

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761065Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761065
PDUFA Goal Date	January 3, 2018
OSE RCM #	2017 – 856 2017 – 857
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	September 22, 2017
Subject	Evaluation of Need for a REMS
Established Name	Ibalizumab
Trade Name	Trogarzo
Name of Applicant	TaiMed Biologics
Therapeutic Class	To be determined
Formulation(s)	200 mg (150 mg/mL) sterile solution for intravenous infusion
Dosing Regimen	Loading dose: 2000 mg IV once Maintenance dose: 800 mg IV every 2 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Trogarzo (ibalizumab) is necessary to ensure the benefits outweigh its risks. TaiMed Biologics submitted a Biologic Licensing Application (BLA 761065) for ibalizumab with the proposed indication: in combination with other antiretroviral(s), for the treatment of adults infected with HIV-1 resistant to at least one agent in three different classes. The risks associated with ibalizumab include immune reconstitution inflammatory syndrome (IRIS), diarrhea, dizziness, nausea and rash. The applicant did not submit a proposed REMS or risk management plan with this application.

IRIS is a common adverse event of antiretroviral therapy initiation, therefore likely prescribers such as infectious diseases practitioners should be aware of this risk.¹ If approved, the labeling will communicate the risks of ibalizumab with Warnings and Precautions specifically highlighting the risk of IRIS. DRISK and the Division of Antiviral Products (DAVP) agree that a REMS is not needed to ensure the benefits of ibalizumab outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Trogarzo (ibalizumab) is necessary to ensure the benefits outweigh its risks. TaiMed Biologics submitted a Biologic Licensing Application (BLA 761065) for ibalizumab with the proposed indication: in combination with other antiretroviral(s), for the treatment of adults infected with HIV-1 resistant to at least one agent in three different classes. The risks associated with ibalizumab include immune reconstitution inflammatory syndrome (IRIS), diarrhea, dizziness, nausea and rash. This application is under review in the Division of Antiviral Products (DAVP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Trogarzo (ibalizumab), a new molecular entity,^a is a CD4 ^{(b) (4)} directed ^{(b) (4)} post-attachment inhibitor ^{(b) (4)} with the proposed indication: in combination with other antiretroviral, for the treatment of adults infected with HIV-1 resistant to at least one agent in three different classes. Ibalizumab is proposed as a 200 mg (150 mg/mL) sterile solution for intravenous administration. The recommended dose is as follows: 2,000 mg IV once as a loading dose then 800 mg IV every two weeks indefinitely. Treatment is continued until disease progression or unacceptable toxicity occurs.^b Ibalizumab has been granted both orphan drug and breakthrough therapy designations and is not currently approved in any jurisdiction.

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761065 relevant to this review:

- 04/16/2001: IND 009776 submission for the treatment of HIV infection received
- 10/20/2014: Orphan drug designation granted
- 02/23/2015: Breakthrough therapy designation granted
- 05/03/2017: BLA 761065 submission received
- 08/18/2017: Mid-cycle Communication; applicant informed that there are currently no major safety concerns that would require a REMS

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Nearly 37 million people are living with human immunodeficiency virus (HIV) around the world.² Of the 1.2 million people living with HIV in the U.S., about 10,000 patients have multidrug resistant HIV and are left with few,^c if any, treatment options.³ These patients often die of AIDS (stage 3 HIV) related illnesses, also known as opportunistic infections, because of the inability of their antiretroviral therapy (ART) to keep HIV RNA levels sufficiently low.^d Because drug resistance can either be developed or transmitted with the initial HIV infection, ART regimens often have to be modified for effectiveness.⁴ With 2.1 million new infections occurring worldwide in 2015, there is a strong need for novel ART options.²

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment of multidrug resistant (MDR) HIV is complex. Antiretroviral therapy (ART) selection is based upon the assessment of patient-specific factors including adherence, drug interactions, tolerability, HIV RNA and CD4 T-lymphocyte cell counts, treatment history and resistance testing.⁵ Current drug options in the six mechanistic classes include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor (FI), a CCR5 antagonist, and integrase strand transfer inhibitors (INSTIs). Because discontinuing or interrupting ART can lead to clinical progression, it's imperative that the ART regimen includes two to three fully active drugs. If maximal virologic suppression cannot be achieved, drugs with partial response are often continued because disease progression may be delayed. However, the potential benefit of delaying disease progression should be balanced with the risk of acquiring additional drug resistance. Due to the complexity of ART regimens, investigational drugs are recommended for consideration as treatment in patients with MDR HIV.⁵

