APPLICATION NUMBER:

761051Orig1s000

OTHER REVIEW(S)
### CDER Breakthrough Therapy Designation Determination Review Template

<table>
<thead>
<tr>
<th>IND #</th>
<th>101843</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request Receipt Date</td>
<td>6/30/2017</td>
</tr>
<tr>
<td>Product</td>
<td>Mogamulizumab (KW-07671)</td>
</tr>
<tr>
<td>Indication</td>
<td>CTCL</td>
</tr>
<tr>
<td>Drug Class/Mechanism of Action</td>
<td>anti-CCR4 monoclonal antibody</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Kyowa Kirin Pharmaceutical Development, Inc.</td>
</tr>
<tr>
<td>ODE/Division</td>
<td>DHP</td>
</tr>
<tr>
<td>Breakthrough Therapy Request Goal Date (within 60 days of receipt)</td>
<td>8/29/2017</td>
</tr>
</tbody>
</table>

**Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs**

1. Briefly describe the indication for which the product is intended:

   **Sponsor’s proposed indication:** Mogamulizumab for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

   **DHP’s recommended indication:** Mogamulizumab for the treatment of mycosis fungoides or Sezary syndrome after at least one prior systemic therapy.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

   | YES | ☒ NO |

3. Consideration of Breakthrough Therapy Criteria:

   a. Is the condition serious/life-threatening?

      ☒ YES  ☐ NO

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

      ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review

      ☐ Undetermined

      ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

      i. Only animal/nonclinical data submitted as evidence ☐

      ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐

      iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

      iv. Endpoint does not assess or is not plausibly related to a serious

---

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b: N/A

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Drug: Mogamulizumab (moga), a new molecular entity, is a defucosylated, humanized IgG monoclonal antibody that selectively binds to CCR4 (CC chemokine receptor 4) and promotes antibody-dependent cellular cytotoxicity. CCR4 is expressed on nonmalignant T-cell subsets and is overexpressed or frequently expressed in various T-cell malignancies, including CTCL. Moga is approved in Japan for CTCL and adult T-cell leukemia/lymphoma. BLA submission is planned 9/2017 for moga for CTCL, based on the phase 3 study underlying this BTDR.

Disease background: Mycoses fungoides (MF) and Sezary syndrome (SS), the main types of CTCL, comprise approximately 5% of non-Hodgkin lymphomas and are usually incurable. These rare diseases cause major morbidity and shortened survival. MF primary presents in the skin, with potential involvement of nodes, blood, and viscera. Prognosis varies widely and is related to stage. Skin lesions may be localized or widespread, manifesting as patches or plaques, tumors (which may be disfiguring), erythroderma, and occasionally large-cell transformation (median OS of ~ 2 years). SS, a rare and aggressive leukemic variant, has a median OS of ~ 3 years. In either disease, pruritus is a leading symptom and can be debilitating. Skin erosion and superinfection from constant scratching are common, as are opportunistic infections.

MF/SS tends to be resistant to chemotherapy. Approximately 30-40% of patients respond to a variety of biologic agents, although durable, deep remissions are rare. Skin directed therapies are used for early-stage disease, whereas systemic therapies are used for refractory early-stage and advanced-stage disease.

---

Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Refer to Question 10.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

Overall response rate (ORR) has been the primary basis for U.S. approval for all drugs for CTCL (Table 1 below). Durable ORR (mostly PR) has supported regular approval in other rare lymphomas, whereas PFS has been the usual endpoint for regular approval (with durable ORR supporting accelerating approval) in more common lymphomas.

Of note, all drugs for CTCL received regular approval on the basis of single-arm studies. Additionally, ORR was determined primarily in the skin, whereas the moga phase 3 study uses more rigorous, multi-compartmental response criteria developed by international consensus (Olsen EA et al, JCO 2011).

Particularly given the symptom burden of advanced CTCL, patient-reported outcomes (PROs) could be supportive.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval. None

7. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

Refer to Table 1.
<table>
<thead>
<tr>
<th>Drug (Year Approved)</th>
<th>Approved Indication</th>
<th>Pivotal Trial Design</th>
<th>Primary &amp; Key Secondary Approval Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Istodax (romidepsin) (2009)</td>
<td>CTCL following at least one prior systemic therapy</td>
<td>Two single-arm studies (N=167)</td>
<td>ORR 34% (Study 1) mDOR 15 months ORR 35% (Study 2) mDOR 11 months</td>
</tr>
<tr>
<td>Zolinza (vorinostat) (2006)</td>
<td>Treatment of cutaneous manifestations of CTCL in pts with progressive, persistent, or recurrent disease on/ following 2 systemic therapies</td>
<td>Two single-arm studies (N=107)</td>
<td>Overall Objective Response 29.5% (≥ IIB) 29.7% (all stages) mDOR not reached</td>
</tr>
<tr>
<td>Targettin (bexarotene) (1999)</td>
<td>Treatment of cutaneous manifestations of CTCL in patients who are relapsed to at least one prior systemic therapy</td>
<td>Two single-arm, historically-controlled studies (N=152) One post-marketing study (N=59)</td>
<td>RR (CA) 30% (Clinical study) For 300mg/m²/day group (Post-marketing study): RR (CA) 34.5% RR (PGA) 37.9%</td>
</tr>
<tr>
<td>Methotrexate (1959)</td>
<td>Alone or in combination with other anticancer agents in the treatment of advanced mycosis fungoides (CTCL)</td>
<td>Not included in USPI</td>
<td>Responses up to 50% (single agent)</td>
</tr>
</tbody>
</table>

Note: All have regular approval. Romidepsin and vorinostat are HDAC inhibitors; bexarotene is a retinoid.

In addition, Ontak (Denileukin diftitox) received regulator approval for but is no longer marketed.

Other treatments: Total skin electron beam irradiation and phototherapy are widely used. Drugs used off-label for CTCL include IFN-alpha and cytotoxic chemotherapy alone (e.g., liposomal doxorubicin) or in combination.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation.

Brentuximab vedotin (Adcentris; an anti-CD30 antibody drug conjugate) was granted BTD (11/2016) for patients with CD30-expressing MF and primary cutaneous anaplastic large cell lymphoma who require systemic therapy and have received one prior systemic therapy. The drug is not approved for these indications.

