CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	761065
Drug Name:	Trogarzo™ (Ibalizumab), intravenous injection with a single loading dose of 2000 mg followed by a maintenance dose of 800 mg every two weeks
Indication:	Treatment of adults infected with HIV resistant to at least one agent in three different classes
Applicant:	TaiMed Biologics, Inc.
Date(s):	Receipt Date: 04/28/2017 Additional Data Receipt Date: 05/03/2017 and 05/11/2017 PDUFA Date: 01/03/2018
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Keywords: single-arm, McNemar's test, Fisher's exact test, Wald Chi-Square test, placebo-controlled, ibalizumab

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1. EXECUTIVE SUMMARY

TaiMed Biologics, Inc. submitted a Biologics License Application (BLA) to support ibalizumab in treatment of HIV treatment-experienced (TE) adult subjects with multi-class drug resistance. The proposed regimen was a single loading dose of 2000 mg ibalizumab followed by a maintenance dose of 800 mg ibalizumab every two weeks in combination with optimized background regimen (OBR). Orphan drug status was granted by FDA due to potentially small sample size of the patient population with multi-class drug resistance and limited treatment choices.

Evidence supporting the BLA comes from a Phase 3 single-arm study referred to as TMB-301. The study enrolled 40 subjects and consisted of three periods: a control period from Day 0 to Day 6, an essential monotherapy period from Day 7 to Day 13, and maintenance period from Day 14 through Week 25. During the control period, subjects were monitored on current failing therapy or received no therapy if subjects had failed and discontinued treatment within the eight weeks preceding screening. Thus, subjects served as their own control. In the essential monotherapy period, subjects received 2000 mg loading dose of ibalizumab on Day 7 while continuing on their current failing therapy up to Day 13. Ibalizumab was anticipated to be the only active antiretroviral agent in this period. Subjects were administered OBR in the beginning of the maintenance period on Day 14. Meanwhile subjects received 800 mg maintenance dose of ibalizumab every two weeks starting on Day 21 up to Week 23. The baseline HIV RNA was assessed prior to the first injection of ibalizumab on Day 7, and HIV RNA level at the end of the essential monotherapy period was obtained prior to receiving the first dose of OBR on Day 14. The primary efficacy endpoint was the percentage of subjects achieving a ≥ 0.5 $\log_{10}$ reduction in HIV RNA from Day 7 to Day 14. The study results showed that 33 of the 40 subjects (82.5%) achieved a ≥ 0.5 $\log_{10}$ reduction in HIV RNA from Day 7 to Day 14. By contrast, only one subject had a ≥ 0.5 $\log_{10}$ decrease in HIV RNA from the beginning to the end of the control period, and this one subject actually violated protocol by taking an OBR at the end of the control period. Furthermore, 42.5% of the subjects had HIV RNA < 50 copies/mL at Week 25.

Additionally, limited supportive data were reviewed from a Phase 2b study (TMB-202) conducted in a similar patient population to that of TMB-301. The study evaluated two ibalizumab dosing regimens: 800 mg ibalizumab every two weeks plus OBR and 1200 mg ibalizumab every four weeks plus OBR. Subjects were randomized equally to receive one of the two regimens for 24 weeks. The primary efficacy endpoint was the percentage of subjects with HIV RNA below 50 copies/mL at Week 24. In this study, 44.1% of the subjects achieved HIV RNA below 50 copies/mL at Week 24 in patients who received 800 mg ibalizumab every two weeks plus OBR, as compared to 27.8% in the 2000 mg ibalizumab every four weeks plus OBR group. This result supported the use of 800 mg ibalizumab every two weeks plus OBR in the maintenance period in TMB-301.

2. INTRODUCTION

2.1 Overview

There are approximately 1.1 million people in the US are living with HIV, according to Center for Disease Control and Prevention. More than 30 antiretroviral agents are approved by FDA for the treatment of HIV infection. These drugs belong to six drug classes which include nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, entry inhibitors, integrase inhibitors and pharmacokinetic enhancers. Combinations of these medications effectively control HIV replication. However, development of drug resistance among patients who initially benefit from the therapies remains one of the major concerns. According to the applicant, there are approximately 5,000 HIV TE patients with multiple-class drug resistance in the US. The disease is rare, and there is an unmet medical need to develop new therapies to treat these patients since their treatment choices are very limited. Therefore, the applicant conducted clinical trials to evaluate the efficacy and safety of ibalizumab that is a HIV entry inhibitor for the treatment of this patient population. Due to the small patient population, the rare disease designation was granted for this drug.

This review will focus on the efficacy of two studies submitted in this BLA: a pivotal Phase 3 trial, TMB-301, as well as a Phase 2b trial, TMB-202, which serves as a supportive study. The two studies recruited similar patients, but the study designs were different. Study TMB-202 was conducted earlier, and its results provided the basis to design TMB-301. Summaries of the key elements of the study designs for the two studies are displayed in Table 1.

Table 1: List of Studies Included in Review

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
TMB-301	single-arm, multicenter, subjects served as their own control	24 weeks	4 weeks	40 subjects	Treatment-experienced patients infected with multi-class drug resistant HIV
TMB-202	Randomized, double-blind, multicenter	24 weeks	4 weeks	Group 1: 800 mg of Trogarzo every two weeks plus OBR for 24 weeks (sample size[1] = 59 subjects) Group 2: 2000 mg of Trogarzo every four weeks plus OBR for 24 weeks (sample size[1] = 54 subjects)	same as TMB-301

2.2 Data Sources

The original BLA is located in \\CDSESUB1\evsprod\BLA761065\0010. The datasets for TMB-301 is located in \\CDSESUB1\evsprod\BLA761065\0013\m5\datasets\tmb-301.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted efficacy data for evaluation for both TMB-301 and TMB-202. An adeffout.xpt data file that was formatted in accordance with the FDA guidance on Efficacy Data Submission on ADaM Conversion for HCV Drugs was provided for TMB-301. An adeffout.xpt for the integrated summary of effectiveness (ISE) including TMB-301 and TMB-202 was also submitted, and data for TMB-202 could be obtained from it.

The quality of the submitted data was not high. The labels of some variables in the datasets were not informative. Additionally, the reviewer identified some minor discrepancies between the study report and the submitted datasets in TMB-202. According to the applicant's responses to the information requests, the study report was based on the SAP for TMB-202 but the dataset was based on the SAP for TMB-301. However, the SAPs for the two studies were slightly different, which may have caused the discrepancies between the study report and the dataset. The detailed description of discrepancies will be provided in the relevant sections later.

3.2 Evaluation of Efficacy

Evaluation of efficacy for TMB-301 and TMB-202 will be provided separately since the two studies had different study designs.

3.2.1 TMB-301

3.2.1.1 Study Design and Endpoints

TMC-301 was a phase 3, single-arm, multicenter study to access the efficacy and safety of IV ibalizumab in TE adult subjects with multi-drug resistant HIV infection. The study was composed of the following three 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 safety and virologic stability of the current failing regimen and to establish baseline HIV viral load and CD4 cell counts. In general, HIV viral load and CD4 cell counts were anticipated to maintain the same levels throughout this period since subjects received the failing regimen or did not receive therapy.

2) Essential monotherapy period (Day 7 to Day 13): All subjects received 2000 mg loading dose of ibalizumab on Day 7. Subjects on a failing therapy continued to receive the therapy in addition to the loading dose. Ibalizumab was expected to be the only active antiretroviral agent in this period. Therefore, the short-term safety and efficacy contribution of ibalizumab

could be assessed by comparison to the control period, as subjects could serve as their own control.

3) Maintenance period (Day 14 to Week 25): On Day 14, the OBR was initiated and was supposed to include at least one agent to which the subject's virus was susceptible. Subjects received OBR throughout this period. Beginning at Day 21, 800 mg maintenance dose of ibalizumab was administered every two weeks through Week 23. This period was to establish the durability of efficacy as well as the safety of ibalizumab when used in combination of an OBR.

HIV viral load and CD4 cell counts were measured at screening, on Day 0, prior to infusion of the loading dose of ibalizumab on Day 7, prior to receiving the first dose of OBR on Day 14, on Day 21 and then every four weeks up to Week 25. The measurements on Day 7 were considered as baseline values, while the measurements on Day 14 were regarded as the values at the end of the essential monotherapy period.

The primary objective of the study was to demonstrate the antiviral activity of ibalizumab at Day 14 and at Week 25/End of Study (EOS).

The primary efficacy endpoint was the percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease from Day 7 (baseline) in viral load at Day 14. The following secondary efficacy endpoints were evaluated:

- percentage of subjects achieving a ≥ 0.5 $\log_{10}$ and ≥ 1 $\log_{10}$ decrease from Day 7 (baseline) in viral load at Week 25
- percentage of subjects with HIV RNA level < 50 copies/mL and < 400 copies/mL at Week 25
- mean change from Day 7 (baseline) in viral load at Day 14 and Week 25
- mean change from Day 7 (baseline) in CD4 cell count at Week 25

During the course of the protocol development, the review team recommended the study should include a short term (7 days – 2 weeks) monotherapy lead-in phase and subjects should be randomized to either continue their current failing regimen plus placebo or to receive ibalizumab in addition to their current failing regimen in this lead-in phase. However, the applicant was concerned about the difficulty in enrolling subjects infected with multiple drug resistant HIV due to the limited patient population. Therefore they proposed a single-arm design including a control period and an essential monotherapy period so that subjects could serve as their own controls, as described above. This single-arm design required a smaller sample size as compared to the two-arm, placebo-controlled design. The review team agreed with the applicant's concern and deemed the proposed single-arm design to be acceptable.

Additionally, the primary objective of demonstrating the antiviral activity of ibalizumab at Day 14 could be assessed by the primary efficacy endpoint. However, another primary objective of demonstrating the sustained antiviral activity of ibalizumab at Week 25 could not be evaluated in the study. Based on the study design, all subjects were switched from the failing background

therapy to the OBR starting on Day 14 up to Week 25. The secondary efficacy endpoints at Week 25 could investigate the efficacy of ibalizumab in combination with an OBR instead of ibalizumab alone.

