CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761051Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Indication/Breakthrough/Priority Review: for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sezary syndrome (SS) after at least one prior systemic therapy.

Recommendation: Approval

BLA STN 761051
Review Number: 1
Review Date: July 09, 2018

Drug Name/Dosage Form	mogamulizumab/injection (POTELIGEO®)
Strength/Potency	20 mg/5 mL (4 mg/mL) single-dose vial
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy.
Applicant/Sponsor	Kyowa Kirin Inc.

Product Overview

Mogamulizumab is a defucosylated humanized IgG1, κ monoclonal antibody produced in a CHO cell line. Mogamulizumab selectively binds to chemokine (C-C motif) receptor 4 (CCR4), a G protein-coupled receptor for C-C chemokines. The complementarity-determining regions (CDRs) were derived from mouse anti-human CCR4 mAb, and constant regions were derived from human IgG1. Mogamulizumab is a glycoprotein with a molecular weight of 149 KDa. The N-glycosylation site is Asn-299 on each heavy chain and the main oligosaccharide structures are asialo-, biantennary, and nonfucosylated complex type structures containing 0, 1, and 2 galactose residues.

The Mechanism of Action (MOA) of mogamulizumab is Antibody-Dependent Cellular cytotoxicity (ADCC) via interactions between the CCR4 antigen on the target cells, the antibody, and the Fc Gamma Receptor IIIa (FcγRIIIa) on the Natural Killer (NK) effector cells. Mogamulizumab exhibits enhanced ADCC activity due to its decreased fucose content.

Mogamulizumab drug substance is manufactured at Kyowa Hakko Kirin Co., Ltd. (Takasaki, Gunma, Japan). (b) (4)

(b) (4)

Mogamulizumab drug product (DP) is manufactured at [redacted]. Mogamulizumab DP manufacturing involves [redacted] The primary container closure for mogamulizumab DP includes a single-use, 10-mL Type [redacted] glass vial, [redacted] rubber stopper, and an aluminum seal with a [redacted] flip-off cap. Mogamulizumab DP is supplied at 20 mg/5 mL in a single-dose vial. Mogamulizumab DP is formulated at 20 mg/5 mL in 2.1 mmol/L citric acid monohydrate, 300 mmol/L glycine, and 0.2 mg/mL polysorbate 80, pH 5.5. For mogamulizumab DP, the data provided in the BLA submission support an expiration dating period of 36 months when stored at 2˚C to 8˚C.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Jun Liu	DBRR III/OBP/OPQ
Drug Product	Jun Liu	DBRR III/OBP/OPQ
Immunogenicity	Susan Kirshner	DBRR III/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Steven Fong	DIA/OPF/OPQ
Microbiology (DS)	Bo Chi	DMA/OPF/OPQ
Microbiology (DP)	Lakshmi Narasimhan	DMA/OPF/OPQ
Business Process Manager	Andrew Shiber	RBPMB I/OPRO/OPQ
Team Lead for OBP	Ramesh Potla	DBRR III/OBP/OPQ
Tertiary Reviewer for OBP	Susan Kirshner	DBRR III/OBP/OPQ
Microbiology Team Lead (DS)	Reyes Candau-Chacon	DMA/OPF/OPQ
Microbiology Tertiary Reviewer	Patricia Hughes	DMA/OPF/OPQ
Facilities Team Lead	Peter Qiu	DIA/OPF/OPQ
Application Team Lead	Ramesh Potla	DBRR III/OBP/OPQ

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Katie Chon	DHP/OHOP
Cross-disciplinary Team Lead	Angelo De Claro	DHP/OHOP
Medical Officer	Yvette Kasamon	DHP/OHOP
Pharm/Tox	Michael Manning	DHOT/OHOP
Clinical Pharmacology	Liang Li	DCPV/OCP/OTS
Statistics	Chia-Wen Ko	DBIV/OB/OTS