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

4 Benefit Assessment^e

The efficacy and safety of ibalizumab for the treatment of MDR HIV-1 was demonstrated in two pivotal studies, TMB-301 and TMB-202. Both studies enrolled patients who had an HIV viral load greater than 1000 c/mL despite ART and were on stable ART for 8 weeks or had failed and off ART. Enrolled patients could not have had an opportunistic infection in the past 3 months. Patients were required to have a life expectancy greater than 3 months and had to be fully susceptible to another ART drug. As shown in Table 1 below, the primary and secondary endpoints in both studies were similar.

TMB-301 was a Phase 3, single arm, 24-week, multicenter study of ibalizumab plus an optimized background regimen (OBR). Forty patients received ibalizumab 2000 mg IV once as a loading dose then 800 mg IV every two weeks. The primary efficacy endpoint was the proportion of patients with a ≥ 0.5 \log_{10} decrease in viral load after 7 days. At day 7, 82.5% of patients had a ≥ 0.5 \log_{10} decrease in the RNA viral load.

TMB-202 was a phase 2b, randomized, double-blind, 48-week, multicenter, dose-response study of ibalizumab plus an OBR. The trial was amended to 24 weeks. A total of 113 patients were enrolled in the study with Arm 1 (59 patients) receiving 800 mg IV every two weeks and Arm 2 (54 patients) receiving 2000 mg IV every 4 weeks. The primary endpoint was the proportion of patients with HIV RNA less than 50 c/mL at week 24. At week 24 in Arm 1 (800 mg IV every two weeks), 44.1% of patients had an HIV RNA less than 50 c/mL. At week 24 in Arm 2 (2000 mg IV every four weeks), 27.8% of patients had an HIV RNA less than 50 c/mL.

The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness for both studies (TMB-301 and TMB-202) based on the primary and secondary endpoints table 1 below.⁶

Table 1: Ibalizumab Studies TMB-301 and TMB-202 – Primary and Secondary Efficacy Endpoints

Efficacy Endpoints	Study TMB-301	Results	Study TMB-202 Arm 1: 800 mg IV Q2W Arm 2: 2000 mg IV Q4W	Results Arm 1	Results Arm 2
Primary	Proportion achieving a ≥ 0.5 \log_{10} decrease from Day 7 (baseline) in viral load at Day 14	N = 33 (82.5%) p-value <0.0001	Proportion with HIV-1 RNA <50 copies/mL at Week 24	N = 26 (44.1%)	N = 15 (27.8%)
Secondary ^a	Proportion with HIV-1 RNA levels at week 25: • < 50 copies/mL • < 400 copies/mL	N = 17 (42.5%) N = 21 (52.5%)	Proportion with HIV-1 RNA <200 copies/mL at Week 24	N = 31 (52.5%)	N = 23 (42.6%)
	Mean change in viral load from Day 7 (baseline) to: • Day 14 and • Week 25/EOS	\log_{10} copies/mL N = 40 -1.07 (0.618) -1.64 (1.541)	Proportion with HIV-1 RNA < 400 copies/mL at Week 24	N = 34 (57.6%)	N = 25 (46.3%)

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

	Proportion achieving a decrease in viral load from Day 7 (baseline), to Day 25/EOS: <ul style="list-style-type: none"> • $\geq 0.5 \log_{10}$ • $\geq 1.0 \log_{10}$ 	N = 25 (62.5%) N = 22 (55.0 %)	Proportion achieving $\geq 1.0 \log_{10}$ decrease from Baseline in viral load at Week 24	N = 37 (62.7%)	N = 32 (59.3%)
	Mean change in CD4+ cell count from Day 7 (baseline) at Week 25/EOS [Mean (SD)]	Cells/ μ L N = 27 62.4 (105.75)	Proportion achieving $\geq 0.5 \log_{10}$ decrease from Baseline in viral load at Week 24	N = 40 (67.8%)	N = 32 (59.3%)

EOS = end of study; HIV = human immunodeficiency virus; RNA = ribonucleic acid; SD = standard deviation

^a Described in Study TMB-202 Statistical Analysis Plan as other primary efficacy endpoints

5 Risk Assessment & Safe-Use Conditions

The safety and tolerability of ibalizumab was assessed from the results of the pivotal studies, TMB-301 and TMB-202, in addition to Study TMB-311. TMB-311, an ongoing expanded access study, provides long-term safety data for patients exposed to ibalizumab from investigator-initiated INDs for up to 8 years. The serious adverse reaction (referred to as risk) determined to be associated with ibalizumab is IRIS.^f If approved, the Warnings and Precautions section of the label will address this risk. The serious risk IRIS and the deaths that occurred are discussed in the sections below.