3.2.1.2 Patient Disposition, Demographic and Baseline Characteristics

Table 2 displays the patient disposition in TMB-301. Among all 40 subjects receiving at least one dose of study drug, 80% of the subjects completed the study treatment. The most common reason for discontinuation of study drug was AE (10%).

Table 2: Applicant's Result for Patient Disposition in TMB-301

Number of subjects enrolled	40
Number of subjects treated	40 (100%)
Number of subjects completed study drug	32 (80%)
Number of subjects discontinued study drug	8 (20%)
Adverse event	4 (10%)
Physician decision	1 (2.5%)
Withdrawal by patient	1 (2.5%)
Patient noncompliant	1 (2.5%)
Lost to follow-up	1 (2.5%)

Source: Table 3 in clinical study report for TMB-301

Table 3 shows patient demographics. Among all treated subjects, the median age was 53 years, 85% were male, 55% were white, and 90% were enrolled in US sites.

Table 3: Applicant's Result for Patient Demographics in TMB-301 (ITT)

	Ibalizumab (N=40)
Age	
Mean (SD)	50.5 (11.0)
Median	53.0
Min, Max	23.0, 65.0
Gender	
Male	34 (85.0%)
Race	
White	22 (55.0%)
African American	13 (32.5%)
Asian	4 (10.0%)
Unknown	1 (2.5%)
Ethnicity	
Hispanic or Latino	11 (27.5%)
Non Hispanic or Latino	27 (67.5%)
Unknown	2 (5.0%)
Region[1]	
USA	36 (90.0%)
Taiwan	4 (10.0%)

Source: Table 6 in clinical study report for TMB-301
[1]generated by statistical reviewer

Table 4 displays the selected baseline disease characteristics. The median duration of diagnosis of HIV was 23 years, and the median number of ARV a subject received prior to the study was

10. The median baseline viral load was 4.5 $\log_{10}$ copies/mL, and the median baseline CD4 cell was 73 cells/mm^3.

Table 4: Selected Baseline Disease Characteristics in TMB-301 (ITT)

	Ibalizumab (N=40)
Years since HIV diagnosis	
Mean (SD)	20.3 (7.8)
Median	23.0
Min, Max	2.0, 30.0
Total number of ARV per patient	
Mean (SD)	11.0 (5.0)
Median	10.0
Min - Max	3.0, 22.0
Baseline (Day 7) viral load ($\log_{10}$ copies/mL)	
Mean (SD)	4.5 (0.8)
Median	4.5
Min, Max	2.5, 5.9
Baseline (Day 7) CD4 cell counts (cells/mm^3)	
Mean (SD)	150.2 (181.8)
Median	73.0
Min, Max	0, 676.0
< 50	17 (42.5%)
50 – 200	10 (25.0%)
≥ 200	13 (32.5%)

Source: Table 7 in clinical study report for TMB-301

3.2.1.3 Statistical Methods

A. Analysis Population

The efficacy analyses were performed using the intent-to-treat (ITT) population which included all subjects enrolled into the study.

B. Baseline Values

As mentioned in the previous section, baseline in TMB-301 was defined as the last assessment on Day 7, prior to receiving the 2000 mg loading dose of ibalizumab. If the value at baseline was missing, then the last value from the screening visit was used as baseline. If there were multiple baseline assessments, the most recent one was used for the analysis.

C. Visit Window

In the efficacy analyses proposed in the SAP, the applicant proposed to use visit windows constructed based on the midpoint between planned study visits and the study days calculated from Day 0 visit date (Table 5).

Table 5: Applicant's Visit Window for TMB-301

Visit	Window (Days)
Day 7	3-10
Day 14	11-17
Day 21	18-28
Week 5	29-42
Week 7	43-56
Week 9	57-70
Week 11	71-84
Week 13	85-98
Week 15	99-112
Week 17	113-126
Week 19	127-140
Week 21	141-154
Week 23	155-168
Week 25	169-182

Source: SAP for TMB-301

The applicant defined study day from Day 0. However, the study days in the submitted datasets were calculated from Day 7 visit date because Day 7 was defined as the baseline in the protocol and SAP. Also, HIV viral load and CD4 cell counts were not measured at Weeks 7, 11, 15, 19 and 23. Therefore, the reviewer used the visit windows for HIV viral load and CD4 cell counts based on the midpoint between two consecutive visits and the study days calculated from Day 7 visit date (Table 6).

Table 6: Reviewer's Visit Window for TMB-301

Visit	Window (Days)
Day 7	0 – 4
Day 14	5 – 11
Day 21	12 – 22
Week 5	23 – 43
Week 9	44 – 71
Week 13	72 – 99
Week 17	100 – 127
Week 21	128 – 155
Week 25	156 - 182

D. Handling Missing Data

According to the SAP, the Screening visit value was used as the Day 0 result for patients missing data at Day 0. Similarly, the Day 0 visit value was used as the Screening result for patients with missing data at Screening. If necessary, imputation of partial dates was performed during the data analysis and documented (e.g., missing month=July; missing day=15). In addition, the quantification range of the assay to measure HIV RNA levels in serum was from 20 to 10,000,000 copies/mL. HIV RNA values <20 were reported as either "Target detected" or "Target not detected". A value of 19 (LLOQ–1) was imputed for samples with "Target detected"

and a value of 10 (LLOQ/2) was imputed for samples with "Target not detected" in the statistical analysis.

The applicant applied the "missing equals failure" (MEF) approach as the primary method in the analysis of efficacy endpoints. The MEF analysis was defined as follows:

> Patients with missing efficacy data at Day 14 or Week 25 (EOS) had this result set to failure for all dichotomous efficacy variables. If a viral load measurement was missing at any visit, the value was replaced with the baseline viral load measurement. Also all visits after a confirmed VF were imputed as failures through Week 25, even if the patient discontinued early.

Of note, a confirmed virologic failure (VF) was defined as two consecutive viral load measurements of <0.5 $\log_{10}$ decline from the baseline viral load beginning at Day 14. Additionally, the MEF approach was also applied to the continuous endpoints. For instance, if a subject missed the HIV RNA level at Week 25 or had experienced VF, then the change from baseline in HIV RNA level at Week 25 for the subject would be imputed as zero.

Both SAP and study report stated that the snapshot approach defined in FDA Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment (2013) was also applied to summarize virologic success or failure and to impute the missing virologic failure in the analyses of the virologic efficacy endpoints with a dichotomized outcome. The snapshot approach was used to summarize efficacy of other recently approved HIV drugs. The following three reasons for missing viral load results in a visit were tabulated based on the snapshot approach:

1) Discontinued study due to AE or death. Any subjects who discontinues because of an AE or death before the window will be classified as discontinued due to AE or death.
2) Discontinued study for other reasons. Any subject who discontinues because of any reasons other than AE or death before the window will be classified as discontinued for other reasons.
3) On study but missing data in window. Only data in the window can be used for subjects remaining on study.

Based on the MEF approach, once a subject had a confirmed virologic failure at a visit after Day 14, he/she was considered as a virologic failure at all visits afterwards, regardless of whether HIV viral load was available or not at later visits. The MEF approach was not applicable to the primary efficacy endpoint since it was evaluated on Day 14. Also, the MEF approach was more stringent than the snapshot approach. The snapshot algorithm first determined whether a subject was a virologic success or failure at a specific visit based on the available HIV viral load measurements within the visit window. Then, if a subject discontinued study treatment due to lack of efficacy or was a virologic failure at the time of discontinuation, he/she was considered as virologic failure. Otherwise, the reason that a subject missed HIV RNA level within the visit window would be determined and tabulated as listed in Items 1) to 3) above. The snapshot approach could lead to different results from the MEF analysis. However, neither method addressed the confounding of changing from failing background regimen to OBT on Day 14.

With respect to the change in OBR, the study report stated that "any patient who had a change in OBR medications between Day 14 and Week 25 (EOS) had their efficacy set to failure if their HIV RNA was ≥ 50 copies/mL at the specific visit. A change in OBR was defined as any replacement or addition of an OBR medication, regardless of medication class, but did not include removal of an OBR medication."

The applicant's proposal of how to handle the change in OBR was similar to the description of the snapshot approach in the appendix of the FDA HIV guidance document. Upon consulting with the medical officer, Dr. Virginia Sheikh, adding or switching to an new antiviral agent should have insignificant impact on efficacy mainly because the study enrolled patients who had been infected with HIV for an average of 20 years and treated with many medications with multi-drug resistant HIV, and developed multi-class drug resistance. Therefore, it was determined that switching OBR would not be taken into account in the efficacy analysis.

For the endpoints mean change from baseline in HIV RNA and CD4 cell counts at Day 14 and Week 25, the applicant proposed to use baseline observation carried forwards (BOCF) to impute the missing data at Day 14 or Week 25. However, the approach of last observation carried forwards (LOCF) instead of BOCF is usually applied to impute the missing CD4 cell counts in HIV trials since CD4 cell counts change more slowly based on the treatment as compared to the HIV RNA level.

E. Statistical Analysis

The applicant applied McNemar's test to analyze the primary efficacy endpoint of the percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease from Day 7 in viral load at Day 14 as compared to the percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decreases from Day 0 in viral load at Day 7. Summary statistics and the 95% CIs (if applicable) were presented for the secondary efficacy endpoints. The applicant rounded the $\log_{10}$ value of HIV RNA to one decimal point prior to calculating change from baseline in viral load.

The following subgroups analyses for the primary efficacy endpoint were undertaken: sex (male vs. female), age (< 50 vs. ≥ 50 years old), race (Caucasian, Asian, or other), and geographic locations (US vs. Taiwan).