1. Names:

a. Proprietary Name: Poteligeo
b. Trade Name: Poteligeo
c. Non-Proprietary Name/USAN: mogamulizumab
d. CAS Name: 1159266-37-1
e. INN Name: mogamulizumab

f. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P51679 (CCR4_HUMAN) [KW0761]

g. Other names: KW-0761, KM8761

Submissions Reviewed

Submission(s) Reviewed	Document Date
STN 761051/SN0001 (Original)	10/04/2017
STN 761051/SN0022 (response to OBP IR#1)	12/07/2017
STN 761051/SN0034 (response to OBP IR#2)	01/12/2018
STN 761051/SN0036 (response to DMA IR)	01/19/2018
STN 761051/SN0037 (response to DMA IR)	01/22/2018
STN 761051/SN0046 (response to DMA IR)	02/20/2018
STN 761051/SN0050 (CCIT Validation Protocol)	02/28/2018
STN 761051/SN0056 (response to DMA IR)	03/16/2018
STN 761051/SN0060 (Amendment)	03/30/2018
STN 761051/SN0061 (response to OBP IR#3)	04/02/2018
STN 761051/SN0063 (response to DMA IR)	04/09/2018
STN 761051/SN0064 (response to OBP IR#3)	04/10/2018
STN 761051/SN0065 (CCIT Validation Results)	04/20/2018
STN 761051/SN0066 (response to DMA IR)	04/30/2018
STN 761051/SN0070 (response to OBP IR#4)	06/13/2018
STN 761051/SN0071 (response to DMA IR)	06/29/2018
STN 761051/SN0072 (response to OBP IR#5)	07/02/2018

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Comments
(b) (4)	III	(b) (4)		3	N/A	Not reviewed. Sufficient information related to compatibility with the product is provided in the BLA.
	III			3	N/A	

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

B. Other documents: None.

3. Consults: None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval.

The Office of Product Quality, CDER, recommends approval of BLA STN 761051 for POTELIGEO® (mogamulizumab) manufactured by Kyowa Kirin Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of POTELIGEO® is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance: Kyowa Hakko Kirin Co., Ltd., Takasaki, Gunma, Japan.
- Drug Product: (b) (4)

- Fill size and dosage form – 20 mg/5 mL in a single-dose vial

- Dating period:
  - Drug Product: 36 months: 2-8 °C
  - Drug Substance: (b) (4)

- Exempt from lot release
  - POTELIGEO® is excepted from lot release per FR Doc. 95–29960

C. Benefit/Risk Considerations:

POTELIGEO® (mogamulizumab) is for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sezary syndrome (SS) after at least one prior systemic therapy.

The data submitted in this application support the conclusion that the manufacture of mogamulizumab is well controlled and yields a consistently high quality product. The conditions used in manufacturing have been sufficiently validated, and a consistent product was prepared from the multiple production runs presented. From a product quality perspective, this product is approvable for human use. Review of manufacturing has identified that the methodologies used for drug substance and drug product manufacturing, release, and stability testing are robust and

sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents.

The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of mogamulizumab drug substance at Kyowa Hakko Kirin Co., Ltd. in Takasaki, Gunma, Japan, and commercial manufacture of mogamulizumab drug product at (b) (4) The OBP product quality and immunogenicity, DMA microbiological drug substance and drug product, DIA facility, and OBP labeling technical assessments are located as separate documents in Panorama.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable: None.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to both drug substance and drug product.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA		Risk	Origin	Control Strategy				*Reviewer Comments*
				Analytical Method	IPC/IPM	Release	Stability	
Potency		Efficacy	Intrinsic to the molecule	(b) (4)				*Acceptable*
Identity		Safety and Efficacy	Intrinsic to the molecule					*Acceptable*
Product-related impurities	Aggregates	Safety and efficacy • Decrease in potency observed • There is a high potential to impact PK and induce immunogenicity	Protein aggregation during production and storage					*Acceptable*
	Fragments	Safety and efficacy • Decrease in potency observed • There is a high potential to impact PK and induce immunogenicity	Degradation on stability					*Acceptable*
	Non-glycosylated species	Safety and efficacy • Decrease in potency observed • Insufficient information available to assess clinical safety	(b) (4)					*Acceptable*
	Non-consensus glycosylated species (NCGS)	Safety and efficacy • Decrease in potency observed • There is a high potential to impact PK	(b) (4)					(b) (4)