10. Information related to the preliminary clinical evidence:

---

3 Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

4
a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design\(^4\), trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

One clinical trial forms the basis of this BTDR:

**ID:** Study 0761-010 (ClinicalTrials.gov: NCT01728805)

**Phase:** 3

**Design**
- International, open-label, randomized controlled trial for adults with MF/SS (stage IB or higher; any CCR4 status) failing ≥ 1 systemic therapy
- 1:1 randomization to moga (1.0 mg/kg on days 1, 8, 15, and 22 of cycle 1; days 1 and 15 of subsequent 28-day cycles) vs vorinostat (standard of-care dosing), until PD or unacceptable toxicity

**Endpoints**
- Primary: PFS by investigator (IRC secondary)
- Key secondary: confirmed ORR, based on global composite score in all disease compartments
- Other secondary endpoints: include quality of life (QOL)

**Treatment groups**
- Per Table 2. This was a heavily pretreated patient population, with >60% of patients having 4 or more prior systemic therapies, and >60% of patients having advanced-stage disease. The arms were well balanced.

<table>
<thead>
<tr>
<th>Table 2: Patient characteristics (N = 374) in Study 0761-010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Median age</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>MF</td>
</tr>
<tr>
<td>SS</td>
</tr>
<tr>
<td>Current stage III or IV</td>
</tr>
<tr>
<td># of prior systemic therapies</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>≤ 2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>≥ 4</td>
</tr>
</tbody>
</table>

\(^4\) Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.
Top-line efficacy results:
- Table 3 summarizes the efficacy data.
- The study met its primary objective, demonstrating a statistically significantly higher, investigator-assessed PFS with moga as compared to vorinostat (Figure). ORR (CR + PR) and DOR were also superior in the moga arm.
- Results of blinded IRC review were consistent with investigator assessments.
- The treatment effect (PFS, ORR, DOR) in SS were consistent with those in MF.
- The treatment effect (ORR) was consistent in individual disease compartments, with a 3-4 fold greater ORR with moga compared to vorinostat in the skin, nodes, and blood.
- The Sponsor additionally reported improved QOL in the moga arm.

![Study 0761-010: PFS (ITT) per investigator](image)

**Table 3: Top-line efficacy results in Study 0761-010**

<table>
<thead>
<tr>
<th>Population</th>
<th>Variable</th>
<th>Moga (N = 186)</th>
<th>Vorinostat (N = 186)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>Median PFS (inv), months</td>
<td>7.7 (95% CI: 5.7, 10.3)</td>
<td>3.1 (95% CI: 2.9, 4.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HR for PFS (inv)</td>
<td>0.53 (0.41, 0.69)</td>
<td>3.8 (CI: 3.0, 4.7)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Median PFS (IRC)</td>
<td>6.7 (CI: 5.6, 9.4)</td>
<td>5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HR for PFS (IRC)</td>
<td>0.65 (CI: 0.50, 0.85)</td>
<td>9 (CI: 5, NE)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Confirmed ORR (inv)</td>
<td>28%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median DOR (inv), months</td>
<td>14 (CI: 9, 19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR for OS a</td>
<td>0.93 (CI: 0.61, 1.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sezary syndrome</strong></td>
<td>Median PFS (inv), months</td>
<td>13.3 (CI: 7.7, 17.1)</td>
<td>3.1 (CI: 2.8, 3.9)</td>
<td>2%</td>
</tr>
<tr>
<td><strong>(N = 168)</strong></td>
<td>Confirmed ORR (inv)</td>
<td>37%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median DOR (inv), months</td>
<td>17.3 (CI: 12.2, 20.6)</td>
<td>6.9 (-)</td>
<td></td>
</tr>
</tbody>
</table>

Inv = investigator

a Unadjusted for cross-over (73%)
b. Include any additional relevant information.

– The overall safety profile with moga appeared acceptable.

– The poor performance of the control arm (5% ORR with vorinostat, compared to ~30% historically) is notable. Cross-trial comparisons are limited in particular because
  - The present study used more stringent response criteria that assessed multiple disease compartments, and that additionally required confirmation of response.
  - All registration studies in CTCL are single-arm, precluding cross-trial comparisons of PFS.
  - Patients in the various trial are likely to be prognostically heterogeneous.

Data on the subjects’ prior exposure to vorinostat, if any, were not included. If patients randomized to the vorinostat arm had prior exposure to vorinostat, the efficacy of vorinostat in the present study would be lower.

– Strengths of this study include:
  - Sample size: This is the largest randomized, active-control trial conducted in CTCL.
  - Efforts to minimize bias: In addition to blinded independent review, skin photographs were archived for each response assessment.

11. Division’s recommendation and rationale (pre-MPC review):

☐ GRANT:

Provide brief summary of rationale for granting:

The Sponsor has met the two key requirements for BTD:

- MF and SS are rare, serious, and life-threatening conditions.
- Preliminary clinical evidence demonstrates substantial improvement over existing therapies on one or more clinically significant endpoints: PFS, ORR, and DOR.

Although the Sponsor requested BTDR in CTCL, the data in this application are restricted to MF and SS. Therefore, DHP’s recommended indication is restricted to MF and SS.

☐ DENY:

Provide brief summary of rationale for denial:

12. Division’s next steps and sponsor’s plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

Based on Study 0761-010, the Sponsor plans to submit a BLA in 9/2017 to support regular approval for moga in CTCL. A face-to-face pre-BLA meeting was held in 7/2017. Based on CDRH consultation, and given the high frequency of CCR4 expression in CTCL, the Agency advised the Sponsor that a companion diagnostic (for tumor CCR4 expression) would likely not be required.
13. List references, if any:


14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: Yvette Kasamon, MD {See appended electronic signature page}
Team Leader Signature: R. Angelo de Claro, MD {See appended electronic signature page}
Division Director Signature: Ann Farrell, MD {See appended electronic signature page}
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YVETTE L KASAMON
08/21/2017

ROMEO A DE CLARO
08/21/2017

ANN T FARRELL
08/22/2017
1 PURPOSE OF MEMO
The Division of Hematology Products (DHP) requested that we review the revised carton label for Poteligeo (mogamulizumab-kpkc) Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION
The revised carton label for Poteligeo is acceptable from medication error perspective, we have no further recommendation at this time.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LEEZA RAHIMI
07/27/2018

HINA S MEHTA
07/27/2018
MEMORANDUM OF REVIEW

STN: BLA 761051 Mogamalizumab
Subject: Assessment of ADA assays for original application.
PRIMARY REVIEWER: Susan Kirshner, Ph.D.
APPLICANT: Kyowa Hakko Kirin
PRODUCT: Mogamalizumab (KW-0761; anti-CCR4)
INDICATION: Treatment of Cutaneous T cell lymphoma

I. SUMMARY BASIS OF RECOMMENDATION:

a. Recommendation: The ADA screening, confirmatory and titer assays are suitable. The NAb assay has poor sensitivity in the presence of expected levels of drug. The sponsor is aware of this and designated all ADA positive samples as NAb inconclusive. The Sponsor will be advised to develop a better NAb assay for other drug development programs.