3.2.1.4 Efficacy Results

Table 7 summarizes the applicant's results for the primary efficacy endpoint. Thirty-three subjects (82.5% with 95% CI of [67.2%, 92.7%]) achieved a ≥ 0.5 $\log_{10}$ decrease from Day 7 to Day 14. By contrast, only one subject (2.5% with 95% CI of [0.06%, 13.2%]) achieved a ≥ 0.5 $\log_{10}$ decrease from Day 0 to Day 7. However, this subject violated the protocol by taking an OBR at the end of the control period on Day 6. 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). The reviewer agrees with the applicant's results.

Table 7: Applicant's Results for Primary Efficacy Endpoint in TMB-301 (ITT)

		Subjects achieving a ≥ 0.5 log_{10} decrease from Day 7 to Day 14		
		Yes	**No**	**Total**
Subjects achieving a ≥ 0.5 log_{10} decrease from Day 0 to Day 7	**Yes**	0	1	1
	No	33	6	39
Total		33	7	40

Source: Table 9 in clinical study report for TMB-301

Table 8 summarizes the applicant's results for the secondary efficacy endpoints at Week 25. The applicant's results for all secondary virologic efficacy endpoints were based on the MEF analysis.

Table 8: Applicant's Results from Secondary Efficacy Endpoints in TMB-301 (ITT)

Secondary Endpoints	Ibalizumab (N=40)
Change from baseline (Day 7) in HIV RNA at Day 14 (log10 copies/mL)	
n	40
Mean (SD)	-1.1 (0.6)
Median	-1.1
Min, Max	-2.0, 0.3
Percentage of subjects with HIV RNA < 50 copies/mL at Week 25 – % (n) [95% CI]	42.5% (17) [27.0%, 59.1%]
Percentage of subjects with HIV RNA < 400 copies/mL at Week 25 – % (n) [95% CI]	52.5% (21) [36.1%, 68.5%]
Percentage of subjects achieving a ≥ 0.5 log_{10} decrease from baseline (Day 7) in HIV RNA at Week 25 – % (n) [95% CI]	62.5% (25) [45.8%, 77.3%]
Percentage of subjects achieving a ≥ 1 log_{10} decrease from baseline (Day 7) in HIV RNA at Week 25 – % (n) [95% CI]	55.0% (22) [38.5%, 70.7%]
Change from baseline (Day 7) in HIV RNA at Week 25 (log_{10} copies/mL)	
n	40
Mean (SD)	-1.64 (1.54)
Median	-1.75
Min, Max	-4.3, 0.1
Change from baseline (Day 7) in CD4 cell counts at Week 25 (cells/mm^3) (Observed case analysis)	
n	27
Mean (SD)	62.4 (105.7)
Median	42.0
Min, Max	-119.0, 341.0

Sources: Tables10, 11, 13, 14 and 15 in clinical study report for TMB-301

In addition, the reviewer applied the snapshot approach to analyze the secondary virologic efficacy endpoints with a dichotomous outcome. The reviewer used the LOCF approach to impute the missing CD4 counts at Week 25. The reviewer's results are displayed in Table 9, and the findings are highlighted as follows:

- The snapshot approach led to the same results as those based on the MEF analyses for the percentages of subjects with HIV RNA < 50 copiles/mL and HIV RNA < 400 copies/mL at Week 25.

- The snapshot approach led to almost identical results to those based on the MEF analyses for the percentages of subjects achieving a ≥ 0.5 $\log_{10}$ and a ≥ 1 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA at Week 25.

- Compared with the observed case analysis, the LOCF resulted in lower mean and median for the change from baseline in CD4 cell counts at Week 25.

Table 9: Reviewer's Analysis for Selected Secondary Efficacy Endpoints at Week 25 in TMB-301 (ITT)

	Ibalizumab (N=40)
HIV RNA < 50 copies/mL at Week 25 - % (n)	42.5% (17)
HIV RNA ≥ 50 copies/mL at Week 25[1] - % (n)	45.0% (18)
No virologic data at Week 25 - % (n)	12.5% (5)
Reasons	
Discontinued due to AE or death - % (n)	12.5% (5)
HIV RNA < 200 copies/mL at Week 25 - % (n)	50.0% (20)
HIV RNA ≥ 200 copies/mL at Week 25[2] - % (n)	37.5% (15)
No virologic data at Week 25 - % (n)	12.5% (5)
Reasons	
Discontinued due to AE or death - % (n)	12.5% (5)
HIV RNA < 400 copies/mL at Week 25 - % (n)	52.5% (21)
HIV RNA ≥ 400 copies/mL at Week 25[3] - % (n)	25.0% (14)
No virologic data at Week 25 - % (n)	12.5% (5)
Reasons	
Discontinued due to AE or death - % (n)	12.5% (5)
Achieving a ≥ 0.5 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA at Week 25 - % (n)	65.0% (26)
Not Achieving a ≥ 0.5 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA at Week 25[4] - % (n)	17.5% (7)
No virologic data at Week 25 - % (n)	17.5% (7)
Reasons	
Discontinued due to AE or death - % (n)	12.5% (5)
Discontinued due to other reasons - % (n)	5.0% (2)
Achieving a ≥ 1 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA at Week 25 - % (n)	57.5% (23)
Not Achieving a ≥ 1 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA at Week 25[5] - % (n)	27.5% (11)
No virologic data at Week 25 - % (n)	15.0% (6)
Reasons	
Discontinued due to AE or death - % (n)	12.5% (5)
Discontinued due to other reasons - % (n)	2.5% (1)
Change from baseline (Day 7) in CD4 cell counts at Week 25 (cells/mm^3) (LOCF)	
n	40
Mean (SD)	44.4 (92.6)
Median	17.0
25th, 75th percentile	0, 72.5
Min, Max	-119.0, 341.0

[1]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

[2]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

[3]included subjects who had ≥ 400 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 ≥ 400 copies/mL

[4]included subjects who did not achieve a ≥ 0.5 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA in the Week 25 window, subjects who discontinued 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 < 0.5 $\log_{10}$ decrease from baseline

[5]included subjects who did not achieve a ≥ 1 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA in the Week 25 window, subjects who discontinued study 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 < 1 $\log_{10}$ decrease from baseline

3.2.2 TMB-202

3.2.2.1 Study Design and Endpoints

TMB-202 was submitted as a supportive study and had different study design from TMB-301. It was a Phase 2b, multicenter, randomized, double-blind trial. The primary objective was to evaluate the dose-response effectiveness of antiviral activity of the ibalizumab dose regimens at Week 24 in order to determine the optimal dose and regimen for treatment of TE adult subjects infected with multi-antiviral class resistant HIV. The applicant submitted the study to support the dosing of ibalizumab in the maintenance period in TMB-301. The following two dosing regimens were evaluated in the study.

1) 800 mg of ibalizumab every two weeks (Q2W) plus OBR
2) 2000 mg of ibalizumab every four weeks (Q4W) and placebo on the intervening 2-week period visit plus OBR

Eligible subjects were randomized in a 1:1 ratio to receive one of the two regimens. The randomization was stratified by use or non-use of a viral entry inhibitor and use and non-use of an integrase inhibitor in OBR. The treatment duration was 24 weeks. Subjects were to have a follow-up visit at Week 28. Of note, subjects were scheduled to receive 48 weeks of treatment in the original protocol. Amendment 2 of protocol changed the treatment duration to 24 weeks. Also, the applicant considered Week 24 as end of study although subjects would have a follow-up visit at Week 28 in the study.

All subjects in the study received an investigator-selected OBR consisting of two to four antiviral agents. 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 subject's viral isolate demonstrate viral sensitivity/susceptibility and which the subject was willing and able to take. After randomization, the OBR was not to be changed until the last infusion of the study drug with the following exception: one OBR substation was allowed for tolerability reasons provided the subject continued to meet inclusion criteria with the new OBR.

To assess the efficacy of the regimens, HIV RNA and CD4 cell counts were measured at screening, at baseline, Week 4 and then every four weeks until at the end of treatment at Week 24. Subjects who experienced virologic failure were discontinued from study. Virologic failure was defined as two consecutive measurements (at least 14 days apart) of viral load indicating the following:

- a decrease of $< 1.0 \log_{10}$ from baseline starting at Weeks 14 and 14 (non-response), or
- a viral load > 50 copies/mL starting at Weeks 22 and 24 (suboptimal response or rebound).

The primary efficacy endpoint was the percentage of subjects with HIV RNA levels below the assay limit (<50 copies/mL) at Week 24. Other key efficacy endpoints were as follows:

- percentage of subjects with HIV RNA levels <200 copies/mL at Week 24
- percentage of subjects with HIV RNA levels <400 copies/mL at Week 24
- percentage of subjects achieving a ≥1.0 $\log_{10}$ decrease from baseline in HIV RNA level at Week 24
- percentage of subjects achieving a ≥0.5 $\log_{10}$ decrease from baseline in HIV RNA level at Week 24
- mean change from baseline in HIV RNA levels at Week 24
- mean change from baseline in CD4 cell count at Week 24

The study consisted of two ibalizumab-involved dosing regimens without a placebo arm. While reviewing the protocol under the IND, the statistical reviewer, Dr. Thomas Hammerstrom, commented that there should be a third arm in which subjects received OBR plus every two weeks IV placebo; otherwise, the uncontrolled nature of the trial would make it difficult to conclude the effectiveness of ibalizumab. The reviewer agrees with his assessment.

3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

Table 10 shows the patient disposition for TMB-202. Fifty-nine subjects were randomized to receive ibalizumab 800 mg Q2W + OBR, and 54 subjects were randomized to receive 2000 mg Q4W + OBR. Of the randomized and treated subjects, 86.4% of the subjects in the ibalizumab 800 mg Q2W group and 83.3% of the subjects in the ibalizumab 2000 mg Q4W group completed the study regimens. The most common reasons for discontinuation of study drug in the ibalizumab 800 mg Q2W group were lost to follow-up (3.4%) and investigator decision (3.4%); while the most common reason for discontinuation of treatment in the ibalizumab 2000 mg Q4W group was lost to follow-up (7.4%) followed by voluntary withdrawal (5.6%).