	Fucosylated species	Safety and efficacy • Decrease in potency observed • There is a low to moderate potential to impact clinical safety	(b) (4)	(b) (4)	(b) (4)
	High Mannose species	Safety and efficacy • Decrease in potency observed • Low to moderate potential to impact PK • Insufficient information available to assess clinical safety			(b) (4)
Product-related Substances	Charge variants	Process consistency No significant negative impact on bioactivity	• Intrinsic to the molecule (b) (4) • Storage conditions		*Acceptable*
	Oxidized species	Process consistency No significant negative impact on bioactivity	• Intrinsic to the molecule (b) (4) • Storage conditions		(b) (4)
	Sialylated species	Process consistency No significant negative impact on bioactivity	• Intrinsic to the molecule (b) (4) • Storage conditions		

	Galactose variants	Process consistency No significant negative impact on bioactivity	• Intrinsic to the molecule (b) (4) • Storage conditions	(b) (4)	*Acceptable*

B. Drug Substance [mogamulizumab] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

	CQA	Risk	Origin	Control Strategy				*Reviewer Comments*
				Analytical Method	IPC/IPM	Release	Stability	
Process-related Impurities	Host Cell Protein	Safety	Process-related impurity (b) (4)	(b) (4)				*Acceptable*
	Host Cell DNA	Safety	Process-related impurity (b) (4)					*Acceptable*
	(b) (4)	PK, Immunogenicity, and Safety	Process-related impurity from (b) (4)					*Acceptable*
	Contaminants: Bioburden	Safety and Purity	Contamination: Bioburden can be introduced throughout the manufacturing process and from raw materials					(b) (4)
	Contaminants: Endotoxin	Safety and Purity	Contamination: Endotoxin can be introduced throughout the manufacturing process and from raw materials					
	Contaminants: Mycoplasma	Safety and Purity	Contamination: Mycoplasma can be introduced during cell culture from raw materials and cell culture					*Acceptable*
	Contaminants: Virus	Safety	Contamination: Adventitious virus can be introduced during cell culture from raw materials and cell culture					*Acceptable*

	Media/Buffer components		(b) (4)	(b) (4)	(b) (4)
Formulation Related	(b) (4)	Bioactivity and product stability	Formulation component		
	Protein concentration	Bioactivity	(b) (4)		*Acceptable*
	pH	Bioactivity and product stability	Formulation		*Acceptable*

- Description:
  POTELIGEO® (mogamulizumab) is a defucosylated humanized IgG1, κ monoclonal antibody produced in a CHO cell line. Mogamulizumab selectively binds to chemokine (C-C motif) receptor 4 (CCR4), a G protein-coupled receptor for C-C chemokines. The complementarity-determining regions (CDRs) were derived from mouse anti-human CCR4 mAb, and constant regions were derived from human IgG1. Mogamulizumab consists of two identical gamma 1 heavy chains of 449 amino acids and two identical kappa light chains of 219 amino acids. The heavy and light chains are stabilized by multiple inter- and intra- chain disulfide bonds. The heavy chain constant region contains a single N-linked oligosaccharide chain, comprised primarily of neutral biantennary-type oligosaccharides. The heavy chain contains a C-terminal lysine residue, the variants of which are a potential source of heterogeneity.

- Mechanism of Action (MoA):
  Mogamulizumab binds with high affinity to CCR4 receptor. CCR4 is overexpressed in skin lesions of patients with cutaneous T-cell lymphoma (CTCL). The Mechanism of Action (MOA) of mogamulizumab is Antibody-dependent Cellular cytotoxicity (ADCC) via interactions between the CCR4 antigen on the target cells, the antibody, and the Fc Gamma Receptor IIIa (FcγRIIIa) on the Natural Killer (NK) effector cells.
  Mogamulizumab exhibits enhanced ADCC activity due to its decreased fucose content.

