

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761065Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # STN 761065
Product Name: Trogarzo™ (ibalizumab)

PMC #1 Description: To develop, validate, and implement an appropriate pharmaceutical grade container closure system for ibalizumab bulk drug substance.

The final study report(s) will be submitted according to 21 CFR 601.12 by October, 2019.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>10/31/2019</u>
	Other: _____	<u>MM/DD/YYYY</u>

PMC #2 Description: NA

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The current ibalizumab bulk drug substance (BDS) container closure system

(b) (4)

(b) (4)

(b) (4) The available stability data for ibalizumab BDS does not indicate that the current BDS container closure negatively impacts product quality. However, laboratory grade materials are not appropriate for use as the BDS container closure because the materials may not be sufficiently controlled to ensure consistent performance throughout the lifecycle of the product. Therefore a new BDS container closure system should be developed, validated, and implemented using appropriate pharmaceutical grade materials.

2. Describe the particular review issue and the goal of the study.

The goal of the study will be to validate a new container closure system for ibalizumab bulk drug substance that is of appropriate pharmaceutical grade materials.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The new container closure system will be validated to ensure compatibility with ibalizumab BDS, stability of BDS stored in the container, and that there is no risk of extractable and leachable material to the quality of product. Prior to implementation of the new container closure system for ibalizumab BDS, the BLA license will be updated through the submission of a prior approval supplement (PAS).

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

STEVEN E BOWEN
03/02/2018

SUSAN L KIRSHNER
03/02/2018

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # STN 761065
Product Name: Trogarzo™ (ibalizumab)

PMC #1 Description: To perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality.

The final study report(s) will be reported by November, 2018.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>11/30/2018</u>
	Other: _____	<u>MM/DD/YYYY</u>

PMC #2 Description: NA

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

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1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The shipping qualification study for ibalizumab did not include an assessment of product quality after the shipment of ibalizumab drug product from Wuxi, China to the United States.
Analytical testing should be performed on the product to assess product quality before and after shipping to evaluate the impact of the shipping conditions on ibalizumab drug product.

2. Describe the particular review issue and the goal of the study.

TaiMed did not perform a product quality assessment of ibalizumab drug product after shipment from the manufacturing site in Wuxi, China to the United States. The goal of the study will be to evaluate the impact of shipment on the product quality of ibalizumab drug product.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The real-time shipping study will capture the worst-case scenario of the proposed shipping conditions (temperature, containers, and mode of transportation) that will be used for commercial product shipping. These studies will be performed using commercial shipping lane(s) that adequately represent the product's distribution network and modes of transport. To assess the effect of real-time shipping conditions on product quality, ibalizumab product will be tested both pre- and post-shipment against adequate pre-determined acceptance criteria.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

STEVEN E BOWEN
03/02/2018

SUSAN L KIRSHNER
03/02/2018

BLA STN: 761065
Product: Ibalizumab
Manufacturer: TaiMed Biologics

Immunogenicity Review

BLA#: 761065, Immunogenicity Review

Product: Ibalizumab, humanized monoclonal IgG4 anti-human CD4

Indication: Treatment of HIV-1 in treatment-experienced patients

Review Date: September 25, 2017

PDUFA Goal Date: January 3, 2018

Primary Review Team:

- a. Medical Officer: Virginia Sheikh, Adam Sherwat
- b. Pharm/Tox: David McMillan, Chris Ellis
- c. Product Quality: Steven Bowen, Ramesh Potla, Susan Kirshner
- d. Immunogenicity: Steven Bowen, Susan Kirshner
- e. Product Quality Microbiology: Bo Chi, Virginia Carroll, Dupeh Palmer, Patricia Hughes
- f. Facilities: Michael Shanks, Marion Michaelis, Peter Qiu
- g. Clinical Pharmacology: Qin Sun, Shirley Seo, Ada Zhuang, Jeffrey Florian, Kellie Reynolds
- h. Clinical Virology: Eric Donaldson, Jules O'Rear
- i. Statistics: Karen Qi, Thamban Valappil
- j. OBP Labeling: Vicky Borders-Hemphill
- k. RBPM: Christian Yoder

Primary Immunogenicity Reviewer: Steven Bowen Ph.D.

Secondary Immunogenicity Reviewer: Susan Kirshner Ph.D.

Dosage Form/Strength: Injection, each vial contains a 1.33 mL deliverable volume of ibalizumab drug product at 150 mg/mL

Route of Administration: Intravenous

Summary basis of recommendation:

Ibalizumab is an anti-CD4 humanized IgG4 monoclonal antibody that has been developed by TaiMed Biologics for the treatment of HIV-1 in patients who are refractory to available antiretroviral therapies. TaiMed has conducted phase 2b (TMB-202) and phase 3 (TMB-301) clinical studies evaluating the safety and efficacy of ibalizumab in patients infected with HIV-1. Immunogenicity was monitored in both studies at baseline and at multiple points throughout the trial. Anti-drug antibodies (ADA) were measured in serum samples using appropriately validated assays. One patient in study TMB-202 tested positive for binding and neutralizing antibodies at Week 24 of the trial. The presence of ADA did not have any apparent impact on safety or efficacy of ibalizumab treatment. Overall, the sampling and testing strategy for ADA was appropriate to support the conclusion that ibalizumab immunogenicity poses a minimal risk to the safety and efficacy of the product.

Background:

Ibalizumab is a humanized IgG4 monoclonal antibody against domain 2 of human CD4. Ibalizumab has been developed by TaiMed Biologics for the treatment of HIV-1 infection in patients who are refractory to one or more component of the conventional anti-retroviral therapy for HIV-1.

HIV infection of CD4 T-cells is initiated through interactions between the viral glycoprotein gp120 and the CD4 T-cell coreceptor. Interaction between gp120 and CD4 leads to a conformational change in CD4 that allows HIV to bind to secondary receptors including CCR5 and CXCR4 which leads to membrane fusion and infection of the T-cell. Ibalizumab binds to a conformational epitope on domain 2 of human CD4 that prevents the conformational change required for HIV to bind CCR5 or CXCR4 and thus blocks viral entry into CD4 T-cells.

Ibalizumab poses a minimal risk for immunogenicity for the following reasons:

1. Ibalizumab is a humanized monoclonal IgG4 and therefore contains minimal foreign amino acid sequences.
2. Because it is a monoclonal antibody, anti-drug antibodies to ibalizumab are unlikely to cross-react with or neutralize endogenous proteins leading to a deficiency syndrome.
3. The patient population treated with ibalizumab are immune-compromised, reducing the likelihood of a robust ADA response. However, as patients recover lymphocyte counts following treatment with ibalizumab the risk of an ADA response may increase.

Ibalizumab has been investigated in HIV patients in two Phase 1 studies (Hu5A8.01 and TNX-355.02), two Phase 2 studies (TNX-355.03 and TMB-202) and one Phase 3 study (TMB-301) under IND 9776. Additionally an extension study (TMB-311) enrolled patients who had previously been treated in studies TMB-202 or TMB-301. This review focuses on the phase 2b study TMB-202 and the pivotal phase 3 study TMB-301 (boxed in red).

Study Type	Regimen	Study Type	Regimen		
Hu5A8.01 (Phase 1a, open label, Single Dose N=30)	0.3 mg/kg	TNX-355.03 (Phase 2a, Double blind, placebo controlled, Multidose, 48 wks DB, total up to 216 wks, N=82)	800 mg q 2 wks		
	1.0 mg/kg		TMB 202 Investigator-sponsored INDs open-label		
	3.0 mg/kg			2000 mg q 4 wks	
	10 mg/kg		25 mg/kg		
TNX-355.02 (Phase 1b, open label, Multidose, 10 week duration N=22)	Arm A: 10 mg/kg q wk for 10 doses, N = 9	Placebo (Upon VF, switch to 15 mg/kg), N = 27 placebo (23 switched to active)	TMB 301 (Phase 3, treatment experienced pts, 24 wks, N=30)	2000 mg single dose with failing therapy and 800 mg q 2 wks ibalizumab and OBR	
	Arm B: 10 mg/kg single dose and 6 mg/kg q 2 wks for 5 doses, N = 10				TMB 311 Expanded access
	Arm C: 25 mg/kg q 2 wks for 5 doses, N = 3				
TMB 202 (Phase 2b, Double blind, dose response, ibalizumab and OBR, treatment experienced, 24 wks, multidose, N=113)	800 mg q 2 wks, N = 59	TMB 301 (Phase 3, treatment experienced pts, 24 wks, N=30)	TMB 311 Expanded access	2000 mg q 4 wks, N = 54	
	2000 mg q 4 wks, N = 54				

The pivotal Phase 3 study (TMB-301) conducted in 40 treatment-experienced HIV patients involved an initial ibalizumab loading dose of 2000mg followed by bi-weekly maintenance doses of 800 mg concurrent with the optimized background regimen (OBR) of anti-retroviral therapy. The doses and schedule used in TMB-301 is consistent with the proposed ibalizumab treatment program recommended in the label. Serum samples were collected from TMB-301 patients at baseline (day 7), week 13, and week 29 (5-weeks after the final dose). The samples were tested using a tiered strategy consisting of screening, confirmatory, and titering assays developed by (b) (4). A ligand binding assay for the detection of neutralizing ADA was developed at (b) (4). Of the 110 serum samples tested, 28 samples from 15 patients screened positive for ADA. No samples were confirmed positive in the confirmatory assay and therefore no samples from TMB-301 were tested for titer or neutralizing activity.

The screening, confirmatory, and titering assays were validated at (b) (4) as described in the following section.

Screening and Confirmatory Assay Validation- (b) (4)

A bridging electrochemiluminescence (ECL) assay was validated at (b) (4) for the detection of anti-ibalizumab antibodies in human serum (Study number 8322-269). Acid dissociation is used to improve the drug tolerance of the assay which has been problematic for previous assays used to test samples from earlier ibalizumab clinical trials. The acid dissociation step involves treatment of sera with 600 mM acetic acid followed by neutralization with 1M Tris and assay buffer. The samples are then incubated with biotin and SULFO-TAG-labeled ibalizumab. Bi-valent ADA form a bridge between the two labeled forms of ibalizumab. The mixture is then added to a microplate coated with streptavidin which binds the biotin-labeled ibalizumab reagent in complex with ADA and SULFO-TAG ibalizumab. The levels of SULFO-TAG labeled ibalizumab bound to the plate are proportional to the levels of ADA in

the sample, and is detected by electrochemiluminescence using a meso-scale discovery (MSD) platform. The minimum required dilution for the assay is 1:10.

Positive control

The positive control antibody used for assay validation as the routine suitability control is referred to as a mouse anti-idiotypic monoclonal antibody. An IR was sent on August 29, 2017 requesting information on the development and qualification of the positive control antibody. The Sponsor responded on September 13, 2017 stating that the antibody was developed at Tanox Inc. prior to TaiMed obtaining the license and that the development data was no longer available. A figure from a 2003 Tanox laboratory notebook was provided showing the inhibitory effect of the anti-Id antibody on ibalizumab in the cell-cell fusion inhibition assay used to test potency.



Validation runs included the following PC concentrations:

- Low positive control (LPC): 48.0 ng/mL
- High positive control (HPC): 4000 ng/mL

A summary of the major assay parameters is provided below:

TMB 301 (b) (4)

Format	ECL bridging assay
Screening cut-point	1.55 x NC Plate-specific, 5% FP 50 HIV-1 Serum samples
Sensitivity	25 ng/mL
Drug Tolerance	2500 ng/mL with acid dissociation
Confirmatory assay	Competition with unlabeled ibalizumab
Confirmatory cut-point	55.77% inhibition, 0.1% false positive 43.35% inhibition, 1% false positive

Screening assay cut-point

Separate assay cut-points were calculated for healthy and HIV serum. Since study TMB-301 enrolled only HIV-positive patients only the HIV-specific cut-points will be discussed. Serum samples from 50 individual HIV patients were tested in the screening assay 2 independent times by 2 analysts (200 total data points). Data were pooled into a single data set and outliers were identified as follows:

- values greater than the upper quartile + 1.5 x interquartile range
- values less than the lower quartile – 1.5 x interquartile range

One outlier was removed from the HIV serum data set.

