mg IV q4 weeks) provided further support. The duration of trial TMB-202 was changed after enrollment initiated, therefore some TMB-202 participants were treated and followed on trial for up to 48 weeks whereas other participants were treated and followed for only 24 weeks. In order to be consistent, this clinical review focuses only on the safety events that occurred in the first 24 weeks of the trial. Data provided by the applicant in summary form for the Phase 2a Trial TNX 355.03, single patient INDs, and the expanded access protocol (TMB-311) provided additional support for the safety analysis.

As discussed in **Section 2.2 (Analysis of Condition)**, the ibalizumab clinical development program focused on the rare patient population of highly treatment-experienced (HTE) patients with MDR HIV. Therefore, nearly all of the participants in the trials discussed in this review had advanced HIV-infection and, therefore, would be expected to experience a relatively high incidence of AEs related to the underlying condition of HIV/AIDS. As discussed in **Section 3.2 (Regulatory History)**, neither the pivotal trial (TMB-301) nor the main supportive trial (TMB-202) included a placebo arm. Among the studies that provide additional support, only TNX-355.03 included a placebo arm, and most of the participants on that arm received open-label ibalizumab after experiencing virologic failure beyond trial week 16. Because of the small safety database (discussed below) and the limited placebo-controlled safety data, this safety review focuses on frequent and significant adverse events and may not detect uncommon events related to ibalizumab. The clinical reviewer relied on investigator's assessment and on the reviewer's clinical expertise to assess the likelihood that safety events might be related to ibalizumab rather than the underlying disease or chance.

Because ibalizumab is a monoclonal antibody that targets the host's CD4 T cell molecule, the review of safety placed special attention to adverse events related to immunogenicity, immunosuppression, infusion-reactions, and drug allergy.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

For overall drug exposure data across the ibalizumab development program, this clinical review relies on the summary data provided by TaiMed. TaiMed reported that a total of 303 participants were exposed to intravenous ibalizumab. One hundred and fifty-three participants took part in the trials TMB-301 and TMB-202. A total of 143 participants took part in the Phase 1a (Hu5A8.01), Phase 1b (TNX 355.02), Phase 2a (TNX 355.03) and the TaiMed-Sponsored Expanded Access Protocol (TMB-311). An additional seven patients received intravenous ibalizumab through investigator-sponsored INDs.

**Table 25 Ibalizumab Safety Database**

<b>Trial Phase</b>	<b>Trial Name</b>	<b>Dose and regimen evaluated</b>	<b>Drug</b>	<b>Placebo</b>	<b>Duration</b>
<b>1a</b>	<b>Hu5A 8.01</b>	0.3 mg/kg	6	0	Single dose
		1.0 mg/kg	6	0	
		3.0 mg/kg	6	0	
		10 mg/kg	6	0	
		25 mg/kg	6	0	
<b>1b</b>	<b>TNX 355.02</b>	10 mg/kg q week for 10 doses;	9	0	9 weeks
		10 mg/kg single dose, then 6 mg/kg q 2 weeks for 5 doses	10	0	
		25 mg/kg q 2 weeks for 5 doses	3	0	
<b>2a</b>	<b>TNX-355.03</b>	15 mg/kg q 2 weeks for 48 wks	28	0	48 weeks, up to 216 weeks
		10 mg/kg q week for 9 weeks, then 10 mg q2 week for 39 weeks	27	0	
		Placebo, cross over to 15 mg/kg for virologic failure	23*	27	
<b>2b</b>	<b>TMB-202</b>	2000 mg IV q4 weeks	54	0	24-48 weeks
		800 mg IV q2 weeks	59	0	
<b>3</b>	<b>TMB-301</b>	2000 mg IV once, then 800 mg q2 weeks	40	0	24 weeks
<b>EAP</b>	<b>TMB-311**</b>	2000 mg IV once, then 800 mg q2 weeks	13	0	
<b>Investigator-Sponsored INDs</b>		2000 mg IV q4 weeks	6	0	Up to 8 years
		800 mg IV q2 weeks	1	0	
<b>Total</b>			<b>303</b>	<b>27</b>	

\*TNX-355.03 participants exposed to ibalizumab after experiencing virologic failure on the placebo arm are included in both “placebo” and “drug” columns.

\*\*Only TMB-311 participants who did not participate in previous ibalizumab trials are included.

### 8.2.2. **Relevant characteristics of the safety population:**

Please see Section 6 for characteristics of the patient populations included in each individual trial. Differences in trial design, dosing regimens, and availability of OBR drugs precluded pooling of safety data between the trials in the ibalizumab development program. Across all trials, women were underrepresented. Although the racial and ethnic diversity is similar to that of the U.S. population, the safety database is small therefore the numbers of participants in ethnic minority groups is very small. All of the participants in the ibalizumab development program were HIV-infected and the majority of participants in the Phase 2b and Phase 3 trials had advanced disease, which appropriately reflects the target patient population.

### 8.2.3. **Adequacy of the safety database:**

Although the majority of participants in the clinical trials did not receive the to-be-marketed dosage regimen, the target population is rare (~5000 individuals in the US) and the condition is life-threatening. The safety database for patients exposed to the intended dose is small, but sufficient to assess frequent adverse events, and acceptable for this serious disease with great unmet medical need. Post-marketing pharmacovigilance will play an important role in further defining the safety profile of this drug, especially for rare adverse reactions.

## 8.3. **Adequacy of Applicant’s Clinical Safety Assessments**

### 8.3.1. **Issues Regarding Data Integrity and Submission Quality**

No issues regarding data integrity were identified. All narratives for deaths, related SAEs, related AEs leading to treatment discontinuation, and significant events were reviewed carefully. Additionally, rates of specific safety events as reported by the Applicant were verified by this reviewer (results were either identical to those of the Applicant or varied by only 1-2 subjects).

### 8.3.2. **Categorization of Adverse Events**

The clinical reviewer identified no issues with respect to recording, coding, or categorizing AEs. The applicant categorized AEs in accordance with standard, regulatory definitions. Investigators assessed the severity of AEs using the following criteria:

- **Mild (Grade 1):** Symptoms causing no or minimal interference with usual social and functional activities.
- **Moderate (Grade 2):** Symptoms causing greater than minimal interference with usual social and functional activities.

- **Severe (Grade 3):** Symptoms causing inability to perform usual social and functional activities.
- **Potentially Life-Threatening (Grade 4):** Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.

### 8.3.3. Routine Clinical Tests

The frequency and scope of routine clinical testing was appropriate in each of the trials reviewed. Routine clinical evaluation and laboratory testing occurred in pre-specified regular intervals in each of the relevant trials. Safety assessments primarily included clinical evaluation of AEs and other safety parameters including vital signs, physical examinations, 12-lead ECGs, standard laboratory safety tests, and HIV RNA and CD4 T cell counts at specified time points. Additional testing occurred as indicated or deemed clinical necessary by the investigator.

## 8.4. Safety Results

**Table 26** displays the incidence of adverse events (without regard to causality) reported in the pivotal Phase 3 (TMB-301) and supportive Phase 2b (TMB-202) trials. The majority of participants in TMB-301 (32, 80.0%), and both arms of TMB-202 (44, 81.5% receiving 2000mg IV q4 weeks and 50, 84.7% receiving 800mg q2 weeks) experienced at least one treatment-emergent adverse event in the 24 weeks that followed initiation of ibalizumab.

There were six deaths in these two trials (four in TMB-301 and two in the 800mg q2 week arm of TMB-202), none of which were deemed related to ibalizumab by the investigator. Nine TMB-301 participants and eleven TMB-202 participants (three receiving 2000mg IV q4 weeks and eight receiving 800 mg IV q2 weeks) experienced SAEs, one of which (progressive multifocal leukoencephalopathy- immune reconstitution inflammatory syndrome) was deemed related to ibalizumab. Six TMB-301 participants and twelve TMB-202 participants (nine receiving 2000mg IV q4 weeks and three receiving 800 mg IV q2 weeks) experienced severe AEs. Three of the TMB-301 participants experienced severe events considered to be related to ibalizumab. Five TMB-202 participants (three 2000mg IV q4 week and two 800mg IV q2 week) experienced severe events considered related to ibalizumab (Table 26).

**Table 26 Safety Overview: TMB-301 and TMB-202**

	<b>TMB-301 (Pivotal)</b>	<b>TMB-202 (Supportive)</b>	
	<b>2000 mg LD then 800mg IV q2 wks n=40</b>	<b>2000 mg IV q4 wks N=54</b>	<b>800 mg IV q2 wks N=59</b>
<b>Any TEAE</b>	32 (80.0%)	44 (81.5%)	50(84.7%)
<b>Any TEAE-Related</b>	7(17.5%)	23(42.6%)	21(35.6%)
<b>Mild AEs</b>	15(37.5%)	39(72.2%)	41(69.5%)
<b>Mild AEs-Related</b>	4(10.0%)	17(31.5%)	11(18.6%)
<b>Moderate AEs</b>	7(17.5%)	27(50.0%)	29(49.1%)
<b>Moderate AEs-Related</b>	0	12(22.2%)	10(16.7%)
<b>AEs Severe</b>	6(15.0%)	9(16.7%)	3(5.1%)
<b>AEs Severe -Related</b>	3(7.5)	3(5.6%)	2(3.4%)
<b>SAEs</b>	9 (22.5%)	3(5.6%)	8(13.6%)
<b>SAEs-Related</b>	1(2.5%)	0	0
<b>TEAEs leading to</b>	5(12.5%)	1(1.9%)	3(5.1%)
<b>Deaths</b>	4(10.0%)	0	2(3.3%)
<b>Deaths –Related</b>	0	0	0

TEAE: Treatment emergent adverse event (without regard to causality), SAE: Serious adverse event (without regard to causality). Mild AE: Grade 1. Moderate AE: Grade 2. Severe: Grade 3. Number and percentage of participants with at least one of the described events are shown.

Additional Support for Ibalizumab Safety

Safety results in the Phase 2a Trial TNX 355.03 were similar; at least one TEAE was experienced by 93% of participants in Ibalizumab arms A and B and by 89% of participants in the placebo arm (many of whom received open label Ibalizumab during the trial period). Three (3.7%) participants died (two in Arm A and one in Arm B). Fifteen (18.3%) TNX 355.03 participants experienced 28 non-fatal SAEs and six (7.3%) participants permanently discontinued Ibalizumab due to an AE.

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

The majority of participants in each of the TNX-355.02 arms also experienced TEAEs (9, 88.9% in 10mg/kg; 7, 70% in 10mg/kg + 6m/kg; and 3, 100% in 25mg/kg). Approximately half of the participant's events were attributed to study drug. No deaths occurred during the study.

Twenty of the 30 (66.7%) participants in Hu5A8.01 experienced a least one TEAE. Ten (33%) participants experienced AEs considered related to study drug. No participants experienced SAEs, AEs that led to death, or AEs that led to study drug discontinuation.

#### Expanded Access as Support for Longer-Term Ibalizumab Safety

The overall safety results for the expanded access trial TMB-311 were also similar to the results of TMB-301 and TMB-202; 37 (69.8%) participants experienced TEAEs and 6 (11.3%) experienced AEs related to study drug. Three deaths occurred, none of which was related to study drug. Nine (16.9%) participants experienced 16 SAEs, none of which was considered related to study drug. Three participants experienced AEs that led to ibalizumab discontinuation.

Twenty-two (34.3%) patients enrolled in investigator-sponsored INDs reported AEs. Seven deaths (10.9%) occurred and thirteen (20.2%) participants experienced non-fatal SAEs. One patient discontinued Ibalizumab because of an AE.

*Reviewer comment: The types, frequency, and severity of safety events observed in the Ibalizumab development program are not unexpected in a patient population with advanced AIDS.*

#### **8.4.1.Deaths**

A total of 18 deaths occurred in the ibalizumab development program, including eleven patients who received Ibalizumab through expanded access studies.

#### TMB-301

Four TMB-301 trial participants died during the study. None of the deaths were attributed to Ibalizumab. Narratives for each of these participants follow.