- Potency Assay:
  ADCC (antibody-dependent cellular cytotoxicity) involves activation of Natural Killer (NK) cells; a NK cell expresses an Fc receptor, which binds to the Fc portion of the antibody bound to the surface of the target cell. Activation of NK cells consequently

results in cell death. The current test method uses human lymphocyte cell line HH as a target cell and human natural killer cell line KC9775 as an effector cell. The calcein-labeled HH cells, the effector KC9775 cells, and mogamulizumab are incubated in 96-well microplates, which results in cytotoxic reaction releasing Calcein-AM from the target cell due to ADCC activity. Fluorescent intensity derived from fluorescent-tagged Calcein-AM (calcein acetoxymethyl ester) can be measured by a fluorescent plate reader, to calculate the biological activity level of mogamulizumab. The potency is expressed as a percent value of the reference material's activity.

- Reference Materials:
(b) (4)

- Critical starting materials or intermediates:
(b) (4)

- Manufacturing process summary:
(b) (4)

- (b) (4)

- Dating period and storage conditions:
The data support an expiration dating period of (b) (4) months when stored at (b) (4) C.

C. Drug Product [mogamulizumab] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy				*Reviewer Comments*
			Analytical Method	IPC/IPM	Release	Stability	
Appearance (Physical state, color, clarity/opalescence)	Bioactivity, stability, and safety	Product, formulation	(b) (4)				*Acceptable*
Volume in Container (Extractable volume)	Efficacy	(b) (4)					*Acceptable*
Protein Concentration	Bioactivity						*Acceptable*
Particulate matter	Safety	Particulates can be introduced throughout the manufacturing process and on stability					*Acceptable*
Sterility	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the manufacturing process					(b) (4)
Container closure integrity (maintenance of sterility during shelf life)	Safety	Container closure breaches during storage					
Endotoxin	Safety, purity, and immunogenicity	Raw materials, contamination may be introduced throughout the manufacturing process					

- Potency and Strength:
  Mogamulizumab is supplied at 20 mg/5 mL in a single-dose vial. Potency is defined as the percent activity relative to the current mogamulizumab reference standard. The potency assay is the same as described in the DS section of this review memo.

- Summary of Product Design:
  Mogamulizumab is supplied as a sterile, preservative-free solution in a single-dose vial for intravenous infusion. Mogamulizumab DP is formulated at 20 mg/5 mL in 2.1 mmol/L citric acid monohydrate, 300 mmol/L glycine, and 0.2 mg/mL polysorbate 80, pH 5.5.

- List of Excipients:
  Excipients include 2.1 mmol/L citric acid monohydrate, 300 mmol/L glycine, and 0.2 mg/mL polysorbate 80.

- Reference Materials:
  The same reference material is used for DS and DP.

- Manufacturing process summary:
  (b) (4)

- Container closure:
  The primary container closure system for mogamulizumab DP consists of a (b) (4) 10 mL (b) (4) glass vial (b) (4) and a (b) (4) flip-off cap with aluminum overseal (b) (4)

- Dating period and storage conditions:
  The dating period for mogamulizumab DP is 36 months when stored at 2˚C to 8˚C, protected from light.

D. Novel Approaches/Precedents: None.

E. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2˚C to 8˚C (36˚F to 46˚F).

- Protect from light until use.
- Do not freeze. Do not shake.

F. Establishment Information:

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
• Bulk DS manufacture • DS IPC testing. • DS release testing. • DS stability testing. • General QC testing. • (b) (4) • Stability sample storage. • Master and working cell bank manufacture and storage.	Kyowa Hakko Kirin Co., Ltd (KHK) 100-1 Hagiwara-Cho, Takasaki-Shi, Gunma-Ken Prefecture, JAPAN 3700013	3007588904	Pre-License Inspection (12/21/2017)	VAI	Approve
(b) (4)				NAI	Approve

DRUG PRODUCT					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
(b) (4)				VAI	Approve

(b) (4)					
• DP release and stability testing for (b) (4) ADCC potency assay.	Kyowa Hakko Kirin Co., Ltd (KHK) 100-1 Hagiwara-Cho, Takasaki-Shi, Gunma-Ken Prefecture, JAPAN 3700013	3007588904	Pre-License Inspection (12/21/2017)	VAI	Approve