The data was determined not to be normally distributed using a Shapiro-Wilk normality test. A non-parametric 95th percentile value of 130.615 was used was used to calculate a floating cut-point normalization factor by dividing by the mean of the negative control sample. The normalization factor for the HIV serum data was determined to be 1.55263.

Screening cut-point determination - HIV Serum

Negative control mean		Normalisation factor (95th percentile of normalised data set)	Screening cut-point value
84.125		1.55263	130.615
Run	N	Mean	STD
Val-009	25	89.320000	19.3341666
Val-010	25	83.520000	16.7782597
Val-011	25	89.920000	20.5546426
Val-012	24	102.083333	23.8380709
Val-013	25	92.160000	23.5065239
Val-014	25	95.280000	23.4547792
Val-015	25	87.960000	22.5526791
Val-016	25	96.160000	23.9055084
Analyst	N	Mean	STD
CDC	100	90.0700000	21.0977786
HD	99	93.9494949	23.0670601

The plate-specific cut-point (PSCP) is calculated as:

$$\text{PSCP} = \text{NC mean} \times 1.55263$$

Reviewer comment: It is not clear why the data was not log-transformed and retested for normality. However, the PCSP calculation based on the non-parametric 95th percentile of the non-normalized data is reasonable. The LPC of 48 ng/mL consistently tested positive in the screening assay using this PSCP. Out of the 40 baseline samples tested for TMB-301, 4 tested positive in the screening assay, suggesting an actual false positive rate of 10% in the clinical population. This is within the 2-11% range generally accepted for the in-study false positive rate.

Sensitivity

The assay sensitivity is reported as 24.8 ng/mL. Assay sensitivity was determined by 2-fold serial dilution of the positive control starting at 4000 ng/mL. Each concentration was measured in triplicate in 4 independent experiments. For each dilution curve the interpolated PC concentration at the PSCP was calculated and the average of the 4 independent runs was reported as the sensitivity.

The LPC concentration of 48.0 ng/mL was calculated as the upper 99th percentile of the interpolated PC concentration at the PSCP (12 values total).

Reviewer comment: The approach to estimate the assay sensitivity and the LPC is appropriate. The screening assay sensitivity of 24.8 ng/mL is consistent with the FDA guidance: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016). The upper 99th percentile of the interpolated concentrations at the cut-point will give a theoretical failure rate of 1% which is consistent with FDA guidance.

Drug tolerance

Clinical samples are treated with 600mM acetic acid and neutralized with 1M Trizma base buffer prior to analysis to dissociate ADA from on-board drug and improve drug tolerance of the assay. Drug tolerance was evaluated by spiking PC samples with ibalizumab at concentrations ranging from 0.00-6000 ng/mL. The results are shown in the table below.

Table 8
Drug Tolerance
Analytical Run Val-027

Ibalizumab Concentration (ng/mL)	PSCP	Anti-Idiotypic Antibody Concentration (ng/mL)				
		0.00	48.0	250	500	4000
		Observed Response (RLU)				
0.00 (Baseline)		66	155	427	769	8733
250		69	127	323	586	7979
500		75	104	251	457	7168
1000	99	79	86	162	273	5781
2500		70	73	102	125	2455
4000		71	76	82	92	884
6000		71	72	75	82	320

Bold: Positive Result ≥ PSCP
PSCP = Plate Specific Cut Point

Reviewer comment: At a PC concentration of 500 ng/mL the assay has a drug tolerance of 2500 ng/mL. However, the drug tolerance observed with the positive control antibody may not be representative of clinical ADA. The PK data from patients enrolled in TMB-301 indicates that a substantial number of samples had on-board ibalizumab levels in excess of 2500 ng/mL (34 samples out of 110, ~31%). Of the 14 samples that tested positive in the screening assay, 3 samples had on board drug >2500 ng/mL (21%). Therefore, among the samples that screened positive there does not appear to be a strong bias against on-board drug levels > 2500 ng/mL. This suggests that on-board drug interference may not have significantly confounded the screening assay results.

Selectivity

Spike/recovery studies were performed in which 10 individual HIV serum samples were spiked with the LPC or HPC concentration of the PC antibody. Out of 10 samples tested, 9/10 were positive in the screening assay and 10/10 were positive in the confirmatory assay at the LPC level. All 10 samples were positive in both the screening and confirmatory assay at the HPC level.

Assay Acceptance Criteria

- PSCP = 1.55263 X Average signal of NC on that plate
- At least 4 out of the 6 NC replicates must have a signal below plate PSCP. NC wells with a signal above the plate PSCP must be masked and excluded from the PSCP calculations.

- At least 3 out of 4 (75%) Low and High Positive Control (LPC and HPC) must have a CV \leq 25% between replicates and must classify correctly as positive with the CP < LPC < HPC.
- The numerical ranges for the NC, LPC, and HPC system suitability are shown below.

Ranges	NC	LPC 48.0 ng/mL	HPC 4000 ng/mL
Mean + 3 x Stdev (OD)	116	245	13820
Mean - 3 x Stdev (OD)	56	119	7856

For unknown samples:

- Each sample is run in duplicate.
- Samples with both replicate signal values above the PSCP are considered to be positive.
- Positive samples with %CV >25% will be re-assayed.
- Samples with one signal value at or above the PSCP and the other signal value below the PSCP with a % CV between replicates < 25% are considered to be negative if their mean values are below the PSCP and are considered to be positive if their mean values are at or above the PSCP.
- Samples with one signal value at or above the PSCP and the other signal value below the PSCP with a CV between replicates >25% will be re-assayed.

Confirmatory assay

Samples that test positive in the screening assay are tested in a confirmatory assay in which the serum samples are spiked with unlabeled ibalizumab and the inhibition of the signal is measured. If the signal is inhibited beyond the cut point are classified as ADA positive. The cut-point for the confirmatory assay was determined in parallel with the screening assay cut-point by spiking 30 serum samples from HIV-positive patients with unlabeled ibalizumab and calculating the % inhibition compared to the unspiked samples using the following equation.

$$[1 - (\text{Mean Signal Depleted} / \text{Mean Signal undepleted})] \times 100$$

One outlier was removed prior to the assessment of normality. The data was normally distributed and so a parametric 99.9% cut-point was calculated.

Reviewer comment: Initially the confirmatory assay cut-point of 52.8% inhibition was calculated using a 0.1% false positive rate. The LPC of 48 ng/mL consistently tested above this cut-point during validation but a 0.1% false positive rate could potentially increase the risk of false negative samples during clinical testing. The Sponsor was advised in an IR on August 29, 2017 to recalculate the confirmatory cut-point with a 1% false positive rate and to re-evaluate the data from TMB-301 with the new cut-point. The Sponsor responded that the re-calculated cut-point with a 1% false positive rate was 43.3534% inhibition and that no additional samples tested in the confirmatory assay from TMB-301 are confirmed positive.

Confirmatory Assay acceptance criteria

- The NC and undepleted PC samples must meet the same acceptance criteria as for the screening assay.
- All PC levels must be analyzed depleted and undepleted.
- Depleted PCs must demonstrate a reduction in signal response from undepleted PCs of $\geq 41.0\%$, as determined in (b) (4) Study No. 8322-269.

Precision

Intra and inter assay precision of the screening and confirmatory assays was evaluated by running 6 replicates of the NC, LPC, and HPC with and without ibalizumab in 6 independent runs.

Intra assay precision- Screening Assay

NC- $\leq 12\%$ CV
LPC- $\leq 8.3\%$ CV
HPC- $\leq 7.8\%$ CV

Inter assay precision- Screening Assay

NC- 11% CV
LPC- 9.5 % CV
HPC- 8.5% CV

Intra Assay Precision- Confirmatory Assay

LPC- $\leq 7.0\%$ CV
HPC- 0.00% CV

Inter Assay Precision- Confirmatory Assay

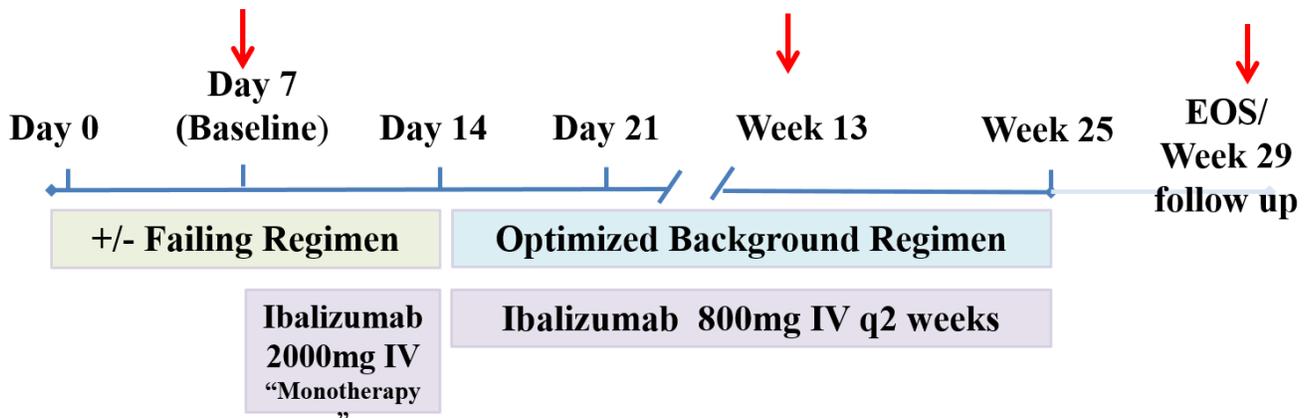
LPC- 5.2% CV
HPC- 0.00% CV

Reviewer comment: The approach to evaluate assay precision is appropriate. The %CV values for the NC and the PC samples are within a reasonable range.

Reviewer comment: The Sponsor evaluated prozone effect, freeze thaw stability (up to 6 cycles), Benchtop stability (up to 25 hours), refrigerator stability and long term stability of the positive control. Under refrigerated conditions the LPC was above the acceptance range after 70 hours 45 minutes. Shorter periods were not tested. Extended storage of the PC at 2-8°C is not recommended. The long term frozen stability study is ongoing.

Clinical Data from TMB-301

The 40 patients enrolled in TMB-301 received a single loading dose of ibalizumab (2000 mg) followed by biweekly infusions of 800 mg in combination with an optimized background regimen of antiretroviral therapy. A schematic of the study design is shown below with the ADA sampling points for most patients indicated by the red arrows. Patients that continued to receive ibalizumab therapy after the 25 week trial period had the final ADA sample taken at week 25.



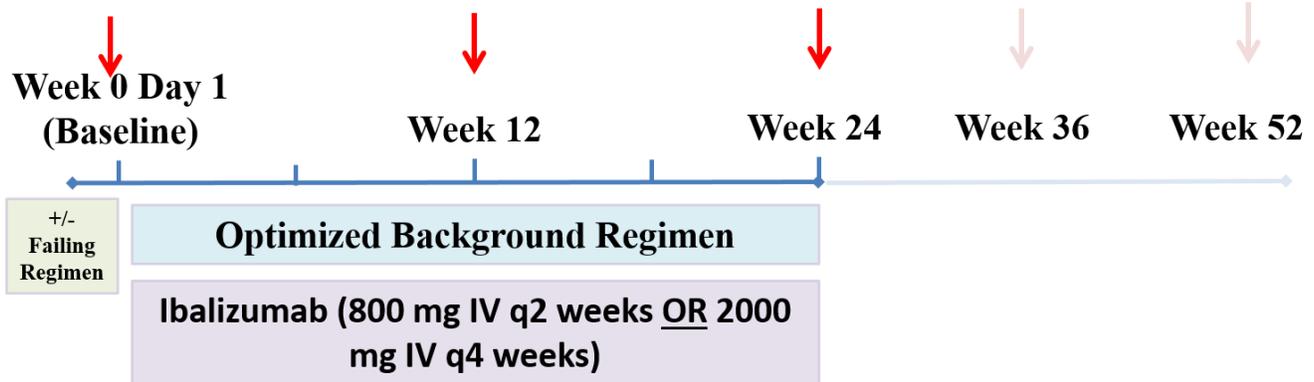
Adapted from Dr. Virginia Sheikh M.D., DAVP

Reviewer comment: In total, 110 samples from 40 patients were analyzed for ADA. In the screening assay 14 samples from 7 patients tested positive. No samples were confirmed positive with the 99% confirmatory cut-point of 43.3534% .