**301-01-001** was a 26 year-old white man who enrolled on the trial with a baseline CD4 T cell count of 2 cells/ $\mu$ l and an HIV RNA of 27,700 c/ml. His past medical history included PCP, recurrent oral thrush, progressive multifocal leukoencephalopathy (PML), and neutropenia. The participant experienced five SAEs including UTI (requiring hospitalization), septic shock, fever, and two Kaposi's sarcoma (KS) events. 301-01-001 died of respiratory arrest secondary to KS on Study day 156, after his final dose of Ibalizumab at week 23 but prior to the week 25 EOS visit.

**301-01-002** was a 44 year-old black man whose baseline CD4 T cell count was 1 cell/ $\mu$ l and HIV RNA was 217,700 c/ml. His past medical history included HCV with cirrhosis, idiopathic thrombocytopenic purpura, gastrointestinal bleeding, rectal hemorrhoids, cryptococcal

meningitis, subarachnoid hemorrhage, cerebrovascular accident, and KS. He experienced four SAEs including rectal hemorrhage, hepatic encephalopathy, liver masses, and liver failure. He was withdrawn from the trial on study day 146 and subsequently died of hepatic failure.

**301-02-002** was a 61 year-old white man whose baseline CD4 T cell count was 44 cells/ $\mu$ l and HIV RNA was 75,100 c/ml. His past medical history included chronic obstructive pulmonary disease, hypertension, and peripheral neuropathy. On study day 33, the participant was admitted for dehydration and acute renal insufficiency and work-up revealed a new diagnosis of lymphoma. He experienced two SAEs severe acidosis and severe hypoglycemia, which were attributed to tumor lysis syndrome and lymphoma. Critical care measures including inotropic support and chemotherapy were continued until he died (from lymphoma) on study day 39.

**301-18-002** was a 64 year old white woman with a baseline CD4 T cell count of 3 cells/ $\mu$ l and HIV RNA of 14,600 c/ml. She had a past medical history of hypertension, esophageal candidiasis, opioid dependence, and depression. The participant experienced symptoms consistent with failure-to-thrive as well as diarrhea, colitis, right lower lobe atelectasis, splenomegaly, and diffuse adenopathy. Two SAEs were reported, both as asthenia, on study days 60 and 66. The participant's family determined that a do not resuscitate (DNR) order would be appropriate and the participant died on Day 66.

*Reviewer comment: This likely represents a case of HIV wasting syndrome.*

#### TMB-202

Two TMB-202 trial participants died during the study. Neither death was considered related to Ibalizumab. The narratives for both cases follow.

**202-25-007** was a 54 year old black man with a baseline CD4 T cell count of 118 cells/ $\mu$ l and HIV RNA of 152,000 c/ml. His past medical history included AIDS, lower extremity edema, co-infection with HBV, and chronic smoking. He was randomized to ibalizumab 800 mg IV q2 weeks and his OBR included ETR, TPV, FTC, and FTC. His baseline GSS score was 1 and baseline OSS score was 2. The patient presented on study Day 122 with shortness of breath, which progressed to respiratory failure. The participant died on study day 153 of Acute Respiratory Distress Syndrome and cardiac arrest. The investigator did not attribute the participant's death to Ibalizumab.

**202-45-002** was a 55 year-old black man with a baseline CD4 T cell count of 19 cells/ $\mu$ l and HIV RNA of 23,400 c/ml. His past medical history included diabetes, neuropathy, and osteoporosis. He was randomized to receive ibalizumab 800 mg IV q2 weeks and his OBR included DRV/r, TDF, FTC, MVC, and RAL. His baseline GSS score was 0 and his OSS score was 1. At week 2, his HIV RNA was 148 c/ml and his CD4 T cell count rose to 88 cells/ $\mu$ l. By week 4, his HIV RNA was 868 c/ml. Although his CD4 T cell count peaked at 190 cells/ $\mu$ l and HIV RNA was 333 c/ml at week 8, this participant's HIV RNA rose to 3800 c/ml at week 12 and remained in that range for the remainder of the trial. On trial day 152, the participant was found

dead at his home. An autopsy was not performed and cause of death was listed as progression of AIDS. The investigator determined that the participant's death was not related to Ibalizumab.

#### Additional supportive studies

One TNX 355.03 participant died of myocardial infarction, considered unrelated to Ibalizumab. No deaths occurred in study TNX 355.02 or Hu5A8.01.

#### Expanded access studies

A total of eleven patients who received Ibalizumab through expanded access studies died.

Three TMB-311 participants have died; 311-03-051 died of metastatic tonsil cancer (head and neck cancer), 311-19-003 died of sepsis, and 311-23-051 died from trauma after a fall. None of the deaths were deemed related to ibalizumab.

Eight patients receiving ibalizumab through investigator-sponsored INDs died. None of the deaths were considered related to ibalizumab. The causes of death were as follows:

- HIV disease progression
- Aortic aneurysm and abdominal lymphoma
- Unspecified (2 patients)
- Chronic obstructive pulmonary disease (COPD)
- Mass in cecum, post-operative pneumonia, abdominal abscess, sepsis, septic shock, acute respiratory failure, acute renal failure, and Kaposi's sarcoma
- Non-Hodgkins Lymphoma, Pyrexia, adrenal insufficiency, tachycardia, and hypotension.

*Reviewer comment: Analysis of deaths throughout the ibalizumab development program reveals no pattern of fatal AEs related to ibalizumab. None of these deaths stands out as unusual given the mortality associated with advanced HIV infection and MDR HIV. The high proportion of deaths that occurred in the expanded access portion of the program likely reflects a sicker patient population and a longer duration of follow-up.*

#### **8.4.2.Serious Adverse Events**

Nine TMB-301 participants experienced 16 SAEs, including ten SAEs that were reported in participants who died. The six SAEs experienced by participants who survived included: diplopia, pulmonary hypertension, progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome, cytomegalovirus (CMV) viremia, fever, and squamous cell carcinoma of the anus and rectum. The only event considered to be related to ibalizumab was immune reconstitution inflammatory syndrome.

*Reviewer comment: The TMB-301 database included 22 SAE events, however, six of those persistent events were repeated twice for the same participant (Kaposi Sarcoma, asthenia, and lymphoma) or are entered using two different AE terms describing the same event on the same*

*day (liver masses and liver failure, progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome, and squamous cell carcinoma of the anus and squamous cell carcinoma of the rectum). Therefore, this summary includes 16 events.*

Eleven TMB-202 participants experienced thirteen SAEs. Three participants receiving the 2000 mg IV q4 week dose of ibalizumab experienced four events including amnesia, CMV viremia (two), and toxoplasmosis. Eight participants receiving the 800mg IV q2 week dose of ibalizumab experienced nine SAEs including two events (AIDS, ARDS) that occurred in participants who died, as described in **Section 8.4.1 Deaths**. The remaining SAEs include paresthesia, anemia, chronic obstructive pulmonary disease, parotid abscess, acute renal failure, gastroenteritis, and traffic accident. None of these SAEs were considered related to ibalizumab.

#### Additional supportive studies

Eleven TNX 355.03 participants experienced 15 non-fatal SAEs, which included bradycardia, coronary artery disease, angina pectoris, myocardial infarction, abdominal pain, rectal hemorrhage, pyrexia, hepatic failure, rhabdomyolysis, rectal cancer, hepatic encephalopathy, depression, acute renal failure, maculopapular rash, and hypotension. No two participants experienced the same SAE. None of the SAEs was considered related to ibalizumab although one event (lower abdominal pain) was considered clinical intolerance to OBR. One SAE (rash) led to permanent discontinuation of ibalizumab and will be discussed in Section 8.4.3.

On study TNX 355.02, three SAEs occurred including renal failure, depression, and grand mal convulsion, none of which was considered related to study drug. Participant 208-04 developed lightheadedness, dizziness, and sweating during phlebotomy prior to the second planned infusion of study drug. The participant then experienced 1-2 minutes of limb jerking without loss of consciousness. Neurologic work-up was negative and the investigator reported the event as new-onset grand-mal seizure secondary to vasovagal reaction, possibly related to study drug. Eighteen months later the investigator determined that the event was actually a vasovagal reaction unrelated to study drug. Participant 105-04, who had a history of depression, bipolar disorder, and substance abuse disorder presented to an ER on study Day 22 (one day after the third study drug infusion) with suicidal ideation and depression. These symptoms prompted a psychiatric admission and the event was attributed to prescription opioid abuse, unrelated to study drug. Participant 103.04, who had a complicated medical history that included hyponatremia, proteinuria, irritable bowel syndrome, and wasting syndrome, was admitted for acute renal failure and vomiting 38 days after his 9<sup>th</sup> and final dose of study drug. The event was attributed to the concomitant use of a diuretic and non-steroidal anti-inflammatory drug.

No SAEs were reported occurred in study Hu5A8.01.

#### Expanded access studies

Nine of 53 TMB-311 participants had experienced 16 non-fatal SAEs at the time of data cutoff. No two participants experienced the same or similar SAE. The SAEs, none of which were

deemed related to ibalizumab, included the following events:

- Renal failure, acute dehydration, blood potassium decreased, hypokalemia
- Cellulitis
- Tonsil cancer (head and neck cancer)
- Deep vein thrombosis
- Lactic acidosis
- Diarrhea and sepsis
- Pyrexia, anal squamous cell carcinoma, rectal cancer
- Pneumonia
- Multiple fractures and injury (trauma from fall)

In addition to the events above, TaiMed reported a Cryptococcal IRIS event via MedWatch in July 2017 (after the data-cutoff). The IRIS event was deemed related to ibalizumab.

*Reviewer comment: The case described in the MedWatch Report is consistent with IRIS. As is described above, a TMB-301 participant developed PML-IRIS. IRIS is a known complication of antiretroviral therapy and will be included in the label.*

Seven patients receiving ibalizumab through investigator-sponsored INDs experienced non-fatal SAEs. The SAEs, none of which was related to the study drug, included were as follows:

- Ileus (bowel obstruction)
- Dehydration, electrolyte imbalance, and bronchitis.
- Giardiasis
- Viral febrile illness
- Invasive squamous cell carcinoma
- Gastroenteritis, myocardial infarction, chest pain, and deep vein thrombosis
- Cerebrovascular accident

*Reviewer comment: The pattern of SAEs reported in the ibalizumab development program are consistent with the events one would expect in a predominately male, middle-aged population of patients with advanced AIDS and MDR HIV. One SAE, immune reconstitution inflammatory syndrome (IRIS) was deemed to be related to ibalizumab. IRIS is a common event following the initiation of effective ART in severely immunosuppressed patients, therefore it is reasonable to assume that this event is related to ibalizumab.*

#### **8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects**

Four TMB-301 participants stopped study drug due to an AE, including three participants who died (described in Section 8.4.1, Deaths). The only AE considered to be related to ibalizumab was Immune Reconstitution Inflammatory Syndrome (described in Section 8.4.2, Severe Adverse Events).

Two TMB-202 participants discontinued ibalizumab due to non-serious AEs deemed to be

related to ibalizumab.

202-13-003 was a 60 year old black woman who was treated for HIV with abacavir, etravirine, lamivudine, and ritonavir-boosted darunavir since the year prior to study screening. She was not eligible for the trial because her HIV RNA was below 1000 copies/ml at screening (HIV RNA 56 copies/ml) and on Day 1 (HIV RNA 74 copies/ml). Because of investigator error, she was enrolled on the trial and started ibalizumab 800 mg IV on Day 1. She continued on her “failing” regimen as her OBR. On Day 2 or 3, she developed allergic rhinitis, vomiting, myalgia, headache, diarrhea, cough, and chills which were all deemed to be moderate (Grade 2) in severity and probably related to ibalizumab by the investigator. She was prescribed acetaminophen as needed for each of these symptoms and these symptoms resolved completely by Day 16. She received her second dose of ibalizumab on Day 22. Her second dose of study drug was reported as a partial dose; however the investigator did not provide any reason for this partial dose and did not report any AEs or other findings that occurred during the infusion. Vital signs were significant for hypertension prior to and after infusion (152/90 mmHg before and 170/94 after). Other vital signs including temperature, heart rate, and respiratory rate were within normal limits and essentially unchanged before and after drug infusion. On the same day as the infusion, the investigator reported “severe allergic reaction”, which was mapped to PT code “hypersensitivity” by the applicant. Oral Benadryl was prescribed the event was reported as resolved two days later. Anti-drug antibodies were tested and negative at baseline, but not repeated at the time of the event. Her peripheral blood eosinophil count and percent were within normal limits and essentially unchanged on the day of the hypersensitivity event. Her CD4 T cell count was also essentially unchanged during her trial participation [Day -27 (330 cells/ $\mu$ L) Day 1 (417 cells/ $\mu$ L) and Day 22 (327 cells/ $\mu$ L)]. TaiMed was unable to obtain further clarifying information from the investigator at the time of the event or during the BLA review process.

