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APPLICATION NUMBER:

761065Orig1s000

SUMMARY REVIEW

Combined Cross-Discipline Team Leader, Division Director, and ODE Director Summary Review

Date	March 4, 2018
From	Adam Sherwat, Jeffrey Murray, and John Farley
Subject	Cross-Discipline Team Leader, Division Director, and ODE Summary Review
NDA/BLA #	BLA 761065
Applicant	TaiMed Biologics Inc.
Date of Submission	May 3, 2017
PDUFA Goal Date	April 3, 2018
Proprietary Name / Non-Proprietary Name	Trogarzo/ Ibalizumab
Dosage form(s) / Strength(s)	2000 mg intravenous (IV) loading dose followed by 800 mg IV every 2 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of adults infected with HIV-1 resistant to at least one agent in three different classes
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV infection failing their current antiretroviral regimen

1. Benefit-Risk Assessment

We agree with the detailed Benefit-Risk Assessment provided by Dr. Virginia Sheikh in her Clinical Review. The following abbreviated Benefit-Risk Assessment highlights the key issues.

Benefit-Risk Summary and Assessment

Heavily treatment experienced patients infected with multidrug resistant (MDR) human immunodeficiency virus (HIV) represent a rare, but important subset of patients living with HIV. Patients with MDR HIV who cannot achieve complete virologic suppression with anti-retroviral treatment (ART) are at high risk for Acquired Immune Deficiency Syndrome (AIDS)-related morbidity and mortality. A need exists in this

population for new and effective antiretroviral products that lack cross-resistance with commercially available products. Ibalizumab, a drug with both Breakthrough and Orphan Drug designation, is one such product.

Ibalizumab has clearly demonstrated shorter-term virologic activity in heavily treatment experienced patients infected with MDR HIV. The pivotal trial, TMB-301, demonstrated a significantly higher percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease in HIV viral load after completion of the Essential Monotherapy Period compared with the percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease in HIV viral load after completion of the Control Period. The lack of a concurrent control arm through Week 25 (i.e., end of study) in TMB-301 limits the ability to precisely quantify the contribution of ibalizumab to longer-term virologic suppression. However, both TMB-301 and the 800 mg q 2 week arm of the supportive Phase 2b trial TMB-202 demonstrated highly similar rates of longer-term virologic suppression at 25 and 24 weeks, respectively. The concordance of these results, generated with virtually identical treatment regimens in similar patient populations, may reflect ibalizumab's contribution to durability.

Based on the data submitted in support of this Biologics License Application (BLA), ibalizumab has a favorable safety profile. The nature and frequency of the significant safety events (deaths, serious adverse events [SAEs], and discontinuations due to adverse events [AEs]) reported in the BLA largely reflect the patient population targeted for enrollment, i.e., advanced HIV/AIDS patients infected with MDR HIV and failing current ART. Although the safety database was limited for the proposed dosing regimen, it was sufficient for the assessment of safety for the rare population for which this drug will be indicated.

The overall benefit-risk profile of ibalizumab is favorable for the treatment of HIV-1 infection in heavily treatment-experienced adults with MDR HIV-1 infection failing their current antiretroviral regimen. In our decision to approve ibalizumab, we considered the available safety and efficacy data, and the recommendation for approval by all other review disciplines.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The US Centers for Disease Control and Prevention estimates that greater than 1.1 million people in the US are living with HIV. Many of these people can achieve virologic suppression and immunologic recovery with an ART regimen comprised of currently approved drugs. However, there is a rare subset of HIV-infected patients who cannot achieve virologic suppression due to the presence of MDR HIV.	Heavily treatment experienced patients with MDR HIV and evidence of ongoing HIV replication despite ART are at high risk of AIDS-related morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	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 often burdensome, less well tolerated, and associated with inadequate HIV viral suppression.	Heavily treatment experienced patients with MDR HIV infection need new and effective antiretroviral products that lack cross-resistance with commercially available products.
Benefit	A reduction in HIV RNA ≥ 0.5 $\log_{10}$ is associated with reduction in disease progression. The pivotal trial, TMB-301, demonstrated a significantly higher percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease in HIV viral load after completion of the Essential Monotherapy Period compared with the percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease in HIV viral load after completion of the Control Period. Additionally, both TMB-301 and the 800 mg q 2 week arm of TMB-202 demonstrated similar longer-term rates of virologic suppression. In Trial 301, 43% of subjects had HIV RNA < 50 copies/mL at week 25. In Trial 202, 44% of subjects had HIV RNA < 50 copies/mL at week 24. Apart from the 2000 mg IV loading dose in TMB-301, these were identical treatment regimens in similar patient populations.	Ibalizumab has clearly demonstrated virologic activity in heavily treatment experienced patients infected with MDR HIV. As TMB-301 was an uncontrolled trial, there remains some uncertainty surrounding the contribution of ibalizumab to the maintenance of virologic suppression. However, the similarity of the Week 25 and Week 24 virologic outcomes in Trials 301 and 202, respectively, may reflect ibalizumab's contribution to longer-term durability.
Risk	Based on the data submitted in support of this BLA, ibalizumab has a favorable safety profile. The nature and frequency of the significant safety events (deaths, SAEs, and discontinuations due to AEs) reported in the BLA largely reflect the patient population targeted for enrollment, i.e., advanced HIV/AIDS patients infected with MDR HIV and failing current ART.	Based on the available data, ibalizumab has a favorable safety profile. The safety database, albeit limited for the proposed dosing regimen, was sufficient for the assessment of safety for the rare population for which this drug will be indicated.
Risk Management	Ibalizumab has a favorable safety profile.	Safety risks have not been identified that require risk management beyond standard pharmacovigilance.