Clinical data from TMB-202

TMB-202 was a phase 2b study conducted in 110 treatment experienced patients with HIV-1. Patients were given either 800 mg or 2000 mg of ibalizumab I.V. every two weeks in conjunction with the optimized background regimen of antiretroviral therapy for up to 24 weeks. Serum samples were collected at baseline, week 12, and week 24. Some patients had additional samples collected at weeks 36

and 52. The schematic of the study design shown below indicates the ADA sampling points as red arrows.



Adapted from Dr. Virginia Sheikh M.D., DAVP

The assays used to test samples from TMB-202 for binding antibodies were developed and validated at (b) (4) using a bridging ELISA format. Plates coated with ibalizumab were incubated with diluted serum samples, followed by detection with HRP-conjugated ibalizumab and tetramethylbenzidine (TMB) substrate. The intensity of the colorimetric signal generated is proportional to the concentration of anti-ibalizumab antibodies present in the serum sample. A summary of the major assay parameters is provided below:

TMB 202 (b) (4)	
Format	Bridging ELISA
Screening cut-point	1.09 Fixed, 5% FP 50 normal human sera
Sensitivity	6.67 ng/mL
Drug Tolerance	500 ng/mL without acid dissociation
Confirmatory assay	Competition with unlabeled ibalizumab
Confirmatory cut-point	>40% inhibition, not statistically justified

The positive control used for TMB-202 is the same mouse monoclonal antibody used for TMB-301. The PC concentrations are run during validation and clinical sample testing are:

PC1: 50 ng/mL
PC2: 200 ng/mL

Reviewer comments:

1. *The Sponsor uses a fixed screening assay cut-point of 1.09. The use of a fixed cut-point was not appropriately justified by demonstrating that the means and variances observed between runs and analysts were not different. However, the NC, PC1, and PC2 performed consistently throughout the 23 assay runs suggesting that run-to-run variability did not impact the appropriateness of the cut-point. Of the 110 baseline samples analyzed 9 were positive in the screening assay (8.2 % false positive rate) suggesting that the cut-point is appropriate for the clinical population.*
2. *The Sponsor uses a confirmatory cut-point of >40% inhibition, which was not set using statistical analysis of negative serum samples. According to the Sponsor, at the time of validation (2008) it was not widely accepted to use a statistical approach using negative serum samples to set the confirmatory assay cut-point. Based on the existing validation data it is not possible to re-calculate the confirmatory assay cut-point using statistics from negative samples. However, PC2 (200 ng/mL) consistently confirmed positive in the range of >70% inhibition. Thus the confirmatory cut-point of >40% is unlikely to pose a risk of false negative samples.*
3. *The drug tolerance of the assay (500 ng/mL) is below the levels of on-board drug observed in many samples from TMB-202. The poor drug tolerance led the sponsor to develop a new ECL assay with an acid dissociation step to test the phase 3 samples. However, there is a risk that there was interference from on-board drug in a portion of the clinical samples from TMB-202 that could have potentially resulted in false negative results.*

Of the 315 samples from 110 patients tested, 33 samples from 24 patients were positive in the screening assay. One sample from patient 10008 was confirmed positive at week 24. This sample was reported as having a titer of 160 (including the MRD of 1:10). The sample was tested in a ligand binding assay for neutralizing ADA and was positive. There was no discernable impact of ADA on PK or efficacy in patient 10008. The serum ibalizumab levels increased for this patient at each evaluable time point during the study and the patient completed Week 24 with undetectable HIV-1 RNA and a 4.1 log₁₀ reduction from Baseline in HIV viral load, accompanied by an increase in CD4+ T cell count (+131 cells/ μ L). Also, the patient reported no adverse events associated with the positive immunogenicity result. It should be noted, too, that patient 10008 enrolled in a physician initiated IND after completing TMB-202 and received ibalizumab therapy for an additional 1.5 years before discontinuing voluntarily with a viral load <50 copies/mL.

The Week 24 sample from patient 10008 was the only sample tested in the ligand binding NAb assay. The ligand binding assay used to detect neutralizing ADA was developed and validated at (b) (4). Ibalizumab is immobilized on a 96 well plate followed by incubation with serum. The plates are washed and incubated with ruthenylated recombinant CD4. Neutralizing antibodies in the serum prevent the interaction of CD4 and ibalizumab resulting in a reduction of the electrochemiluminescent signal proportional to the concentration of NAb in the sample.

The major assay parameters are summarized below:

Format	Ligand binding ECL
Cut-point	0.78 Sample/Negative control 1% False positive rate 50 normal human sera
Sensitivity	76.29 ng/mL
Drug Tolerance	<160 ng/mL ibalizumab at 100 ng/mL of PC 2.5 µg/mL of ibalizumab at 2µg/mL of PC
Intra-assay Precision	HPC (2µg/mL): 0.00% CV LPC (100 ng/mL): 1.76% CV
Inter-assay Precision	HPC (2µg/mL): 15.65% CV LPC (100 ng/mL): 5.12% CV

Reviewer comment:

- 1. The drug tolerance for the assay is poor (<160 ng/mL ibalizumab at 100 ng/mL of PC). However, only one sample from the ibalizumab clinical program was tested, and it was determined to be positive. Thus there is no risk of false negative samples due to poor on-board drug tolerance.*
- 2. The ligand binding assay for neutralizing ADA was appropriately validated consistent with FDA guidance: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016).*



Susan
Kirshner

Digitally signed by Susan Kirshner
Date: 2/28/2018 11:31:18AM
GUID: 508da6db000266b77da0ba4bfa620030



Steven
Bowen

Digitally signed by Steven Bowen
Date: 2/28/2018 11:22:07AM
GUID: 542e18bc0004450166b274ce843bb4f2

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the instructions (see Appendix A) and by referring to MAPP 6010.9, “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

BLA 761065
PMR/PMC Set 3283-1
Product Name: TROGARZO (ibalizumab)
Applicant Name: TaiMed Biologics
ODE/Division: OAP/DAVP

SECTION B: PMR/PMC Information

1. PMR Description

Complete and provide a risk assessment of the carcinogenic potential of ibalizumab.

2. PMR Schedule Milestones^{2, 3}

Final Report Submission: 11/2018

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

Ibalizumab is intended for chronic use in certain HIV-1-infected populations. A risk assessment of

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

⁴ A “study” is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A “clinical trial” is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.”

carcinogenicity is therefore required and should be submitted to the BLA.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- PREA PMR:** Meets PREA postmarketing pediatric study *requirements* *[Skip to Q.5]*
- FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial *[Go to Q.3]*
- PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. *[Go to Q.3]*

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed prior to approval.]

4. For FDAAA PMRs only *[for PMCs skip to Q.5]*. Complete this entire section

a. The purpose of the study/clinical trial is to: *[Select one, then go to Q.4.b]*

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient? *[Select either “Yes” or “No” and provide the appropriate responses.]*

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

f. Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study
- Registry-based observational study
- Other (describe) A risk assessment of the carcinogenic potential

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

Yes

No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

For non-PREA pediatric studies/trials only: Pediatric population

Geriatric population

Lactating/nursing mothers

Medical Countermeasures (e.g. anthrax exposure, bioterrorism)

Orphan or rare disease population

Pregnant women

Racial/ethnic population

Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: [Select all that apply]

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Refer to DARRTS electronic signature (Deputy Director for Safety)

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the instructions (see Appendix A) and by referring to MAPP 6010.9, “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

BLA	761065
PMR/PMC Set	3283-2
Product Name:	TROGARZO (ibalizumab)
Applicant Name:	TaiMed Biologics
ODE/Division:	OAP/DAVP

SECTION B: PMR/PMC Information

1. PMR Description

Submit the final study report for the enhanced pre/postnatal development study in cynomolgus monkeys.

2. PMR Schedule Milestones^{2, 3}

Final Report Submission: 05/2018

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

Ibalizumab may be administered to women of reproductive potential. An assessment of developmental and reproductive toxicity is therefore required and should be submitted to the BLA.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

(Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- PREA PMR:** Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** [for PMCs skip to Q.5]. Complete this entire section

a. The purpose of the study/clinical trial is to: [Select one, then go to Q.4.b]

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either “Yes” or “No” and provide the appropriate responses.]

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

f. **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?**

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study
- Registry-based observational study

TYPE OF STUDY

Other (describe) _____

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- Yes
- No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

Refer to DARRTS electronic signature (Deputy Director for Safety)

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

BLA	761065
PMR/PMC Set	3283-3
Product Name:	TROGARZO (ibalizumab)
Applicant Name:	TaiMed Biologics
ODE/Division:	OAP/DAVP

SECTION B: PMR/PMC Information

1. PMR Description

Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: P236E, K303R, P367L, I369V, R474K, K615R/N, N649I/R, L774S, and L831V. In addition, determine the phenotypes of the substitutions observed in the various coding sequences noted: C1cons_V75I; gp41cons_E229G/Q229P/R and gp41cons_L274V/A274T; V1V2_N12K and V1V2_N14D/V14M/deletion; V4_T23N/deletion.

2. PMR Schedule Milestones^{2, 3}

Final Report Submission: 11/2018

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

There are limited clinical data defining resistance pathways for ibalizumab, and there were several amino acid substitutions identified in the HIV-1 envelope of virologic failures that are of unknown significance. Given that ibalizumab is indicated for highly treatment-experienced patients, virologic failures of ibalizumab are at serious risk of developing HIV-1 infection that is resistant to most or all HIV-1 drugs. It is important to identify the specific resistance pathways of ibalizumab so that cross-resistance with other antiretroviral drugs can be assessed when determining optimized drug regimens for highly treatment-experienced patients.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- PREA PMR:** Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination

Other reason (describe in text box below)

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

FAERS data do not routinely include detailed genotypic or phenotypic resistance data.

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either “Yes” or “No” and provide the appropriate responses.]

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

The phenotypic analyses need to be evaluated by introducing changes into the HIV-1 envelope protein using site-directed mutagenesis. It will take several months to complete the characterization of all of the identified amino acid substitutions.

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

f. **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?**

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study

TYPE OF STUDY

- Registry-based observational study
- Other (describe) _____

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- Yes
- No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

Refer to DARRTS electronic signature (Deputy Director for Safety)

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

BLA 761065
PMR/PMC Set 3283-4
Product Name: TROGARZO (ibalizumab)
Applicant Name: TaiMed Biologics
ODE/Division: OAP/DAVP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: S143P, K171E, N186K/S/R, Q308H/P, G352K/E, and V547A/G.

2. PMR/PMC Schedule Milestones^{2, 3}

Final Report Submission: 11/2018

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

There are limited clinical data defining resistance pathways for ibalizumab, and there were several amino acid substitutions identified in the HIV-1 envelope of virologic failures that are of unknown significance. Given that ibalizumab is indicated for highly treatment-experienced patients, virologic failures of ibalizumab are at serious risk of developing HIV-1 infection that is resistant to most or all approved HIV-1 drugs. It is important to identify the specific resistance pathways of ibalizumab to assess the susceptibility of a patient's virus to reduce the serious risk of developing multidrug resistant HIV-1 infection..

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- PREA PMR:** Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only [for PMCs skip to Q.5]. Complete this entire section**

a. The purpose of the study/clinical trial is to: [Select one, then go to Q.4.b]

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

FAERS data do not routinely include detailed genotypic or phenotypic resistance data.

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either “Yes” or “No” and provide the appropriate responses.]

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

The phenotypic analyses need to be evaluated by introducing changes into the HIV-1 envelope protein using site-directed mutagenesis. It will take several months to complete the characterization of all of the identified amino acid substitutions.