*Reviewer comment: For any drug, and especially a monoclonal antibody targeting a human epitope, hypersensitivity is a potential risk. Because of the importance of this risk, it is particularly unfortunate that the information provided for this case is limited and perplexing.*

*First, it is unclear why this participant was included in the trial and given two doses of ibalizumab after not meeting the key inclusion criteria of failing her current regimen. In addition to having HIV RNA less than 100 copies/ml during the screening and enrollment period, the participant had GSS and PSS scores of 4 and 4, corroborating the conclusion that the participant was not taking a “failing” regimen at study entry.*

*Secondly, there seems to be confusion about why the participant stopped ibalizumab and the study. The investigator reported that the participant was removed from study by the physician because the participant was “non-complaint and had a reaction to the medication”. The applicant concludes that the participant was removed because she was not eligible for the trial. Because of the timing of events and because supportive details to the contrary were not presented, I am considering this event as one which led to treatment discontinuation.*

*Lastly and most importantly, the information provided in the applicant’s narrative (including a*

*more detailed narrative prompted by an information request) and in the datasets is not consistent with a hypersensitivity reaction or more broadly, a drug allergy.*

- *The events described and documentation of vital signs provide no evidence of anaphylaxis, angioedema, bronchospasm, urticaria, or hypotension, which would suggest a Type I, immediate, IgE-mediated hypersensitivity reaction.*
- *Unfortunately, ADA testing was not performed after ibalizumab administration. ADA testing would have been a reasonable diagnostic step in determining whether the participant experienced an antibody-dependent, Type II allergic reaction. The results of the complete blood count, however, are normal; there is no evidence of hemolytic anemia, thrombocytopenia, or neutropenia that would suggest an antibody dependent Type II drug allergy.*
- *The timing and description of events are unlikely to represent a Type III drug allergy such as serum sickness or arthus reaction.*
- *The symptoms reported are not consistent with a Type IV allergic reactions (delayed hypersensitivity reaction), which might manifest as morbilliform rash, Stevens-Johnson syndrome, or DRESS syndrome (rash, eosinophilia, lymphadenopathy, and end-organ involvement).*

*In conclusion, this series of events that led to treatment discontinuation is not consistent with hypersensitivity reaction or allergic reaction. Although the events may represent drug intolerance, the limited and inconsistent information provided about the case make it challenging to provide any useful information to potential prescribers as a result of the events.*

202-25-001 was a 41 year-old white man who started 2000mg IV q4 weeks of ibalizumab with an OBR consisting of maraviroc, etravirine, tenofovir, and emtricitabine. Five days after his first dose of ibalizumab, he developed a moderate (Grade 2) maculopapular rash without concomitant AEs. The investigator determined that the rash was unrelated to study drug. He was prescribed antihistamines and corticosteroids and the rash resolved by Day 25. On Day 30, the participant received a second dose of ibalizumab. The following day he developed another moderate rash, prompting permanent discontinuation of the study drug. The second rash, which resolved by day 65, was deemed related to ibalizumab.

*Reviewer comment: This case likely represents a moderate rash related to Ibalizumab. Please see section 8.5.2 for a review of all rash events that occurred in the Ibalizumab development program.*

#### Additional supportive studies

A total of six TNX 355.03 participants discontinued study drug due to AE. Among participants receiving 15 mg/kg, one stopped because of allergic dermatitis definitely related to ibalizumab, one stopped because of petechiae and pruritus possibly related to ibalizumab, and another stopped because of hepatic failure, unrelated to ibalizumab. One TNX 355.03 participant, who was receiving the 10mg/kg dose, discontinued ibalizumab due to a Grade 3 maculopapular rash. Of the two participants randomized to the placebo arm, one discontinued study drug due to rectal

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

hemorrhage and the other discontinued due to depression.

Two TNX 355.02 participants discontinued ibalizumab due to AE; grand mal convulsion unrelated to ibalizumab (described in Section 8.4.2) and one due to drug abuse, also unrelated to ibalizumab.

No Hu5A8.01 participants discontinued ibalizumab due to AE.

#### Expanded access studies

In TMB-311, one participant, who had previously been enrolled in TMB-202, permanently discontinued ibalizumab due to pyrexia and drug eruption, both considered possibly related to ibalizumab. Both symptoms resolved.

One patient who received ibalizumab through an investigator-sponsored IND discontinued study drug because of non-Hodgkins lymphoma (described in Section 8.4.2, Serious Adverse Events).

*Reviewer Comment: Review of AEs leading to permanent ibalizumab discontinuation in the drug's development program reveals five participants who discontinued ibalizumab due to moderate rash related to ibalizumab. A detailed review of all rash events will be described in **Section 8.5.1 Analysis of Submission-Specific Safety Issues**. The information provided for the TMB-202 case reported as hypersensitivity, is not consistent with a drug allergy, although some of the individual AEs reported in this case may potentially be related to ibalizumab. Infusion Reactions and Drug Allergy will be also be addressed **Section 8.5.1 Analysis of Submission-Specific Safety Issues**. IRIS, as described in Section 8.4.2 (Serious Adverse Events) is a known and expected adverse reaction to ART in patients with advanced HIV.*

#### **8.4.4. Significant Adverse Events**

This section summarizes severe (Grade 3) that were not discussed in the sections described in the sections on deaths, SAEs, and AEs leading to discontinuations. Refer to section 8.3.2 Categorization of Adverse Events for the applicant's definition of mild, moderate, and severe AEs.

Nine (22%) TMB-301 participants experienced 17 Grade 3 events. Two of the participants who died (301-01-001 and 301-01-002) experienced seven of these events, which are discussed in Section 8.4.1 (Deaths). Six of the events (IRIS and PML, diplopia, pulmonary hypertension, pyrexia, CMV viremia), which occurred in five participants, were considered non-fatal SAEs and are described in Section 8.4.2 (SAEs). The participant who experienced IRIS and PML also experienced Grade 3 hemiplegia. IRIS, as described above in Sections 8.4.2 (SAEs) and 8.4.3. (AEs leading to discontinuation), was considered related to ibalizumab. The remaining Grade 3 events are described below.

301-02-001 was a 52 year old white man with a history of HIV and diffuse large B-cell

lymphoma with a baseline HIV RNA of 70,300 copies/ml and CD4 T cell count of 77 cells/ $\mu$ L. His HIV RNA was 20,000 copies on Day 14, 1100 by Day 21 and below 100 copies/ml between week 9 and the end-of-study. He experienced eight rash events over the course of the trial beginning on study day 13. These events included two moderate rashes possibly related to ibalizumab and one severe rash deemed probably related to ibalizumab by the investigator. The events were described as either maculopapular, macular, or generalized. The participant was taking a long list of concomitant medications during the studies including bactrim, azithromycin, cyclosporine, omeprazole and numerous herbal extracts and supplements as well as his OBR, which included DTG, FTC, TDF, and fostemsavir. Other AEs included neutropenia, intermittent diarrhea, pruritus, pyrexia, and pain in the extremity. Ibalizumab was continued. The rash was ongoing and classified as moderate in severity at the end of study.

301-05-005 was a 65 year old white man with HIV/AIDS, liver cirrhosis, thrombocytopenia, Type 2 Diabetes, and hypertension. On Day 10, he developed severe fatigue, which was considered possibly related to ibalizumab, and moderate gastroenteritis, unrelated to ibalizumab. He was diagnosed with presumed pneumonia (moderate, unrelated) on Day 15 for which he was prescribed Azithromycin. By Day 18, the severity of the fatigue improved to moderate. The fatigue resolved on Day 92.

Nine (8%) TMB-202 participants experienced 13 Grade 3 events that were not previously discussed. Six of these events (all unrelated) were elevations in laboratory results (three liver-associated tests, one amylase, one uric acid, and one glucose) and will be discussed in **Section 8.3.6 Laboratory Findings**. The remaining events included CMV infection, fever, oral candidiasis, weight loss, cellulitis, esophagitis, and fatigue. None of the events led to discontinuation of ibalizumab. Only CMV and esophagitis were deemed unrelated to ibalizumab. CMV, esophagitis, and fatigue were ongoing at the end of study but the remaining events were resolved.

#### Additional supportive studies

Sixteen (20%) TNX 355.03 participants experienced severe AEs not previously described, including five (18%) participants in the 15 mg/kg arm, six (22%) participants in the 10 mg/kg, and five (19%) participants in the placebo arm. None of the severe events in the 15mg/kg arm were considered related to ibalizumab, two of the events in the 10 mg/kg arm were deemed related, and four events in the placebo arm were deemed potentially related to treatment. The severe events are listed below by treatment arm.

- 15 mg/kg arm: hepatic failure, hyperglycemia, and neutropenia (two participants). In addition, one participant experienced the following severe AEs; liver disorder, hepatic encephalopathy, mental status changes, increased ammonia, malnutrition, and alkaline phosphatase increased.
- 10 mg/kg arm: rash, elevated lipase, elevated triglyceridemia, and depression. In addition, one participant experienced intestinal obstruction and two episodes of severe fatigue, one of which was deemed related to ibalizumab.

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

One TNX 355.02 participants experienced a severe AE not previously described; a participant receiving 10mg/kg + 6 mg/kg experienced a severe headache, which was deemed possibly related to ibalizumab. Ibalizumab was continued. The headache resolved.

One Hu5A8.01 participant experienced a severe AE; a participant receiving 1 mg/kg experienced aggravated hypertension.

*Reviewer Comment: Review of severe AEs reveals no pattern of safety events not already identified.*

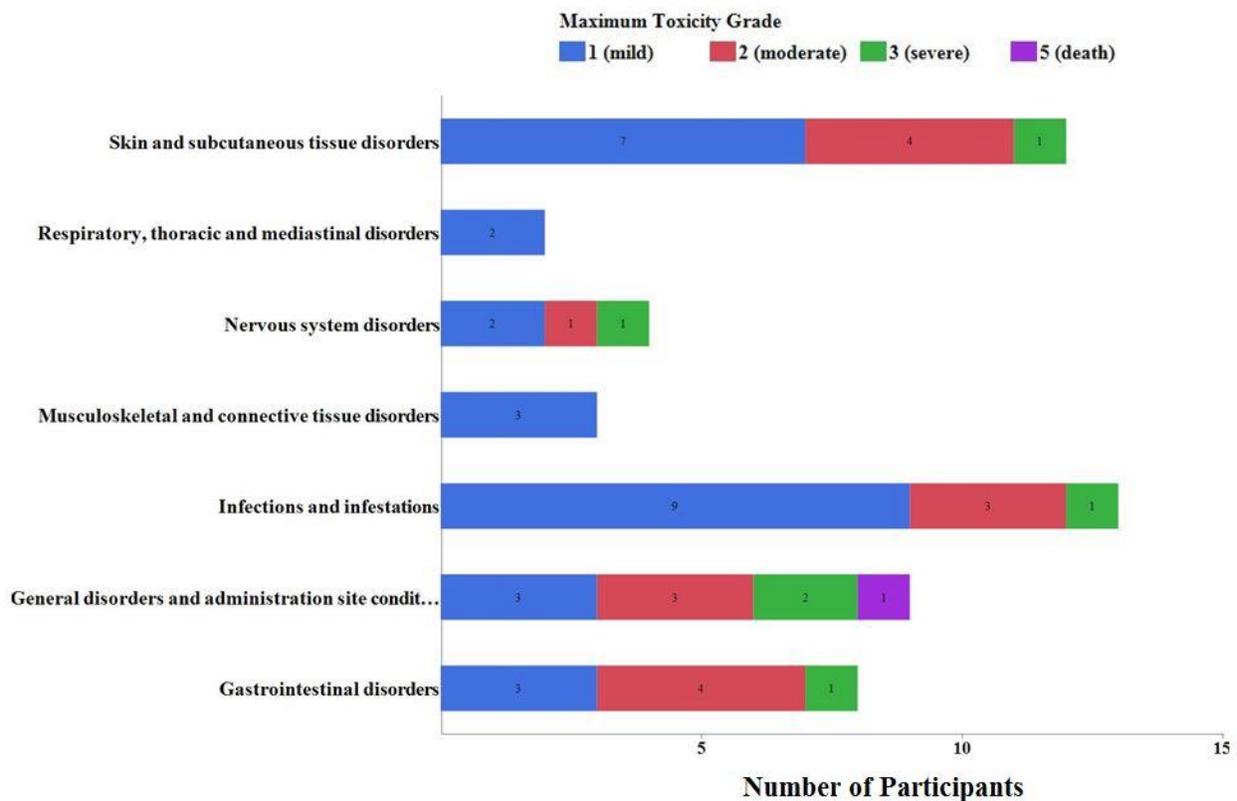
#### **8.4.5. Treatment Emergent Adverse Events and Adverse Reactions**

##### **TMB-301**

The following treatment-emergent adverse events (TEAEs) occurred in two (5%) or more TMB-301 participants; rash, diarrhea, nausea, vomiting, gastroenteritis, decreased appetite, pyrexia, fatigue, headache, dizziness, and peripheral edema. The system organ classes represented by events occurring in two or more (5%) TMB-301 participants include; skin and subcutaneous tissue disorders (12 events), respiratory, thoracic, and mediastinal disorders (2 events), nervous system disorders (4 events), musculoskeletal and connective tissue disorders (3 events), infections and infestations (13 events), general disorders and administration site conditions (9 events), and gastrointestinal disorders (8 events).