Justification:
The Sponsor used a bridging method and ECL platform for the ADA screening, confirmatory and titer assays. These are commonly used and acceptable approaches. The Sponsor included an acid dissociation step to improve the assays’ drug tolerance. Acid dissociation is a commonly used method to improve drug tolerance and was appropriately validated. When the Sponsor validated the assay FDA Guidance published in 2009 indicated that a sensitivity of 500 ng/ml was acceptable, and for low risk products such as KW-0761 (mogamalizumab) it still may be acceptable. The Sponsor evaluated the drug tolerance of the assay and found that 200 ng/ml of positive control antibody could not be detected if drug levels were higher than 16 ug/ml. Cmin is ~20 ug/ml in cycles after the first cycle. Results indicate that ADA levels of around 500 ng/ml may still be detected in the assay at expected drug levels. The Sponsor tested ADA samples to determine the amount of drug in the serum. When serum drug levels exceeded 16 ug/ml samples non-positive test results were categorized as inconclusive rather than negative. The screening, confirmatory, and titer assays are acceptable.

The Sponsor used a ligand binding assay to determine whether ADA were neutralizing, because KW-0761 is not an agonist. However, because the drug’s mechanism of action is ADCC a cell based assay that evaluated inhibition of killing would have been a better choice. The Sponsor will be advised to develop an ADCC assay for future studies.

The NAb assay has poor drug tolerance. The Sponsor is aware of that and measured drug concentration in ADA samples. When the concentration was above the assay tolerance negative sample results were considered inconclusive and when drug concentration
levels were not measured sample results were considered unknown. This is an acceptable approach to reporting results although developing a suitably drug tolerant assay is preferred.

The Sponsor uses a tiered approach to sample testing that is comprised of testing all samples in a screening assay, confirming the specificity of ADA positive test results in a confirmatory assay, and testing confirmed positive samples in titer and neutralization assays. This tiered approach is recommended in FDA Guidance and is acceptable. The Sponsor created sample and patient status definitions that are not described in Guidance but are discussed in literature and are acceptable (Shankar G et al. AAPS J. 2014 Jul;16(4):658-73. doi: 10.1208/s12248-014-9599-2. Epub 2014 Apr 24.) These definitions include the status of inconclusive if drug concentration in the sample is greater than the assay drug tolerance, and unknown if drug levels are unknown. This is acceptable.

The pooled incidence of ADA positive subjects from studies 07601-007, -009, and -010 was 3.4% (11/328 subjects) and 3.9% in the CTCL population (10/258 subjects). ADA inconclusive subjects’ incidence was 25.3% in the pooled population and 29.1% in the CTCL population. FDA evaluation of the impact of ADA on pharmacokinetics, safety, and efficacy is under the purview of clinical pharmacology and clinical divisions and is not included in this memo.

II. REVIEW OF SUBMISSION:

Reviewer comment:

Documents reviewed:

P11-29203 Method Validation Report – Validation of an electrochemiluminescence-based ligand binding assay for the detection of neturalizing antibodies against KW-0761 in human serum or plasma.


Integrated Summary of Immunogenicity

1. Background:
The FDA Draft Guidance for Industry Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016) will be referred to as FDA Guidance in this memo.

Results for the screening and confirmatory assays are found in report P11-2902. Results for hyperlipidemic and whole blood samples and the titer and neutralizing assays are found in report P11-2903 and P14-29210.

Controls:
Positive – anti-KW-0761 Ab at 12.62 mg/ml supplied by KHK. No other information provided.

Serum from 5 healthy individuals male (3) and female (2).
Hyperlipidemic serum from 5 individuals male (3) and female (2).
Hemolytic serum samples from 5 individual.
Whole blood from 3 healthy individuals male (1) and female (2).

Negative – pooled human serum from 13 individuals, 6 males and 7 females, and 44 individual samples from healthy males (20) and females (24).
Plasma from Caucasian male (5) and female (5) and Japanese male (7) and female (3) individuals.

Screening and confirmatory assay methods validation (Report P11-2902):
The screening and confirmatory bridging assays use electrochemiluminescence (ECL) to detect antibodies to detect anti-KW-0761 antibodies in plasma from mogamulizumab treated patients. The assay includes an acid dissociation step to reduce interference from on-board drug. The table below summarizes the results from the validation studies.

Reviewer comment: The bridging method and ECL platform are commonly used for ADA assays and are acceptable approaches. FDA Guidance states that the Agency has no preferred method or approach. No action indicated.
Reviewer comment: A more detailed analysis of the assay validation is provided below. The Sponsor included an acid dissociation step to help with the assay drug tolerance. Acid dissociation is a commonly used method to improve drug tolerance and was appropriately validated. Overall the screening, confirmatory, and titer assays are acceptable.

Cut points:
Screening assay: 54 individual serum samples were analyzed by 2 analysts on 3 days. No outlier samples were identified. Log transformed data were normalized to the negative control samples (Sample/Negative control). The log transformed data were not normally distributed so the cut point was determined using the 95\textsuperscript{th} percentile. The screening cut point was determined to be 1.09. The confirmatory cut point was 23.81\% inhibition. The lower limit of reliable detection threshold was 1.19 (S/N).

Reviewer comment: Using S/N is an acceptable approach for evaluating cut-point and is similar mathematically to calculating a floating cut point. Calculating the cut point as the 95\textsuperscript{th} percentile of the responses is an appropriate method for data that are not normally distributed. The cut point is acceptable.

Sensitivity:
Serum and plasma samples at 6.25, 12.5, 25, 50, 100, 200, 500, 2000 ng/ml with and without 100 \text{ ug/ml} KW-0761 were analyzed on 3 different days. The concentration at which the %inhibition of the positive control exceeded the confirmatory cut point was considered to be the assay sensitivity. The screening assay sensitivity in serum was determined to be 19.4 ng/ml with a lower limit of reliable detection of 35.3 ng/ml. The screening assay sensitivity in plasma was determined to be 18.1 ng/ml with a lower limit of reliable detection of 35.5 ng/ml. The confirmatory assay sensitivity ranged from 25 – 100 ng/ml depending on the day.

Drug tolerance:
Positive control diluted to 0, 400, 1000, 2000, and 4000 ng/ml. KW-0761 diluted to 0, 2, 4, 8, 16, 32, 64, 128, and 256 ug/ml. Samples were analyzed three times. Positive control at 200 ng/ml could be detected in the presence of 16 ug/ml of KW-0761.