G. Facilities:

POTELIGEO® (mogamulizumab) DS and DP are manufactured at Kyowa Hakko Kirin Co., Ltd, Takasaki-Shi, Gunma-Ken Prefecture, Japan (FEI #3007588904), (b) (4) Drug product labeling and secondary packaging will take place at (b) (4)

A pre-license inspection was conducted between December 11, 2017 and December 21, 2017 of Kyowa Hakko Kirin Co., Ltd, the drug substance manufacturing facility for mogamulizumab. The inspection covered the manufacturing operations and testing of mogamulizumab including the following five quality systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. A 9-item FDA-483 was issued to the firm during the closeout meeting on December 21, 2017. The final classification of acceptable (VAI) has been made after satisfactory resolution of inspectional deficiencies by the firm.

A pre-license inspection was conducted between (b) (4) the drug product manufacturing facility for mogamulizumab. The inspection covered the manufacturing operations and testing of mogamulizumab including the following five quality systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. A 5-item FDA-483 was issued to the firm during the closeout meeting on (b) (4). The final classification of acceptable (VAI) has been made after satisfactory resolution of inspectional deficiencies by the firm.

Overall, the DS and DP manufacturing sites, and the proposed (b) (4) testing facility, (b) (4) are currently in a state of compliance. This BLA application is recommended for approval from a facilities perspective.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols:
   1. Validation of (b) (4) at commercial scale
   2. Requalification/annual retesting of primary and secondary reference materials
   3. Qualification of a new working cell bank
   4. Post-approval DS stability protocol

ii. Outstanding review issues/residual risk: None.

iii. Future inspection points to consider:

   1. Adequacy of method verification for compendial methods used for DS lot release and stability testing.

b. Drug Product

i. Protocols:
   1. Post-approval DP stability protocol

ii. Outstanding review issues/residual risk: None.

iii. Future inspection points to consider:

   1. Adequacy of method verification for compendial methods used for DP lot release and stability testing.

Ramesh Potla

Digitally signed by Ramesh Potla
Date: 7/25/2018 02:22:51PM
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Susan Kirshner

Digitally signed by Susan Kirshner
Date: 7/27/2018 09:33:43AM
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BLA STN 761051

POTELIGEO® (mogamulizumab)

Kyowa Kirin, Inc.

Jun Liu, Ph.D., Quality Reviewer
Ramesh Potla, Ph.D., Team Lead

Division of Biotechnology Review & Research III (DBRR-III)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP CMC Review Data Sheet

1. **BLA#**: STN 761051

2. **REWIEW DATE**: October 24, 2017

3. **PRIMARY REVIEW TEAM:**

a.	Medical Officer:	Yvette Kasamon
b.	Pharm/Tox:	Michael Manning
c.	Product Quality Team:	Ramesh Potla (ATL) (OPQ/OBP) Susan Kirshner (Immunogenicity) (OPQ/OBP) Jun Liu (DS and DP) (OPQ/OBP) Bo Chi (DS) (OPQ/OPF/DMA) Lakshmi Narasimhan (DP) (OPQ/OPF/DMA)
d.	Facilities:	Steven Fong (OPQ/OPF/DIA)
e.	Clinical Pharmacology:	Liang Li
f.	Statistics:	Kiki Ko
g.	OBP Labeling:	Vicky Borders-Hemphill
h.	OBP RBPM:	Andrew Shiber
i.	OND RBPM:	Katie Chon (DHP)

4. **MAJOR GRMP DEADLINES:**

a.	Filing Meeting:	November 01, 2018
b.	Primary review due:	July 20, 2018
c.	Secondary review due:	July 23, 2018
d.	PDUFA action date:	September 04, 2018

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Filing review memo	12/03/2017
Information Request #1	11/29/2017
Information Request #2	01/10/2018
Information Request #3	03/19/2018
Information Request #4	06/01/2018
Information Request #5	06/26/2018
Mid-cycle meeting (internal)	01/04/2018
Mid-cycle meeting (with sponsor)	01/17/2018
Late-cycle meeting (internal)	03/14/2018
Late-cycle meeting (with sponsor)	03/28/2018

6. **SUBMISSION(S) REVIEWE**D:

Submission	Date Received	Review Completed (yes or no)
STN 761051/SN0022 (response to IR#1)	12/07/2017	Yes
STN 761051/SN0034 (response to IR#2)	01/12/2018	Yes
STN 761051/SN0061 (response to IR#3)	04/02/2018	Yes
STN 761051/SN0064 (response to IR#3)	04/10/2018	Yes
STN 761051/SN0070 (response to IR#4)	06/13/2018	Yes
STN 761051/SN0072 (response to IR#5)	07/02/2018	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**

a. Proprietary Name: POTELIGEO®
b. Trade Name: POTELIGEO®
c. Non-Proprietary Name/USAN: mogamulizumab

d. CAS Registry Number: 1159266-37-1
e. INN Name: mogamulizumab
f. OBP Systematic Name: MAB HUMANIZED (IGG1) ANTI P51679 (CCR4_HUMAN) [KW0761]
g. Other Name (s): KW-0761, KM8761

8. **PHARMACOLOGICAL CATEGORY:**

Therapeutic recombinant humanized anti-C-C chemokine receptor 4 (CCR4) monoclonal antibody.

9. **DOSAGE FORM:**

Injection

10. **STRENGTH/POTENCY:**

i. The concentration/strength of the Drug Product (DP): 20 mg/5 mL (at 4 mg/mL) in a single-dose vial.
ii. Type of potency assay(s): Potency is defined as percent activity relative to reference material using a cell-based Antibody-dependent Cellular Cytotoxicity (ADCC) assay.

11. **ROUTE OF ADMINISTRATION:**

Intravenous Infusion

12. **REFERENCED MASTER FILES (DMF):**

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Provided	Type III, Sufficient information was provided in the BLA for its intended use.
			Provided	Type III, Sufficient information was provided in the BLA for its intended use.

13. **INSPECTIONAL ACTIVITIES:**

A pre-license inspection was conducted between December 11, 2017 and December 21, 2017 of Kyowa Hakko Kirin Co., Ltd, Takasaki-Shi, Gunma-Ken Prefecture, Japan (FEI #3007588904), the drug substance manufacturing facility for mogamulizumab. The inspection was conducted by Thuy Nguyen (OPQ/DIA), Scott Nichols (OPQ/DMA), Chikako Torigoe (OPQ/OBP), Ramesh Potla (OPQ/OBP), and Jun Liu (OPQ/OBP) and covered the manufacturing operations and testing of mogamulizumab including the following five quality systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. A 9-item FDA-483 was issued to the firm during the closeout meeting on December 21, 2017. See Appendix 1 for a copy of FDA-483.

A pre-license inspection was conducted between (b) (4) the drug product manufacturing facility for mogamulizumab. The inspection was conducted by Marion Michaelis (OPQ/DIA) and Steven Fong (OPQ/DIA) and covered the manufacturing operations and testing of mogamulizumab including the following five quality systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. A 5-item FDA-483 was issued to the firm during the closeout meeting on (b) (4) See Appendix 2 for a copy of FDA-483.

Dr. Steven Fong (OPQ/DIA), the facilities reviewer for mogamulizumab BLA, is recommending approval from a facilities perspective.

14. **CONSULTS REQUESTED BY OBP:**

None.

15. **QUALITY BY DESIGN ELEMENTS**:

The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
X	Design of Experiments
	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. **PRECEDENTS:** None

17. **ADMINISTRATIVE:**

Signature Block

Name and Title	Signature and Date
Ramesh Potla, Ph.D. Team Leader, DBRRIII/OBP/OPQ/CDER	(At the end of the document)
Jun Liu, PhD Primary reviewer, DBRRIII/OBP/OPQ/CDER	(At the end of the document)

SUMMARY OF QUALITY ASSESSMENTS

A. **Primary Reviewer Summary Recommendation**

The data submitted in this Biologics License Application support the conclusion that the manufacture of POTELIGEO® (mogamulizumab) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that POTELIGEO® (mogamulizumab) be approved for human use and under conditions specified in the package insert.

I recommend an expiration dating period of 36 months for mogamulizumab drug product when stored at 5 ± 3°C, protected from light.