**Figure 6 TEAEs occurring in ≥5% (two or more) TMB-301 participants by system organ class (SOC).**

Horizontal bars represent the number of participants experiencing an event in that SOC. The color of the bar indicates the maximum AE severity experienced by each participant (blue = mild, red = moderate, green = severe, purple = death). The number inside each colored section represents the number of participants who experienced an AE of the indicated maximum severity.



Five TMB-301 participants experienced a total of 12 skin and subcutaneous tissue disorder events. These events will be described in detail in Section 8.5.1. Analysis of Submission-Specific Safety Issues: Rash.

Five participants experienced TEAEs in the respiratory, thoracic, and mediastinal disorders SOC. These events include mild cough (two events), mild productive cough, mild dyspnea, and, as described in Section 8.4.2 Severe Adverse Events, pulmonary hypertension. Dyspnea was the only event in this SOC deemed related to ibalizumab.

Nine participants experienced 12 TEAEs in the nervous system disorders SOC. Seven of these events [headache (2 events), convulsion, hemiplegia, motor neuron disease, dizziness, and hepatic encephalopathy)] are described in four narratives found in **Section 8.4.2 Severe Adverse**

**Events** and one narrative in **Section 8.4.1 Deaths**. The remaining events included mild dizziness (4 events) and mild headache (one event) and were deemed related to ibalizumab.

Eight TMB-301 participants experienced various mild or moderate musculoskeletal and connective tissue disorders TEAEs including back pain (two events), groin pain (one event), joint swelling (one event), musculoskeletal pain (one event), myalgia (one event), neck pain (one event), osteoarthritis (one event), and pain in extremity (one event). Only two of those events (back pain and myalgia), which occurred in one participant, were deemed related to ibalizumab.

Thirty infection and infestation SOC TEAEs occurred in 18 TMB-301 participants. Four of these events (septic shock, PML, UTI, and CMV viremia) were severe or life-threatening are described in **Section 8.4.2 (Serious Adverse Events)**. The remaining events were mild or moderate in severity. The most common events in this SOC were nasopharyngitis, URI, and oral candidiasis. None of these events were deemed related to ibalizumab.

Thirty-seven Gastrointestinal SOC TEAEs occurred in 16 TMB-301 participants. One event was severe and the remaining events were mild or moderate. No participants discontinued ibalizumab due to GI events. The most common GI AEs were diarrhea (15 events occurring in eight participants), nausea (6 events), vomiting (4 events), and abdominal pain (3 events). The following GI events were deemed related to ibalizumab; nausea (two mild events), vomiting (one mild event), and diarrhea (one mild event, three moderate events).

Fourteen TMB-301 participants experienced 20 TEAEs in the General disorders and administrative site conditions. One Grade 5 event (asthenia) is described in **Section 8.4.1 Deaths**. Four other severe events in this SOC were reported: fatigue, generalized edema, peripheral edema, and pyrexia. The remaining events were mild and moderate. The most common events in this SOC were pyrexia, fatigue, and asthenia. Only two events; mild asthenia and severe fatigue were deemed related to ibalizumab.

The following TEAEs occurring in two or more participants were deemed possibly, probably, or definitely related to ibalizumab: diarrhea, nausea, dizziness, and rash. **Table 27** includes all TMB-301 adverse reactions (i.e., adverse events judged related to ibalizumab per investigator).

**Table 27 Adverse Reactions occurring in one or more participants in TMB-301**

Adverse Reactions	Number of Participants (%)
Diarrhea	3 (8%)
Dizziness	3 (8%)
Nausea	2 (5%)
Rash	2 (5%)
Asthenia	1 (3%)
Back pain	1 (3%)
Decreased appetite	1 (3%)
Dry skin	1 (3%)
Dyspnea	1 (3%)
Fatigue	1 (3%)
Feeling of despair	1 (3%)
Headache	1 (3%)
Hemiplegia	1 (3%)
Lymphadenopathy	1 (3%)
Myalgia	1 (3%)
Night sweats	1 (3%)
Papule	1 (3%)
Pruritus	1 (3%)

*Reviewer Comment: Review of TMB-301 TEAEs and adverse reactions (ARs) by frequency demonstrate that the most common events related to ibalizumab were rash, nausea, diarrhea, and dizziness. Refer to Section 8.4.2 for further details about rash events.*

**TMB-202**

The distribution of TEAEs in TMB-202 was similar to that of TMB-301. TEAEs occurring in  $\geq 5\%$  participants were in the following SOCs; skin and subcutaneous tissue disorders (28 events in 11% participants), respiratory, thoracic, and mediastinal disorders (24 events, 20% of participants), nervous system disorders (4 events, 4% of participants), infections and infestations (80 events in 45% of participants), general disorders and administration site conditions (34 events in 21%), and gastrointestinal disorders (53 events in 30% participants). The following TEAEs occurred in six (5%) or more TMB-202 participants; rash, diarrhea, nausea, vomiting, fatigue, headache, upper respiratory infection (URI), and nasopharyngitis.

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

The following TEAEs were deemed related to ibalizumab and occurred in three (2%) or more participants; rash, diarrhea, nausea, vomiting, fatigue, headache, dizziness, and fever.

*Reviewer Comment: Review of TMB-202 TEAEs and ARs by frequency reveals a pattern of AEs consistent with those seen in TMB-301.*

#### Additional supportive studies

The most frequently reported TEAEs in TNX 355.03 were rash, diarrhea, nausea, vomiting, abdominal pain, fatigue, pyrexia, headache, bronchitis, URI, candidiasis, and sinusitis. The following ARs occurred in two or more participants (>7%) in any treatment arm; rash, abdominal pain, constipation, flatulence, nausea, cellulitis, elevated triglycerides, somnolence, and abnormal dreams.

The following TEAEs were reported in at least two participants in a TNX 355.02 treatment group; headache, nausea, and cough. The following ARs were reported in at least two participants overall: headache and mouth ulceration.

The following TEAEs were reported in 3 or more Hu5A8.01 participants (>10%); headache and rash. The most common AR was headache. ARs of the skin and subcutaneous tissue system organ class were also common including pruritus, rash, and urticaria.

*Reviewer Comment: The TEAEs and ARs seen in the Phase 1a, 1b, and Phase 2a trials are consistent with those seen in TMB-301.*

#### **8.4.6.Laboratory Findings**

This section provides general summaries of graded laboratory abnormalities observed in trials TMB-301 and TMB-202 followed by descriptions of severe (Grade 3 and 4) and frequent abnormalities, regardless of grade, by laboratory category. Laboratory evaluations were assigned grades according to the Division of Acquired Immune Deficiency Syndrome (AIDS) Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Grade 0, 1, 2, 3, 4) as specified in the trial protocol.

*Reviewer comment: Although the TMB-301 and TMB-202 protocols specified that serum creatinine, urine protein, and urine glucose would be collected and reported, results from these three laboratory tests were omitted from the datasets and were not summarized in TaiMed's summaries of clinical safety. These results have been requested from TaiMed but have not yet been received at the time of this review. An addendum to the clinical review will provide the reviewer's analysis of those data, once received.*

All reported graded laboratory abnormalities that increased in grade from baseline in TMB-301 are presented in **Table 28**, by maximum grade. Thirty-five (88%) TMB-301 participants

experienced at least one Grade 1-4 laboratory abnormality that increased in grade from baseline. Fourteen (35%) and thirteen (33%) of participants experienced laboratory abnormalities with maximum of Grade 1 and 2, respectively. Only eight (20%) participants experienced laboratory abnormalities that were Grade 3 or higher. Specific abnormalities, including all Grade 3 or higher abnormalities, will be discussed in the sections following the summary tables.

All reported graded laboratory abnormalities that occurred within the first 168 days (24 weeks) and increased in grade from baseline in TMB-202 are presented in **Table 28**, by maximum grade. Fifty-eight (51%) TMB-202 participants experienced at least one Grade 1-4 laboratory abnormality consisting of an elevation above baseline. Among these, only twelve (11%) participants experienced Grade 2 or higher and only five experienced Grade 3 or higher laboratory changes. No participants experienced a Grade 4 laboratory abnormality consisting of an elevation above baseline. Seventy-one (63%) TMB-202 participants experienced at least one Grade 1-4 laboratory abnormality consisting of a decrease from baseline. Among these participants, 51 participants experienced Grade 2 or higher abnormalities, 29 experienced Grade 3 or higher abnormalities, and eight experienced Grade 4 or higher abnormalities. Specific abnormalities, including all Grade 3 or higher abnormalities, will be discussed in the sections following **Table 28**.

**Table 28 TMB-301 and TMB-202 Laboratory Abnormalities \***

Parameter	Toxicity Grade	Result Range	TMB-301	TMB-202	
			Ibalizumab 2000 mg x1 then 800mg Q2W N=40	Ibalizumab 2000 mg Q4W N=54	Ibalizumab 800 mg Q2W N=59
Alanine Aminotransferase, U/L (ALT/SGPT)	1	1.25 to 2.50 x ULN	8 (20%)	4 (8%)	6 (10%)
	2	>2.50 to 5.0 x ULN	2 (5%)	6 (11%)	6 (10%)
	3	>5.00 to 10.00 x ULN	0	1 (2%)	0
	4	>10.00 x ULN	0	1 (2%)	1 (2%)
Aspartate Aminotransferase, U/L (AST/SGOT)	1	1.25 to 2.50 x ULN	8 (20%)	4 (8%)	9 (15%)
	2	>2.50 to 5.00 >ULN	2 (5%)	3 (6%)	1 (2%)
	3	<5.00 to 10.00 x ULN	0	1 (2%)	0
	4	>10.00 x ULN	0	0	1 (2%)
Bilirubin (umol/L)	1	1.1 to 1.5 xULN	1 (3%)	2 (4%)	3(5%)
	2	≥1.6 to 2.5 ULN	2 (5%)	1 (2%)	1 (2%)
	3	≥ 2.6 to 4.9 x ULN	1 (3%)	0	0
	4	≥ 5.0 x ULN	1 (3%)	0	0

Clinical Review  
 Virginia Sheikh, MD  
 Biologic Licensing Application 761065  
 Ibalizumab/TROGARZO