Table 10: Applicant's Results for Patient Disposition in TMB-202

	Ibalizumab 800 mg Q2W + OBR	**Ibalizumab 2000 mg Q4W + OBR**
Number of subjects randomized	59	54
Number of subjects treated	59 (100%)	54 (100%)
Number of subjects completed study drug	51 (86.4%)	45 (83.3%)
Number of subjects discontinued study drug	8 (13.6%)	9 (16.7%)
Lost to follow-up	2 (3.4%)	4 (7.4%)
Voluntarily withdrew	1 (1.7%)	3 (5.6%)
Investigator decision	2 (3.4%)	1 (1.9%)
Protocol violation	1 (1.7%)[1]	1 (1.9%)
Death	2 (3.4%)	0

Source: Table 6 in clinical study report for TMB-202

Table 11 and Table 12 display the applicant's results for patient demographics and selected baseline disease characteristics. While using the submitted dataset, the reviewer came across slightly different results for age, baseline viral load, baseline CD4 counts, and years since HIV diagnosis presented in the study report. As mentioned in Section 3.1, the applicant explained that the study report was based on the SAP for TMB-202 and the dataset was based on the SAP for TMB-301. The two SAPs differed slightly and might lead to the inconsistencies.

Table 11: Applicant's Results for Patient Demographics in TMB-202 (ITT)

	Ibalizumab 800 mg Q2W + OBR (N=59)	Ibalizumab 2000 mg Q4W +OBR (N=54)	Total (N=113)
Age			
Mean (SD)	48.3 (8.1)	47.9 (6.6)	48.1 (7.4)
Median	48.7	47.3	47.5
Min, Max	29.6, 69.5	32.6, 62.3	29.6, 69.5
Gender			
Female	8 (13.6%)	4 (7.4%)	12 (10.6%)
Male	51 (86.4%)	50 (92.6%)	101 (89.4%)
Race			
White	42 (71.2%)	28 (51.9%)	70 (61.9%)
Black	12 (20.3%)	15 (27.8%)	27 (23.9%)
Asian	1 (1.7%)	3 (5.6%)	4 (3.5%)
Other	4 (6.8%)	8 (14.8%)	12 (10.6%)
Ethnic group			
Hispanic or Latino	20 (33.9%)	20 (37.0%)	40 (35.4%)
Non-Hispanic or Latino	39 (66.1%)	34 (63.0%)	73 (64.6%)

Source: Table 8 in clinical study report for TMB-202

Table 12: Applicant's Results for Selected Baseline Disease Characteristics in TMB-202 (ITT)

	Ibalizumab 800 mg Q2W (N=59)	Ibalizumab 2000 mg Q4W (N=54)	Total (N=113)
Years since HIV diagnosis			
n	23	29	52
Mean (SD)	17.0 (4.4)	16.9 (6.2)	17.0 (5.4)
Median	16.3	17.1	17.0
Min, Max	8.1, 24.8	0.3, 26.3	0.3, 26.3
Total number of ARV per patient[1]			
Mean (SD)	12.0 (4.4)	13.6 (5.2)	12.8 (4.8)
Median	12.0	13.5	12.0
Min - Max	3, 21	3, 25	3, 25
Baseline viral load (log10 copies/mL)			
Mean (SD)	4.6 (0.8)	4.7 (0.7)	4.6 (0.7)
Median	4.6	4.7	4.6
Min, Max	1.8, 6.0	3.3, 6.2	1.8, 6.2
Baseline CD4 cell counts (cells/mm^3)			
Mean (SD)	106.4 (91.3)	112.4 (118.5)	109.3 (104.7)
Median	80.5	54.0	69.5
Min, Max	19.0, 375.0	10.0, 476.5	10.0, 476.5

Source: Table 9 in clinical study report for TMB-202
[1]generated by the reviewer

3.2.2.3 Statistical Methods

A. Analysis Population

The efficacy analyses were performed on the ITT population which included all randomized subjects. The analyses were done according to the treatment the subjects were randomized into.

B. Baseline Values

The baseline HIV RNA level and CD4 cell counts were the averages of the available values of HIV RNA levels and CD4 cell counts between screening visits and Day 1 visit, respectively. This is different from the baseline HIV RNA and CD4 cell counts proposed in the SAP for TMB-301 which were the last measurements prior to the infusion of the first dose of ibalizumab.

C. Visit Window

The SAP proposed to use the visit windows shown in Table 13 for the viral load and CD4 cell counts in the efficacy analysis. These visit windows were based on the midpoint between two consecutive visits when viral load and CD4 cell counts were measured.

Table 13: Applicant's Visit Window for TMB-202

Visit	Study Week	Window (Study Day)
Screening 1	-6 to -4	day < -21
Screening 2	-2 to -1	[-21 ≤ day < 0)
Day 1	0	0
Week 2	2	4 ≤ day < 21
Week 4	4	21 ≤ day < 42
Week 8	8	42 ≤ day < 70
Week 12	12	70 ≤ day < 98
Week 16	16	98 ≤ day < 126
Week 20	20	126 ≤ day < 154
Week 24	24	154 ≤ day < 183

Source: SAP (Version 1.1) for TMB-202 (Amendment 2)

D. Handling Missing Data

The following sections summarize how to handle missing data relevant to efficacy in SAP.

D1. Imputation of Missing Dates

If the screening date was partial, it was imputed as follows:

- If the day was missing, it was set to be the 15th day of the month.
- If the day and the month were missing, it was set to be 15th June of the year.

For all missing or partial dates other than the start date of an adverse event or concomitant medication, it was imputed as follows:

- If the year and month were both present and were the same as the year and month of the first dose date, the onset date was imputed to the first dose date.
- If year and month were not the same as the first dose, the first day of the month recorded were used for a start date and the last day of the month was used for a stop date.
- If the year only was present and was the same as the year of the first dose date, then the onset date was imputed to the first dose date. Otherwise the onset date was set to 1 January of that year.
- If this imputation led to a start date after a stop date then the start date was set to the earliest date possible.
- If partial dates were presented as partial in all listings, i.e. imputed dates were be presented.

D2. Imputation of Missing HIV RNA and CD4 Cell Counts

According to the SAP, missing HIV RNA and CD4 cell counts were imputed using LOCF and BOCF. Both the SAP and the study report mentioned that the primary efficacy endpoint was analyzed with MEF in addition to LOCF. However, the MEF approach in this study differed from the MEF approach in TMB-301. As mentioned in the previous sections, the MEF approach in TMB-301 consisted of two parts: 1) subjects with missing HIV RNA level were set to be failures for all HIV RNA relevant endpoints with a dichotomous outcome; and 2) a subject was considered as a virologic failure at all visits after the visit when he/she had a confirmed virologic failure. The definition of MEF in this study did not include Part 2.

E. Statistical Analysis

Fisher exact test was applied to analyze the primary efficacy endpoint of the percentage of subjects with HIV RNA level below 50 copies/mL at Week 24. The study report further mentioned that a 95% confidence interval of the two dosing regimens was generated to test for the non-inferiority (NI). However, neither the protocol nor the SAP indicated this was an NI trial.

The applicant proposed to use the same procedure as that for primary efficacy endpoint to analyze the binary secondary virologic efficacy endpoints. Furthermore, the applicant planned to analyze mean change from baseline in HIV RNA levels at Week 24 by utilizing a general linear model at each scheduled visit. For mean change from baseline in CD4 cell counts, summary statistics were provided.

3.2.2.4 Efficacy Results

As shown in Table 14, the applicant's results for the primary efficacy endpoint demonstrated that the percentage of subjects with HIV RNA below 50 copies/mL at Week 24 was 44.1% in the 800 mg q2w treatment group and 27.8% in the 2000 mg q4w treatment group. The difference between treatment groups was not statistically significant (p=0.160 based on Wald Chi-Square

test). Instead of using the Fisher's exact test proposed in the SAP, the applicant applied Wald Chi-Square test to compare the treatment difference between the two arms. Since the number of subjects with HIV RNA < 50 copies/mL at Week 24 and the number of subjects with HIV RNA ≥ 50 copies/mL at Week 24 were greater than 5 in each arm, Wald Chi-Square test was acceptable. The reviewer agrees with the applicant's results.

Table 14: Applicant's Results for Primary Efficacy Endpoints (ITT) in TMB-202

	800 mg Q2W (N=59)	2000mg Q4W (N=54)	Treatment Difference	
			Percentage difference [95% CI]	p-value
Percentage of subjects with HIV RNA < 50 copies/mL at Week 24 (number of response) - % (n) [95% exact CI]	44.1% (26) [31.2%, 57.6%]	27.8% (15) [16.5%, 41.6%]	16.3% [-1.1%, 33.7%]	0.160

Source: Table 14 in clinical study report for TMB-202

Table 15 summarizes the applicant's results for the secondary efficacy endpoints. The applicant imputed the missing data as failures as described in Section 3.2.2.3. The reviewer could not reproduce the applicant's results using the same approach, but the reviewer's results were close to those of the applicant. The reviewer also applied the MEF approach for TMB-301 specified in Section 3.2.1.3. The two approaches resulted in the same percentages of subjects with HIV < 200 copies/mL and < 400 copies/mL at Week 24 since no subjects experienced virologic failure during the treatment and eventually achieved HIV < 200 copies/mL or < 400 copies/mL at Week 24. The two approaches had slightly different results in the percentages of subjects achieving a ≥ 0.5 $\log_{10}$ and ≥ 1 $\log_{10}$ decrease from baseline in HIV RNA at Week 24 due to different approach to calculate the baseline HIV RNA levels. In addition, the reviewer used the snapshot approach and obtained similar results to the applicant's. Finally, the reviewer calculated change from baseline in CD4 count at Week 24 using LOCF approach. The reviewer's results are shown in Table 16 and Table 17.