2. Background

The US Centers for Disease Control and Prevention estimates that greater than 1.1 million people in the US are living with HIV. Many of these people can achieve virologic suppression and immunologic recovery with an ART regimen comprised of currently approved drugs. However, there is a rare subset of patients with HIV infection who cannot achieve virologic suppression due to the presence of MDR HIV. In the absence of fully effective ART, these patients are at high risk for AIDS-related morbidity and mortality.

This BLA, submitted by TaiMed Biologics Inc., contains information to support the approval of Trogarzo (ibalizumab) for the treatment of HIV-1 infection in heavily treatment-experienced adults with MDR HIV infection failing current antiretroviral therapy. Ibalizumab, a humanized IgG4 monoclonal antibody that recognizes domain 2 of the extracellular portion of the CD4 molecule, would be the first monoclonal antibody approved for the treatment of HIV infection.

The original IND for ibalizumab was submitted in 2001. Milestone regulatory events included the granting of Fast Track designation in 2003, Orphan Drug designation in 2014, Breakthrough designation in 2015, and Rolling Review in 2016. From the time of IND submission, the Agency has worked closely with the Sponsor to guide and foster ibalizumab's development program.

This review will present the major findings and key issues from the BLA review of Ibalizumab. For a more comprehensive assessment, the reader is referred to the specific discipline reviews for the Ibalizumab BLA.

3. Product Quality

The Product Quality review team recommends approval of this BLA based on their review of the submitted data. Please refer to the Product Quality reviews for additional details.

General product quality considerations

Ibalizumab drug substance and drug product are manufactured at WuXi AppTec (Wuxi, China). Ibalizumab is expressed in mouse NS0 cells. (b) (4) The container closure is a single (b) (4) 2 mL (b) (4) glass vial with a (b) (4) rubber stopper and aluminum flip-off seal.

The multi-disciplinary Product Quality review team noted major concerns with the completeness and organization of the data submitted in support of the BLA. The Product Quality review team (with full support of the review division) worked closely with the Applicant to communicate and

address these issues. This process included numerous information requests as well as telephone conferences and face-to-face meetings with the Applicant, including their Chief Executive Officer, Dr. James Chang. The Applicant was advised that the product quality data must be provided in an organized, complete, and reviewable format to allow for a substantive product quality review. Additionally, the Applicant was advised of the importance of having the infrastructure and expertise in place to successfully manage a BLA license. Addressing the Agency's concerns required the submission of a major amendment to the BLA thus triggering an extension of the goal date by three months to provide time for a full review of the submission. The submitted data was reviewed by the Product Quality review team and deemed acceptable to support the approval of the BLA.

Facilities review/inspection

In July/August 2017, the manufacturing facility, WuXi AppTec, was inspected. The inspection identified manufacturing deficiencies leading to the issuance of a Food and Drug Administration (FDA) Form 483. The Product Quality review team worked closely with WuXi App Tec to successfully address these issues and with the Applicant to appropriately update the BLA to reflect the changes in manufacturing processes. The Office of Product Quality's final determination is that the facilities designated for the manufacture of ibalizumab are acceptable.

4. Nonclinical Pharmacology/Toxicology

Dr. David McMillan recommended approval of this BLA based on his review of the nonclinical safety information provided in the submission. Please refer to the Pharmacology/Toxicology review by Dr. McMillan for additional details.