Reviewer comment: FDA Guidance recommends assay sensitivity of at least 100 ng/ml. The screening and confirmatory assays are more sensitive than recommended. This is acceptable.

C_{min} is ~20 ug/ml after the first cycle. When the assay validation was performed the FDA Guidance published in 2009 indicated that a sensitivity of 500 ng/ml was acceptable, and for low risk products such as KW-0761 (mogamulizumab) it still is acceptable. The Sponsor designates ADA as inconclusive at a sensitivity of around 200 ng/ml of positive control. Results indicate that ADA levels of around 500 ng/ml would still be detected by this assay. In addition, the Sponsor tested drug levels in ADA samples and deemed that negative samples were inconclusive when drug levels were higher than 16 ug/ml. Therefore, no further action is indicated.

Selectivity:
Ten individual blank samples were spiked with positive control at 200 ng/ml with and without KW-0761. The positive control with and without 100 ng/ml of KW-0761 were diluted into 10 individual serum or plasma samples. S/N ratios for all samples spiked with 200 ng/ml of positive control were above the cut point threshold and showed decreased response when spiked with KW-0761.

Five individual blank hemolytic or hyperlipemic samples were analyzed with and without low positive control in the presence and absence of KW-0761. All positive controls tested positive in the absence of KW-0761 and confirmed positive in the presence of KW-0761.

Reviewer comment: The assay specifically detects ADA in the assay matrix. When the assay validation was performed the FDA Guidance published in 2009 indicated that a sensitivity of 500 ng/ml was acceptable, and for low risk products such as KW-0761 (mogamulizumab) it still is acceptable. Therefore, no further action is indicated.

Drug tolerance:
Positive control diluted to 0, 400, 1000, 2000, and 4000 ng/ml. KW-0761 diluted to 0, 2, 4, 8, 16, 32, 64, 128, and 256 ug/ml. Samples were analyzed three times. Positive control at 200 ng/ml could be detected in the presence of 16 ug/ml of KW-0761.

Reviewer comment: C_{min} is ~20 ug/ml after the first cycle. When the assay validation was performed the FDA Guidance published in 2009 indicated that a sensitivity of 500 ng/ml was acceptable, and for low risk products such as KW-0761 (mogamulizumab) it still is acceptable. The assay appears to be able to detect ADA in the presence of expected levels of drug in the serum. In addition, the Sponsor tested drug levels in ADA samples and deemed that negative samples were inconclusive when drug levels were higher than 16 ug/ml. Therefore, no further action is indicated.
Precision:
Intra-assay – Six replicates of serum samples spiked with LPC 200 ng/ml, MPC 500 ng/ml and HPC 2000 ng/ml were analyzed once in a single microtiter plate. Intra-assay precision for the screening assay ranged from 2.9 – 6.8 CV% depending on the concentration of positive control. Intra-assay precision for the confirmatory assay for %inhibition of 200 or 2000 ng/ml positive control ranged from 0.2 - 3.8 CV% respectively.

Reviewer comment: Intra-assay precision is consistent with industry experience for this type of assay and is acceptable. No further action required.

Inter-assay – Three replicates of serum samples spiked with LPC 200 ng/ml, MPC 500 ng/ml and HPC 2000 ng/ml were analyzed on 3 different days by 2 analysts. Inter-assay precision for the screening assay ranged from 6.2 – 7.2% depending on the concentration of positive control. Inter-assay precision for the confirmatory assay for %inhibition of 200 or 2000 ng/ml positive control ranged from 0.5 - 4.8 CV% respectively.

Reviewer comment: Inter-assay precision is consistent with industry experience for this type of assay and is acceptable. No further action required.

Prozone effect:
Serum and plasma samples diluted to 8000, 32000, 128000, 512000 ng/ml and analyzed once. No hook effect was observed.

Reviewer comment: This is acceptable.

Titer (Report P11-2903):
Titer was defined as the one-step lower dilution factor than the lowest dilution factor with a normalized response below the screening cutpoint (1.09). Positive control samples were diluted 4 fold from the high positive control to achieve nominal concentrations of 2000, 500, 125, 31.3, 781, and 1.95 ng/ml or from the low positive control 200, 50, 12.5, 3.13 ng/ml. Samples were analyzed on the same plate on three different days. Assay results were within 4 fold dilution.

Reviewer comment: The Sponsor’s definition of titer is acceptable. FDA guidance recommends two-fold dilutions rather than four-fold dilutions. However, redeveloping this assay is unlikely to provide useful information because of the low immunogenicity of this product. No further action is required.

Neutralizing assay method validation (Report P11-2903):

Controls:
Positive – anti-KW-0761 Ab at 12.62 mg/ml supplied by KHK. No other information provided.

Immunodepletion antigen – KW-0761
Negative – pooled human serum from 13 individuals, 6 males and 7 females, and 44 individual samples from healthy males (20) and females (24).

**Neutralizing assay method validation:**
The Nab assay is an ECLA based method that measures the ability of ADA to interfere with the binding of KW-0761 to a CCR4-derived synthetic peptide. Briefly, KW-0761 is mixed with biotinylated CCR-4 peptide, transferred to streptavidin coated wells and then incubated with ADA samples. After washing, polyhistidine tagged CD16 is added to the plates followed by anti-polyhistidine mouse mAb, and then ruthenylated goat-anti-mouse IgG mAb. The specificity of inhibition is confirmed by adding protein G/L or Sepharose (negative control) to the mixture containing KW-0761, CCR4-peptide and ADA sample.

**Reviewer comment:** The Sponsor used a ligand binding assay to determine whether ADA are neutralizing, presumably because KW-0761 is not an agonist. However, because the drug’s mechanism of action is ADCC a cell based assay that looked for inhibition of killing would have been a better choice. The Sponsor will be advised to develop an ADCC assay for future studies. ADA incidence was low and was not found to impact safety or efficacy so no further action is recommended for this submission.