Table 15: Applicant's Results for Secondary Efficacy Endpoints in TMB-202 (ITT)

	Ibalizumab 800 mg Q2W + OBR (n=59)	**Ibalizumab 2000 mg Q4W + OBR (n=54)**
HIV RNA < 200 copies/mL at Week 24 - % (n)	52.5% (31)	42.6% (23)
HIV RNA < 400 copies/mL at Week 24 - % (n)	57.6% (34)	46.3% (25)
Achieving a ≥ 0.5 $\log_{10}$ decrease from baseline in HIV RNA at Week 24 - % (n)	67.8% (40)	57.4% (31)
Achieving a ≥ 1 $\log_{10}$ decrease from baseline in HIV RNA at Week 24 - % (n)	62.7% (37)	57.4% (31)
Change from baseline in HIV RNA level ($\log_{10}$ copies/mL) at Week 24 (LOCF)		
Mean (SD)	-1.6 (1.3)	-1.5 (1.4)
Median	-1.8	-1.5
Min, Max	-3.8, 0.0	-4.1, 0.1
Change from baseline in CD4 cell counts at Week 24		
Mean (SD)	36.5 (63.0)	39.8 (80.1)
Median	7.0	0.0
Min, Max	-56.0, 285.5	-126.5, 367.5

Sources: Tables 17, 25, 26, 14.2.1.2, 14.2.1.3, 14.2.1.4 and 14.2.1.5 in clinical study report for TMB-202

Table 16: Reviewer's Results for Secondary Efficacy Endpoints based on MEF in TMB-202 (ITT)

	Ibalizumab 800 mg Q2W + OBR (n=59)	**Ibalizumab 2000 mg Q4W + OBR (n=54)**
Missing equals to failure defined in TMB-202		
HIV RNA < 200 copies/mL at Week 24 - % (n)	50.9% (30)	42.6% (23)
HIV RNA < 400 copies/mL at Week 24 - % (n)	55.9% (33)	46.3% (25)
Achieving a ≥ 0.5 $\log_{10}$ decrease from baseline in HIV RNA at Week 24 - % (n)	72.9% (43)	63.0% (34)
Achieving a ≥ 1 $\log_{10}$ decrease from baseline in HIV RNA at Week 24 - % (n)	62.7% (37)	61.1% (33)
Missing equals to failure defined in TMB-301		
HIV RNA < 200 copies/mL at Week 24 - % (n)	50.9% (30)	42.6% (23)
HIV RNA < 400 copies/mL at Week 24 - % (n)	55.9% (33)	46.3% (25)
Achieving a ≥ 0.5 $\log_{10}$ decrease from baseline in HIV RNA at Week 24 - % (n)	71.2% (42)	61.1% (33)
Achieving a ≥ 1 $\log_{10}$ decrease from baseline in HIV RNA at Week 24 - % (n)	61.0% (36)	57.4% (31)

Table 17: Reviewer's Results for Secondary Efficacy Endpoints in TMB-202 (ITT)

	Ibalizumab 800 mg Q2W + OBR (n=59)	Ibalizumab 2000 mg Q4W + OBR (n=54)
Snapshot approach		
HIV RNA < 50 copies/mL at Week 24 - % (n)	44.1% (26)	27.8% (15)
HIV RNA ≥ 50 copies/mL at Week 24[1] - % (n)	50.9% (30)	72.2% (39)
No virologic data at Week 24 - % (n)	5.1% (3)	0%
Reasons		
Discontinued due to AE or death - % (n)	3.4% (2)	0%
Discontinued due to other reasons- % (n)	1.7% (1)	0%
HIV RNA < 200 copies/mL at Week 24 - % (n)	50.9% (30)	42.6% (23)
HIV RNA ≥ 200 copies/mL at Week 24[2] - % (n)	39.0% (23)	53.7% (29)
No virologic data at Week 24 - % (n)	10.2% (6)	3.7% (2)
Reasons		
Discontinued due to AE or death - % (n)	3.4% (2)	0% (0)
Discontinued due to other reasons- % (n)	6.8% (4)	3.7% (2)
HIV RNA < 400 copies/mL at Week 24 - % (n)	55.9% (33)	46.3% (25)
HIV RNA ≥ 400 copies/mL at Week 24[3] - % (n)	33.9% (20)	44.4% (24)
No virologic data at Week 24 - % (n)	10.2% (6)	9.3% (5)
Reasons		
Discontinued due to AE or death - % (n)	3.4% (2)	0% (0)
Discontinued due to other reasons - % (n)	6.8% (4)	9.3% (5)
Achieving a ≥ 0.5 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA at Week 24 - % (n)	72.9% (43)	64.8% (35)
Not Achieving a ≥ 0.5 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA at Week 24[4] - % (n)	11.9% (7)	20.4% (11)
No virologic data at Week 24 - % (n)	15.3% (9)	14.8% (8)
Reasons		
Discontinued due to AE or death - % (n)	3.4% (2)	0%
Discontinued due to other reasons - % (n)	11.9% (7)	14.8% (8)
Achieving a ≥ 1 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA at Week 24 - % (n)	62.7% (37)	59.3% (32)
Not Achieving a ≥ 1 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA at Week 24[5] - % (n)	25.4% (15)	29.6% (16)
No virologic data at Week 24 - % (n)	11.9% (7)	11.1% (6)
Reasons		
Discontinued due to AE or death - % (n)	3.4% (2)	0%
Discontinued due to other reasons - % (n)	8.5% (5)	11.1% (6)

[1]included subjects who had ≥ 50 copies/mL in the Week 24 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

[2]included subjects who had ≥ 50 copies/mL in the Week 24 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

[3]included subjects who had ≥ 400 copies/mL in the Week 24 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 ≥ 400 copies/mL

[4]included subjects who did not achieve a ≥ 0.5 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA in the Week 24 window, subjects who discontinued 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 < 0.5 $\log_{10}$ decrease from baseline

[5]included subjects who did not achieve a ≥ 1 $\log_{10}$ decrease from baseline (Day 7) in HIV RNA in the Week 24 window, subjects who discontinued study 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 < 1 $\log_{10}$ decrease from baseline

(to be continued)

Table 17: Reviewer's Results for Secondary Efficacy Endpoints based on Snapshot Approach in TMB-202 (ITT) (Continued)

	Ibalizumab 800 mg Q2W + OBR (n=59)	Ibalizumab 2000 mg Q4W + OBR (n=54)
Change from baseline in CD4 at Week 24 based on LOCF (cells/mm^3)		
Mean (SD)	53.3 (65.5)	45.1 (83.7)
Median	34.0	16.0
Min, Max	-119.0, 275.0	-121.0, 373.0

3.3 Evaluation of Safety

The reviewer did not review the safety data. Please refer to the clinical review by Dr. Virginia Shiekh for more details.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 TMB-301

The pre-specified subgroup analyses for primary efficacy endpoint included age (< 50 vs. ≥ 50 years), gender (female vs. male), race (white, Asian, vs other) and region (Taiwan vs. US). Table 18 in the Appendix summarizes the applicant's results for the subgroup analyses. In the reviewer's opinion, a small sample size in the study and high percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease in HIV RNA from Day 7 to Day 14 precluded meaningful interpretation of the results of the subgroup analyses.

The protocol prohibited subjects to take any investigational drugs from 30 days before screening and throughout the study except for fostemsavir (BMS 663068). It was of clinical interest to compare efficacy at Week 25 between those subjects who took fostemsavir and those who did not. The determination to add fostemsavir to OBR after Day 14 was made after baseline and was possibly dependent on the subject's response to the loading dose of ibalizumab. Therefore, this was an inappropriate subgroup analysis, and the results were difficult to interpret.

The study report included the results of comparing the percentages of subjects achieving a ≥ 0.5 $\log_{10}$ decrease from Day 0 to Day 7, from Day 7 to Day 14 and from Day 7 to Week 25 (Tables 14.2.2 and 14.2.3 in clinical study report) between subjects with and without fostemsavir. However, these analyses were based 17 subjects receiving fostemsavir. The footnote in section 11.2.2 of study report stated that Subject 301-01-001 received fostemsavir as part of the OBR, but the source documentation in the study file did not include this information, and the error was discovered after the database was locked. Thus the total number of subjects receiving fostemsavir was 18 instead of 17. The submitted datasets such as CM.XPT reflected this correction.

Using the complete data, the reviewer compared demographics, baseline disease characteristics and primary efficacy endpoint between the two subsets (Table 19). It was noticed that subjects receiving fostemsavir had much longer duration of HIV and lower baseline CD4 cell counts. The reviewer's exploratory analysis of comparing the efficacy endpoints at Week 25 are displayed in Table 20. Numerically poorer outcomes at Week 25 were observed in subjects with fostemsavir in comparison to subjects without fostemsavir.

4.2 TMB-202

The applicant's subgroup analyses by selected baseline characteristics for the primary efficacy endpoint are summarized in Table 21 in Appendices. In general, the percentages of subjects with HIV RNA below 50 copies/mL at Week 24 in the 800 mg Q2W plus OBR arm were numerically higher than the percentages in the 2000 mg Q4W plus OBR arm in almost all subgroups. However, the sample sizes in most of the subgroups were too small to be conclusive.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The applicant submitted TMB-301 to support use of ibalizumab in treatment of TE adult subjects infected with multi-class drug resistant HIV. The proposed dosing regimen was a single loading dose of 2000 mg ibalizumab followed by a maintenance dose of 800 mg ibalizumab every two weeks in combination of OBR for 24 weeks.

TMB-301 was a single-arm study that enrolled 40 subjects. Based on the FDA HIV guidance document and the review team's recommendation, the study should have included a short term (7 days – 2 weeks) ibalizumab monotherapy lead-in phase and subjects should have been randomized to either continue their failing regimen plus placebo or to receive ibalizumab plus their failing regimen in this lead-in phase. However, due to the concern about the limited patient population of subjects infected with multi-class drug resistant HIV, the study instead included a control period from Day 0 to Day 6 where subjects were monitored on their failing therapy or received no therapy. With such a design, the subjects served as their own control, and therefore the sample size was smaller than the two-arm, placebo-controlled study.