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

f. **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?**

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study

TYPE OF STUDY

- Registry-based observational study
- Other (describe) _____

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- Yes
- No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

Refer to DARRTS electronic signature (Deputy Director for Safety)

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

BLA 761065
PMR/PMC Set 3283-5
Product Name: TROGARZO (ibalizumab)
Applicant Name: TaiMed Biologics
ODE/Division: OAP/DAVP

SECTION B: PMR/PMC Information

1. PMR Description

Provide the fastq envelope sequences from the next generation sequencing of samples collected from subjects who failed treatment in clinical trials TMB-202, entitled “*A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab plus an Optimized Background Regimen in Treatment-Experienced Patients Infected with HIV-1*” (Amended to 24 Week Study) and TMB-301, entitled “*A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected with Multi-Drug Resistant HIV-1*” to better characterize the HIV-1 gp120 sequence at the time of failure.

2. PMR Schedule Milestones^{2, 3}

Final Report Submission: 04/2018

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

There are limited clinical data defining resistance pathways for ibalizumab, and the entire envelope sequence of HIV-1, which is the viral protein associated with resistance to ibalizumab, was not provided for any of subjects who failed treatment with ibalizumab in TMB-301 or TMB-202. Given that ibalizumab is indicated for highly treatment-experienced patients, virologic failures of ibalizumab are at serious risk of developing HIV-1 infection that is resistant to most or all HIV-1 drugs. It is important to identify the specific resistance pathways of ibalizumab so that cross-resistance with other antiretroviral drugs can be assessed when determining optimized drug regimens for highly treatment-experienced patients.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- PREA PMR:** Meets PREA postmarketing pediatric study *requirements* [\[Skip to Q.5\]](#)
- FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

Other reason (describe in text box below)

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

FAERS data do not routinely include detailed genotypic or phenotypic resistance data.

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either “Yes” or “No” and provide the appropriate responses.]

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

FDA needs to conduct an independent assessment of the genotypic data from individuals failing treatment to identify candidate resistance-associated substitutions. Phenotypic analyses of emergent substitutions will need to be evaluated by introducing changes into the HIV-1 envelope protein using site-directed mutagenesis.

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

f. **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)

TYPE OF STUDY

- Quality stability study
- Registry-based observational study
- Other (describe) _____

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- Yes
- No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

Refer to DARRTS electronic signature (Deputy Director for Safety)

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

BLA	761065
PMR/PMC Set	3283-6
Product Name:	TROGARZO (ibalizumab)
Applicant Name:	TaiMed Biologics
ODE/Division:	OAP/DAVP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Provide integrated virology datasets for clinical trials TMB-202, entitled “*A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab plus an Optimized Background Regimen in Treatment-Experienced Patients Infected with HIV-1*” (Amended to 24 Week Study) and TMB-301, entitled “*A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected with Multi-Drug Resistant HIV-1*”. This should include one database for each clinical trial with baseline data for all subjects who were enrolled, and time of virologic failure data for all subjects who failed treatment and were assessed for resistance.

2. PMR/PMC Schedule Milestones^{2, 3}

Final Report Submission: 07/2018

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

There are limited clinical data defining resistance pathways for ibalizumab, and the resistance datasets provided by the sponsor did not integrate all of the baseline and time-of-failure data for clinical trials TMB-202 and TMB-301. Given that ibalizumab is indicated for highly treatment-experienced patients, virologic failures of ibalizumab are at serious risk of developing HIV-1 infection that is resistant to most or all approved HIV-1 drugs. It is important to identify the specific resistance pathways of ibalizumab to assess the susceptibility of a patient's virus to reduce the serious risk of developing multidrug resistant HIV-1 infection. Comprehensive and integrated datasets are required to perform an optimal resistance analysis.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- PREA PMR:** Meets PREA postmarketing pediatric study requirements *[Skip to Q.5]*
- FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial *[Go to Q.3]*
- PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. *[Go to Q.3]*

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

FAERS data do not routinely include detailed genotypic or phenotypic resistance data.

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either “Yes” or “No” and provide the appropriate responses.]

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

FDA needs to conduct an independent assessment of the genotypic data from individuals failing treatment to identify candidate resistance-associated substitutions. Integrated datasets are necessary to perform these analyses.

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

f. **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?**

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study

TYPE OF STUDY

- Registry-based observational study
- Other (describe) _____

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- Yes
- No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

Refer to DARRTS electronic signature (Deputy Director for Safety)

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

/s/

ELIZABETH G THOMPSON
02/26/2018

POONAM MISHRA
02/26/2018



Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date:	February 14, 2018
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Steven Bowen, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research III
Application:	BLA 761065
Product:	Trogarzo (ibalizumab)
Applicant:	TaiMed Biologics USA Corp.
Submission Date(s):	July 19, 2016, May 3, 2017, July 20, 2017, October 12, 2017, and December 27, 2017

I) RECOMMENDATION

The container labels and carton labeling (submitted on October 12, 2017) and the prescribing information and patient information (submitted on December 27, 2017) for Trogarzo (ibalizumab) Injection, 200 mg/1.33 mL (150 mg/mL) single dose vial for intravenous infusion are acceptable from a quality perspective.

II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant submitted BLA 761065 Trogarzo (ibalizumab) on July 19, 2016, proposed for the treatment of adults infected with HIV-1 resistant to at least one agent in three different classes.

Table 1: Proposed Product Characteristics of Trogarzo (ibalizumab).

Proprietary Name:	Trogarzo (ibalizumab)
Nonproprietary Name:	ibalizumab
Dosage Form:	injection
Strength and Container-Closure:	200 mg/1.33 mL (150 mg/mL) single dose vial
Route of Administration:	intravenous infusion
Storage and Handling:	under refrigeration at 2 to 8°C (36-46 °F). Do not freeze. Protect from light
Indication:	treatment of adults infected with HIV-1 resistant to at least one agent in three different class
Dose and Frequency:	single loading dose: 2,000 mg followed by maintenance dose: 800 mg every 2 weeks after dilution in 250 mL of 0.9% Sodium Chloride Injection, USP

III) MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2: Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B
Relevant Code of Federal Regulations and CDER Labeling Best Practices	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

IV) DISCUSSION

The proposed labels were evaluated for compliance to the applicable code of federal regulations and CDER Labeling Best Practices (see Appendix C).

V) CONCLUSION

The container labels and carton labeling (submitted on October 12, 2017) and the prescribing information and patient information (submitted on December 27, 2017) for Trogarzo (ibalizumab) Injection, 200 mg/1.33 mL (150 mg/mL) single-dose vial were reviewed and found to comply with pertinent regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100), United States Pharmacopeia (USP), and CDER labeling best practices.

The labels and labeling submitted on October 12, 2017 and December 27, 2017 are acceptable (see Appendix D) from a quality perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted July 20, 2017

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Container Labels (submitted 3May17)

(b) (4)

Appendix B: N/A

Appendix C: Applicant Code of Federal Regulations and CDER Best Labeling Practices

Table 3: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
<u>Proper Name</u> 21 CFR 610.60 21 CFR 201.50 21 CFR 201.10			X	considered a partial label
<u>Manufacturer name, address, and license number</u> 21 CFR 610.60			X	considered a partial label
<u>Lot number or other lot identification</u> 21 CFR 610.60 21 CFR 201.18 21 CFR 201.100			X	considered a partial label
<u>Expiration date</u> 21 CFR 610.60 21 CFR 201.17			X	considered a partial label
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.60			X	
<u>Statement: "Rx only"</u> 21 CFR 610.60 21 CFR 201.100		X		Reduce the prominence of the "Rx only" statement and relocate to appear in the upper right corner of the Principal display panel to permit space for the revised storage temperature statement.

¹ Per 21 CFR 1.3 (b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				<i>The applicant revised as requested</i>
<u>Medication Guide</u> 21 CFR 610.60 21 CFR 208.24			X	
<u>No Package for container</u> 21 CFR 610.60			X	
<u>Partial label</u> 21 CFR 610.60 21 CFR 201.10		X		<p>Per 21 CFR 610.60 (c), Remove the distributor information and add the licensed manufacturer (the Applicant listed on the submitted Form FDA 356h) as follows: TaiMed Biologics USA Corp US License No. xxxx <i>The applicant revised as requested</i></p> <p>Revise the dosage form from (b) (4) to the appropriate dosage form for this drug product "Injection" and relocate to appear underneath the proper name (placed in parenthesis) followed by the revised strength presentation as follows:</p> <p>Trogarzo (ibalizumab) Injection 200 mg/1.33 mL (150 mg/mL) For intravenous infusion Single-dose vial. Discard unused portion. (include this line if space permits)</p> <p><i>The applicant revised as requested</i></p>
<u>No container label</u> 21 CFR 610.60			X	
<u>Ferrule and cap overseal</u>		X		<p>Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <7> Labeling</p> <p><i>The applicant responded: TaiMed has implemented the new caps without text starting with Lot 6, June 2017. In June 2017, a change control <CC-17-185> has been initiated to change the caps of ibalizumab product as per the USP <7> Labeling. Lots 3 and 4</i></p>

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				<p>have the old cap. To avoid drug waste, we propose to use Lots 3 and 4 as the initial commercial supplies until these are depleted.</p> <p>We find the applicant's response acceptable.</p>
<u>Visual inspection</u> 21 CFR 610.60		x		<p>Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e).</p> <p>The Applicant responded: To allow visual inspection of the labeled vials, we propose to establish the dimension (e.g. length = 44.5 mm) of the container label so that it creates a 5 mm uncovered space for its full length (between the edges of the affixed label) . In addition, the bottom area of the container will allow the visual inspection.</p> <p>We find the applicant's response acceptable.</p>
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35	x			
<u>Route of administration</u> 21 CFR 201.5 21 CFR 201.100		x		<p>Revise from (b) (4) to read "For Intravenous Infusion Only"</p> <p>The applicant revised as requested</p>
<u>Preparation instructions</u> 21 CFR 201.5			x	<p>considered partial label</p>
<u>Package type term</u> 21 CFR 201.5		x		<p>Revise to the appropriate package type term, from (b) (4) to read "single-dose" (see Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry)</p> <p>The applicant revised as requested</p>
<u>Drugs Misleading statements</u> 21 CFR 201.6			x	
<u>Strength</u>		x		<p>Revise the strength presentation to be expressed as</p>

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
21 CFR 201.10 21CFR 201.100				strength per total volume followed by strength/mL in parenthesis "200 mg/1.33 mL (150 mg/mL)" (see USP General Chapters <7> Labeling (Strength per total volume for single dose and multiple dose injectable drug products) <i>The applicant revised as requested</i>
<u>Drugs Prominence of required label statements</u> 21 CFR 201.15	X			
<u>Bar code label requirements</u> 21 CFR 201.25 21CFR 610.67	X			
<u>Net quantity</u> 21 CFR 201.51		X		
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100		X		This is considered to be a partial label and the usual dose statement is not required information and can be deleted to permit space for required information. However, if space permits once revisions have been made to include the required information, revise usual dosage statement from (b) (4) (b) (4) to read "Dosage: See prescribing information" and relocate to the side panel to allow for critical information to appear on the principal display panel. <i>The applicant revised as requested</i>
<u>Inactive ingredients</u> 21 CFR 201.100			X	considered partial label
<u>Storage requirements</u>		X		Revise the storage requirements to read "2 to 8°C (36-46 °F)" per USP definitions (see USP chapter <659> Packaging and Storage Requirements) <i>The applicant revised as requested</i>
<u>Dispensing container</u> 21 CFR 201.100			X	