General nonclinical pharmacology/toxicology considerations

Non-human primates were selected as the relevant species due to similarity in the binding affinity of ibalizumab to human and monkey CD4, and the similarity in binding patterns between rhesus monkeys and humans in the tissue cross-reactivity studies. Ibalizumab was not associated with any clinically-relevant adverse effects in the repeat-dose general toxicology studies in monkeys up to the highest doses tested. No clear effects on the immune system, including drug-related effects on $CD4^+$ T cell levels, immune cell phenotyping, lymphocyte proliferation, or cytokine production, were observed. Further, no effects on proliferation, activation, or apoptosis in human and monkey lymphocytes were observed *in vitro*.

Reproductive toxicology

Fertility and early embryonic development and embryo-fetal development studies with ibalizumab have not been conducted. An enhanced pre/postnatal development study in cynomolgus monkeys is in progress and will be submitted as a post-marketing requirement.

Genetic toxicology and carcinogenicity

Genotoxicology studies with ibalizumab were not needed in accordance with ICH S6.

Carcinogenicity studies with ibalizumab have not been conducted. A carcinogenicity risk assessment will be submitted as a post-marketing requirement.

5. Clinical Pharmacology

The Office of Clinical Pharmacology reviewed the clinical pharmacology information submitted, and considers the BLA approvable from their perspective. Please refer to the clinical pharmacology review by Dr. Qin Sun for additional details.

General clinical pharmacology considerations

Ibalizumab administered as a single agent exhibits nonlinear pharmacokinetics. Following single-dose administrations of ibalizumab as 0.5 to 1.5-hour intravenous 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 first 800 mg maintenance dose with mean concentrations over 30 mcg/mL throughout the dosing period.

The metabolism of ibalizumab was not studied. In general antibodies are degraded into small peptides and amino acids via catabolic pathways.

Critical intrinsic factors potentially affecting elimination

Renal/Hepatic Impairment:

There were no dedicated studies conducted in patients with renal or hepatic impairment. However, the large size of ibalizumab would suggest that it is not filtered by the kidneys and thus, the pharmacokinetics of ibalizumab is unlikely to be affected by renal impairment. Currently, there is insufficient evidence to conclude that hepatic impairment will not affect PK of ibalizumab.

Demographic/Host Factors:

No clinically relevant effect was found for age, body weight, sex, or baseline CD4+ cell count. Although a population PK analysis suggested that ibalizumab concentration decreases as body weight increases, the effect is unlikely to impact virologic outcome and does not warrant a dose adjustment.

Drug-drug interactions

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 anticipated.

Pharmacodynamic Considerations

Receptor occupancy assessment:

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.

QT assessment:

A thorough QT study was not conducted with ibalizumab. Serial electrocardiography was performed in trials TMB-202 and TMB-301, and no clinically meaningful changes in the QT interval were demonstrated.

Exposure-response relationship: See Section 8, Clinical/Statistical –Efficacy.

Immunogenicity:

All subjects enrolled in clinical trials TMB-301 and TMB-202 were tested for the presence of anti-ibalizumab IgG antibodies throughout their participation. One sample tested positive with low titer anti-ibalizumab antibodies. No adverse reaction or reduced efficacy was attributed to the positive sample reported in this subject. The effect of ADA on PK was inconclusive due to limited ADA positive samples and large variability in ibalizumab concentrations.

Formulation

Trogarzo is formulated in 10 mM histidine, 5.2% sucrose, 52 mM sodium chloride, 0.045% polysorbate 80, and (b) (4) a final pH of 6.0. It is supplied in 200 mg single (b) (4) vials at a concentration of 150 mg/mL.

There were minor differences between the formulations used in the Phase 2b trial (TMB-202) and the pivotal Phase 3 trial (TMB-301). The pivotal trial was performed with the to-be-marketed formulation.

6. Clinical Microbiology

Dr. Eric Donaldson recommended approval of this BLA based on his review of the nonclinical and clinical virology information provided in the submission. Please refer to the virology review by Dr. Donaldson for a detailed assessment of the virology data.

Ibalizumab blocks HIV-1 from infecting $CD4^+$ 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 preventing the viral transmission that occurs via cell-cell fusion. Ibalizumab does not

interact with CD4 domain 1 which binds with major histocompatibility complex (MHC) class II and is critical for normal immune function.

Ibalizumab is active against HIV-1 resistant to all approved antiretroviral agents and exhibits antiretroviral activity against R5-tropic, X4-tropic, and dual-tropic HIV-1.

No antagonism was demonstrated in cell culture studies when ibalizumab was combined with any of the following approved anti-retroviral drugs: maraviroc, enfuvirtide, efavirenz, abacavir, didanosine, emtricitabine, tenofovir, zidovudine, or atazanavir.