Parameter	Toxicity Grade	Result Range	TMB-301	TMB-202	
			Ibalizumab 2000 mg x1 then 800mg Q2W N=40	Ibalizumab 2000 mg Q4W N=54	Ibalizumab 800 mg Q2W N=59
Direct Bilirubin (umol/L)	1	NA	NA	NA	NA
	2	NA	NA	NA	NA
	3	> ULN	1 (3%)	2 (4%)	1 (2%)
	4	> ULN with life	0	0	0
Albumin	1	3.0 g/dL to <LLN	1 (3%)	0	1 (2%)
	2	≥2.0 to 3.0 g/dL	1 (3%)	2 (4%)	4 (7%)
	3	< 2.0	0	0	0
	4	NA	0	0	0
Alkaline Phosphatase, U/L	1	1.25 to < 2.5 x ULN	1 (3%)	5 (9%)	8 (14%)
	2	≥2.5 to <5.0 xULN	1 (3%)	0	1 (2%)
	3	≥5.0 to <10.0 x ULN	0	0	1 (2%)
	4	≥10.00 x ULN	0	0	0
Amylase	1	≥1.1 to <1.5 x ULN	1 (3%)	5 (9%)	1 (2%)
	2	≥ 1.5 to <3.0 x ULN	2(5%)	2 (4%)	3 (5%)
	3	≥ 3.0 to <5.0 x ULN	0	0	0
	4	≥ 5.0 x ULN	0	0	1(2%)
Lipase	1	1.0 to 1.5 x ULN	2 (5%)	8(15%)	4 (7%)
	2	>1.5 to 3.0 x ULN	1 (3%)	3 (6%)	9(15%)
	3	>3.0 to 5.0 x ULN	2 (5%)	1 (2%)	0
	4	> 5.0 x ULN	0	1 (2%)	0
Hemoglobin (Anemia)	1	9.5 to 10.4 g/dL	1 (3%)	0	5 (9 %)
	2	8.5 to <9.5 g/dL	3 (8%)	2 (4%)	2 (3%)
	3	6.5 to <8.5 g/dL	1(3%)	1(2%)	3 (5%)
	4	<6.5 g/dL	0	0	2 (3%)
Platelets	1	100,000 to < 124,999 cells/ mm <sup>3</sup>	1(3%)	1 (2%)	1 (2%)

Clinical Review  
 Virginia Sheikh, MD  
 Biologic Licensing Application 761065  
 Ibalizumab/TROGARZO

Parameter	Toxicity Grade	Result Range	TMB-301	TMB-202	
			Ibalizumab 2000 mg x1 then 800mg Q2W N=40	Ibalizumab 2000 mg Q4W N=54	Ibalizumab 800 mg Q2W N=59
<b>(Thrombocytopenia)</b>	2	50,000 to < 100,000 cells/ mm <sup>3</sup>	1(3%)	0	0
	3	25,000 to < 50,000 cells/ mm <sup>3</sup>	1(3%)	0	0
	4	<25,000 cells/ mm <sup>3</sup>	0	0	0
<b>Leukocytes (Leukopenia)</b>	1	2000 to 2499 cells/ mm <sup>3</sup>	3(8%)	1 (2%)	1 (2%)
	2	1500 to 1999 cells/ mm <sup>3</sup>	1 (3%)	1 (2%)	0
	3	1000 to 1499 cells/ mm <sup>3</sup>	0	0	0
	4	<1000 cells/ mm <sup>3</sup>	2 (5%)	0	0
<b>Neutrophils (Neutropenia)</b>	1	800 to 1000 cells/ mm <sup>3</sup>	3 (8%)	1 (2%)	0
	2	600 to 799 cells/ mm <sup>3</sup>	1 (3%)	0	0
	3	400 to 599 cells / mm <sup>3</sup>	0	0	0
	4	<400 cells / mm <sup>3</sup>	2 (5%)	1 (2%)	0
<b>Sodium (Hyponatremia)</b>	1	130 to 135 mEq/L	15 (38%)	15(28%)	12 (20%)
	2	125 to 130 mEq/L	2 (5.0)	1 (2%)	3 (5%)
	3	121 to 125 mEq/L	0	0	1 (2%)
	4	≤120 mEq/L	0	0	0
<b>Sodium (Hypernatremia)</b>	1	146 to 150 mEq/L	0	2(4%)	2(4%)
	2	150 to 154 mEq/L	0	0	0
	3	154 to <160 mEq/L	0	0	0
	4	≥160 mEq/L	0	0	0
<b>Glucose (Hyperglycemia, non-fasting)</b>	1	116 to 160 mg/dL	14(35%)	9 (17%)	7 (12%)
	2	>160 to 250 mg/dL	6(15%)	3 (6%)	4 (7%)
	3	>250 to 500 mg/dL	1(3%)	0	1 (2%)
	4	>500 mg/dL	0	0	0

Clinical Review  
 Virginia Sheikh, MD  
 Biologic Licensing Application 761065  
 Ibalizumab/TROGARZO

Parameter	Toxicity Grade	Result Range	TMB-301	TMB-202	
			Ibalizumab 2000 mg x1 then 800mg Q2W N=40	Ibalizumab 2000 mg Q4W N=54	Ibalizumab 800 mg Q2W N=59
<b>Glucose (Hypoglycemia)</b>	1	55 to 64 mg/dL	0	0	2 (3%)
	2	40 to <55 mg/dL	2(5%)	0	0
	3	30 to <40 mg/dL	0	0	0
	4	<30 mg/dL	0	0	0
<b>Calcium (Hypocalcemia)</b>	1	7.8 to <8.4 mg/dL	2(5%)	4 (8%)	6 (10%)
	2	7.0 to <7.8 mg/dL	1(3%)	1 (2%)	4 (7%)
	3	6.1 to <7.0 mg/dL	0	1 (2%)	0
	4	<6.1 mg/dL	0	0	1 (2%)
<b>Calcium (Hypercalcemia)</b>	1	10.6 to <11.5 mg/dL	2 (5%)	0	1 (2%)
	2	11.5 to <12.5mg/dL	1(1%)	0	1 (2%)
	3	12.5 to <13.5 mg/dL	0	1 (2%)	0
	4	≥13.5 mg/dL	0	0	0
<b>Potassium (Hypokalemia)</b>	1	3.0 to <3.4 mmol/L	7 (18%)	7 (13%)	2 (3%)
	2	2.5 to <3.0 mmol/L	0	1 (2%)	1 (2%)
	3	2.0 to <2.5 mmol/L	0	0	0
	4	<2.0 mmol/L	0	0	0
<b>Potassium (Hyperkalemia)</b>	1	5.6 to 6.0 mEq/L	1 (3%)	5(9%)	0
	2	6.0 to <6.5 mEq/L	0	0	2 (3%)
	3	6.5 to <7.0 mEq/L	0	0	0
	4	≥7.0 mEq/L	0	0	0
<b>Magnesium (Hypomagnesemia)</b>	1	1.2 to 1.4 mEq/L	2(5%)	1 (2%)	1 (2%)
	2	0.9 to <1.2 mEq/L	1(3%)	0	1 (2%)
	3	0.6 to <0.9 mEq/L	0	1 (2%)	1 (2%)
	4	<0.6 mEq/L	0	0	0
<b>Phosphate, (Hypophosphatemia)</b>	1	2.0 to <LLN	NA	NA	NA
	2	1.4 to <2.0 mg/dL	7(18%)	7(13%)	12 (20%)
	3	1.0 to <1.4 mg/dL	3 (8%)	7(13%)	11(19%)
	4	<1.0 mg/dL	0	2 (4%)	2 (3%)
<b>Urate</b>	1	≥ 7.5 to 10.0 mg/dL	13 (33%)	7(13%)	11(19%)

Parameter	Toxicity Grade	Result Range	TMB-301	TMB-202	
			Ibalizumab 2000 mg x1 then 800mg Q2W N=40	Ibalizumab 2000 mg Q4W N=54	Ibalizumab 800 mg Q2W N=59
<b>(Increased)</b>	2	10.0 to <12.0 mg/dL	1 (3%)	3 (6%)	4(7%)
	3	12.0 to <15.0 mg/dL	1 (3%)	0	2(4%)
	4	≥ 15.0 mg/dL	0	1 (2%)	0
<b>Creatine Kinase (Increased)</b>	1	≥ 3 x ULN	1(3%)	2(4%)	6(10%)
	2	≥ 6 x ULN	0	1(2%)	1(2%)
	3	≥ 10 x ULN	0	2(4%)	0
	4	≥ 20 x ULN	0	0	1(2%)
<b>Creatinine (Increased)</b>	1	Data pending	Data pending	Data pending	Data pending
	2	Data pending	Data pending	Data pending	Data pending
	3	Data pending	Data pending	Data pending	Data pending
	4	Data pending	Data pending	Data pending	Data pending
<b>Urine protein (Increased)</b>	1	Data pending	Data pending	Data pending	Data pending
	2	Data pending	Data pending	Data pending	Data pending
	3	Data pending	Data pending	Data pending	Data pending
	4	Data pending	Data pending	Data pending	Data pending
<b>Urine glucose (Increased)</b>	1	Data pending	Data pending	Data pending	Data pending
	2	Data pending	Data pending	Data pending	Data pending
	3	Data pending	Data pending	Data pending	Data pending
	4	Data pending	Data pending	Data pending	Data pending

\*Increased in grade from baseline.

### Liver-Associated Laboratory Tests

In TMB-301, three participants experienced Grade 3 or higher abnormalities in liver-associated tests, all of which were elevations in bilirubin.

- 301-01-002, whose past medical history included HCV and cirrhosis and whose death due to hepatic failure is described in Section 8.4.1 (Death), had Grade 1 bilirubin and Grade 3 direct bilirubin at baseline. He experienced Grade 4 elevation in bilirubin at his final visit (week 17).
- 301-01-006, whose concomitant medications included atazanavir, and who had mildly (Grade 1) elevated AST, ALT, Alkaline Phosphatase, and bilirubin at baseline, experienced a Grade 3 elevation in bilirubin at the EOS (week 25) visit.

- 301-29-002, who had no history of laboratory abnormalities experienced a Grade 3 elevation in direct bilirubin at the EOS (week 25) visit.

Six TMB-202 participants experienced Grade 3 or higher abnormalities in liver-associated tests, none of which met Hy's Law laboratory criteria.

- 202-10-009, who had a grade 2 elevation in alkaline phosphatase at baseline, developed Grade 3 elevations in alkaline phosphatase and Grade 3 direct bilirubinemia at week 4. He experienced concomitant abdominal pain and was diagnosed with Grade 2 cholangitis, deemed not related to ibalizumab. Ibalizumab was continued without interruption. By week 8, the laboratory abnormalities had returned to baseline and both AEs had resolved.
- 202-32-007 had normal AST and ALT but grade 1 elevation in alkaline phosphatase at baseline. He developed Grade 3 AST and Grade 4 ALT elevations at week 8. Ibalizumab was continued and both abnormalities resolved by week 16.
- 202-33-002, who had Grade 1 ALT elevation at baseline, experienced Grade 3 elevations in ALT, and Grade 2 elevations in AST, which peaked at week 12. Ibalizumab was continued and both laboratory abnormalities returned to baseline levels by week 20.
- 202-34-002, who had a Grade 1 ALT elevation at baseline, experienced Grade 3 direct bilirubin elevation at week 18. He stopped study on the same day due to virologic failure.
- 202-61-002, who had Grade 3 elevation in direct bilirubin during the two visits that proceeded baseline but an ungraded elevation in direct bilirubin at baseline, experienced a Grade 3 elevation in direct bilirubin at week 8. The laboratory abnormality returned to baseline by the following visit.
- 202-51-007, who had a history of chronic HBV and was HBeAg positive, had no abnormalities of liver-associated chemistry tests at baseline. He received 11 doses of ibalizumab (800mg IV q2 weeks), however ibalizumab was discontinued due to virologic failure after week 20. He experienced Grade 4 elevations in AST and ALT at his visit two weeks later (premature end-of-study visit) These abnormalities were reflected in the AE "liver function test abnormal", which was deemed possibly related to ibalizumab. Although the participant's failing regimen included lamivudine and tenofovir, both of which have antiviral activity against HBV, his OBR included only raltegravir and darunavir/ritonavir. Hepatitis B viral load was not reported. Other concomitant drugs included azithromycin and Bactrim. *Reviewer comment: This participant's elevations in AST and ALT are most likely related to an HBV flare, due to discontinuation of lamivudine and tenofovir at the start of study.*

*Reviewer comment: The frequency and distribution of liver-associated laboratory abnormalities observed in trials TMB-301 and TMB-202 are not unexpected in the enrolled patient population. These abnormalities are likely related to advanced HIV/AIDS, concomitant medications, and/or other co-morbidities.*

### **Pancreatic laboratory abnormalities**

Two TMB-301 participants experienced Grade 3 elevations in Lipase. Neither experienced pancreatitis or any related symptom such as nausea, vomiting, or abdominal pain. No TMB-301 participants experienced elevations in amylase increased in grade above baseline.