Package Label⁵ Evaluation

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Proper name</u> 21 CFR 610.61 21 CFR 201.50 21 CFR 201.10		x		Revise the dosage form from (b) (4) to the appropriate dosage for this drug product "Injection" and relocate to appear underneath the proper name (placed in parenthesis) followed by the revised strength presentation as follows: Trogarzo (ibalizumab) Injection 200 mg/1.33 mL (150 mg/mL) For Intravenous Infusion only Single-dose vial. Discard unused portion. <i>The applicant revised as requested</i>
<u>Manufacturer name, address, and license number</u> 21CFR 610.61		x		Per 21 CFR 610.61(b) revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h as follows: Manufactured by: TaiMed Biologics USA Corp Irvine, California 92614 US License No. xxxx <i>The applicant revised as requested</i> Remove the statement (b) (4) " since they are not the applicant listed on Form FDA 356h. <i>The applicant revised as requested</i> Per 21 CFR 610.64 if your intent is to include the distributor's name (Theratechnologies Inc) then it should be listed as follows: "Distributed by: Name and address" <i>The applicant revised as requested</i>
<u>Lot number or other lot identification</u> 21 CFR 610.61	x			

⁵ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Expiration date</u> 21 CFR 610.61 21 CFR 201.17	X			
<u>Preservative</u> 21 CFR 610.61		X		If no preservative, ensure "No preservative" appears on the carton labeling per 21 CFR 610.61 (e). <i>The applicant revised as requested</i>
<u>Number of containers</u> 21 CFR 610.61	X			
<u>Strength/volume</u> 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100		X		Revise the strength presentation to be expressed as strength per total volume followed by strength/mL in parenthesis "200 mg/1.33 mL (150 mg/mL)" (see USP General Chapters <7> Labeling (Strength per total volume for single dose and multiple dose injectable drug products) <i>The applicant revised as requested</i> Remove statement (b) (4) since this is not the appropriate strength presentation for this dosage form. <i>The applicant revised as requested</i>
<u>Storage temperature</u> 21 CFR 610.61	X			
<u>Handling: "Shake Well", "Do not Freeze" or equivalent</u> 21 CFR 610.61	X			
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.61			X	
<u>Route of administration</u> 21 CFR 610.61 21 CFR 201.5 21 CFR 201.100		X		Revise from (b) (4) to read "For Intravenous Infusion Only" <i>The applicant revised as requested</i>
<u>Known sensitizing substances</u>			X	

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21CFR 610.61				
<u>Antibiotics added during manufacturing</u> 21 CFR 610.61			x	
<u>Inactive ingredients</u> 21 CFR 610.61 21 CFR 201.100		x		Revise the list of ingredients based on how much is deliverable in 1.33 mL of solution and by placing the active ingredient first with its quantitative amount followed by the list of all inactive ingredients in alphabetical order (see USP Chapter <1091>) with their quantitative information using the metric system of weight in parenthesis (x mg) except for those inactive ingredients added to adjust pH or tonicity or water for injection as follows: "Each 1.33 mL single dose vial contains 200 mg ibalizumab, L-histidine (xx mg), Polysorbate 80 (xx mg), Sodium Chloride (xx mg), and Sucrose (xx mg)" <i>The applicant revised as requested</i>
<u>Adjuvant, if present</u> 21 CFR 610.61			x	
<u>Source of the product</u> 21 CFR 610.61			x	
<u>Identity of each microorganism used in manufacturing</u> 21 CFR 610.61			x	see PI
<u>Minimum potency of product</u> 21 CFR 610.61		x		Add the words "No U.S. standard of potency" per 21CFR 610.61 (r) <i>The applicant revised as requested</i>
<u>Rx only</u> 21CFR 610.61 21 CFR 201.100		x		Unbold "Rx Only" to reduce the prominence and to allow for prominence of other critical information on the PDP <i>The applicant revised as requested</i>
<u>Divided manufacturing</u> 21 CFR 610.63			x	

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Distributor</u> 21 CFR 610.64		X		see above
<u>Bar code</u> 21 CFR 610.67 21 CFR 201.25	X			
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35	X			Unbold the NDC number to reduce the prominence and to allow for prominence of other critical information on the PDP <i>The applicant revised as requested</i>
<u>Preparation instructions</u> 21 CFR 201.5			X	
<u>Package type term</u> 21 CFR 201.5		X		Revise to the appropriate package type term, from (b) (4) to read "single-dose" (see Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry) <i>The applicant revised as requested</i>
<u>Drugs Misleading statements</u> 21 CFR 201.6			X	
<u>Drugs Prominence of required label statements</u> 21 CFR 201.15		X		see above
<u>Net quantity</u> 21 CFR 201.51	X			
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100		X		Remove the duplicative usual dose statement (b) (4) from the principal display panel to permit space for other important information including package type term and discard unused portion statement <i>The applicant revised as requested</i> Revise the usual dose statement from (b) (4)

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				(b) (4) to read "See prescribing information for dosage, preparation, administration, and storage" <i>The applicant revised as requested</i>
Dispensing container 21 CFR 201.100			X	
Medication Guide 21 CFR 610.60 21 CFR 208.24			X	

Prescribing Information and Patient Labeling Evaluation

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
PRESCRIBING INFORMATION				
Highlights of prescribing information				
PRODUCT TITLE 21 CFR 201.57(a)(2)	X			
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)		X		Ensure diluents and intravenous solutions comply with USP nomenclature. Revise from (b) (4) to read "Sodium Chloride Injection, USP". <i>The applicant revised as requested</i>
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)		X		Per 21 CFR 201.57(a)(8) revised to include the appropriate dosage form, strength presentation expressed as strength per total volume followed by strength/mL in parenthesis, and the appropriate package type term "Injection: 200 mg/1.33 mL (150 mg/mL) of Trogarzo in a single-dose vial" <i>The applicant revised as requested</i>
Full Prescribing Information				
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)		X		Ensure diluents and intravenous solutions comply with USP nomenclature. Revise from (b) (4) to read "Sodium Chloride Injection, USP". <i>The applicant revised as requested</i>

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				<p>Add the temperature range "(20°C to 25°C, 68°F to 77°F)" after the storage requirements for 2nd to last bullet <i>The applicant revised as requested</i></p> <p>Relocated "Appropriate numbers of vials are diluted in 250 mL of 0.9% Sodium Chloride Injection, USP for intravenous infusion. For the 2000 mg loading dose, 10 vials are used. For the 800 mg maintenance dose, 4 vials are used." (b) (4) <i>The applicant revised as requested</i></p> <p>Statement (b) (4) this should be revised to read "1.33 mL" with a "discard unused portion" statement <i>The applicant revised as requested</i></p>
<u>3 DOSAGE FORMS AND STRENGTHS</u> 21 CFR 201.57(c)(4)		x		<p>Add dosage form, identifying characteristics and package type term per 21 CFR 201.57(c)(4) (colorless to slightly yellow and clear to slightly opalescent solution with no visible particles) <i>The applicant revised as requested</i></p>
<u>6.2 IMMUNOGENICITY</u>		x		<p>Per best labeling practices we added standard statement to appear at the beginning of the Immunogenicity subsection preceding the immunogenicity data <i>The applicant revised as requested</i></p>
<u>11 DESCRIPTION</u> 21 CFR 201.57(c)(12)		x		<p>Deleted the proprietary name since this 1st paragraph describes the drug substance <i>The applicant revised as requested</i></p> <p>The identity of the cell line/cell substrate was added "Ibalizumab-uyk is produced by recombinant DNA technology in murine myeloma non-secreting 0</p>

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				<p>(NS0) cells.” <i>The applicant revised as requested</i></p> <p>Included dosage form in second paragraph per 21 CFR 201.57(c)(12) <i>The applicant revised as requested</i></p> <p>Updated to reflect submitted DP specifications for appearance 3.2.P.5.1. PQ reviewer to confirm. <i>The applicant revised as requested</i></p> <p>List all inactive ingredients in alphabetical order (see USP Chapter <1091>) followed by their quantitative information that is deliverable in 1.33 mL using the metric system of weight in parenthesis (x mg) except for those inactive ingredients added to adjust pH or tonicity or water for injection <i>The applicant revised as requested</i></p>
<p><u>16 HOW SUPPLIED/STORAGE AND HANDLING</u> 21 CFR 201.57(c)(17)</p>		x		<p>Per 21 CFR 201.57(c)(17) revised to include the appropriate dosage form, strength presentation expressed as strength per total volume followed by strength/mL in parenthesis, and the appropriate package type term <i>The applicant revised as requested</i></p> <p>Add identifying characteristics <i>The applicant revised as requested</i></p> <p>Relocate “each vial delivers approx....” to section 11 as the appropriate section in PI to describe quantitative ingredient information. <i>The applicant revised as requested</i></p> <p>Relocated “appropriate numbers of vials are diluted in 250 mL of ...” to section 2. Detailed storage conditions for reconstituted and diluted products should be described in the DOSAGE AND</p>

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				<p>ADMINISTRATION section rather than the HOW SUPPLIED/STORAGE AND HANDLING section.</p> <p><i>The applicant revised as requested</i></p> <p>Deleted as distributor information appears at the end of the PI and patient information</p> <p><i>The applicant revised as requested</i></p>
<p><u>MANUFACTURER INFORMATION</u> 21 CFR 610.61, 21 CFR 610.64</p>				<p>Per 21 CFR 610.61(b) Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h as follows: Manufactured by: TaiMed Biologics USA Corp Irvine, California 92614 US License No. xxxx</p> <p>We relocated the US license number to appear with the licensed manufacturer name and address</p> <p><i>The applicant revised as requested</i></p> <p>Per 21 CFR 610.64 include the distributor name and address as follows: "Distributed by: Name and address"</p> <p><i>The applicant revised as requested</i></p> <p>To applicant: We deleted the trademark information as is not required information and may imply that the licensed applicant is Theratechnologies</p> <p><i>The applicant revised as requested</i></p>
PATIENT INFORMATION				
<u>TITLE (NAMES AND DOSAGE FORM)</u>	x			
<u>STORAGE AND HANDLING</u>			x	
<u>INGREDIENTS</u>		x		<p>List inactive ingredients in alphabetical order per USP <1091> Labeling of Inactive Ingredients.</p> <p><i>The applicant revised as requested</i></p>
<u>MANUFACTURER INFORMATION</u>		x		<p>Per 21 CFR 610.61(b) Revise the licensed manufacturer and address to appear as the</p>

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.61, 21 CFR 610.64				<p>Applicant listed on the submitted Form FDA 356h as follows: Manufactured by: TaiMed Biologics USA Corp Irvine, California 92614 US License No. xxxxx</p> <p>We relocated the US license number to appear with the licensed manufacturer name and address</p> <p><i>The applicant revised as requested</i></p> <p>Per 21 CFR 610.64 include the distributor name and address as follows: "Distributed by: Name and address" <i>The applicant revised as requested</i></p> <p>To applicant: We deleted the trademark information as is not required information and may imply that the licensed applicant is Theratechnologies</p> <p><i>The applicant revised as requested</i></p>

APPENDIX D. Acceptable Labels and Labeling

Prescribing Information/Patient information (submitted December 27, 2017)

[\\cdsesub1\evsprod\bla761065\0070\m1\us\draft-physician-labeling-text.pdf](#) and [\\cdsesub1\evsprod\bla761065\0070\m1\us\draft-patient-labeling-text.pdf](#)

Container Labels (submitted October 12, 2017)



(b) (4)

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Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 2/14/2018 11:29:23AM
GUID: 50814c7000007a3d59329f660d8ddf02



Steven
Bowen

Digitally signed by Steven Bowen
Date: 2/14/2018 04:23:07PM
GUID: 542e18bc0004450166b274ce843bb4f2

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 1, 2017

To: Christian Yoder, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TROGARZO™ (ibalizumab-uiyk) injection,
for intravenous use

BLA: 761065

In response to DAVP consult request dated May 5, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original BLA submission for TROGARZO™ (ibalizumab-uiyk) injection, for intravenous use (Trogarzo).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DAVP (Christian Yoder) on November 15, 2017. We have no comments at this time on the PI.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAVP (Christian Yoder) on November 28, 2017, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov.

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/s/

WENDY R LUBARSKY
12/01/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 1, 2017

To: Debra Birnkrant, MD
Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Wendy Lubarsky, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TROGARZO (ibalizumab)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761065

Applicant: TaiMed Biologics

1 INTRODUCTION

On May 3, 2017, TaiMed Biologics submitted for the Agency's review a Biologics License Application (BLA) 761065 for TROGARZO (ibalizumab) injection. TROGARZO (ibalizumab) injection is indicated 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on May 10, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TROGARZO (ibalizumab) injection.