Phenotypic and genotypic test results revealed no evidence of cross-resistance between ibalizumab and any of the approved classes of anti-retroviral drugs (i.e., CCR5 co-receptor antagonists, gp41 fusion inhibitors, integrase strand transfer inhibitors [INSTIs], non-nucleos(t)ide reverse transcriptase inhibitors [NNRTIs], nucleos(t)ide reverse transcriptase inhibitors [NRTIs], or protease inhibitors [PIs]).

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

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.

7. Clinical/Statistical- Efficacy

This section summarizes the efficacy analyses conducted by the review team of the key trials supporting an indication for the treatment of HIV-1 infection in heavily treatment-experienced adults infected with MDR HIV-1 infection. The Applicant's development program for ibalizumab consisted of five clinical trials including two Phase 1 trials, one Phase 2a trial, one Phase 2b trial, and one Phase 3 trial. This section will focus on the supportive Phase 2b trial (TMB-202) and the pivotal Phase 3 trial (TMB-301). The study designs, subject characteristics, and key efficacy results from each of these trials are summarized below.

For information on the early phase clinical trials, and for additional details on the Phase 2b and Phase 3 trials, please refer to the Clinical Review by Dr. Virginia Sheikh and the Statistical Review by Dr. Karen Qi.

Study designs, baseline characteristics, and key efficacy results

Trial TMB-202

TMB-202 was a Phase 2b, multicenter, randomized, double-blind study, which evaluated the safety and efficacy of ibalizumab in heavily treatment-experienced subjects infected with MDR

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HIV-1. Subjects were required to have a viral load greater than 1,000 copies/mL and documented resistance to at least one antiretroviral medication from each of three classes of antiretroviral medications (NRTI, NNRTI, and PI). Enrollment criteria also required that subjects either recently failed ART or were on a failing ART regimen.

Eligible subjects were randomized in a 1:1 ratio to receive one of the following two regimens: 1) 800 mg of ibalizumab every two weeks (Q2W) plus optimized background therapy (OBR) or; 2) 2000 mg of ibalizumab every four weeks (Q4W) and placebo on the intervening 2-week period visit plus OBR. The selection of the OBR was aided by results of screening resistance testing and review of the patient's prior antiretroviral therapy. Once the screening resistance data became available and prior to randomization, the investigator selected an OBR including at least one agent to which the patient's viral isolate demonstrated viral sensitivity/susceptibility and which the patient was willing and able to take. The primary efficacy endpoint for the trial was the percentage of subjects with HIV RNA levels <50 copies/mL at Week 24.

A total of 113 subjects were enrolled. Fifty-nine subjects were randomized to receive ibalizumab 800 mg Q2W + OBR, and 54 subjects were randomized to receive 2000 mg Q4W + OBR. The majority of subjects were male (89%), white (62%), and enrolled in the US (97%). The median number of years since HIV diagnosis was 17. The median CD4 T cell count was 70 cells/μL and the median HIV RNA level was 4.6 $\log_{10}$ copies/ml.

The subjects were heavily treatment-experienced; 73% of subjects were treated with 10 or more antiretroviral drugs prior to study enrollment. The subjects were infected with MDR HIV and were highly resistant to available HIV therapy. The number of active drugs in the OBR was documented by assessing results of current and past genotypic and phenotypic resistance testing. A genotypic susceptibility score (GSS), phenotypic susceptibility score (PSS), and overall susceptibility score (OSS) was calculated for each subject. The GSS, PSS, and OSS are the sum of active drugs in the OBR based on genotypic, phenotypic, and combined resistance testing, respectively. The median GSS, PSS, and OSS scores (IQR) in TMB-202 trial participants were 1 (0-2), 2 (1-2), and 2 (1-2), respectively. The trial arms were well balanced for demographic and other baseline characteristics. Key efficacy findings are outlined in Table 1 below.

Table 1: TMB-202, Primary and Key Secondary Efficacy Outcomes at Week 24

Endpoint	**Variable**	**Ibalizumab 2000mg q4 weeks** **n=54**	**Ibalizumab 800 mg q2 weeks** **n=59**
Primary	HIV RNA < 50 copies/mL, % (n)* [95% exact CI]	27.8% (15) [16.5%, 41.6%]	44.1% (26) [31.2%, 57.6%]
Secondary	HIV RNA < 200 copies/mL, % (n)*	42.6% (23)	50.9% (30)
	Median CD4 T cell count increase from baseline (cells/mm^3)	16.0	34.0

*Snapshot approach
Source: Adapted from the FDA Statistical and Clinical Reviews

Notably, this trial demonstrated: 1) earlier virologic suppression in subjects in the 2000 mg Q4W arm and; 2) a higher percentage of subjects achieving virologic suppression at Week 24 in the 800 mg Q2W arm. Based on these results, the treatment regimen selected for the Phase 3 trial (TMB-301) consisted of a 2000 mg IV loading dose of ibalizumab followed by 800 mg IV every 2 weeks.