TMB-301 included two periods in addition to the control period: 1) an essential monotherapy period from Day 7 to Day 13 where subjects received 2000 mg loading dose of ibalizumab on Day 7 as well as continued with their failing regimen; and 2) a 23-week maintenance period from Day 14 to Week 25 where the subjects received 800 mg ibalizumab every two weeks in combination of OBR. In the study, the HIV RNA level measured prior to the injection of the loading dose of ibalizumab on Day 7 was regarded as baseline, and the value prior to administering OBR on Day 14 was considered as the measurement at the end of the essential monotherapy period. The primary objective demonstrating the antiviral activity of ibalizumab on Day 14 was evaluated by the primary efficacy endpoint of the percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease from Day 7 to Day 14. However, subjects received both

ibalizumab and OBR starting on Day 14 up to Week 25. Therefore, it was impossible to evaluate another primary objective of demonstrating the antiviral activity of ibalizumab at Week 25.

The study results demonstrated that 33 of the 40 (82.5%) subjects achieved a ≥ 0.5 $\log_{10}$ decrease from Day 7 to Day 14. By contrast, only one subject (2.5%) achieved a ≥ 0.5 $\log_{10}$ decrease from Day 0 to Day 7. Moreover, this subject violated the protocol by taking OBR on Day 6. The study also showed that 42.5% of the subjects achieved HIV RNA below 50 copies/mL at Week 25.

Finally, there were 18 subjects in TMB-301 receiving an additional investigational drug, fostemsavir, as part of their OBR after Day 14. It was of clinical interest to compare efficacy endpoints at Week 25 between the subjects who received fostemsavir and those that did not. However, it was difficult to interpret the analysis results since the determination of whether to add fostemsavir in the OBR was after Day 14 and possibly influenced by the subjects' responses to ibalizumab.

The BLA also included TMB-202 which was a supportive trial. The study was a randomized, double-blind trial conducted in a similar patient population to TMB-301. It compared two ibalizumab dosing regimens for the purpose of selecting a dose for TMB-301. All subjects received both ibalizumab and OBR throughout the trial; therefore, the treatment effect of ibalizumab could not be evaluated. The primary efficacy endpoint was the percentage of subjects achieving 50 copies/mL at Week 24. The study resulted in 44.1% of the subjects in the 800 mg ibalizumab Q2W plus OBR group and 27.8% in the 2000 mg ibalizumab Q4W plus OBR group achieved 50 copies/mL at Week 24. Based on the results, 800 mg ibalizumab Q2W plus OBR was selected to use in the maintenance period in TMB-301.

5.2 Conclusions and Recommendations

Based on the results from TMB-301, the reviewer concluded that the proposed ibalizumab regimen was effective in treating the treatment-experienced HIV adult subjects who have multi-class drug resistance and limited treatment choice. Evidence from Study TMB-202 supported the regimen in the maintenance period in TMB-301.

5.3 Labeling Recommendations

The applicant proposed the following efficacy results from the pivotal study TMB-301 in Section 14 of the label.

> Study TMB-301:
>
> Study TMB-301 was a single arm, multicenter study, conducted in 40 treatment-experienced HIV-infected patients with multi-drug resistant HIV-1. Patients must have been treated with antiretrovirals for at least 6 months and failing or had recently failed (i.e., in the last 8 weeks) therapy.

During Days 0 through 6, “the control period”, patients were monitored on current failing background regimen (or no therapy, if the patient had failed and discontinued treatment within the 8 weeks preceding Screening). During Days 7 through 13, "the (b) (4) monotherapy period", patients (b) (4) received one 2000 mg dose (loading dose) of TROGARZO on Day 7. (b) (4) (b) (4) -Week 25). On Day 14 viral load was assessed for the primary end point, thereafter the background regimen was optimized to include at least one agent to which the patient’s virus was susceptible. Beginning at Day 21, 800 mg of TROGARZO was administered every 2 weeks through Week 2 (b) (4) (b) (4)

The majority of patients in Study TMB-301 were males (85.0%), white (55.0%) and between 23 and 65 years of age (mean [SD] age: 50.5 [10.99] years). At Baseline, median viral load and CD4+ T cell counts were (b) (4) (b) (4) (35,350 copies/mL) and 73 cells/mm^3, respectively.

(b) (4)

An increase in the mean number of $CD4^+$ T-cells of 63 cells/mm^3 (42%) was observed from Baseline to Week 25. This increase in $CD4^+$ T-cells is indicative of the therapeutic effect over 24 weeks of treatment.

The reviewer agrees with the clinical team that it is inappropriate to present the results of the primary and secondary efficacy endpoints in one table (Table 4). The primary efficacy endpoint evaluated the 2000 mg loading dose of ibalizumab at the end of the essential monotherapy period, while the secondary efficacy endpoints investigated the 800 mg maintenance dose of ibalizumab in combination of OBR in the maintenance period. After discussing with the clinical team, the reviewer suggested the following table for the primary efficacy endpoint.

Table X. Proportion of Subjects Achieving a ≥ 0.5 log_{10} Decrease in Viral Load at End of Control and Essential Monotherapy Periods

	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

For the secondary efficacy endpoints, the clinical team deemed it adequate to show proportions of subjects with HIV RNA below 50 copies/mL and 200 copies/mL in the label. Because the applicant proposed to present the results based on the snapshot approach for these endpoints, the reviewer suggested the following table, recommended by FDA HIV guidance document, should be adopted.

Table x: Virologic Outcomes (Snapshot Algorithm) at Week 25

	Ibalizumab (N=40)
HIV RNA < 50 copies/mL at Week 25	(b) (4)%
HIV RNA ≥ 50 copies/mL at Week 25[1]	45.0%
HIV RNA < 200 copies/mL at Week 25	50.0%
HIV RNA ≥ 200 copies/mL at Week 25[2]	(b) (4)%
No virologic data at Week 25	%
(b) (4)	
Discontinued due to AE or death	12.5%

[1]included subjects who had ≥ 50 copies/mL in the Week 25 window and who discontinued study drug due to lack of efficacy; 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

[2]included subjects who had ≥ 200 copies/mL in the Week 25 window and who discontinued study drug due to lack of efficacy; 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

With respect to the change from baseline in CD4 cell count at Week 25, the proposed mean change was calculated based on 27 subjects who had CD4 cell count at Week 25 only. The LOCF approach was applied to impute the missing CD4 cell for the recently approved HIV drugs, and the LOCF results were presented in the labels. The reviewer suggested using the same approach to be consistent with other labels. The mean and median change from baseline in CD4 cell count at Week 25 based on LOCF approach was 44 and 17 cells/mm^3, respectively.

For the proposal of results of subgroup analyses for the secondary endpoints at Week 25 shown in Table 5, again the clinical team deemed it sufficient to only show the results for the endpoints of proportion of subjects with HIV RNA below 50 and 200 copies/mL at Week 25. Also, the clinical team disagreed with presenting the results by (b) (4) because our practice is generally not to mention an investigational drug by name in labeling, and the information was not beneficial to providers. The reviewer agreed with the clinical team. Another reason the reviewer supported exclusion of this information from the label was that in the study, the addition of fostemsavir to OBR after Day 14 was determined after baseline and likely dependent on the subject's response to the loading dose of ibalizumab. The analysis was not an appropriate subgroup analysis, and the results were uninterpretable.

(b) (4)

6. APPENDICES

6.1 TMB-301

Table 18: Applicant's Subgroup Analysis by Demographics for Primary Efficacy Endpoint in TMB-301 (ITT)

	Percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease from Day 7 to Day 14 (n/N) [95% CI]
Age	
< 50 years	92.3% (12/13) [64.0%, 99.8%]
≥ 50 years	77.8% (21/27) [57.7%, 91.4%]
Gender	
Female	100% (6/6) [54.1%, 100%]
Male	79.4% (27/34) [62.1%, 91.3%]
Race	
White	81.8% (18/22) [59.7%, 94.8%]
Asian	100% (4/4) [39.8%, 100%]
Other[1]	78.6% (11/14) [49.2%, 95.3%]
Region	
Taiwan	100% (4/4) [39.8%, 100%]
US	80.6% (29/36) [64.0%, 91.8%]

Source: Table 14.2.2 in clinical study report for TMB-301
[1]including 13 African American

Table 19: Reviewer's Results for Comparison of Baseline Characteristics and Primary Efficacy Endpoint between Subjects with or without Receiving Fostemsavir in TMB-301 (ITT)

	With Fostemsavir (n=18)	Without Fostemsavir (n=22)
Age		
Mean (SD)	49.7 (13.0)	51.0 (9.4)
Median	53.0	53.0
Min - Max	23 - 65	25 - 65
Gender		
Male	94.4% (17)	77.3% (17)
Race		
White	55.6% (10)	54.6% (12)
African American	38.9% (7)	27.3% (6)
Asian	0%	18.2% (4)
Unknown	5.6% (1)	0%
Ethnicity		
Hispanic or Latino	16.7% (3)	36.4% (8)
Non Hispanic or Latino	83.3% (15)	54.6% (12)
Unknown	0% (0)	9.1% (2)
Region		
USA	100% (18)	81.8% (18)
Taiwan	0%	18.2% (4)
Years since HIV diagnosis		
Mean (SD)	23.3 (6.5)	18.1 (8.1)
Median	26.0	20.0
Min - Max	8 - 30	2 - 30
Total number of ARV per patient		
Mean (SD)	10.5 (5.6)	11.4 (4.6)
Median	10.5	10.0
Min - Max	3 - 21	5 - 22
Baseline viral load (copies/mL)		
Mean (SD)	84957.7 (172265.1)	112829.4 (174507.3)
Median	31850.0	36350.0
Min - Max	648 - 743000	304 - 577000
Baseline CD4 cell counts (cells/mm^3)[1]		
Mean (SD)	80.6 (96.1)	207.0 (215.4)
Median	27.0	103.5
Min – Max	1 – 268	0 – 676
< 50	55.6% (7)	31.8% (7)
50 – 200	27.8% (5)	22.7% (5)
≥ 200	16.7% (3)	45.5% (10)
Percentage of subjects achieving a ≥ 0.5 $\log_{10}$ decrease in HIV RNA from Day 7 to Day 14	77.8% (14)	86.4% (19)