<table>
<thead>
<tr>
<th>Assay</th>
<th>Validation parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening assay in human serum</td>
<td>Cut point</td>
<td>1.35</td>
</tr>
<tr>
<td></td>
<td>Sensitivity (LLRD)</td>
<td>1.08 µg/mL (1.50 µg/mL)</td>
</tr>
<tr>
<td></td>
<td>Selectivity</td>
<td>Accepted</td>
</tr>
<tr>
<td></td>
<td>Drug interference</td>
<td>Confirmed</td>
</tr>
<tr>
<td></td>
<td>Intra-assay precision</td>
<td>Accepted</td>
</tr>
<tr>
<td></td>
<td>Inter-assay precision</td>
<td>Accepted</td>
</tr>
<tr>
<td>Confirmatory assay in human serum</td>
<td>Cut point</td>
<td>Examined as 2.00</td>
</tr>
<tr>
<td></td>
<td>Selectivity</td>
<td>Accepted</td>
</tr>
<tr>
<td></td>
<td>Intra-assay precision</td>
<td>Accepted</td>
</tr>
<tr>
<td></td>
<td>Inter-assay precision</td>
<td>Accepted</td>
</tr>
<tr>
<td>Screening assay in human plasma (partial validation)</td>
<td>Sensitivity (LLRD)</td>
<td>1.09 µg/mL (1.51 µg/mL)</td>
</tr>
<tr>
<td>Confirmatory assay in human plasma (partial validation)</td>
<td>Selectivity</td>
<td>Accepted</td>
</tr>
</tbody>
</table>

**Reviewer comment:** The assay has poor drug tolerance. The Sponsor is aware of that and measured drug concentration in ADA samples. When the concentration was above the assay tolerance negative sample results were considered inconclusive and when drug concentration levels were not measured sample results were considered unknown. This is an acceptable approach although developing a suitably drug tolerant assay is preferred. Because ADA incidence was low and ADA did not appear to impact safety and efficacy no further action is required. However, the Sponsor will be advised to develop a more drug tolerant assay for future studies.
Cut points:
Screening assay: Fifty-four individual blank samples were analyzed on 3 days by 2 analysts. Outliers were identified and removed. Data were not normally distributed so a non-parametric cut point of 1.35 using the 95th percentile was calculated.

Confirmatory assay: Thirty individual serum samples spiked with 4 ug/ml positive control either treated or untreated with Protein G/L or Sepharose were analyzed once by 2 analysts. An arbitrary cut point of 2 was used.

Reviewer comment: The Sponsor used acceptable approaches to establishing the screening and confirmatory cut points. The cut points are acceptable.

Sensitivity:
Serum or plasma samples spiked with 0.125, 0.250, 0.5, 1, 2, 4, 8, 16, and 32 ug/ml (1 each) were analyzed on 3 different days. The lower limit of reliable detection threshold for the screening Nab assay was 1.55 and corresponds to a sensitivity of 1.08 – 1.5 ug/ml.

Drug tolerance:
Positive control at 4 ug/ml could not be detected in the presence of 125 ug/ml of KW-0761 but 8 ug/ml could be detected in the presence of 125 ug/ml.

Reviewer comment: Assay sensitivity in the absence of drug is acceptable. However, as discussed above, the sensitivity in the presence of drug is poor.

Selectivity:
Ten individual blank samples were spiked with positive control at 4 ug/ml and samples treated or untreated with protein G/L and Sepharose were analyzed once. All PC spiked samples had signal greater than the screening cut point. Screening assay values for 90% of the sample blanks were less than the screening cut point.

Five individual blank hemolytic or hyperlipimic samples were analyzed with and without low positive control treated or untreated with protein G/L or Sepharose. All samples containing low PC or low PC and Sepharose had S/N about the screening cut point (1.35). All blank samples had a S/N ration below the screening cut point. Protein G/L treated samples all S/N greater than the confirmatory cut point (2.0).

Reviewer comment: The assay can specifically detect ADA in the sample matrix.

Precision:
Intra-assay – Six replicates of serum samples spiked with 4 ug/ml of PC or treated with protein G/L or Sepharose were analyzed once in a single microtiter plate. Screening assay precision of the negative control was 3.7%CV and the PC was 4.7%CV. Confirmatory assay precision was 2.3% and 1.7% respectively for Protein G/L and Sepharose treated samples.
Inter-assay – Eighteen replicates of serum samples spiked with 4 μg/ml treated with protein G/L or Sepharose from all assays (n=7) were evaluated. Screening assay precision was 13.5% CV. Confirmatory assay precision was 9.0% and 16% respectively for Protein G/L and Sepharose treated samples.

**Reviewer comment:** Assay precision is consistent with industry standards for this type of assay and is acceptable.

### III. SUMMARY OF CLINICAL RESULTS

Mogamalizumab is an afucosylated humanized IgG1 mAb with specificity for CCR4. Mogamalizumab as a monotherapy has been used in 9 clinical studies (0761-0501, -002, -004, -001, 007, 009, 010 and KW-0761-001, and -002) and in combination with other therapies (0761-003). Results from studies 00761-007, -009, and 010 are the basis for understanding ADA because results can be pooled because they used the same dose, dosing regimen, and ADA assays (see table 4-1 below from Integrated Summary of Immunogenicity.)

<table>
<thead>
<tr>
<th>Study No. (Region)</th>
<th>Design</th>
<th>Dose Route schedule (mogamalizumab)</th>
<th>Study Population</th>
<th>ADA Biosimilar method (Lab)</th>
<th>Number of ADA Analysis Set</th>
<th>ADA Sampling</th>
<th>Assayment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0761-007 (EU)</td>
<td>Phase 2, open-label, multicenter</td>
<td>1.0 mg/kg iv weekly (Day 1, 8, 15 and 22) in Cycle 1, then biweekly (Day 1 and 15) in subsequent cycles</td>
<td>Subjects with relapsed/refractory PTCL</td>
<td>ECLA (TBC)</td>
<td>35 subjects</td>
<td>Cycle 1: Day 1 (Pre dose) and Day 26-28; Subsequent Cycles: every 8 Weeks; EOT</td>
<td>Anti-KW-0761 Antibody (screening) confirmatory assay, KW-0761 concentration, Neutralizing Antibody, Titer</td>
</tr>
<tr>
<td>0761-009 (US, Caribbean, EU, South America)</td>
<td>Phase 2, open-label, multicenter, randomized</td>
<td>1.0 mg/kg iv weekly (Day 1, 8, 15 and 22) in Cycle 1, then biweekly (Day 1 and 15) in subsequent until progression</td>
<td>Subjects with relapsed/refractory ATL</td>
<td>ECLA (TBC)</td>
<td>65 subjects (Data cut off: 31th Mar 2016)</td>
<td>Cycle 1: Day 1 (Pre dose) and Day 26-28; Subsequent Cycles: every 8 Weeks; EOT</td>
<td>Anti-KW-0761 Antibody (screening) confirmatory assay, KW-0761 concentration, Neutralizing Antibody, Titer</td>
</tr>
<tr>
<td>0761-010 (US, EU, Japan, and Australia)</td>
<td>Phase 3, open-label, multicenter, randomized</td>
<td>1.0 mg/kg iv weekly (Day 1, 8, 15 and 22) in Cycle 1, then biweekly (Day 1 and 15) in subsequent cycle until progression</td>
<td>Subjects with relapsed/refractory CTCL</td>
<td>ECLA (TBC)</td>
<td>320 subjects (Data cut off: 31th Dec 2016)</td>
<td>Cycle 1: Day 1 (Pre dose) and Day 26-28; Subsequent Cycles: every 8 Weeks; EOT</td>
<td>Anti-KW-0761 Antibody (screening) confirmatory assay, KW-0761 concentration, Neutralizing Antibody, Titer</td>
</tr>
</tbody>
</table>

ADA=anti-drug antibody; ATL=Adult T-cell leukemia-lymphoma; CCR4=C-C chemokine receptor 4; CTCL=Cutaneous T-cell lymphoma; ECLA=electrochemiluminescence immunoassay; ELISA=enzyme-linked immunosorbent assay; EOT=End of Treatment; EU=European Union; iv=intravenous

PTCL=Peripheral T-cell lymphoma.