Trial TMB-301

TMC-301 was a phase 3, single-arm, multicenter trial which assessed the efficacy and safety of ibalizumab in in heavily treatment-experienced subjects infected with MDR HIV-1. Subjects were required to have a viral load greater than 1,000 copies/mL and documented resistance to at least one antiretroviral medication from each of three classes of antiretroviral medications (NRTI, NNRTI, and PI). Enrollment criteria also required that subjects either recently failed ART or were on a failing ART regimen.

The trial was composed of three discrete periods:

1. Control period (Day 0 to Day 6): Subjects were either monitored on current failing therapy or received no therapy if they had failed and discontinued treatment within the 8 weeks preceding screening. This was an observational period designed to establish the baseline HIV viral load. In general, HIV viral load was anticipated to remain relatively stable throughout this period since subjects received their failing regimen or no therapy.
2. Essential monotherapy period (Day 7 to Day 13): All subjects received a 2000 mg loading dose of ibalizumab on Day 7. Subjects on a failing ART regimen continued to receive their regimen in addition to the loading dose of ibalizumab. This period was to establish the short-term virologic activity of ibalizumab.
3. Maintenance period (Day 14 to Week 25): On Day 14, the OBR was initiated and was to include at least one agent to which the subject's virus was susceptible. Subjects received OBR throughout this period. Beginning at Day 21, an 800 mg maintenance dose of ibalizumab was administered every two weeks through Week 23. This period was to establish the durability of virologic suppression as well as the safety of ibalizumab when used in combination with an OBR.

The approach to the selection of the OBR was consistent with that described above for TMB-202. The primary efficacy endpoint was the proportion of subjects achieving a ≥ 0.5 $\log_{10}$ decrease in viral load at the end of the "Control Period" compared to the proportion of subjects achieving a ≥ 0.5 $\log_{10}$ decrease in viral load at the end of the "Essential Monotherapy Period". The trial design [including the primary (early) virologic endpoint at Day 13 and the secondary durability/safety endpoint at Week 25] was consistent with current FDA guidance for development of antiretroviral drugs in this patient population.

A total of 40 subjects were enrolled. The majority of subjects were male (85%), white (55%), and enrolled in the US (90%). The median number of years since HIV diagnosis was 23. The

median CD4 T cell count was 73 cells/μL and the median HIV RNA level was 4.5 $\log_{10}$ copies/ml.

The subjects were heavily treatment-experienced; 53% of subjects were treated with 10 or more antiretroviral drugs prior to study enrollment. The subjects were infected with MDR HIV and were highly resistant to available HIV therapy. The median GSS, PSS, and OSS scores (IQR) in TMB-301 trial participants were 1 (0-2), 2 (1-3), and 2 (1-2), respectively. Key virologic primary and secondary efficacy outcomes are provided in Tables 2 and 3, respectively.

Table 2: TMB-301, Primary Efficacy Outcomes

	Proportion of Subjects Achieving a ≥ 0.5 $\log_{10}$ Decrease in Viral Load (N=40)	**95% CI***
End of Control Period (Day 7)	3%	(0.06%, 13%)
End of Essential Monotherapy Period (Day 14)	83%	(67%, 93%)

*exact 95% confidence interval
Source: Adapted from the FDA Statistical and Clinical Reviews

The percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease from Day 7 to Day 14 was significantly higher than the percentage of subject achieving a ≥ 0.5 $\log_{10}$ decrease from Day 0 to Day 7 ($p < 0.0001$ based on McNemar's test).

Table 3: TMB-301, Secondary Efficacy Outcomes

	Ibalizumab (N=40)
HIV RNA < 50 copies/mL at Week 25 HIV RNA ≥ 50 copies/mL at Week 25*	43% 45%
HIV RNA < 200 copies/mL at Week 25 HIV RNA ≥ 200 copies/mL at Week 25**	50% 38%
No virologic data at Week 25 Discontinued due to AE or death	13% 13%

*included subjects who had ≥ 50 copies/mL in the Week 25 window, subjects who discontinued study drug due to lack of efficacy, and subjects who discontinued study drug for reasons other than an AE, death and at the time of discontinuation had a viral value ≥ 50 copies/mL
**included subjects who had ≥ 200 copies/mL in the Week 25 window, subjects who discontinued study drug due to lack of efficacy, and subjects who discontinued study drug for reasons other than an AE, death and at the time of discontinuation had a viral value ≥ 200 copies/mL
Source: Adapted from the FDA Statistical and Clinical Reviews

An increase in the mean and median number of CD4+ T-cells (44 cells/mm^3 and 17 cells/mm^3, respectively) was observed from Baseline to Week 25.