Table 20: Reviewer's Results for Comparison of Secondary Endpoints at Week 25 between Subjects with and without Receiving Fostemsavir in TMB-301 (ITT)

	With Fostemsavir (n=18)	Without Fostemsavir (n=22)
HIV RNA < 50 copies/mL at Week 25	33.3% (6)	50.0% (11)
HIV RNA < 400 copies/mL at Week 25	44.4% (8)	59.1% (13)
Achieving a ≥ 0.5 log_{10} decrease from baseline (Day 7) in HIV RNA at Week 25	55.6% (10)	72.7% (16)
Achieving a ≥ 1 log_{10} decrease from baseline (Day 7) in HIV RNA at Week 25	50.0% (9)	63.6% (14)
Change from baseline (Day 7) in HIV RNA at Week 25 (log_{10} copies/mL)		
Observed analysis		
n	13	18
Mean (SD)	-1.90 (1.46)	-2.35 (1.35)
Median	-2.14	-2.90
25th, 75th percentile	-3.15, -0.44	-3.28, -0.94
Min, Max	-3.87, 0.08	-4.31, 0.09
Baseline observation carried forward		
n	18	22
Mean (SD)	-1.37 (1.51)	-1.92 (1.52)
Median	-0.73	-2.50
25th, 75th percentile	-2.54, 0.00	-3.26, -0.11
Min, Max	-3.87, 0.08	-4.31, 0.09
Change from baseline (Day 7) in CD4 cell counts at Week 25 (cells/mm^3)		
Observed analysis		
n	12	15
Mean (SD)	51.9 (63.0)	70.8 (132.2)
Median	49.0	34.0
25th, 75th percentile	4.5, 99	1, 185
Min, Max	-59, 154	-119, 341
Last observation carried forward		
n	18	22
Mean (SD)	36.0 (56.0)	51.3 (115.3)
Median	14.5	17.0
25th, 75th percentile	0, 71	0, 100
Min, Max	-59, 154	-119, 341

6.2 TMB-202

Table 21: Applicant's Subgroup Analyses for Primary Efficacy Endpoint in TMB-202 (ITT)

	Ibalizumab 800 mg Q2W + OBR (N=59)	Ibalizumab 2000 mg Q4W +OBR (N=54)
	% of subjects with HIV RNA below 50 copies/mL (n/N) [95%CI]	% of subjects with HIV RNA below 50 copies/mL (n/N) [95%CI]
Age		
< 45 years	43.5% (10/23)	29.4% (5/17)
≥ 45 years	44.4% (16/36)	27.0% (10/37)
Gender		
Female	12.5% (1/8)	25.0% (1/4)
Male	49.0% (25/51)	28.0% (14/50)
Race		
White	47.6% (20/42)	39.3% (11/28)
Other	35.3% (6/17)	15.4% (4/26)
Baseline CD4 (cells/uL)		
< 20	0% (0/12)	23.5% (4/17)
20 to < 100	38.1% (8/21)	28.6% (4/14)
100 to < 200	75.0% (12/16)	36.4% (4/11)
200 to < 350	66.7% (6/9)	37.5% (3/8)
≥ 350	0% (0/1)	0% (0/4)
Baseline HIV RNA level		
< 100,000 copies/mL	51.2% (22/43)	30.6% (11/36)
≥ 100,000 copies/mL	25.0% (4/16)	22.2% (4/18)

Source: Table 14.2.8.1.1 in clinical study report for TMB-202

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/s/

XIAOJING K QI
10/03/2017

THAMBAN I VALAPPIL
10/03/2017

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

BLA #:	BLA 761065
Related IND #:	9776
Product Name:	Intravenous injection of Trogarzo (ibalizumab) with a single loading dose of 2000 mg followed by a maintenance dose of 800 mg every two weeks after dilution in 250 mL of sterile physiological saline
Indication:	Treatment of adults infected with HIV-1 resistant to at least one agent in three different classes
Applicant:	TaiMed Biologics, Inc.
Dates:	BLA Receipt Date: 04/28/2017 Data Receipt Date: 05/03/2017 and 05/11/2017 PDUFA Date: 01/03/2018
Review Priority:	Priority
Biometrics Division:	DB4
Statistical Reviewer:	Karen Qi, PhD
Concurring Reviewers:	Thamban Valappil, PhD
Medical Division:	Division of Antiviral Products
Clinical Team:	Virginia Sheikh, MD, M.H.S., Clinical Reviewer Adam Sherwat, MD, Clinical Team Leader
Project Manager:	Christian Yoder, BSN, MPH

1. Summary of Efficacy Clinical Trials to be Reviewed

The BLA was submitted to support intravenous (IV) injection of Trogarzo (ibalizumab) for the treatment of the heavily treated HIV-1 subjects with documented multi-drug resistances. Trogarzo has been designated an orphan drug. The proposed indication and dosage was primarily depended on the results from a Phase 3 study, TMB-301, with support from a Phase 2b trial, TMB-202. The statistical reviewer will focus on the efficacy of these two studies.

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
TMB-301	Single-arm, control (Subjects served as their own control, i.e., all subjects were monitored on current failing therapy from Study Day 0 to 6, and began to receive the study drug since Day 7 for 22 weeks. Day 7 was considered as study baseline.)	IV injection of Trogarzo with a single dose of 2000 mg on Day 7, followed by doses of 800 mg administered once every two week for 22 weeks from study Day 21 to Week 23 In addition to Trogarzo, subjects received the optimized background regimen (OBR) from Day 14 through Week 25. The OBR was standard of care regimen selected by the investigator and must have included at least one agent to which the subject's virus was fully susceptible. sample size[1] = 40 subjects	Primary efficacy endpoint: proportion of subjects achieving a ≥ 0.5 $\log_{10}$ IU/mL decrease from Day 7 in viral load at Day 14 Secondary efficacy endpoints: proportion of subjects achieving HIV RNA < 50 copies/mL and < 400 copies/mL at each study visit; proportion of subjects achieving a ≥ 0.5 $\log_{10}$ and ≥ 1 $\log_{10}$ decrease from Day 7 in viral load at each study visit; CD4 cell count and change from Day 7 in CD4 cell at each study visit	Please see Table 2 and Figures 1, 2, and 3 for the applicant's results for primary and some secondary efficacy endpoints.
TMB-202	Randomized, double-blind to evaluate two dose regimens of Trogarzo	Group 1: 800 mg of Trogarzo every two weeks plus OBR for 24 weeks (sample size[1] = 59 subjects) Group 2: 2000 mg of Trogarzo every four weeks plus OBR for 24 weeks (sample size[1] = 54 subjects) Note: The OBR was selected by investigator including at least one agent to which the subject's viral isolate demonstrated viral sensitivity/susceptibility and which the subject 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).	Primary efficacy endpoint: proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 Secondary efficacy endpoints: mean change from baseline in HIV-1 RNA level at Week 24/EOS; mean change from baseline in CD4 cell counts at Week 24/EOS; time to loss of virologic response through Week 24	Please see Tables 3, 4 and 5 for the applicant's results for primary and some secondary efficacy endpoints.

[1]number of enrolled or randomized subjects who received at least one dose of study drug

Table 2: Primary Efficacy Endpoint in TMB-301

	All Patients N=40
Proportion of patients achieving a ≥0.5 $\log_{10}$ decrease from	
Day 0 to Day 7 (Baseline)	
n	1 (2.5%)
95% CI	(0.0006, 0.1316)
Day 7 (Baseline) to Day 14	
n	33 (82.5%)
95% CI	(0.6722, 0.9266)
p-value[a]	<0.0001

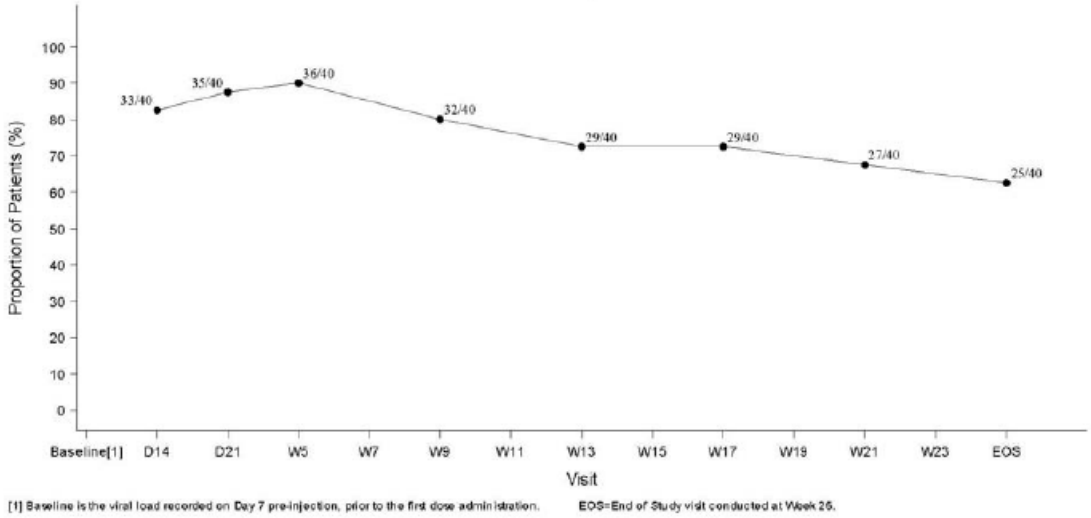
CI=confidence interval; ITT=intent-to-treat; MEF=missing equals failure.