Note: KW-0761 concentration; KW-0761 concentrations were measured at study sites to asses drug tolerance.

**Risk assessment:**

The Sponsor considers mogamalizumab to be low risk because it is not an endogenous protein and it is not an agonist. Epibase 3.0 *in silico* analyses of VH and VL region sequences indicated that it has 496 critical epitopes, which is comparable to the 22 already approved mAb therapies, 484±323. Critical epitopes were “defined as any strong binder to DRB1, DRB3/4/5 and DQ and medium binders to DRB1 and DRB3/4/5, with affected allotypes present in ≥10% of the target population (Strong
binders; Kd<100nM, Medium binders; 100nM≤Kd<1000nM; Weak and non-binders; Kd≥1000nM).

Reviewer comment: The Sponsor stated that the target of mogalizumab, CCR4 is present on malignant and non-malignant T cells. The mechanism of action of mogalizumab is ADCC of target expressing cells. Therefore, mogalizumab reduces the population of T cells that support ADA development. However, CCR4 tends to be expressed on regulatory and Th2 type T cells so the argument that it suppresses its own immunogenicity is suspect. Nevertheless, as a non-agonistic Mab ADA risk is low. KW-0761 does have critical effector function, however ADA are generally directed towards the variable rather than constant regions of human or humanized MAbs so the risk of ADA to the constant region is low.

The Sponsor’s definitions of ADA sample status and tiered testing approach is diagrammed below.

**Figure 7.2-2** Immunogenicity testing scheme for sample ADA status for anti-mogalizumab antibodies (drug tolerance determined)

![Immunogenicity Testing Scheme](image_url)

The Sponsor used a similar tiered approach for NAb sample assessment, diagrammed below.
Reviewer comment: This tiered approach to sample testing is recommended in FDA Guidance and is acceptable. The definitions of sample status are not described in Guidance but are discussed in literature and are acceptable (see Shankar G et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides – harmonized terminology and tactical recommendations. AAPS J. 2014 Jul;16(4):658-73. doi: 10.1208/s12248-014-9599-2. Epub 2014 Apr 24.)

ADA status for individual subjects are defined below:

In addition, one of the following subject ADA statuses was determined.

1) ADA-positive: Samples of a subject meet any of the following criteria.
   - Treatment-induced ADA: The sample ADA status from before the first administration of mogamulizumab was “ADA-negative” and one or more sample ADA status after the first administration of mogamulizumab were “ADA-positive”.
   - Treatment-boosted ADA: The sample ADA status before the first administration of mogamulizumab was “ADA-positive” and one or more titer values of the sample after the first administration of mogamulizumab were more than 4 times of that in the sample before the first administration of mogamulizumab.

2) ADA-negative: Subject ADA status was not defined as “ADA-positive” and sample ADA status at the last evaluable time point was neither “ADA-inconclusive” nor “ADA-unknown”.

3) ADA-inconclusive: Subject ADA status was not defined as “ADA-positive” and sample ADA status at the last evaluable time point was “ADA-inconclusive”.

4) ADA-unknown: Subject ADA status was not defined as “ADA-positive” and sample ADA status at the last evaluable time point was “ADA-unknown”.

Reviewer comment: The definitions of subject status are not described in Guidance but are discussed in literature and are acceptable (see Shankar G et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides – harmonized terminology and tactical recommendations. AAPS J. 2014 Jul;16(4):658-73. doi: 10.1208/s12248-014-9599-2. Epub 2014 Apr 24.)
In study 0761-007, of 33 patients, no patients tested positive for ADA, 3 patients had inconclusive results, two patients had unknown results, and 11 patients were negative.

In study 0761-009, of 63 patients, 1 patient tested positive at baseline and one patient tested positive at an unscheduled visit. In-study sampling was too variable after cycle 1 to get estimates of ADA incidence with samples tested from 1 to 5 patients at the end of any given cycle. At the end of treatment, of 40 patients tested none tested positive, 35 were considered negative, 5 inconclusive, and no unknowns.

In the Phase 3 study, 07610-010, 11 of 295 (3.7%) of subjects tested baseline positive, and 14 of 311 subjects confirmed ADA positive in one (n=5) or more (n=9) post-treatment samples. Four subjects who tested positive at baseline also tested positive at some timepoints in-study with two patients considered treatment boosted. No NAb were detected, however the Sponsor acknowledged the poor drug tolerance of the NAb assay, so most NAb samples were classified as inconclusive. The Sponsor’s analysis indicates that ADA do not impact PK and clearance. The Sponsor states that ADA did not impact progression free survival, however, the number of ADA positive subjects is too small for reliable analysis. Similarly, adverse events did not correlate with ADA status; however the number of ADA positive subjects is too small for reliable analysis.

The pooled incidence of ADA positive subjects from studies 07601-007, -009, and -010 was 3.4% (11/328 subjects) and 3.9% in the CTCL population (10/258 subjects). ADA inconclusive subjects incidence was 25.3% in the pooled population and 29.1% in the CTCL population.

Reviewer comment: The results above reflect the Sponsor’s summary of the impact of ADA on PK, safety, and efficacy. Clinical Pharmacology and clinical review units perform their own assessments of those data and their reviews are not incorporated into this memo.

IV. REVIEWER CONCLUSIONS:

The ADA screening, confirmatory, and titer assays are suitable for use. The NAb assay has poor sensitivity in the presence of expected levels of drug. The Sponsor’s tiered approach to ADA assessment and definitions of subject status are acceptable. The Sponsor will be advised to develop a better NAb assay for future studies.
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: February 15, 2018
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 761051
Product Name and Strength: Poteligeo (mogamulizumab-kpkc) Injection, for intravenous infusion
20 mg/5 mL (4 mg/mL)
Applicant/Sponsor Name: Kyowa Kirin Pharmaceutical Development, Inc.
FDA Received Date: February 01, 2018
OSE RCM #: 2017-2040-1
DMEPA Safety Evaluator: Leeza Rahimi, Pharm.D.
DMEPA Team Leader: Hina Mehta, Pharm.D.