2 MATERIAL REVIEWED

- Draft TROGARZO (ibalizumab) injection PPI received on May 3, 2017, and received by DMPP and OPDP on November 15, 2017.
- Draft TROGARZO (ibalizumab) injection Prescribing Information (PI) received on May 3, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 15, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
12/01/2017

WENDY R LUBARSKY
12/01/2017

BARBARA A FULLER
12/01/2017

LASHAWN M GRIFFITHS
12/01/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: November 3, 2017
Requesting Office or Division: Division of Antiviral Products
Application Type and Number: BLA 761065
Product Name and Strength: Trogarzo (ibalizumab-uiyk) injection,
200 mg/1.33 mL (150 mg/mL)
Applicant/Sponsor Name: TaiMed Biologics, Inc.
Submission Date: October 12, 2017
OSE RCM #: 2017-854-1
DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Antiviral Products requested that we review the revised container label and carton labeling for Trogarzo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and carton labeling for Trogarzo are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Roosta N. Label and Labeling Review for Trogarzo (BLA 761065). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 24. RCM No.: 2017-854.

APPENDIX A. LABEL AND LABELING SUBMITTED ON OCTOBER 12, 2017

Container labels

(b) (4)



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/s/

OTTO L TOWNSEND
11/03/2017

Clinical Inspection Summary

Date	October 6 , 2017
From	Antoine El Hage, Ph.D. Susan Thompson, M.D. Team Leader Kassa Ayalew, M.D., MPH. Branch Chief
To	Christian Yoder, M.P.H. Regulatory Health Project Manager Virginia Sheikh, M.D., Medical Reviewer Adam Sherwat, M.D. Team Leader/ CTDL Division of Antiviral Products (DAVP)
NDA #	BLA 761065
Applicant	TiaMed Biologics, Inc.
Drug	Ibalizumab
NME (Yes/No)	Yes
Therapeutic Classification	Expedited Priority
Proposed Indication(s)	Treatment of adults infected with HIV-1 resistant to at least one agent in three different classes
Consultation Request Date	May 19, 2017
Summary Goal Date	November 15, 2017
Action Goal Date	January 3, 2018
PDUFA Date	January 3, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Fessel, Khanlou, Kumar, and Schrader were inspected in support of BLA 761065. The inspection of the four clinical sites revealed regulatory violations. The preliminary classification of Drs. Fessel, Khanlou, and Schrader’s clinical site inspections is Voluntary Action Indicated (VAI). The final classification for Dr. Kumar is Voluntary Action Indicated (VAI). The minor deviations noted for the four sites would not appear to have a significant effect on safety or efficacy considerations; therefore, the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective application/indication.

The inspection of one clinical investigator (Dr. Schrader) listed above found serious regulatory violations in the conduct of Study TMB-202. Dr. Schrader’s site was issued a Form FDA 483 citing inspectional observations regarding the failure to retain Study TMB-202 records. The field investigator was not able to audit/review Dr. Schrader’s TMB-202 records because the site informed the field investigator at the time of the inspection that the records were “accidentally destroyed”. Subsequently, Dr. Schrader in his amended response to the FDA 483 included copies of the “found/located” study records.

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However, we cannot attest that the copies Dr. Schrader provided with his written response were in fact true copies of the original study records without verification.

OSI recommends that the data generated at this site for Protocol TMB-202 not be used in support of the application since we were unable to verify data from the “found” copies of the study records. In addition, the inspection of Study TMB-301 revealed inadequate record keeping and discrepancies contrary to the signed investigational plan. However, the latter identified discrepancies noted in Study TMB-301 did not appear to significantly impact safety and efficacy considerations. The remainder of the data generated from Study TMB301 may be considered in support of the pending application.

The final classification for the above three sites will be made at a later date after receiving and reviewing the EIRs provided by the field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

Based on the inspections of the four clinical sites, the inspectional findings support validity of the data as reported by the sponsor under this BLA, with the exception noted for Study TMB-202. OSI recommends that the review division may wish to perform a sensitivity analysis with and without data from Dr. Schrader’s site to determine whether overall safety and efficacy in Study TMB-202 are impacted.

II. BACKGROUND

The Applicant has conducted these studies in support of approval for the use of ibalizumab in the treatment of HIV-1 infected patients who acquired resistance and failed antiretroviral medication.

The investigational product, ibalizumab, is a humanized IgG4 monoclonal antibody (MAb) administered via intravenous infusion (IV) over 30 minutes. Ibalizumab blocks HIV entry, in a manner distinct from other entry inhibitors. Ibalizumab binds to a conformational epitope on domain 2 of the extracellular portion of the CD4 receptor. Early trials suggested that the administration of ibalizumab demonstrated clinically significant viral load reduction when compared to a placebo arm, and an increase in CD4 T-cell counts versus no change from baseline for the placebo arm. There is a medical need for potent and well tolerated agents with greater efficacy, an improved safety profile, and less viral resistance to treat HIV-1 infected subjects who have failed currently available antiretroviral drugs. Ibalizumab is the only treatment which offers the potential of reducing viral load and improving CD4 counts and safety profile. Treatment of patients who failed previous antiretroviral regimens represents an opportunity to minimize the risk of long-term HIV-1 related complications.

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These studies are designed to demonstrate that IV ibalizumab is effective in the treatment of patients who failed antiretroviral regimens. The Applicant is seeking the indication of ibalizumab treatment of patients with chronic HIV-1 infection. Treated subjects received ibalizumab intravenously once weekly for 24 weeks with a 2000 mg loading dose on Day 7/Baseline followed by 800 mg maintenance doses every 2 weeks. At Day 14, after 1 week of ibalizumab as monotherapy, all subjects received an optimized background regimen (OBR), which is a standard-of-care regimen selected by the investigator based on treatment history and the results of viral resistance testing.

Study Protocols TMB-301 and TMB-202 were submitted in support of the application. The most common side effects of ibalizumab include headache, dizziness, nausea, cough, fatigue, abdominal pain, and rash.

Protocol TMB-301: A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab Plus Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected With Multi-Drug Resistant HIV-1.

Subjects: 40 subjects enrolled; 31 subjects completed all scheduled visits
Sites: 30 in North America and 2 in Taiwan
Period of Trial: 7/2015 to 10/2016

The primary objective of this study was to demonstrate the antiviral activity of ibalizumab in subjects who failed other anti-retroviral treatment at Day 14 and at Week 25/End of Study. The secondary objectives of the study were 1) to assess the safety and tolerability of ibalizumab assessed through Week 25, 2) to assess the mean change from Day 7 baseline in CD4 cell count at Week 25, and 3) to determine the impact of ibalizumab on quality of life as assessed by the patient-reported outcomes.

This protocol was a phase 3, single arm, multicenter study to evaluate the safety and effectiveness of ibalizumab in treatment-experienced subjects infected with multi-drug resistant HIV-1. Subjects were failures with highly active antiretroviral therapy (HAART) for at least 6 months. After at least 8 weeks of therapy, a baseline viral load was determined.

The primary efficacy and safety analyses were assessed at 7, 14, 24, and 25 weeks after the end of the treatment/principal observation period. Thirty-one (31) centers enrolled subjects in the U.S. and Taiwan. Forty (40) subjects were randomized as follows:

- Days 0-6 of the study were a “control period”. During Days 0 through 6, subjects were monitored on current failing therapy (or no therapy, if the patient has failed and discontinued treatment within the 8 weeks preceding screening).
- Days 7-13 of the study were an “essential monotherapy period”. During Days 7 through 13, patients continued on current failing therapy and received one 2000 mg dose (loading dose) of ibalizumab on Day 7. Day 7 is the Baseline for the treatment period (Day 7-Week 25).

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- Day 14-Week 25 of the study was “maintenance period.” During Day 14 (primary endpoint), the OBR were initiated and included at least one agent to which the patient’s virus was susceptible. Beginning at Day 21, 800 mg of ibalizumab were administered every 2 weeks through Week 23.

- Subjects completed the Week 25/EOS Visit and the Week 29/Follow-up Visit procedures.

Protocol TMB-202: A Phase 2b, Randomized, Double-Blind, 48-Week, Multicenter, Dose-Response Study of Ibalizumab plus Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected with Multi-Drug Resistant HIV-1 (Amended to 24-Week Study).

Subjects: 120 subjects enrolled

Sites: 30 in North America

Period of Trial: 10/14/2008 to 1/26/2011

The primary objectives of this study were 1) to evaluate the dose-response effectiveness of antiviral activity of the ibalizumab dose regimen at Week 24 in order to determine the optimal dose and regimen. The primary evaluation of effectiveness was based on the proportion of patients achieving undetectable viral loads at Week 24; and 2) to evaluate the safety and tolerability of two dose regimens of ibalizumab.

The secondary objectives of the study were 1) to evaluate changes from baseline in viral load, CD4 cell counts, and time to loss of virologic response (TLOVR), and 2) to determine the impact of ibalizumab on quality of life as assessed by the patient-reported outcomes.

This protocol was a phase 2, multicenter, randomized, double-blind study to evaluate the effectiveness and safety of ibalizumab in patients infected with HIV-1. Patients who were treated with HAART for at least 6 months and failed, or had recently failed (i.e., in the last 8 weeks) therapy. The two dose regimens of ibalizumab were randomly assigned in a 1:1 ratio to approximately 120 patients. The random assignment was stratified by (a) use of or non-use of a viral entry inhibitor, and (b) use or non-use of an integrase inhibitor in OBR. Thirty (30) centers enrolled subjects in the U.S. Subjects were randomized to the following two dose regimens as follows:

- 800 mg of ibalizumab every 2 weeks plus OBR
- 2000 mg of ibalizumab every 4 weeks and placebo on the intervening 2-week period visit, plus OBR.

All patients completed the Week 24/End of Study (EOS) and Week 28 Follow-up Visit procedures.

Site Selection for Study Protocols TMB-301 and TMB-202

The CDER review division team selected these sites principally due to relatively high patient accrual in the study and site specific protocol violations. The clinical site inspections were intended to help verify data integrity.

Site #25 (Dr. Khanlou) in the U.S. enrolled a relatively large number of subjects in Study TMB-202 and reported no protocol deviations. This site had a single history of inspection with a VAI classification in 2009.

Site #5 (Dr. Fessel) in the U.S. enrolled a relatively high number of subjects in Study TMB-301 and reported four protocol violations. Also this site enrolled six subjects in TMB-202 with one protocol deviation. This site had no prior history of inspection.

Site #22 (Dr. Schrader) in the U.S. had a relatively high number of subjects in the TMB-301 study, and also enrolled five subjects in TMB-202 with one protocol deviation. This site had no prior history of inspection.

Site #17 (Dr. Kumar) in the U.S. enrolled three subjects in Study TMB-301 with one protocol deviation. This site had no prior history of inspection

III. RESULTS (by site):

Name of CI, Site #, Address, City, State	Protocol # and # of Subjects	Inspection Date	Final Classification
Jeffery Fessel, M.D. Kaiser Permanente Medical Center, Clinical Trial Unit 4141 San Francisco, CA 98118 Site #5	TMB-301 & TMB-202 Subjects enrolled: 4 & 6	7/31-8/8/2017	Pending (preliminary classification VAI/)
Shannon Schrader, M.D. Research Access Network Houston, TX 77098 Sites #22 &43	TMB-301 & TMB-202 Subjects enrolled: 4 & 5	7/10-14/2017	Pending (preliminary classification VAI)
Homayoon Khanlou, M.D. Laveeza Bhatti, M.D., Ph.D Health Care Foundation Center Cienega Blvd. Suite 200 Beverly Hills, CA 90211	TMB-202 Subjects enrolled: 13	7/31- 8/18/2017	Pending (preliminary classification VAI)
Princy N Kumar, M.D. 3800 Reservoir Rd Washington, DC 20007	TMB-301 Subjects enrolled: 3	7/13-17/2017	VAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

NOTE: Site inspections focused on 100% review of informed consent documents, IRB, ethics committee correspondence, financial disclosures, training records, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, vital signs, subject source documents, including medical history records, drug accountability, and the use of concomitant medications. Source documents were compared to data listing for primary efficacy endpoints and adverse events reporting.