Subgroup analyses of interest are provided in Table 4. There appeared to be less durable HIV viral suppression in subjects with CD4 cell counts < 50 cells/mm^3, HIV viral load > 100,000 copies/mL and OSS=0; however, given the small number of subjects in each subgroup, these results should be viewed with caution.

Table 4: Trial 301, Subgroup Analyses

	Subjects achieving <50 HIV-1 RNA copies/mL (%)	**Subjects achieving <200 HIV-1 RNA copies/mL (%)**
CD4 Cell Counts		
<50 (n=17)	17.6	23.5
50-200 (n=10)	60.0	70.0
>200 (n=13)	61.5	69.2
Viral Load		
≤100,000 (n=33)	48.5	57.6
>100,000 (n=7)	14.3	14.3
OSS		
0 (n=5)	20.0	20.0
1 (n=12)	41.7	50.0
2 (n=18)	50.0	61.1
3 (n=3)	33.3	33.3
4 (n=2)	50.0	50.0

Conclusions on effectiveness

Trial TMB-301 demonstrated a highly significant difference in the percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease in HIV viral load after completion the Essential Monotherapy Period versus after completion of the Control Period. This was the primary endpoint of the trial and is an acceptable variation of the primary endpoint recommended in the FDA Guidance for Industry for pivotal trials in this patient population. Allowing subjects to serve as their own controls (versus employing a short-term placebo comparison arm) helps to address issues of inter-participant variability and sample size, that are particularly problematic for studies in this population.

The key secondary endpoint for Trial 301 was the percentage of subjects who achieved virologic suppression at Week 25, a measurement of longer-term durability. At Week 25, 43% and 50% of subjects remained undetectable at < 50 copies/mL and < 200 copies/mL respectively. Results from the 800 mg q 2 week arm of Trial 202 were remarkably similar with 44% and 51% of subjects remaining undetectable at < 50 copies/mL and < 200 copies/mL, respectively, at Week 24. As trial 301 was an uncontrolled trial, there remains some uncertainty surrounding the contribution of ibalizumab to the maintenance of virologic suppression. However, both TMB-301 and the 800 mg q 2 week arm of the supportive Phase 2b trial TMB-202 demonstrated highly similar rates of longer-term virologic suppression at 25 and 24 weeks, respectively. The concordance of these results, generated with virtually identical treatment regimens in similar patient populations, may reflect ibalizumab's contribution to durability. Longer term placebo-controlled comparisons in this population would not be expected to be acceptable to physicians

or patients as continued use of the unmodified (failing) regimen, or modified but suboptimal background regimen, increases the risk of emergence of resistance to the investigational drug and/or the background drugs.

8. Safety

This section will provide a summary of safety focusing on TMB-301, the Phase 3 pivotal trial using the to-be-marketed treatment regimen. As no unique safety signals were demonstrated in the earlier clinical trials, the safety profile of ibalizumab as demonstrated in TMB-301 is illustrative of the overall safety profile of the product. For a complete description of the Agency's safety assessment for ibalizumab, please refer to the Clinical Review performed by Dr. Virginia Sheikh.

Adequacy of the safety database, Applicant's safety assessments, and submission quality

The safety database at the time of BLA submission included 303 subjects who had been exposed to IV ibalizumab (at any dose and for any duration) across the entire development program, including 20 patients who received ibalizumab through expanded access. Given ibalizumab's restricted indication, Breakthrough and Orphan Drug designation, and favorable safety profile, the Agency deemed the safety database to be adequate.

The Sponsor provided a basic assessment of safety as a component of the BLA submission; however, numerous requests for additional safety-related information and analyses were required to complete the review. No substantive issues with data integrity were identified.

Key safety results, including deaths, serious adverse events (SAEs), discontinuations due to AEs, results of laboratory tests, and immunogenicity

The safety profile of ibalizumab was favorable. The most common adverse reactions (i.e., adverse events deemed related to study drug by investigator) reported in at least 5% of subjects were diarrhea (8%), dizziness (8%), nausea (5%), and rash (5%). Most (90%) of the adverse reactions reported were mild or moderate in severity. Two subjects experienced severe adverse reactions: one subject had a severe rash and one subject developed immune reconstitution inflammatory syndrome (IRIS) manifested as an exacerbation of progressive multifocal leukoencephalopathy.

Four deaths occurred in TMB-301, none of which were attributed to ibalizumab. They included: 1) respiratory arrest secondary to Kaposi's sarcoma; 2) hepatic failure secondary to cirrhosis due to hepatitis C infection; 3) lymphoma and; 4) presumed HIV wasting syndrome.