I recommend an expiration dating period of (b) (4) months for mogamulizumab drug substance when stored at (b) (4)

B. **List of Deficiencies to Be Communicated**

None

C. **List of Post-Marketing Commitments/Requirement**

None

D. **Review of Common Technical Document- Quality Module 1**

Environmental Assessment of Claim of Categorical Exclusion

KHK claims categorical exclusion from the requirements of environmental assessment under 21 CFR 25.31 (c). The claim of categorical exemption is accepted.

E. **Primary Container Labeling Review:**

The CMC labeling review was performed by Dr. Vicky Borders-Hemphill, CDER/OPQ/OBP. The review memo is uploaded to CDER informatics separately.

F. **Review of Common Technical Document- Quality Module 2.3 and Module 3.2, Quality Overall Summary**

The review of Modules 2.3 and 3.2 are included in this review.

G. **Review of Immunogenicity Assays- Module 5.3.1.4**

The review of immunogenicity assays was performed by Dr. Susan Kirshner, CDER/OPQ/OBP. The review memo is uploaded to CDER informatics separately.

TABLE OF CONTENTS

Description of Drug Substance and Drug Product

2.3 Quality Overall Summary

Review Comment: Review of Section 2.3 did not identify anything that was not included in Module 3. Therefore, the review document will only cover Module 3. Note that updates to Module 3 have not yet been updated in Module 2.3 at the time of finalizing this review memo.

S. DRUG SUBSTANCE

3.2.S.1 General information

3.2.S.1.2 Structure

Mogamulizumab is a defucosylated humanized immunoglobulin G subclass 1 (IgG1) kappa monoclonal antibody that selectively binds to chemokine (C-C motif) receptor 4 (CCR4), a G protein-coupled receptor for C-C chemokines. The complementarity-determining regions (CDRs) were derived from mouse anti-human CCR4 mAb, and constant regions were derived from human IgG1. Mogamulizumab is a glycoprotein (molecular weight: ~149,000) composed of two H-chain (γ1-chain) molecules consisting of 449 amino acid residues each and two L-chain (κ-chain) molecules consisting of 219 amino acid residues each. The chains are linked together via covalent heavy-heavy and heavy-light chain disulfide bonds. Mogamulizumab is a glycoprotein. The N-glycosylation site is Asn-299 on each heavy chain and the main oligosaccharide structures are asialo-, biantennary, and nonfucosylated complex type structures containing 0, 1, and 2 galactose residues.

3.2.S.1.3 General Properties

The Mechanism of Action (MOA) of mogamulizumab is Antibody-dependent Cellular cytotoxicity (ADCC) via interactions between the CCR4 antigen on the target cells, the antibody, and the Fc Gamma Receptor IIIa (FcγRIIIa) on the Natural Killer (NK) effector cells. Mogamulizumab exhibits enhanced ADCC activity due to its decreased fucose content. A more detailed description of the physicochemical, biochemical, and biological properties of mogamulizumab molecule is provided in Section 3.2.S.3.1, Elucidation of Structure and Other Characteristics, below.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Table 3.2.S.2.1-1 Manufacturing and Quality Control Testing Sites for Mogamulizumab Drug Substance

Site Name and Address	Responsibility

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Jun Liu

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Ramesh Potla

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

LABELS AND LABELING REVIEW

Date:	June 13, 2018
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Jun Liu, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research III
Application:	BLA 761051
Applicant:	Kyowa Kirin Pharmaceutical Development, Inc.
Submission Date(s):	October 4, 2017, November 20, 2017
Product:	Poteligeo (mogamulizumab)
Dosage form(s):	injection
Strength and Container-Closure:	20 mg/5 mL (4 mg/mL) single-dose vial
Indication, dose, route, and frequency of administration:	for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy 1 mg/kg administered as an intravenous infusion over at least 60 minutes. Administered weekly on days 1, 8, 15, and 22 of the first 28-day cycle, followed by infusions every two weeks on days 1 and 15 for each subsequent 28-day cycle until disease progression or unacceptable toxicity
Background and Summary Description:	The Applicant submitted BLA 761051 Poteligeo (mogamulizumab) on October 4, 2017 which provides for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.
Recommendations:	The container labels (submitted on February 1, 2018), and carton labeling, prescribing information, and patient information labeling (submitted on March 13, 2018) for Poteligeo (mogamulizumab) injection, 20 mg/5 mL (4 mg/mL) single-dose vial for intravenous infusion acceptable from an OBP labeling perspective