5.1 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

Immune reconstitution inflammatory syndrome was reported in one patient in Study TMB-301. The patient was a 60 year old white male with concomitant progressive multifocal leukoencephalopathy who permanently discontinued study drug. He remained chronic and stable after discontinuation.

5.2 DEATHS

There were a total of six deaths for Studies TMB-301 and TMB-202. None were considered treatment-related by the clinical reviewer. In TMB-301, the four deaths were attributed to Kaposi's sarcoma, hepatic failure, lymphoma, and asthenia (AIDS).⁷ In TMB-202, the two deaths in Arm-1 (800 mg IV Q2W) were attributed to acute respiratory distress syndrome and AIDS.⁶ As of February 27, 2017, there were three deaths in the ongoing expansion Study TMB-311. The applicant attributed these deaths to metastatic tonsil cancer, sepsis, and injury (trauma from fall).⁸

^f Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6 Expected Postmarket Use

Ibalizumab will be primarily prescribed in the outpatient setting and the likely prescribers will be infectious diseases providers specializing in HIV management. These providers are likely to be familiar with the management of adverse events associated with antiretroviral therapy including IRIS.^{1,9} The draft prescribing information (PI) currently addresses the associated serious risk and management of IRIS in the Warnings and Precautions section.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for ibalizumab beyond labeling and routine pharmacovigilance for ibalizumab.

8 Discussion of Need for a REMS

The Division of Antiviral Products favors approval of ibalizumab based on the efficacy and safety information currently available. MDR HIV is a serious disease with an estimated 10,000 people currently living with the disease in U.S. Treatment options for this subgroup of HIV are limited due to the development of transmission of drug resistance. Ibalizumab is a novel monoclonal antibody with a unique mechanism which may reduce the likelihood of cross-resistance with other drugs treating HIV.

The serious risk associated with ibalizumab is IRIS. HIV-associated IRIS is a common adverse event of early ART initiation especially in patients with advanced disease.¹ The incidence of IRIS varies (6.4% to 37.7%) and is dependent upon the targeted antigen and associated opportunistic infection.^{1,9} Prescribers specializing in the management of HIV, such as infectious diseases providers, are likely to be familiar with managing the risk of IRIS as it is well known in this specialty.¹⁰ The labeling will be used to communicate this risk. DRISK recommends that, should ibalizumab be approved, a REMS is not necessary to ensure its benefits outweigh its risks.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

1. Walker NF, Scriven J, Meintjes G, Wilkinson RJ. Immune reconstitution inflammatory syndrome in HIV-infected patients. *HIV/AIDS (Auckland, NZ)*. 2015;7:49-64.
2. HIV/AIDS. National Institute of Allergy and Infectious Diseases. Available at: <https://www.niaid.nih.gov/diseases-conditions/hivaids>. Accessed June 26, 2017.
3. IDSA: New Drug Benefits Patients with Multi-Drug Resistant HIV [press release]. Infectious Diseases Society of America, October 28, 2016.
4. Understanding HIV/AIDS, Drug Resistance Fact Sheet. AIDSinfo. Available at: <https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/21/56/drug-resistance#>. Accessed June 26, 2017.
5. 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. Available at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed June 22, 2017.
6. Sheikh V. Division of Antiviral Products (DAVP). Trogarzo (ibalizumab) Mid-Cycle Meeting, Clinical Reviewer Slides. August 11, 2017.
7. Sheikh V. Division of Antiviral Products (DAVP). Trogarzo (ibalizumab) Global Assessment Meeting #1, Clinical Reviewer Slides June 13, 2017.
8. TaiMed Biologics. Trogarzo (ibalizumab). TMB-311, 60-Day Safety Update. July 3, 2017.
9. Meintjes G, Scriven J, Marais S. Management of the Immune Reconstitution Inflammatory Syndrome. *Current HIV/AIDS Reports*. 2012;9(3):238-250.
10. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed September 6, 2017.

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/s/

INGRID N CHAPMAN
09/22/2017

CYNTHIA L LACIVITA
09/22/2017
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