1 PURPOSE OF MEMO
The Division of Hematology Products (DHP) requested that we review the revised carton and container labels for Poteligeo (mogamulizumab-kpkc) Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION
The revised container label for Poteligeo is acceptable from medication error perspective, however, we identified an area of improvement in the carton labeling to enhance clarity and readability of the information. We have made a recommendation in section 3 below.

3 RECOMMENDATIONS FOR APOPHARMA
We recommend the following be implemented prior to approval of this BLA:


Reference ID: 4222191
A. Carton Labeling:

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

____________________________________
LEEZA RAHIMI
02/15/2018

____________________________________
HINA S MEHTA
02/15/2018
In response to DHP's consult request dated January 9, 2018, OPDP has reviewed the proposed product labeling (PI) for the original NDA POTELIGEO® (mogamulizumab-kpc) injection, for intravenous use (Poteligeo).

**PI:** OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on February 7, 2018, and are provided below.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or rachael.conklin@fda.hhs.gov.
PI
OPDP does not have any comments on the PI at this time.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHAEL E CONKLIN
02/13/2018
PATIENT LABELING REVIEW

Date: February 7, 2018

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

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: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Rachel Conklin, MS, RN
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): POTELIGEO (mogamulizumab)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761051

Applicant: Kyowa Kirin Pharmaceutical Development, Inc.
1 INTRODUCTION
On October 4, 2017, Kyowa Kirin Pharmaceutical Development, Inc., submitted for the Agency’s review an original Biologics License Application (BLA) 761051 for POTELIGEO (mogamulizumab) injection. The proposed indication is for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

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 Hematology Products (DHP) on October 31, 2017 and January 9, 2018, respectively, for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) for POTELIGEO (mogamulizumab) injection.

2 MATERIAL REVIEWED
- Draft POTELIGEO (mogamulizumab) injection PPI received on October 4, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 29, 2018.
- Draft POTELIGEO (mogamulizumab) injection Prescribing Information (PI) received on October 4, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 29, 2018.

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.

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

/s/

SUSAN W REDWOOD
02/07/2018

RACHAEL E CONKLIN
02/07/2018

LASHAWN M GRIFFITHS
02/07/2018
1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Musiek and Kim) were selected by the Division of Hematology Products (DHP) for inspection of study conduct for Study 0761-010, submitted in support of BLA 761051. The sponsor was also inspected. The study data from these clinical sites as reported by the sponsor to the BLA are considered to be reliable in support of the requested indication.

The preliminary regulatory classification for Drs. Musiek and Kim is No Action Indicated (NAI). The preliminary regulatory classification for the sponsor is Voluntary Action Indicated (VAI).
2. BACKGROUND

Mogamulizumab [KW-0761] is an anti-CCR4 monoclonal antibody that has shown promising efficacy against various T-cell lymphomas. This new molecular entity is proposed for the treatment of patients with cutaneous T cell lymphomas (CTCL), who have failed at least one prior course of systemic therapy.

Study 0761-010

Study 0761-010 was an open-label, multicenter, randomized Phase 3 study evaluating the effectiveness of mogamulizumab compared to that of vorinostat in subjects with CTCL, who had failed at least one prior course of systemic therapy. The 1:1 randomization to treatment groups was stratified by disease type (mycosis fungoides [MF] or Sézary syndrome [SS]) and disease stage (IB/II or III/IV). All treatments were administered on an outpatient basis and each treatment cycle was 28 days. The primary study objective was to compare the progression-free survival (PFS) of mogamulizumab versus vorinostat for subjects with relapsed or refractory CTCL.

The median number of cycles initiated during the randomized treatment period was 6.0 in the mogamulizumab group and 3.0 in the vorinostat group. The median duration of drug exposure was approximately twice as long for mogamulizumab (170.0 days) compared to vorinostat (84.0 days).

The primary endpoint was the comparison of disease progression free survival (PFS) between mogamulizumab and vorinostat. The analysis was performed on the intent-to-treat (ITT) study population, based upon the results of the Investigator’s Assessment.

This multicenter study was conducted at 63 centers internationally, mainly in Western Europe, Australia, Japan and the U.S. There were 372 study subjects who enrolled in the study (186 subjects were randomized to mogamulizumab and 186 subjects were randomized to vorinostat). The first subject was treated on Dec 12, 2012 (First Dose) and the clinical data cut-off date was Dec 31, 2016.

3. RESULTS (by site):

<table>
<thead>
<tr>
<th>Name of Clinical Investigator/Sponsor Address</th>
<th>Protocol #: Site #/## Subjects</th>
<th>Inspection Dates</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amy C. Musiek, M.D. Washington University School of Medicine Siteman Cancer Center 4921 Parkview Place, 7th floor St. Louis, MO 63110</td>
<td>0761-010 Site #103 13 total</td>
<td>December 12 to 18, 2017</td>
<td>NAI</td>
</tr>
</tbody>
</table>

Reference ID: 4214360
Name of Clinical Investigator/Sponsor | Protocol #/ Site #/# Subjects | Inspection Dates | Classification
---|---|---|---
Youn H..Kim, M.D. Stanford Cancer Center Stanford University Medical Center 875 Blake Wilbur Drive Stanford, CA 94305 | 0761-010 Site #112 17 total | December 4 to 8, 2017 | NAI
Kyowa Kirin Pharmaceutical Development Inc. 212 Carnegie Center, Suite 101 Princeton, New Jersey 08540 | Sponsor for Study Protocol 0761-010 | November 16 to 29, 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.

Clinical Investigator

1. Amy C. Musiek, M.D./ Site #103

The inspection was conducted from December 12 to 18, 2017. A total of 15 subjects were screened and thirteen subjects were enrolled. Thirteen subjects completed the treatment phase of the study. A comprehensive review of study subjects’ records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 (Inspectional Observations) was issued.
2. Youn H. Kim, M.D./Site #112

The inspection was conducted from December 4 to 8, 2017. A total of 19 subjects were screened and 17 subjects were enrolled. Seventeen subjects completed the treatment phase of the study. An audit of all the subjects’ records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. No Form FDA 483 was issued.

Sponsor


This inspection was conducted from November 16 to 29, 2017.