1. Jeffrey Fessel, M.D./Site #5 / Studies TMB-301 & TMB-202
San Francisco, CA 94118

For Study TMB-301, at this site there were five subjects screened, one subject was reported as a screen failure, four subjects were enrolled in the study, and all four subjects completed the study. All five subjects' records were reviewed.

For Study TMB-202, at this site there were seven subjects screened, one subject was reported as a screen failure, six subjects were enrolled, and all completed the study. All seven subjects' records were reviewed.

The medical records for all 12 subjects in both studies were reviewed. The ORA investigator reported that the records reviewed were organized and legible. Medical records/source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse event reporting. There were minor transcription errors, cross-outs, and out of window visits; some adverse events were not reported. For example, a subject (not identified) in Study TMB-202 had a history of hypertension of (160/110) and on hypertensive medication experienced a significant rise in blood pressure level to 196/128 shortly after drug infusion. The rise in blood pressure was not reported as an adverse event. The clinical investigator stated that he had seen this patient for a long time prior to the study, and the spikes in blood pressures were common. Similar observations were noted in subjects enrolled in Study TMB-301. Subject 05-001 experienced edema of the trunk, arms, and legs. These adverse events were not reported. Subject 05-005 experienced onchomycosis that was not reported as an adverse event, condition although it was reported as an adverse event for Subject 05-001.

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The inspection revealed adequate adherence to the regulations and investigational plan. There were no major objectionable conditions noted, and no Form FDA 483 was issued to Dr. Fessel. However, these observations were noted and discussed with the clinical investigator at the conclusion of the inspection. The clinical investigator agreed with the inspectional findings and promised to err on the side of reporting possible adverse events in the future. OSI finds his verbal response to be acceptable.

With the exceptions noted above, the data generated by this site appear acceptable. The inspection did not indicate serious deviations/findings that would impact the acceptability of the data submitted in support of the application.

2. Shannon Schrader, M.D./ Sites #22 & 43/Studies TMB-301 & TMB202
Houston, TX 77098

For Study TMB-202, at this site eight subjects were screened, two subjects were reported as screen failures, and one subject withdrew consent. During the inspection, the ORA investigator reported that the study records were “accidentally destroyed”, as described in a memo dated 6/18/2017. Dr. Schrader in his amended response to the FDA inspectional findings included copies of the “found” records. OSI cannot attest that the “found/located” study records were in fact true copies of the original study records without verification at the site.

The OSI reviewer was notified by the field investigator (shortly after the inspection was concluded) that the clinical investigator contacted the field investigator to let him know that he was able to locate the “destroyed records”. The OSI reviewer recommended to the field investigator to return to the site and try to review and verify the “found” records. The field investigator was advised repeatedly to return to the site as soon as possible and to let the Center know the date he plans to visit the clinical investigator in order to complete the inspection. As of 9/12/2017 the field investigator e-mailed the Center stating that due to “time constraints and scheduling conflicts with another inspection (for-cause).....was not able to go back out to the site”.

OSI recommends that the data submitted from this site for Protocol TMB-202 should not be used in support of the application under review because we were unable to verify the data from the “found/located” copies of the study records. OSI recommends that the review division consider conducting a sensitivity analysis with and without the data from Dr. Schrader’s Study TMB-202 from their final analyses to detect differences in the efficacy and/or safety outcome..

For Study TMB-301, at this site four subjects were enrolled and all completed the study. The medical records for all subjects were reviewed. The inspection revealed inadequate record keeping practices contrary to the signed investigational plan: our investigator found discrepancies between the source documents and what was reported in the electronic case report forms (e-CRF) for all four subjects. The discrepancies noted included, but were not limited to the following:

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Subject PID22-001/DS - Source document lacked the following data found in the e-CRF; dose, unit, route of administration, and frequency of ART medications taken.

Subject PID22-002/LA - Source document lacked data found in the e-CRF for start and stop dates of OBR medications.

Subject PID-003/DS - Source data for previous and concomitant medications and e-CRF are not identical. For example, source data listed Lyrica 200 mg TID starting in 2003, while the e-CRF listed the Lyrica 300 mg QD start date as 2012 and the source data listed the Bactrim start date as 2015, while the e-CRF listed the Bactrim start date as 2014. In addition, the concomitant medications page lacks the initials/signatures and frequency of dosing”.

It is not clear from the report whether the field investigator reviewed the Electronic Medical Records (EMR) to determine if the data initially were directly recorded in the electronic case report forms (e-CRFs).

These objectionable conditions were listed on Form FDA 483 and were discussed with Dr. Schrader.

Overall, the data generated at Dr. Schrader’s site for protocol TMB-301 in support of the clinical efficacy and safety is considered reliable and acceptable. However, the data from Site TMB-202 (Dr. Schrader) submitted to Study TMB -202 could not be verified using the copies of “found” study records provided by the clinical investigator without the benefit of access to original study records.

3. Homayoon Khanlou, M.D./ Site #25/Study TMB-202 Beverly Hills, CA 90211

There were 15 subjects screened, two subjects were reported as screen failures, 13 subjects were enrolled, five subjects were discontinued and the reasons were documented. One subject withdrew consent, two subjects were reported as lost to follow-up, and one subject was reported as a virologic failure. Eight subjects completed the study. The medical records for all subjects were reviewed.

The medical records/source documents were compared to case report forms and data listings for the primary efficacy endpoint and adverse event reporting. For five subjects minor protocol deviations were found. The deviations included physical exams, ECGs, vital signs, and Functional Assessment of HIV Infection (FAH) questionnaires were not always completed at certain visits as required by the protocol.

At the conclusion of the inspection, a 1-item Form FDA 483 was issued to Dr. Michael Wolfheiler, Chief Medical Officer for The AIDS Healthcare Foundation located in Miami.

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The ORA investigator discussed her findings with Dr. Wolfheiler due to the absence of the clinical investigator during the inspection and the exit interview. The Chief Medical Officer provided a verbal corrective action response, and he promised to respond in writing to the FDA 483 inspectional findings. The field investigator reported that the medical records were organized and legible. It is unlikely that the deviations note above would impact the outcome of the study in terms of validity or reliability of the submitted data.

With the exceptions noted above, the data generated by this site in support of the clinical efficacy and safety is considered acceptable and may be used in support of the pending application.

4. Princy N. Kumar, M.D./Site #17/Study TMB-301
3800 Reservoir Rd.
Washington, DC 20007

There were four subjects screened, one subject was reported as a screen failure, and three subjects were enrolled. One subject was terminated for non-compliance and two subjects completed the study. The medical records for all subjects were reviewed.

The medical records/source documents were compared to case report form and data listings for the primary efficacy endpoint and adverse event reporting. No major deficiencies were noted. The inspection revealed minor protocol deviations.

At the conclusion of the inspection, a 1-item Form FDA-483 was issued to Dr. Kumar. The field investigator noted a protocol deviation: Grade 3 or 4 neutropenia is an exclusionary criterion according to the protocol. This subject was enrolled and later was discontinued due to non-compliance.

The clinical investigator agreed with the observation and stated that the subject's neutropenia level fluctuates depending on taking the medication, Neulasta. The subject was enrolled and later was discontinued due to non-compliance. OSI finds his response to be acceptable. It is unlikely that the deviation impacted the outcome of the study in terms of validity or reliability of the submitted data.

With the exception noted above, the data generated by this site appear acceptable. The inspection did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

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{See appended electronic signature page}

Antoine El Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Susan Thompson, M.D., Team Leader for
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/s/

ANTOINE N EL HAGE
10/10/2017

SUSAN D THOMPSON
10/10/2017

LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: August 24, 2017
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: BLA 761065
Product Name and Strength: Trogarzo (ibalizumab) injection, 150 mg/mL
Total Product Strength: 200 mg/1.33 mL
Product Type: Single-ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: TaiMed Biologics, Inc.
Submission Date: May 3, 2017 and July 20, 2017
OSE RCM #: 2017-854
DMEPA Safety Evaluator: Nasim Roosta, PharmD
DMEPA Team Leader: Otto L. Townsend, PharmD

1 REASON FOR REVIEW

The Division of Antiviral Products (DAVP) requested that we assess the proposed Prescribing Information (PI), the Patient Package Insert, container labels and carton labeling submitted for BLA 761065 from a medication error prospective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, patient information leaflet, container labels, and carton labeling to identify deficiencies that may lead to medication errors and to identify other areas that could be improved.

Prescribing Information:

(See appended PI in Appendix H for an illustration of recommendations)

We note that the table in Section 2.1 “Recommended Doses” contains information for preparing the loading dose and maintenance doses. This table would more appropriately be placed in Section 2.2 “Preparation” with the other preparation information. We recommend to move the table in Section 2.1 to Section 2.2.

We also note Section 2.1 “Recommended Doses”, contains a table that is not titled or numbered. All tables within the PI should be numbered and contain a title to introduce the information presented in the table. We recommend the addition of a table number (e.g. “Table

1”) and proper title above the table (e.g. “*Preparation of TROGARZO*”) in Section 2.1. All subsequent tables must be numbered accordingly.

The second column of this table, lists the number of vials associated with the recommended doses of 2,000 mg and 800 mg. As this drug product is a solution, the user should be instructed on the total volume of drug required to prepare the dose. Therefore, in addition to the number of vials required to prepare the dose, the corresponding volume of drug required should be included in the table. For example, for a loading dose of 2,000 mg, 13.3 mL must be added to the infusion bag. The number of vials for this corresponding amount can be presented in parentheses next to the volume to be administered dose. We also recommend to change the heading of this column from (b) (4) to “*Volume to Withdraw From Trogarzo Vials*”.

We note the loading dose is listed as “2000 mg” throughout the PI. Commas should be used for numbers 1,000 and above to improve legibility of larger numerals.^a Throughout the PI, all instances of the numeral “2000” should be replaced with “2,000”.

In Sections 2.1 and 2.2, the PI recommends the user to dilute the product in 250 mL of (b) (4). This is not commonly used language for diluents and may become a source of confusion and error when diluting the product. The Applicant should clarify which solution represents (b) (4). For example, “0.9% Normal Sodium Chloride Injection, USP”. Additionally, we note diluent information is contained in Section 16: “*How Supplied*”. Since the diluent information is more applicable to preparation and administration, we would recommend this information be deleted because it is contained in the Section 2: “*Dosage and Administration*”.

In Section 2.2 “*Preparation*”, the statement (b) (4) does not clearly convey to the user what actions are required to prepare the drug product. To prevent the user from preparing this product incorrectly, the Applicant needs to clarify instructions (b) (4).

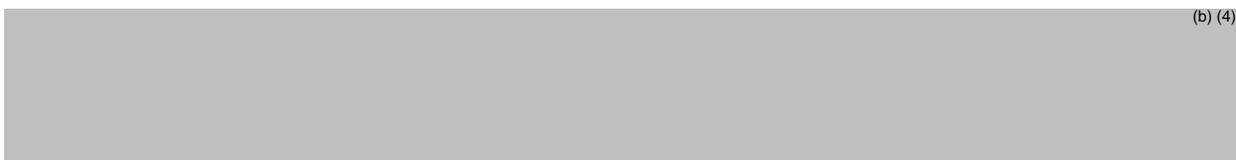
In Section 2.2 “*Preparation*”, the second bullet point contains the statement (b) (4). To prevent a potential wrong dose (overdose) medication error, the statement should instruct the user to withdraw the exact volume required to prepare an 800 mg and 2,000 mg dose.

Section 2.3 “*Administration*”, instructs the user to flush the intravenous line with 30 mL of “normal saline”. The Applicant should clarify if “normal saline” is 0.9% Sodium Chloride Injection, USP that must be used.

^aGuidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

In section 2.3, we also noted the use of the symbol (b) (4) within a sentence. According to the ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations^b, these symbols may be confused or misinterpreted and should be replaced with their full meaning as this may be a source of potential dosing errors. We recommend to replace the symbol, (b) (4) with its full meaning (e.g., 3 or more days) within this sentence.