Two TMB-202 participants experienced transient lipase elevations (one Grade 3 and one Grade 4) and one experienced a Grade 4 elevation in amylase. None experienced pancreatitis or any related concomitant symptom such as nausea, vomiting, or abdominal pain. One TMB-202 participant, who did not have a Grade 3 or 4 laboratory abnormality, was diagnosed with Grade 1 pancreatitis.

*Reviewer Comment: Review of pancreas-related laboratory results in TMB-301 and TMB-202 reveal no pattern of pancreatic toxicity associated with ibalizumab.*

### **Electrolytes and other chemistry tests**

*Reviewer comment: As mentioned above, three important laboratory abnormalities (serum creatinine, urine protein, and urine glucose) were not included in the data submitted by the applicant. An addendum to the clinical review will provide the reviewer's analysis of those data, once received.*

Five TMB-301 participants experienced Grade 3 or higher abnormalities of electrolytes and other non-liver or pancreas-related chemistry tests. 301-02-002, who died of lymphoma while receiving intensive care, experienced a Grade 3 elevation in urate. 301-05-003 experienced a Grade 3 elevation in glucose. Three participants, two whom were taking tenofovir, experienced transient Grade 3 hypophosphatemia. None of these were reported as AEs. None were reported to have a history of renal toxicity or any new renal diagnosis over the course of the study. Serum creatinine, urine protein, and urine glucose data are pending from the applicant, so further analyses investigating the possibility that this represents a side-effect of tenofovir is deferred until that information is available.

The most common Grade 3 and 4 laboratory abnormalities on TMB-202 were hypophosphatemia. Twenty-two (19%) participants experienced this laboratory abnormality including 18 (16%) participants who experienced maximum Grade 3 hypophosphatemia and 4 (4%) who experienced maximum values of Grade 4. In most cases, hypophosphatemia was transient and resolved by the time of the subsequent visit. None of these abnormalities were reported as AEs. None of these participants were reported to have experienced concomitant fatigue, weakness, or myopathy and none was prescribed concomitant oral phosphate. One participant had concomitant diarrhea. None were reported to have a relevant renal diagnosis. Before ibalizumab administration, seventeen (15%) TMB-202 participants had Grade 3 or higher hypophosphatemia demonstrating that hypophosphatemia, as defined in the study, was very common in the trial population in the absence of ibalizumab. Nearly all of the participants who experienced hypophosphatemia during the study were also taking tenofovir. As noted previously,

serum creatinine, urine protein, and urine glucose results were not available for analysis at the time of this review. Only one of participants with hypophosphatemia had a laboratory abnormality “proteinuria” reported as an AE. None of these participants were reported to have “creatinine increased” as an AE. Comprehensive analysis comparing serum phosphorus with serum creatinine and urine protein to investigate the possibility that these abnormalities represent tenofovir toxicity will be performed when the data is submitted by the applicant.

Other Grade 3 or 4 electrolyte/chemistry abnormalities were uncommon in TMB-202. Two participants experienced hypocalcemia (one Grade 3 and one Grade 4) and one participant experienced Grade 3 hypercalcemia. Three participants, none of whom experienced concomitant symptoms of myositis, had elevations in CK (two Grade 3 and one grade 4). One participant experienced Grade 3 glucose elevation and two participants experienced Grade 3 hypomagnesemia. One participant experienced Grade 3 hyponatremia (low sodium). Three participants had asymptomatic elevation in urate (two Grade 3 and one Grade 4).

Although Grade 3 or higher hyperglycemia was rare in both TMB-301 and TMB-202, Grade 1 hyperglycemia was frequent; 14 (35%) of TMB-301 and 16 (14%) of TMB-202 participants experienced this abnormality. In addition, 6 (15%) TMB-301 participants and 7 (6%) TMB-202 participants experienced Grade 2 hyperglycemia. However, hyperglycemia was also common at baseline: nine (23%) TMB-301 and 16 (14%) TMB-202 participants had Grade 1 or higher elevations in glucose at one of three time points prior to ibalizumab administration.

*Reviewer Comment: Grade 3 or 4 hypophosphatemia was common in TMB-202 and also occurred in TMB-301, albeit at a much lower frequency. The abnormality was frequently reported at baseline prior to ibalizumab administration, occurred intermittently, was not associated with clinical symptoms, and resolved spontaneously. Grade 1 hyperglycemia was common in both studies, however the abnormality was equally common at baseline prior to Ibalizumab and therefore is most likely related to the underlying co-morbidities. Review of the remaining electrolyte laboratory results in TMB-301 and TMB-202 revealed no pattern toxicity associated with ibalizumab.*

### **Hematologic Abnormalities**

Four TMB-301 participants experienced Grade 3 or 4 abnormalities of hematologic tests. Three of these participants (301-18-002, 301-01-001, and 301-01-002) were severely ill and died of lymphoma, Kaposi’s sarcoma, and severe asthenia (failure to thrive), respectively. The fourth participant (301-17-001) experienced Grade 4 leukopenia and Grade 4 neutropenia at week 5 and subsequently missed several visits and ibalizumab injections. When the participant returned for follow-up at week 25, both abnormalities had persisted despite being off ibalizumab for twenty weeks.

Seven TMB-202 participants experienced Grade 3 or higher abnormalities of hematologic tests. Six participants experienced Grade 3 (n=5) or Grade 4 (n=2) decreases in hemoglobin. One participant, 202-48-001, who was also diagnosed with hypergammaglobulinemia, experienced

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

grade 4 neutropenia, which was reported as an AE related to Ibalizumab. The participants neutropenia resolved on treatment with filgrastim.

*Reviewer Comment: The frequency and distribution of hematologic abnormalities seen in TMB-301 and TMB-202 is expected in this patient population. TMB-301 and TMB-202 revealed no pattern of hematologic toxicity associated with ibalizumab.*

### **Summary of TMB-301 and TMB-202 Laboratory Abnormalities**

In summary, review of reported TMB-301 and TMB-202 laboratory abnormalities reveals no clear ibalizumab-related safety signal. Grade 3 or higher hypophosphatemia was common during the TMB-202 study and this will be noted in labeling. Analysis of serum creatinine, urine protein, and urine glucose will be provided in an addendum to this clinical review. In addition, the reviewer will analyze the relationship between the hypophosphatemia results and these three renal parameters.

#### **8.4.7. Vital Signs**

In both trials TMB-301 and TMB-202, heart rate, blood pressure, respiratory rate, and body temperature were measured at each on-treatment study visit, both pre-infusion and post-infusion. A summary of vital signs pre-and post ibalizumab in Trial TMB-301 are shown in the Table below. Of note, two participants experienced fevers on the day of infusion; 301-01-001 had a fever (38.9 degrees C) pre-infusion at week 7 and 301-17-001 had fevers pre (38.3 C) and post (38.3 C) infusion at week 5. Five participants had 17 recorded temperatures below 36.0 degrees Celsius; ten of those values were recorded pre-infusion and seven were recorded post-infusion. Comparison of vital signs between pre-and post-infusion reveals no clinically meaningful changes (**Table 29**). Results of the same analysis of vital sign parameters from TMB-202 were similar.

**Table 29 Vital Signs Pre and Post Ibalizumab infusion in TMB-301(all visits)**

Parameter	Statistic	Pre-Infusion	Post-Infusion
<b>Temperature</b> (degrees Celsius)	Median (IQR)	36.7(36.5-36.9)	36.7(36.4-36.9)
	Min, Max	35.0-38.9	35.2-38.3
<b>Heart rate</b> (beats per minute)	Median (IQR)	76(69-84)	73(68-82)
	Min, Max	43-117	45-108
<b>Respiratory Rate</b> (breaths/minute)	Median (IQR)	16(15-18)	16(14-17)
	Min, Max	12-24	12-24
<b>Systolic Blood Pressure</b> (mmHg)	Median (IQR)	122(114-132)	122(112-132)
	Min, Max	92-172	89-172
<b>Diastolic Blood Pressure</b> (mmHg)	Median (IQR)	78(71-84)	78(70-84)
	Min, Max	50-102	48-100

#### 8.4.8. Electrocardiograms (ECGs)

In trials TMB-301 and TMB-202, ECG was performed at screening, week 12 (TMB-301 and TMB-202) and at EOS (week 25 for TMB-301 and week 24 for TMB-202). Clinically meaningful changes were to be recorded as AEs however no such changes were observed.

#### 8.4.9. QT

As described above, ECG was performed three times during the trial period in both TMB-301 and TMB-202. The QT interval, the QT interval with Fredericia's formula correction (QTcF), and the QT interval with Bazett's formula correction (QTcB) were reported by the sponsor for trial TMB-301. The results, shown below in **Table 30**, do not suggest any clinically meaningful changes in QT after initiating ibalizumab.

**Table 30 Changes in QT interval in TMB-301**

	QT in msec Median (IQR)	QTcB in msec Median (IQR)	QTcF in msec Median (IQR)
<b>Baseline</b>	388 (366-420)	424 (395-436)	402(394-435)
<b>Week 13</b>	364(364-408)	423(407-438)	415(402-440)
<b>EOS (Week 25)</b>	388(367-410)	423(411-435)	410(399-445)

For Trial TMB-202, Investigator interpretations of EKG were reported. There were no QT-related abnormalities reported.

#### 8.4.10. Immunogenicity

The review of data related to the development and potential impact of anti-drug antibodies was ongoing by the Office of Biotechnology Products at the time this review was finalized.

### 8.5. Analysis of Submission-Specific Safety Issues

On the basis of preclinical data and findings in standard safety analyses performed in **Section 8.4 Safety Results**, two potential submission-specific safety issues, infusion reactions and rash, were identified. In addition, although no evidence of a safety signal emerged during standard safety analysis, AEs within the SOC Infections and Infestations will be addressed because ibalizumab binds to the host CD4 T cell molecule. These issues are discussed in further detail in this section.

#### 8.5.1. Infusion Reactions

As discussed in **Section 8.4, Dropouts and/or Discontinuations due to Adverse Events**, there was one poorly defined report of hypersensitivity reaction in trial TMB-202. Although the data and narrative provided by the investigator are not consistent with hypersensitivity reaction in that case, the potential seriousness of infusion reactions and the frequent association of infusion reactions with the monoclonal antibody drug class necessitate careful review of the database for manifestations of infusion reaction.

There were no reports of anaphylaxis or hypersensitivity AEs in trial TMB-301 and none, other than the case (202-13-003) mentioned above, in trial TMB-202.

The TMB-301 and TMB-202 datasets, excluding 202-13-003, were reviewed for evidence of any of the following ARs occurring on the day of or the day following an infusion; acute respiratory distress syndrome, pyrexia, chills, arthralgia, musculoskeletal pain, myalgia, joint swelling, obstructive airways disorder, pulmonary oedema, generalized oedema, peripheral oedema, flushing, bronchospasm, stridor, dysphonia, headache, fatigue, asthenia, pruritus, urticaria, hypotension, hypertension, chest pain, palpitations, arrhythmia, bradycardia, syncope, rhinorrhea, allergic rhinitis, nausea, vomiting, angioedema, dyspnea, dizziness/lightheadedness, angioedema, convulsion, and cytokine release syndrome reactions.

Ten participants (three in TMB-301 and seven in TMB-202) experienced one or more of the ARs above with onset or duration possibly consistent with an infusion reaction. The ARs included dizziness (eight events, five participants), vomiting (two events, two participants), fatigue (five events, three participants), nausea (two events, one participant), and feverishness (one event). Five of the participants experienced one or more of these ARs during a single infusion without subsequent recurrence. All ARs were mild in severity except for four fatigue events,

experienced by two TMB-202 participants, which were moderate in severity. One of the participants who experienced fatigue with ibalizumab infusion also experienced fatigue with the placebo infusion. None of the ARs resulted in any change in ibalizumab dosing and all resolved.