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

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investigator's causality determination as IRIS is a common event following the initiation of effective ART in severely immunosuppressed patients.

Four TMB-301 subjects stopped study drug due to an AE, including three participants who died (described above) and one participant who developed IRIS (described above). The nature and frequency of the significant safety events (deaths, SAEs, and discontinuations due to AEs) reported largely reflect the patient population targeted for enrollment, i.e., advanced HIV/AIDS patients with MDR HIV infection, failing current ART.

Overall, laboratory analyses did not reveal any significant safety concerns. Table 5 displays the combined grade 3 and 4 laboratory abnormalities that occurred in TMB-301. Although Grade 3 creatinine elevation occurred in 10% of subjects in TMB-301, these abnormalities occurred only in subjects with underlying renal disease, risk factors for renal disease, and/or concomitant medications known to be nephrotoxic or to cause modest elevations in creatinine via inhibition of tubular secretion (e.g., cobicistat). There was no apparent causal relationship between ibalizumab administration and elevation in creatinine.

Table 5: Trial TMB-301, Selected Laboratory Abnormalities (Grade 3 or 4)

	% Subjects N=40
Bilirubin (≥ 2.6 x ULN)	5%
Direct Bilirubin (> ULN)	3%
Creatinine (> 1.8 x ULN or > 1.5 x baseline)	10%
Hyperglycemia (> 250 mg/dL)	3%
Lipase (> 3.0 x ULN)	5%
Phosphate (< 1.0 mg/dL)	8%
Uric Acid (> 12 mg/dL)	3%
Hemoglobin (< 8.5 g/dL)	3%
Platelets (< 50,000/mm^3)	3%
Leukocytes (< 1.5 10^9 cells/L)	5%
Neutrophils (< 0.6 10^9 cells/L)	5%

Submission-specific safety issues

Rash was identified as an adverse event of interest prior to the conduct of the Phase 3 trial. Rash events, which were primarily mild or moderate in severity, were common in both TMB-202 and TMB-301. One subject in TMB-202 experienced a grade 2 rash which led to drug discontinuation, and one subject in TMB-301 experienced a grade 3 rash; both of these events were judged related to study drug. No serious dermatologic adverse reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic

symptoms) have been reported in ibalizumab's development program to date. The available data indicates that rash may be associated with ibalizumab use in some patients.

As ibalizumab is an intravenously administered monoclonal antibody, special attention was given to assessing for evidence of infusion-related toxicity. There was no convincing evidence of clinically significant infusion reactions (e.g., hypersensitivity reactions, anaphylaxis) in ibalizumab's development program to date.

Although non-clinical studies demonstrated that ibalizumab does not interact with CD4 domain 1 (see Section 6, Clinical Microbiology), special attention was also given to assessing for evidence of negative clinical impact on immune function. No evidence of increased susceptibility to opportunistic infections with ibalizumab treatment was found. The frequency and distribution of infection-related adverse events described in TMB-301 and TMB-202 were consistent with that expected in the enrolled populations.

9. Advisory Committee Meeting

As there were no issues identified that would benefit from an Advisory Committee discussion, an Advisory Committee was not convened to discuss this application.

10. Pediatrics

No pediatric trials were submitted in support of this BLA. Notably, ibalizumab has orphan drug status and is therefore exempt from Pediatric Research Equity Act (PREA) requirements.

11. Other Relevant Regulatory Issues

- *Financial disclosures*

Financial disclosures were provided and reviewed for investigators involved in TMB-202 and TMB-301. There were no financial disclosures of significant concern, individually or collectively. The financial disclosures do not impact the approvability of Trogarzo. Please refer to the Clinical Review for additional details.

- *Other Good Clinical Practice (GCP) issues*

The clinical trials discussed in this review were 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.

- *Office of Scientific Investigations (OSI) audits*

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 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 only if irregularities were identified in the TMB-301 records.

Per OSI's assessment, the deviations noted at the four sites were generally minor and would not have significant impact on safety or efficacy considerations; therefore, the data generated by these sites and submitted by the Applicant appeared acceptable in support of the respective application/indication.

The notable exception involved Site #43 from Study TMB-202. This site was issued a Form FDA 483 citing inspectional observations regarding the failure to retain Study TMB-202 records. In his response to the 483, the site's primary investigator noted that he was able to locate the records in question and provided these records as a component of his response. However, at present, OSI has not re-inspected the site and therefore cannot attest that the documents the primary investigator provided with his written response were in fact true copies of the original study records. As such, OSI recommended that the review division consider performing a sensitivity analysis with and without data from Site #43 to determine whether overall safety and efficacy in Study TMB-202 were impacted. The review division determined that the exclusion of data from Site #43 in Study TMB-202 would not significantly impact our conclusions.