In section 16, some of the temperatures indicated do not include a corresponding degree measurement. All numbers within the PI must be followed by an appropriate unit of measure. We recommend to add °C after the number '2' and °F after the number '36' within this section.



Container Label and Carton Labeling

We note the total drug strength is listed as “200 mg/vial” on both the container label and carton labeling, which is the strength presentation intended for dry powder dosage forms. For injection solution dosage forms, the strength should be presented as the total drug strength per total volume followed in close proximity by the strength per mL.^c

Both the container label and carton labeling include the statement, (b) (4) next to the established name of the drug. This would be appropriate for dry powder dosage form, but this product is a liquid dosage form. We recommend to delete the (b) (4) statement on both the container label and the principle display panel of the carton labeling and instead add “injection” underneath “ibalizumab”.

We note the use of the package-type term, (b) (4) vial in the PI and on the container label and carton labeling. We defer to the Office of Pharmaceutical Quality on the determination of the appropriate package-type term for this product.

^b ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Sep 16]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

^c USP General Chapter: Injections; Labels and Labeling; strength and total volume for single- and multiple dose injectable drug products. USP has announced plans to relocate this information to General Chapter Labeling in the near future.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed PI, container label, and carton labeling that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

We find the proposed Patient Package Insert for Trogarzo acceptable from a medication error perspective.

If you have questions or need clarifications, please contact Danyal Chaudhry, OSE Project Manager, at 301-796-3813.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

(See appended PI in Appendix H for an illustration of all recommended changes)

1. Move the table containing dose preparation information in Section 2.1 *“Recommended Doses”* to Section 2.2 *“Preparation”*. This table will more appropriately correspond to preparation information presented in Section 2.2.
2. To introduce the contents of the table in Section 2.1 *“Recommended Doses”*, add a number and title. Adjust numbering for all subsequent tables accordingly.
3. In addition to adding a number and title for the table listed above, change the title of the second column to *“Volume to Withdraw From Trogarzo Vials”* and within the table, include the volume that must be administered for each corresponding dose being prepared. The number of vials for this corresponding amount may be presented in parentheses next to the volume to be administered.
4. All doses within the PI that are larger than 1,000 should have an appropriately placed comma in the dose presentation to avoid confusion (i.e., 200 vs. 2000). Change all instances of *“2000 mg”* to read *“2,000 mg”*.
5. The use of “(b) (4)” in Sections 2.1 and 2.2 and the use *“normal saline”* in section 2.3 should be clarified. For example, *“0.9% Normal Sodium Chloride Injection, USP”*.
6. Delete the diluent information that is contained in Section 16: *“How Supplied”*. This is redundant information that is contained in Section 2: *“Dosage and Administration”*.

7. In Section 2.2 “Preparation”, clarify the statement (b) (4). This statement does not clearly instruct the user what actions need to be performed. (b) (4)
8. In Section 2.2 “Preparation”, instructs the user to (b) (4). Revise this statement to instruct the user to withdraw the actual volume of drug required for preparing the 800 mg and 2,000 mg doses or refer the user to the table in Section 2.1.
9. In Section 2.3, “Administration”, we recommend to replace the symbol (b) (4) with its full meaning (e.g., 3 or more days).
10. In section 16, we recommend to add °C after the number “2” and °F after the number “36” to ensure all corresponding units of measure are included.

4.2 RECOMMENDATIONS FOR TAIMED BIOLOGICS, INC.

We recommend the following recommendation be implemented prior to approval of this BLA:

1. On both the proposed container label and the carton labeling, the strength statement is listed as (b) (4).^d This is the format used for dry powder dosage forms. Change the strength statement from (b) (4) to the total drug strength per total volume “200 mg/1.33 mL” followed by the strength per mL, “150 mg/mL”.
For example:
200 mg/1.33 mL
(150 mg/mL)
2. On both the proposed container label and the carton labeling, the dosage form is listed as (b) (4) but this product is an injection solution. Change all instances of (b) (4) to “Injection”.

^d Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Trogarzo (ibalizumab) that TaiMed Biologics, Inc. submitted on May 3, 2017.

Table 2. Relevant Product Information for Trogarzo (ibalizumab)	
Initial Approval Date	N/A
Active Ingredient	Ibalizumab
Indication	(b) (4) in combination with other antiretroviral(s), is indicated for the treatment of adults infected with HIV-1 resistant to at least one agent in three different classes.
Route of Administration	Intravenously
Dosage Form	Injection
Strength	150 mg/mL
Dose and Frequency	A single loading dose of 2,000 mg is followed by a maintenance dose of 800 mg every 2 weeks.
How Supplied	Available in a carton containing two single (b) (4) vials.
Storage	Store vials under refrigeration at 2 to 8°C (36-46 °F). Do not freeze. Protect from light.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 31, 2017, we searched the L:drive and AIMS using the terms, 'Trogarzo' and 'Ibalizumab' to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any other reviews for this product.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^e along with postmarket medication error data, we reviewed the following Trogarzo labeling submitted by TaiMed Biologics, Inc. on May 3, 2017.

- Prescribing Information
- Patient Package Insert
- Carton labeling
- Container label

G.2 Label and Labeling Images

Container Label:



24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

NASIM N ROOSTA
08/24/2017

OTTO L TOWNSEND
08/24/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 761065	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: TROGARZO Established/Proper Name: ibalizumab Dosage Form: injectable Strengths: 150 mg/mL; 200 mg/vial Route(s) of Administration: intravenous		
Applicant: TaiMed Biologics USA Corp. Agent for Applicant (if applicable):		
Date of Application: May 3, 2017 Date of Receipt: May 3, 2017 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: January 3, 2018	Action Goal Date (if different): December 6, 2017	
Filing Date: July 2, 2017	Date of Filing Meeting: May 25, 2017	
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication: For the treatment of adults infected with HIV-1 resistant to at least one agent in three different classes.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	

Review Classification:		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority		
The application will be a priority review if: <ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 		<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>			
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)			
<input checked="" type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 9776				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Product name corrected in DARRTS

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Submitted on 7/19/16 on initiation of rolling review
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</i>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:	<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>		

<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 	<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p>	<input type="checkbox"/>	<input type="checkbox"/>																		
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%;">Application No.</th> <th style="width: 30%;">Drug Name</th> <th style="width: 25%;">Exclusivity Code</th> <th style="width: 20%;">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<ul style="list-style-type: none"> If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If no, include template language in the 74-day letter.</p> <p>Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]</p> <p><i>Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>																		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
NDA only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Exclusivity was not requested; may be eligible

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Initial application included an incomplete Form 356h. Resubmitted on 5/8/17.
<p>Index: Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA</i> efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Revised 356h submitted 5/8/17
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Requested in Acknowledgement Letter – submitted 5/11/17
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p>For non-NMEs: <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Exemption for orphan drugs
<p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>BPCA:</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 12/05/2016

8

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Request submitted on 09/06/16; Proprietary name conditionally accepted on 11/17/16
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting? Date: June 14, 2011	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Dates: February 3, 2016 (CMC) & September 26, 2016	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>			

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 25, 2017

BACKGROUND: The new molecular entity, ibalizumab, is being reviewed for the treatment of HIV-1 infection in adults resistant to at least one agent in three different classes. New biologic application 761065 for TROGARZO (ibalizumab) injection for intravenous use was initially received in a pre-submission under rolling review on July 19, 2016, as agreed to by the Division for CMC information, and the full application was received on May 3, 2017. TROGARZO has been granted Fast Track, Orphan status, and Breakthrough designation and the application will be given priority review. The pivotal data to support the use of this product is from the TMB-301 clinical trial.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christian P. Yoder	Y
	CPMS/TL:	Elizabeth Thompson	Y
Cross-Discipline Team Leader (CDTL)	Adam Sherwat		Y
Division Director/Deputy	Debra Birnkrant, Director		N
	Jeffrey Murray, Dep Director		Y
Office Director/Deputy	Edward Cox, Director		N
	John Farley, Dep Director		Y
Clinical	Reviewer:	Virginia Sheikh	Y
	TL:	Adam Sherwat	Y
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Eric Donaldson	Y
	TL:	Julian O'Rear	N
Clinical Pharmacology	Reviewer:	Qin Sun	N
	TL:	Shirley Seo Islam Younis	N Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Karen Qi	Y
	TL:	Thamban Valappil	Y

Nonclinical Pharmacology/Toxicology)	Reviewer:	David McMillan	Y
	TL:	Chris Ellis Hanan Ghantous	Y Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Ramesh Potla	Y
	RBPM:	Anita Brown	N
• Drug Substance	Reviewer:	Steven Bowen	N
• Drug Product Quality	Reviewer:	Susan Kirshner	N
• Process	Reviewer:		
• Microbiology	Reviewer:	Patricia Hughes	Y
• Microbiology (Drug Substance)		Maria Lopez-Barragan	Y
• Microbiology (Drug Product)		Virginia Carrol	Y
• Microbiology TL		Dupeh Palmer	Y
• Facility	Reviewer:	Michael Shanks	Y
	TL:	Peter Qiu	Y
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:	Vicky Borders-Hemphill	Y
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Morgan Walker	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Wendy Lubarsky	N
	TL:	Sam Skariah	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Nasim Roosta	Y
	TL:	Otto Townsend	N
OSE/DRISK (REMS)	Reviewer:	Ingrid Chapman	Y
	TL:	Elizabeth Everhart	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Antoine el Hage	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline	Reviewer:		
	TL:		
Other attendees – OND ADRA	Stacey Min, Associate Director for Labeling		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The application did not raise significant safety or efficacy issues.
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> Comments: Does not apply to biologics	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment ready for inspection? Comments: Inspection in China scheduled for July 17-August 2, 2017	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments: Fileable, however, application is incomplete and additional information is being requested by separate IR's and not being sent in filing letter.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments: No CMC labeling reviewer comments at this time.</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Office

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 8/11/17

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

CHRISTIAN P YODER
06/27/2017

ELIZABETH G THOMPSON
06/27/2017

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 761065

Application Type: New BLA

Drug Name(s)/Dosage Form(s): TROGARZO (ibalizumab) injection

Applicant: TaiMed Biologics

Receipt Date: May 3, 2017

Goal Date: January 3, 2018

1. Regulatory History and Applicant's Main Proposals

The new molecular entity, ibalizumab, is currently being reviewed under PDUFA V's "The Program" for the treatment of HIV-1 infection in adults resistant to at least one agent in three different classes. New biologic application 761065 for TROGARZO (ibalizumab) injection for intravenous use was initially received in a pre-submission under rolling review on July 19, 2016, as agreed to by the Division for CMC information, and the full application was received on May 3, 2017. TROGARZO was granted Orphan status and Breakthrough designation and the application will be given priority review. The pivotal data to support the use of this product is from the TMB-301 clinical trial.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review. Also, it was noted that Section 15 was not properly formatted and contained references that should be removed from that section. In addition, Section 16 contains subsections and applicant will be notified that this section should not include subsections.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 4, 2017. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Selected Requirements of Prescribing Information

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *Font is in 11-point. We will suggest that sponsor use 8-point*

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- NO** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment: *There is no horizontal line between TOC and the FPI*

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required

Selected Requirements of Prescribing Information

• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

Selected Requirements of Prescribing Information

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at**

Selected Requirements of Prescribing Information

(insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION** and **FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**

Comment: *This should NOT be underlined*

Revision Date in Highlights

NO 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment: *The revision date is not right justified.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment: *Should be all on one line*
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

Selected Requirements of Prescribing Information

Comment: *Note: there is a lack of cross-referencing which will be addressed during the content review*

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment: *There are no Recent Major Changes.*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Selected Requirements of Prescribing Information

Comment: No postmarketing adverse reaction data are included, however, applicant utilized the reserved subsection for lab abnormalities. Applicant will be notified to remove from subsection 6.2 and add this under subsection 6.1.

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

CHRISTIAN P YODER
05/31/2017

ELIZABETH G THOMPSON
05/31/2017