*Reviewer Comment: Except for one TMB-202 case, which does not appear clinically consistent with hypersensitivity reaction, there were no reports of infusion reaction, hypersensitivity reaction, or anaphylaxis in the ibalizumab development program. Comprehensive review of TMB-301 and TMB-202 ARs associated with infusion reactions reveals no additional pattern of ARs to suggest unrecognized cases of infusion reaction.*

### 8.5.2. Rash

As described in Section 8.4. Safety Results, rash was a common, sometimes severe AR in the ibalizumab clinical development program. This section summarizes rash events that occurred in trials TMB-301 and TMB-202. For both trials, the analysis includes events with the following preferred terms (PTs) “rash”, “rash erythematous”, “rash generalized”, “rash macular”, “rash maculopapular”, and “rash papular”, which are collectively referred to as “rash” in this review.

Five TMB-301 trial participants experienced 12 rash events, including one participant (301-02-001) who experienced 8 such events including one severe rash, which resolved despite continuing ibalizumab without interruption, and one moderate event that was ongoing at the end of study. All of this participant’s rashes were deemed related to ibalizumab. The four other participants who experienced rashes experienced single rash events, one of which was deemed related to ibalizumab. Three of the rashes were mild in severity and one was moderate.

Twenty-three (20.3%) participants experienced 28 rash events over the course of the TMB-202 trial. Seventeen of the events were Grade 1 and eleven events were Grade 2. No Grade 3 or higher rash AE events were reported. Investigators determined that 14 rash events were related to ibalizumab. One participant, (202-25-01) stopped ibalizumab because of two Grade 2 rashes; one rash began on Day 5 after his first dose of ibalizumab (2000mg IV) and resolved on Day 25 after treatment with an antihistamine and corticosteroids. He developed a second rash on Day 31, one day after receiving his second and final dose of ibalizumab (2000mg IV).

*Reviewer comment: Rash events, which were primarily mild or moderate in severity, were common in both TMB-301 and TMB-202. Rash ARs were also relatively common. Two participants experienced significant rash AR; one was deemed severe and the other rash led to ibalizumab discontinuation. In conclusion, data from TMB-301 and TMB-202 data suggest that ibalizumab administration may be associated with rash in some patients. Rash will be included in Section 6 of the ibalizumab label.*

### 8.5.3. Infections and Infestations

Ibalizumab binds to the host’s CD4 T cell molecule at domain 2 and does not interfere with the interaction between CD4 domain 1 and MHC (*major histocompatibility complex*) class II

complex, which is essential for CD4 T cell immune function. As is discussed in **Section 4.3 Microbiology**, investigations performed on human and non-human primates treated with ibalizumab demonstrated that ibalizumab treatment did not interfere with the number or function of CD4 T cells. Furthermore, as described in **Sections 6.1 TMB-301** and **6.2 TMB-202**, the majority of participants in both TMB-301 and TMB-202 experienced increases in CD4 T cell number, rather than decreases, over the course of the trial. Nonetheless, because any impairment in cellular immunity could be clinically important in the targeted patient population, a thorough review of the trial data was performed to detect any signal of increased risk for infections or infestations.

Eighteen (45%) TMB-301 participants experienced one or more AEs within the infection and infestations SOC, including four AEs considered severe or potentially life-threatening (CMV viremia, progressive multifocal leukoencephalopathy (PML), urinary tract infection (UTI), and sepsis). These events are described in detail in **Section 8.4.2 (Serious Adverse Events)**. Regarding the case of PML, the treating physician's impression was that the patient had PML prior to ibalizumab treatment and that ibalizumab treatment led to a recovery of the immune system and Immune Reconstitution Inflammatory Syndrome (IRIS). The following AEs occurred in two or more participants; nasopharyngitis (n=4), upper respiratory infection (n=3), pneumonia (n=2), gastroenteritis (n=2), herpes zoster (n=2), UTI (n=2), and bronchitis (n=2). CMV viremia, an opportunistic infection associated with AIDS and CD4 T cell impairment was also reported in one participant. None of the infection or infestations AEs were deemed related to ibalizumab.

Fifty-one (45%) TMB-202 participants experienced one or more AEs within the infection and infestations SOC, including five AEs considered severe (AIDS, cellulitis, CMV infection, CMV viremia, and gastroenteritis). The following AEs occurred in three or more participants; CMV infection (CMV viremia or CMV infection), upper respiratory infection, oral candidiasis, nasopharyngitis, sinusitis, urinary tract infection, gastroenteritis, folliculitis, and conjunctivitis. Other infection and infestation AEs associated with AIDS and CD4 T cell impairment occurred less commonly and included herpes zoster (n=1), CMV chorioretinitis (n=1), bronchopneumonia (n=1), Mycobacterium Avium Infection (n=1), and Toxoplasmosis (n=1). Six AEs were considered related to ibalizumab (cellulitis, giardiasis, herpes zoster, oral candidiasis (n=2), and urinary tract infection).

*Reviewer comment: Review of AEs and ARs within the Infectious and Infestations SOC reveal no evidence of increased susceptibility to opportunistic infections with ibalizumab treatment. The frequency and distribution of AEs described in both TMB-301 and TMB-202 are consistent with that expected in the trial populations.*

## 8.6. Safety Analyses by Demographic Subgroups

The frequencies of ARs were analyzed by race, ethnicity, and sex. Because TMB-301 was not powered to detect differences between these individual populations, the analyses are exploratory. One (25%) Asian participant and six (27%) white participants experienced ARs. No black

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

participants or participants with unspecified race experienced ARs. Three (30%) Hispanic/Latino participants experienced ARs compared to three (10%) participants who were non-Hispanic/Latino. Seven (21%) male participants and no female participants experienced ARs. Frequencies of ARs experienced by two or more TMB-301 participants by race, ethnicity, and gender are presented in the table below (**Table 31**).

*Clinical Comment: Although there are differences in the frequency of ARs by race, ethnicity, and sex, the small number of patients enrolled in TMB-301 precluded any meaningful conclusions.*

**Table 31 ARs occurring in two or more TMB-301 participant by race, ethnicity, and sex**

Preferred Term	Overall N=40	Race				Ethnicity		Sex	
		Asian n=4	Black/ African American n=13	Not reported n=1	White n=22	Hispanic /Latino n=10	Not Hispanic /Latino or unknown n=30	Male n=34	Female n=6
Diarrhea	3(8%)	1	0	0	2(9%)	0	3(10%)	3(9%)	0
Nausea	2(5%)	1(25%)	0	0	1(5%)	1(10%)	2(7%)	2(6%)	0
Rash*	3(8%)	0	0	0	2(9%)	1(10%)	2(7%)	3(9%)	0
Dizziness	3(8%)	0	0	0	3(14%)	1(10%)	2(7%)	3(9%)	0

\*As described in Section 8.5.2, the term “rash” represents several PTs, all of which are specific descriptions of types of rashes.

## 8.7. **Specific Safety Studies/Clinical Trials**

No additional trials have been conducted to evaluate specific safety concerns.

## 8.8. **Additional Safety Explorations**

### 8.8.1. **Human Carcinogenicity or Tumor Development**

A carcinogenicity risk assessment will be submitted as a post-marketing requirement.

### 8.8.2. **Human Reproduction and Pregnancy**

Fertility and early embryonic development and embryo-fetal development studies with ibalizumab have not been conducted. An enhanced pre/postnatal development study is in progress and will be submitted as a post-marketing requirement. Female patients who were pregnant were excluded from all clinical trials and expanded access studies.

### 8.8.3. **Pediatrics and Assessment of Effects on Growth**

This application requests approval of ibalizumab for the treatment of adults. No pediatric studies have been performed and therefore none will be discussed in this review. In addition, ibalizumab has orphan drug status and is therefore exempt from Pediatric Research Equity Act (PREA) requirements.

### 8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Because of its mechanism of action, ibalizumab is unlikely to be associated with abuse, withdrawal, or rebound.

## 8.9. **Safety in the Postmarket Setting**

### 8.9.1. **Safety Concerns Identified Through Postmarket Experience**

The study drug is a novel biologic, and thus, there is no postmarket experience.

### 8.9.2. **Expectations on Safety in the Postmarket Setting**

The safety database of patients exposed to the intended dosage regimen is small, but sufficient to assess frequent adverse events, and acceptable for this serious disease with great unmet medical need. Post-marketing pharmacovigilance will play an important role in further defining the safety profile of this drug, especially for rare adverse reactions.

## 8.10. **Additional Safety Issues From Other Disciplines**

All safety issues from other disciplines have been incorporated into relevant sections elsewhere in this review.

### 8.11. **Integrated Assessment of Safety**

The safety data submitted with this BLA demonstrate a favorable safety profile for ibalizumab. The safety database of patients exposed to the intended dosage regimen is small, but sufficient to assess frequent adverse events, and acceptable for this serious disease with great unmet medical need. The following adverse reactions occurred in at least five percent of participants in the Phase 3 clinical trial (TMB-301): dizziness, diarrhea, rash, and nausea. One serious adverse reaction, immune reconstitution inflammatory syndrome, occurred in TMB-301. Analysis of the supportive Phase 2b trial TMB-202 and review of safety from early phase trials and expanded access studies show similar safety results. Post-marketing pharmacovigilance will play an important role in further defining the safety profile of this drug, especially for rare adverse reactions

## **9 Advisory Committee Meeting and Other External Consultations**

---

No advisory committee or other external consultations were held to discuss this application.

## **10 Labeling Recommendations**

---

### 10.1. **Prescribing Information**

Negotiations pertaining to the prescribing information are ongoing at the time of completion of this review. The summary that follows reflects the major changes to the Sponsor's labeling that have been proposed by the Agency.

Section 1 Indications and Usage. The Phase 3 ibalizumab clinical study was designed for heavily-treatment experienced, HIV-infected patients with multi-drug (and often multi-class) resistance, a rare population with limited treatment options. Important aspects of the pivotal trial (TMB-301), such as its small sample size, early virologic primary endpoint, and the absence of a control group, were acceptable only in the context of this rare patient population at high risk for progression to AIDS and death absent viable treatment options. Notably, ibalizumab's orphan disease designation was granted specifically for this population, i.e., the treatment of HIV-1 infection in treatment experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy. For these reasons, the indication will be narrowed to be consistent with the patient population studied and ibalizumab's orphan designation.

Section 6.1 Adverse Reactions. Clinical Trials Experience.

- Because TMB-301 was the only study that used the ibalizumab dose proposed in the label, Section 6.1 will focus on the safety results in TMB-301. Other safety events of significance from other studies will only be included if those safety events are not reflected in the TMB-301 safety results.
- In accordance with FDA guidance for adverse reactions section of labeling<sup>19</sup> the listing of adverse events will be limited to events for which there is a basis to believe that there is a causal relationship with the drug (adverse reactions).
- Also in accordance with the referenced guidance<sup>19</sup>, Section 6.1 was consolidated to be concise. One table of adverse reactions will be included and will list frequent events (occurring in 5% or more of participants) by specific term in order of event frequency.

Section 6.2 Adverse Reactions. Laboratory Evaluations. A table of Grade 3 and 4 laboratory abnormalities that occurred in trial TMB-301 will be included.

Section 12.3 Pharmacokinetics.

(b) (4)

Section 14. Efficacy. According to FDA guidance for Clinical Studies Section of Labeling<sup>20</sup>, Section 14 should not include information from clinical studies with results that imply effectiveness for an unapproved dose regimen. Therefore, this section will be limited to results from study TMB-301.

**10.2. Patient Labeling**

Patient labeling will be updated in accordance with the final agreed upon prescribing information in the Package Insert. Because negotiations pertaining to prescribing information are ongoing at the time of completion of this review, patient labeling is not yet updated.

**10.3. Nonprescription Labeling**

Ibalizumab will be available only by prescription; therefore this section is not applicable.

## **11 Risk Evaluation and Mitigation Strategies (REMS)**

---

No concerns necessitating REMS were identified.

**11.1. Safety Issue(s) that Warrant Consideration of a REMS**

Not applicable.

**11.2. Conditions of Use to Address Safety Issue(s)**

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

Not applicable.

### 11.3. **Recommendations on REMS**

Not applicable.

## **12 Postmarketing Requirements and Commitments**

---

Final determinations related to PMRs and PMCs are pending at the time of finalization of this review.