Please refer to the OSI Consult Review for further details.

12. Labeling

Prescribing Information

The summary that follows reflects the major changes to the Applicant's labeling that have been proposed by the Agency and accepted by the Applicant. Please refer to the individual FDA reviews from each of the review disciplines for additional details.

- INDICATIONS AND USAGE section:

The indication for ibalizumab was narrowed from the Sponsor's proposed indication to one consistent with the patient population studied and ibalizumab's orphan designation. The final indication reads as follows:

TROGARZO, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.

- ADVERSE REACTIONS section:

The section was revised to focus primarily on TMB-301, as this was the only clinical trial that used the to-be-recommended dosing regimen (i.e., a 2000 mg IV loading dose followed by 800 mg IV every 2 weeks).

In accordance with FDA guidance, the listing of adverse events was limited to those events for which there was at least a possible causal relationship with the drug (i.e., adverse reactions).

- CLINICAL PHARMACOLOGY section:

(b) (4)

Although a formal renal impairment study was not conducted, a statement was included in labeling indicating that it is not anticipated that renal impairment will impact the pharmacokinetics of ibalizumab. A similar statement was not included for hepatic impairment as the potential impact of hepatic impairment on the pharmacokinetics of ibalizumab is less certain.

- CLINICAL STUDIES section:

In accordance with FDA guidance, this section was limited to describing clinical trials that used the to-be-recommended dosing regimen (i.e., TMB-301).

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Based on the overall safety profile of ibalizumab, a REMS is not recommended.

Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs)

To date, the Agency has determined that the following PMCs and PMRs should be issued:

Pharmacology/Toxicology PMRs

1. Provide a risk assessment of the carcinogenic potential of ibalizumab.
2. Submit of the final study report for the enhanced pre/postnatal development study in cynomolgus monkeys.

Clinical Virology PMRs

3. Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: P236E, K303R, P367L, I369V, R474K, K615R/N, N649I/R, L774S, and L831V. In addition, determine the phenotypes of the substitutions observed in the various coding sequences noted: C1cons_V75I; gp41cons_E229G/Q229P/R and gp41cons_L274V/A274T; V1V2_N12K and V1V2_N14D/V14M/deletion; V4_T23N/deletion.
4. Provide the fastq envelope sequences from the next generation sequencing of samples collected from subjects who failed treatment to better characterize the HIV-1 gp120 sequence at the time of failure.

5. Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: S143P, Kl71E, Nl86K/S/R, Q308II/P, G352K/E, and V54'7A/G.
6. Provide integrated virology datasets for clinical trials TMB-202, entitled "A Phase 2b Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of lbalizumab plus an Optimized Background Regimen in Treatment Experienced Patients Infected with HIV-l" (Amended to 24 Week Study) and TMB-301, entitled "A Phase 3, Single Arm, 24- Week. Multicenter Studv of lbalizumab plus an Optimized Background Regimen (OBR) in Treatment Experienced Patients Infected with Multi-Drug Resistant HIV-1". This should include one database for each clinical trial with baseline data for all subjects who were enrolled, and time of virologic failure data for all subjects who failed treatment and were assessed for resistance.

Product Quality PMCs

7. To develop, validate, and implement an appropriate pharmaceutical grade container closure system for ibalizumab bulk drug substance.
8. To perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality.

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ADAM I SHERWAT
03/05/2018

JEFFREY S MURRAY
03/05/2018

JOHN J FARLEY
03/06/2018

Cross-Discipline Team Leader (CDTL) Memorandum

Date	November 8, 2017
From	Adam Sherwat
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	BLA 761065
Applicant	TaiMed Biologics Inc.
Date of Submission	May 3, 2017
PDUFA Goal Date	January 3, 2018
Proprietary Name / Non-Proprietary Name	Trogarzo/ Ibalizumab
Dosage form(s) / Strength(s)	2000 mg intravenous (IV) loading dose followed by 800 mg IV every 2 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of adults infected with HIV-1 resistant to at least one agent in three different classes
Recommendation on Regulatory Action	Pending based on the Applicant's ability to satisfactorily address the outstanding manufacturing issues
Recommended Indication(s)/Population(s)	Treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV infection failing current antiretroviral therapy

The CDTL Summary Review is complete. I recommend the approval of ibalizumab once the deficiencies outlined by the Product Quality review discipline are satisfactorily addressed. The CDTL Summary Review will be placed in the FDA's Document Archiving, Reporting and Regulatory Tracking System later in the review cycle as a Combined CDTL, Division Director, and ODE Summary Review.

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/s/

ADAM I SHERWAT
11/05/2017