The sponsor inspection included review of the following: regulatory site set up, financial disclosures, site management and monitoring, and the Clinical Trial Management System. Clinical sites for which monitoring files were reviewed during the inspection included: Sites 103, 112 and 304. Sites 103 and 112 were the two sites selected for clinical site inspection. Site 304 was chosen to be reviewed based on the ORA investigator’s request for a listing for root cause analyses of all reasons why a corrective and preventive action plan (CAPA) was created for the sponsor, and the list identified problems at the site which are described below.

Clinical site monitoring was performed by a contract research organization (CRO). Monitoring reports indicated that the sites received adequate periodic monitoring to determine that they had obtained appropriate IRB approvals, and reported protocol deviations and serious adverse events. There was no under-reporting of serious adverse events.

Oversight by the sponsor appeared to be adequate in general. However, a one-item Form FDA 483 was issued to the sponsor at the end of the inspection for failure to promptly bring into compliance or subsequently terminate participation of a clinical investigator (CI) who had failed to comply with the signed investigator agreement, the general investigational plan, and applicable regulatory requirements. The CRO site monitor for Site #304 initially noted problems with compliance in December 2014 including issues with CI oversight, procedures being performed by persons not listed on the delegation log, and timely verification of source data. A Site Corrective Action Plan was implemented, however again at the August 30, 2017 monitoring visit, the site showed continued noncompliance. For example,
(a) The CI failed to co-sign documents (i.e physical exams, follow-up letters to referring physicians) completed by medical interns that were not delegated on the site responsibility logs and supervised by sub-investigators. Additionally, the medical interns were prescribing the comparator drug (vorinostat oral capsule), until the sponsor requested that this practice be suspended in March 2015.

(b) Source documents for two study subjects were missing, not filed or had delayed signatures placed more than one year after the Site Corrective Action Plan was filed.

The sponsor responded adequately to the Form FDA 483 on December 19, 2017, with their corrective and preventive action plans. The sponsor, Kyowa Kirin, provided reassurance that data source verification for the seven study patients at this study site was documented by the monitoring CRO and no data integrity issues were found. The sponsor and the monitoring CRO are working to ensure that this study site is monitored adequately, prior to the planned close out at the end of December 2017, with a single remaining patient in the study to be discontinued.

The above regulatory deficiencies observed at the sponsor site did not appear to impact study subject safety and data integrity did not appear to be compromised.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Reference ID: 4214360
CC: Central Doc. Rm.
DHP/Division Director/ Ann Farrell
DHP /Medical Team Leader/ Tanya Wroblewski
DHP/Medical Officer/ Elizabeth Pulte
DHP/Project Manager/ Beatrice Kallungal
OSI/Office Director/David Burrow (Acting)
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman
OSI/DCCE/GCP MO/Anthony Orenzia
OSI/ GCP Program Analyst/Yolanda Patague
OSI/Database PM/Dana Walters
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY J ORENCIA
01/31/2018

JANICE K POHLMAN
01/31/2018

KASSA AYALEW
01/31/2018
**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***

<table>
<thead>
<tr>
<th>Date of This Review:</th>
<th>January 26, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Hematology Products (DHP)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>BLA 761051</td>
</tr>
</tbody>
</table>
| Product Name and Strength:  | Poteligeo (mogamulizumab-xxxx) Injection, for intravenous infusion  
                                 20 mg/5 mL (4 mg/mL) |
| Product Type:               | Single-Ingredient |
| Rx or OTC:                  | Rx               |
| Applicant/Sponsor Name:     | Kyowa Kirin Pharmaceutical Development, Inc. |
| Submission Date:            | October 04, 2017, October 23, 2017, November 20, 2017 |
| OSE RCM #:                  | 2017-2040        |
| DMEPA Safety Evaluator:     | Leeza Rahimi, Pharm.D. |
| DMEPA Team Leader:          | Hina Mehta, Pharm.D. |
1 REASON FOR REVIEW

Kyowa Kirin Pharmaceuticals submitted a Biological License Application (BLA) 761051 for Poteligeo (mogamulizumab-xxxx) Injection for the proposed indication of treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. Poteligeo (mogamulizumab-xxxx) injection for infusion will be available in a single-dose vial of 20 mg/5 mL (4mg/mL) concentration.

The Division of Hematology Products (DHP) requested that we review the labels and labeling of the product and evaluate for areas of vulnerability that may lead to medication errors.

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>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C-N/A</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D-N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E-N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F-N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

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

DMEPA evaluated the Prescribing Information (PI), carton and container labels for areas of vulnerability in regards to medication error. Our review identified areas in the labels and labeling that can be improved to increase readability and prominence of important information.

We note the use of the term  in Section 3 Dosage Forms and Strengths and Section 16 How Supplied of the PI. We defer to Office of Pharmaceutical Quality (OPQ) for the appropriateness of the terminology. We provide our recommendations in Sections 4.1 and 4.2 and recommend their implementation prior to approval of this application.
4 CONCLUSION & RECOMMENDATIONS

We identified areas on the 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.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information (HPI):

1. Dosage and Administration:

   a. Consider adding the statement “See Full Prescribing Information for important preparation and administration instructions”.

B. Full Prescribing Information (FPI):

1. Section 2 Dosage and Administration:

   a. Please to read: “POTELIGEO can be administered within two days of the scheduled dose”

2. Section 2.2 Preparation and Administration:

   b. Preparation: We recommend revising the second bullet to read: “Calculate the dose (mg/kg) and the number of vials of POTELIGEO needed to prepare the infusion solution based on patient weight.

   c. Preparation: Add a bullet after each sentence following the first sentence to separate the preparation instructions and to increase the prominence of each important instruction.

   d. Administration: Please move the administration instructions to appear under “Preparation” instructions and before “Storage of Diluted Solution” section.
4.2 RECOMMENDATIONS FOR KYOWA KIRIN PHARMACEUTICALS

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

A. Carton and Container Labels:

B. Carton Labels:

---

C. Container Labels:
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Poteligeo that Kyowa Kirin submitted on November 20, 2017.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Poteligeo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
</tr>
<tr>
<td><strong>Strength</strong></td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
</tr>
<tr>
<td><strong>Storage</strong></td>
</tr>
</tbody>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 10, 2017, we searched DMEPA’s previous reviews using the terms, Poteligeo. Our search did not identify any previous labeling reviews.
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, along with postmarket medication error data, we reviewed the following Poteligeo labels and labeling submitted by Kywowa Kirin on October 04, 2017.

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

G.2  Label and Labeling Images

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

___________________________________________________________________________________________________________________

__________

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

/s/

----------------------------------------
LEEZA RAHIMI
01/26/2018

----------------------------------------
HINA S MEHTA
01/30/2018