## 13 Appendices

---

### 13.1. References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. . 2016.
2. Zaccarelli M, Tozzi V, Lorenzini P, et al. Multiple drug class-wide resistance associated with poorer survival after treatment failure in a cohort of HIV-infected patients. *AIDS* 2005;19:1081-9.
3. Heather Bradley HIH, Richard J. Wolitski, Michelle M. Van Handel, Amy E. Stone,, Michael LaFlam JS, MD1, Darrel H. Higa,, Joseph Prejean, Emma L. Frazier, Roshni Patel,, Ping Huang QA, Ruiguang Song, Tian Tang,, Linda A. Valleroy. Vital Signs: HIV Diagnosis, Care, and Treatment Among Persons Living with HIV — United States, 2011. *Morbidity and Mortality Weekly Report, MMWR*; 2014:1618-23.
4. Hanna DB, Buchacz K, Gebo KA, et al. Trends and disparities in antiretroviral therapy initiation and virologic suppression among newly treatment-eligible HIV-infected individuals in North America, 2001-2009. *Clin Infect Dis* 2013;56:1174-82.
5. Kantor R, Shafer RW, Follansbee S, et al. Evolution of resistance to drugs in HIV-1-infected patients failing antiretroviral therapy. *AIDS* 2004;18:1503-11.
6. Hofstra LM, Sauvageot N, Albert J, et al. Transmission of HIV Drug Resistance and the Predicted Effect on Current First-line Regimens in Europe. *Clin Infect Dis* 2016;62:655-63.
7. Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. *J Infect Dis* 2004;189:2174-80.
8. Bruyand M, Thiebaut R, Lawson-Ayayi S, et al. Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. *Clin Infect Dis* 2009;49:1109-16.
9. Estrella M, Fine DM, Gallant JE, et al. HIV type 1 RNA level as a clinical indicator of renal pathology in HIV-infected patients. *Clin Infect Dis* 2006;43:377-80.
10. Mocroft A, Ledergerber B, Viard JP, et al. Time to virological failure of 3 classes of antiretrovirals after initiation of highly active antiretroviral therapy: results from the EuroSIDA study group. *J Infect Dis* 2004;190:1947-56.
11. Grover D, Copas A, Green H, et al. What is the risk of mortality following diagnosis of multidrug-resistant HIV-1? *J Antimicrob Chemother* 2008;61:705-13.
12. Lohse N, Jorgensen LB, Kronborg G, et al. Genotypic drug resistance and long-term mortality in patients with triple-class antiretroviral drug failure. *Antivir Ther* 2007;12:909-17.

Clinical Review  
Virginia Sheikh, MD  
Biologic Licensing Application 761065  
Ibalizumab/TROGARZO

13. Paquet AC, Solberg OD, Napolitano LA, et al. A decade of HIV-1 drug resistance in the United States: trends and characteristics in a large protease/reverse transcriptase and co-receptor tropism database from 2003 to 2012. *Antivir Ther* 2014;19:435-41.
14. Napravnik S, Keys JR, Quinlivan EB, Wohl DA, Mikeal OV, Eron JJ, Jr. Triple-class antiretroviral drug resistance: risk and predictors among HIV-1-infected patients. *AIDS* 2007;21:825-34.
15. De Luca A, Dunn D, Zazzi M, et al. Declining prevalence of HIV-1 drug resistance in antiretroviral treatment-exposed individuals in Western Europe. *J Infect Dis* 2013;207:1216-20.
16. Vergel N. Is There a Future for HIV-Infected Patients in "Deep Salvage? TheBodyPROcom2011.
17. FDA Guidance. Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry. U.S. Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). 2015.
18. Bureau USC. Population estimates, July 1, 2016 (V2016).
19. FDA Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. Department of Health and Human Services. . 2006.
20. FDA Guidance for Industry. Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. 2006.

Clinical Review  
 Virginia Sheikh, MD  
 Biologic Licensing Application 761065  
 Ibalizumab/TROGARZO

### 13.2. Financial Disclosure

There were no financial disclosures of concern.

#### Covered Clinical Study (Name and/or Number): TMB-301

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>139</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in Stock: <u>0</u></p> <p>Sponsor of covered study: <u>Taimed Biologics</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

#### Covered Clinical Study (Name and/or Number): TMB-202

Clinical Review  
 Virginia Sheikh, MD  
 Biologic Licensing Application 761065  
 Ibalizumab/TROGARZO

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>152</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in Stock: <u>0</u></p> <p>Sponsor of covered study: <u>Taimed Biologics</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>5</u>		
Is an attachment provided with the reason: Applicant cannot locate investigators	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

VIRGINIA M SHEIKH  
10/03/2017

ADAM I SHERWAT  
10/03/2017

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: BLA 761065      Applicant: TaiMed Biologics Inc.      Stamp Date: 5/3/2017**

**Drug Name: Ibalizumab      NDA/BLA Type: 351(a)      Expedited, Priority Review**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
<b>LABELING</b>					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see <a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm</a> )	X			
<b>SUMMARIES</b>					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			2.7.4: Summary of Clinical Safety  5.3.5.3: ISS Tables and Figures
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			2.7.3: Summary of Clinical Efficacy  5.3.5.3: ISE Tables and Figures
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			2.5: Clinical Overview (Section 6, page 28)
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			351(a)
<b>505(b)(2) Applications</b>					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
<b>DOSAGE</b>					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g.,	X			Module 5.3.3.5 describes results of

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	appropriately designed dose-ranging studies)?				study Hu5A8.01 (Phase I MAD study in HIV-infected subjects). In addition, TMB-202 compared 2000 mg IV q4 weeks with 800mg IV q2 weeks.
<b>EFFICACY</b>					
16.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p><i>This BLA submission is intended to support approval of the new molecular entity, Ibalizumab, in combination with other HIV drugs, for the treatment of HIV-1 in treatment-experienced patients with multidrug resistant HIV-1 viral infection and virologic failure despite antiretroviral therapy. Because this patient population is rare (orphan disease designation), the Division agreed with the sponsor that a single successful Phase 3 trial, supported by Phase 2 data, would be adequate to support approval of Ibalizumab for this rare patient population.</i></p> <p><b>Pivotal Study #1</b></p> <p><u>Study Number:</u> TMB-301  <u>Study Name:</u> 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  <u>Patient population:</u> HIV-infected adults with VL &gt;1000 c/ml despite ART and with at least 6 months of ART experience, resistant to at least one drug in each of the following (NRTI, NNRTI, PI), no OIs in the past 3 months. Life expectancy &gt; 6 months  <u>Dosing:</u> 2000 mg IV loading dose then 800mg IV q 2 weeks  <u>Efficacy Endpoints:</u>                      Primary                      • Proportion of participants with <math>\geq 0.5</math> log<sub>10</sub> decrease in VL after 7 days (Day 14 vs Day 7/Baseline)                      Secondary                      • Proportion of participants with:                          ○ HIV RNA &lt;50 c/ml at week 25                          ○ HIV RNA &lt;400 c/ml at week 25                          ○ <math>\geq 0.5</math> log<sub>10</sub> decrease in HIV RNA at week 25 (verses Day 7/Baseline)                      Mean change in CD4 T cell count at week 25 (Week 25 vs Day 7/Baseline)</p> <p><b>Pivotal (Supportive) Study #2</b></p> <p><u>Study Number:</u> TMB-202  <u>Study Name:</u></p>	X			<p>Note: The applicant has proposed the following indication in the submitted label:</p> <p>“TROGARZO, (b) (4) [redacted] [redacted] [redacted] in combination with other antiretroviral(s), is indicated for the treatment of adults infected with HIV-1 resistant to at least one agent in three different classes.”</p> <p>Sample size and trial design are c/w what was agreed upon by the Division and c/w FDA guidance for <u>treatment-experienced patients with multidrug resistant HIV.</u></p>

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<ul style="list-style-type: none"> <li>• <u>Patient population</u>: HIV-infected adults with VL &gt;1000 c/ml despite ART, decreased susceptibility to at least one drug in each of the following (NRTI, NNRTI, PI), no OIs in the past 3 months. Life expectancy &gt; 6 months</li> </ul> <p><u>Dosing</u>:                      ARM 1: 2000 mg IV q 4 wks                      ARM 2: 800mg IV q 2 wks</p> <p><u>Efficacy Endpoints</u>: A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab Plus an Optimized Background Regimen in Treatment- Experienced Patients Infected With HIV-1 (Amended to 24-Week Study)</p> <p><u>Endpoints</u>:                      Primary:</p> <ul style="list-style-type: none"> <li>• Proportion with HIV RNA &lt;50 c/mL at week 24</li> </ul> <p>Secondary</p> <ul style="list-style-type: none"> <li>• Proportion of participants with:                             <ul style="list-style-type: none"> <li>○ HIV RNA &lt;400 c/ml at week 24</li> <li>○ <math>\geq 0.5 \log_{10}</math> decrease in HIV RNA at week 24 (vs. Week 0/Day 1)</li> </ul> </li> <li>• Mean change in CD4 T cell count at week 24 (vs. Week 0/Day 1)</li> </ul> <p>Location in submission: Module 5.3.5.1</p>				
17.	<p>Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?</p> <p><i>Because treatment-experienced patients with MDR HIV infection are rare and heterogeneous with regard to HIV viral load, adherence, and viral resistance, the Division agreed that participants would serve as their own controls (Day 7 verses Day 14 HIV-1 RNA level).</i></p>				The FDA agreed to the study design including the use of internal rather than external control during the Type C End-of-Phase 2 Meeting.
18.	<p>Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.</p> <p><i>Because treatment-experienced patients with MDR HIV infection are rare and prolonged exposure to a single drug is unethical due to the risk of developing viral resistance, the Division agreed that the primary endpoint for the registration trial (TMB-301) would be the proportion of participants with HIV RNA &lt;50 c/mL after 7 days of essential monotherapy (+/- continued current failing HIV therapy) After the seven day period of monotherapy (Days 7-13), participants w started optimized background therapy (OBR) for the remaining duration of the trial.</i></p>				Because the target population is rare and heterogeneous, the Division agreed to the 7 day virologic endpoint. This is consistent with the Division's published guidelines for development of HIV drugs.

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		IR to sponsor requesting rationale for assuming applicability of small number of participants from Taiwan. A total of 7 subjects in the Phase 3/2b program are from Taiwan. 4/113 (3.5%) of TMB-202 subjects & 3/40 (7.5%) TMB-301
<b>SAFETY</b>					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Ibalizumab is not approved in any country.
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dosage (or dosage range) believed to be efficacious?  <i>A total of 299 participants have been exposed to Ibalizumab. Although the majority of participants did not receive the dosage believed to be efficacious, the target population is rare (~5000 individuals in the US) and the condition is life-threatening. Therefore, a smaller safety database is reasonable.</i>	X			Because the target population is rare, the Division agreed that a safety base of slightly fewer than 300 subjects is acceptable.
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?		X		IR to sponsor requesting coding dictionary. Review of verbatim verses AEDECOD suggests coding is adequate.
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Ibalizumab is the first CD4 receptor antagonist HIV drug to be approved in the US

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Narratives for deaths, SAEs, and AEs leading to discontinuations are included. Locations: TMB-202 CSR Section 12.3.2.1 TMB-301 CSR "Body" Appendix 14.3.3.1
<b>OTHER STUDIES</b>					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Orphan Drug Designation, therefore exempted from required pediatric assessment
<b>PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE</b>					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see <a href="http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm">http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm</a> )?	X			None of the Ibalizumab clinical trial participants were pregnant. Label follows PLLR format in section 8.
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		IR to sponsor requesting rationale for assuming applicability of small number of participants from Taiwan. A total of 7 subjects in the Phase 3/2b program are from Taiwan. 4/113 (3.5%) of TMB-202 subjects & 3/40 (7.5%) TMB-301.
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously by the Division?				
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes**

The clinical section of the application is fileable. We have identified one review issue related to assuming applicability of the data from the small number of trial participants from Taiwan to U.S. patients. We will communicate this concern to the applicant in an IR.

Virginia Sheikh, MD  
 \_\_\_\_\_  
 Reviewing Medical Officer

June 6, 2017  
 \_\_\_\_\_  
 Date

Adam Sherwat, MD  
 \_\_\_\_\_  
 Clinical Team Leader

June 6, 2017  
 \_\_\_\_\_  
 Date

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

VIRGINIA M SHEIKH  
06/15/2017

ADAM I SHERWAT  
06/15/2017