Note: Log_{10} viral load measurements were rounded to one decimal place prior to calculating change from Day 0 or change from baseline. For analysis of viral load only, if a measurement was missing for a given visit, the value was imputed by replacing it with the Baseline value such that change from Baseline=0 and the visit was treated as a failure. Baseline was defined as the viral load recorded on Day 7 pre-injection, prior to the first dose administration.

[a] McNemar's test comparing the proportion of patients achieving a ≥0.5 $\log_{10}$ decrease from Day 0 to Day 7 to the proportion of patients achieving a ≥0.5 $\log_{10}$ decrease from Day 7 to Day 14 for the same set of patients in each time period.

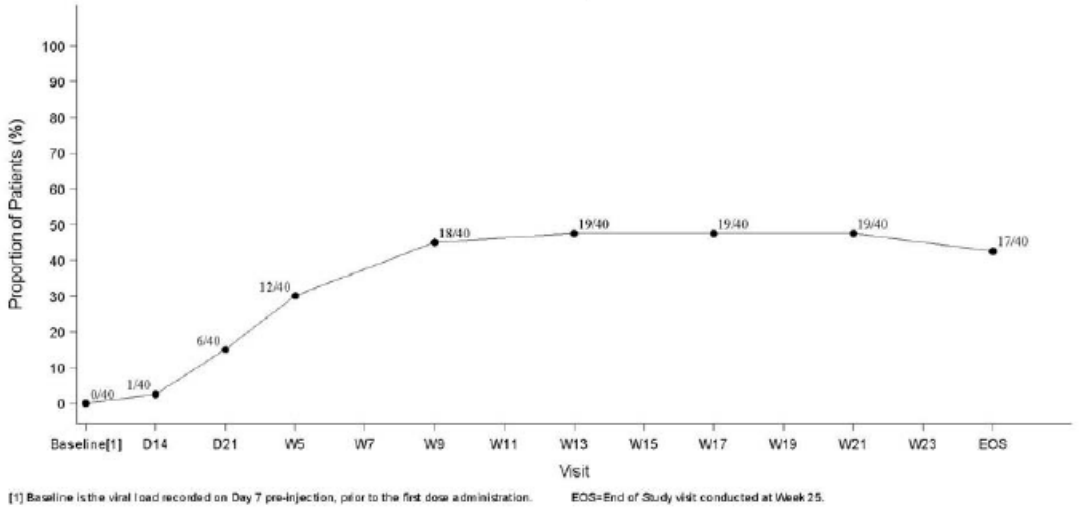
Source: Table 9 in Clinical Study Report for TMB-301

Figure 1: Proportion of Subjects Achieving a ≥ 0.5 $\log_{10}$ Decrease from Day 7 (Baseline) in Viral Load by Visit in TMB-301



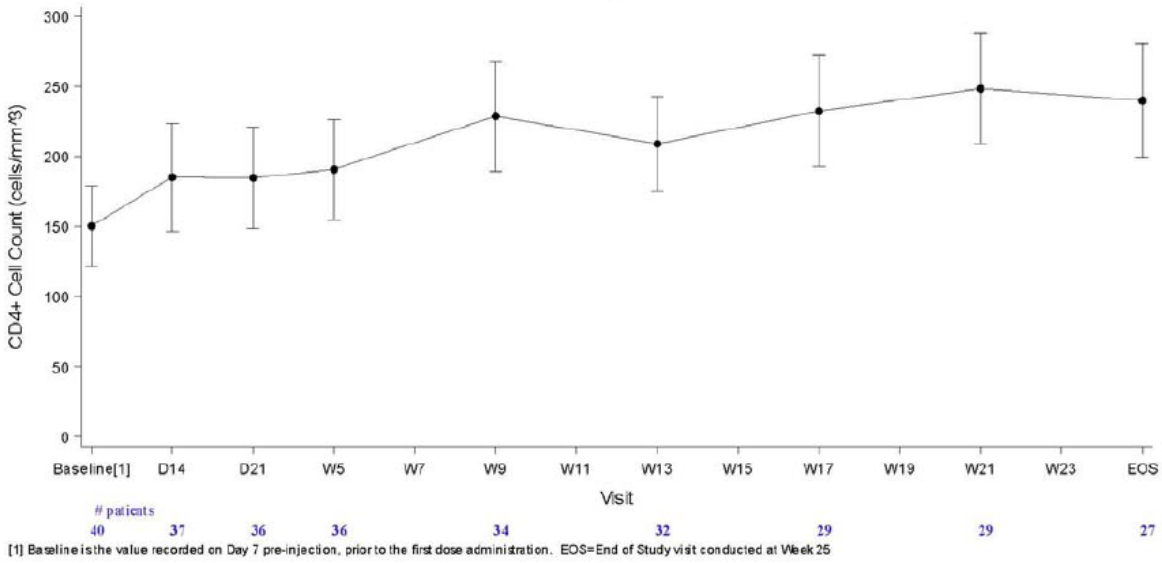
Source: Figure 2 in Clinical Study Report for TMB-301

Figure 2: Proportion of Subjects Achieving < 50 copies/mL in HIV-1 RNA by Visit in TMB-301



Source: Figure 3 in Clinical Study Report for TMB-301

Figure 3: Mean (±SE) CD4 Cell Counts by Visit in TMB-301



Source: Figure 10 in Clinical Study Report for TMB-301

Table 3: Primary Efficacy Endpoint of Proportion of Subjects Achieving HIV RNA < 50 copies/mL at Week 24 (EOS) in TMB-202

	Ibalizumab + OBR		
Description	**800 mg q2wk (N=59)**	**2000 mg q4wk (N=54)**	**Total (N=113)**
Proportion of patients (<50 copies/mL), n/N (%)	26/59 (44.1)	15/54 (27.8)	41/113 (36.3)
95% exact CI	(31.2, 57.6)	(16.5, 41.6)	(27.4, 45.9)
Observed difference between treatment groups, %	—	-16.3	—
95% exact CI	—	(-33.7, 1.1)	—
Hazard ratio	—	0.63	—
95% CI	—	(0.3, 1.2)	—
p-value	—	0.160[a]	—

[a] P-value calculated using Wald chi-square test
CI=confidence interval; OBR=optimized background regimen; q2wk=every 2 weeks; q4wk=every 4 weeks

Source: Table 14 in Clinical Study Report for TMB-202

Table 4: Mean Change from Baseline in HIV-1 RNA Level at Week 24 (EOS) in TMB-202

	Ibalizumab + OBR		
Time point Statistic	**800 mg q2wk (N=59)**	**2000 mg q4wk (N=54)**	**Total (N=113)**
HIV-1 RNA level (log_{10} copies/mL)			
Baseline			
n	59	53	113
Mean (SD)	4.6 (0.8)	4.7 (0.7)	4.6 (0.7)
Median	4.6	4.7	4.7
Minimum to maximum	1.8 to 6.0	3.3 to 6.2	1.8 to 6.2
Week 24			
n	59	54	113
Mean (SD)	2.9 (1.5)	3.2 (1.4)	3.0 (1.5)
Median	1.9	2.8	2.4
Minimum to maximum	1.4 to 5.9	1.4 to 5.9	1.4 to 5.9
Change from baseline to Week 24			
n	59	54	113
Mean (SD)	-1.6 (1.3)	-1.5 (1.4)	-1.6 (-1.4)
Median	-1.8	-1.5	-1.7
Minimum to maximum	-3.8 to 0.0	-4.1 to 0.1	-4.1 to 0.1

OBR=optimized background regimen; q2wk=every 2 weeks; q4wk=every 4 weeks; SD=standard deviation

Source: Table 25 in Clinical Study Report for TMB-202

Table 5: Mean Change from Baseline in CD4 Cell Counts at Week 24 (EOS) in TMB-202

	Number (%) of Patients		
	Ibalizumab + OBR		
Time point Statistic	**800 mg q2wk (N=59)**	**2000 mg q4wk (N=54)**	**Total (N=113)**
$CD4^+$ T-cell count (cells/μL)			
Baseline			
n	59	54	113
Mean (SD)	106.4 (91.3)	112.4 (118.5)	109.3 (104.7)
Median	80.5	54.0	69.5
Minimum to maximum	19.0 to 375.0	10.0 to 476.5	10.0 to 476.5
Week 24			
n	59	54	113
Mean (SD)	142.9 (120.8)	152.2 (155.3)	147.3 (137.8)
Median	120.0	105.0	111.0
Minimum to maximum	19.0 to 587.0	19.0 to 666.0	19.0 to 666.0
Change from baseline to Week 24			
n	59	54	113
Mean (SD)	36.5 (63.0)	39.8 (80.1)	38.0 (71.4)
Median	7.0	0.0	3.0
Minimum to maximum	-56.0 to 285.5	-126.5 to 367.5	-126.5 to 367.5

Source: Table 26 in Clinical Study Report for TMB-202

2. Assessment of Protocols and Study Reports

Table 6: Summary of Information Based Upon Review of the Protocols and the Study Reports

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	The study design for TMC-301 was appropriate for indications requested, but the design for TMC-202 was not. Therefore, the proposed indication is primarily reliable in TMC-301 with support from TMC-202.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	Yes
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	Yes
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Yes

3. Electronic Data Assessment

Table 7: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	TMC-301: \\CDSESUB1\evsprod\BLA761065\0013\m5\datasets\tmb-301 TMC-202: \\CDSESUB1\evsprod\BLA761065\0010\m5\datasets\tmb-202\datasets
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM and ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	ADSL.XPT
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 8: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	✓			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	✓			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	✓			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	✓			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?

Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

None

5.2. Information Requests/Review Issues

None

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/s/

XIAOJING K QI
07/05/2017

THAMBAN I VALAPPIL
07/05/2017