Materials Considered for this Label and Labeling Review	
Materials Reviewed	**Appendix Section**
Proposed Labels and Labeling	A
Other	B (n/a)
Evaluation Tables	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance to the applicable requirements in the Code of Federal Regulations and United States Pharmacopeia (USP) standards (see Appendix C).

The container labels (submitted on February 1, 2018), and carton labeling, prescribing information, and patient information labeling (submitted on March 13, 2018) for Poteligeo (mogamulizumab) injection, 20 mg/5 mL (4 mg/mL) single-dose vial for intravenous infusion were reviewed and found to comply with relevant 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) and USP standards.

The labels and labeling are acceptable (see Appendix D) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted November 20, 2017 **\\cdsesub1\evsprod\bla761051\0015\m1\us\0761-bla-m114131-draft-labeling-text-en.docx**)

Patient Information (submitted October 4, 2017 **\\cdsesub1\evsprod\bla761051\0001\m1\us\0761-bla-m11413-patient-information-en.pdf**)

Container Labels (submitted October 4, 2017)

(b) (4)

(b) (4)

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(b) (4)

Prescribing Information and Patient Labeling Evaluation

Regulations	Conforms
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	☐ No ☒ Yes ☐ N/A
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	☐ No ☒ Yes ☐ N/A
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: The appropriate package-type term for this product is "single-dose". Revise the package type term (b) (4) to read "single-dose" throughout the prescribing information. A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. *The applicant revised as requested*	
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	☐ No ☒ Yes

	☐ N/A
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: We added identifying characteristics per 21 CFR 201.57(c)(4) *The applicant revised as requested* Revise the package type term (b) (4) to read "single-dose" throughout the prescribing information. *The applicant revised as requested*	
6.2 IMMUNOGENICITY Draft Guidance for Industry: Labeling for Biosimilar Products	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: We relocated and revised the language for this standard statement based on our current labeling best practice. *The applicant revised as requested*	
11 DESCRIPTION (21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q))	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: We added the identity of the microorganism/cell substrate used in manufacture per 21 CFR 610.61(q). *The applicant revised as requested* We added the dosage form per 21 CFR 201.57(c)(12) *The applicant revised as requested*	
16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: We added the dosage form and identifying characteristics per 21 CFR 201.57(c)(17) *The applicant revised as requested*	
MANUFACTURER INFORMATION 21 CFR 610.61, 21 CFR 610.64	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: The licensed manufacturer must appear as the Applicant on Form FDA 356h and the license number must be included per 21 CFR 610.61(b): (b) (4) US License No. xxxx The Distributor information may be included. Confirm that that the distributor (b) (4) *The applicant revised the manufacturer information to coincide with the most recent FDA form 356h and removed the distributor information from the labeling. We find this acceptable*	

PATIENT INFORMATION	
TITLE (NAMES AND DOSAGE FORM)	☐ No ☒ Yes ☐ N/A
STORAGE AND HANDLING	☐ No ☐ Yes ☒ N/A
INGREDIENTS	☐ No ☒ Yes ☐ N/A
MANUFACTURER INFORMATION 21 CFR 610.61, 21 CFR 610.64	☒ No ☐ Yes ☐ N/A

Comment/Recommendation: see above for full prescribing information
Ensure the manufacturer information is revised in the Patient Information Labeling.
Revise the manufacturer information as follows Manufactured by:
Kyowa Kirin, Inc.
Bedminster, NJ 07921
US License No. XXXX
You may include the distributor information, confirm the distributor (b) (4)

The applicant revised the manufacturer information to coincide with the most recent FDA form 356h and removed the distributor information from the labeling. We find this acceptable

APPENDIX D. Acceptable Labels and Labeling
Prescribing Information (submitted March 13, 2018
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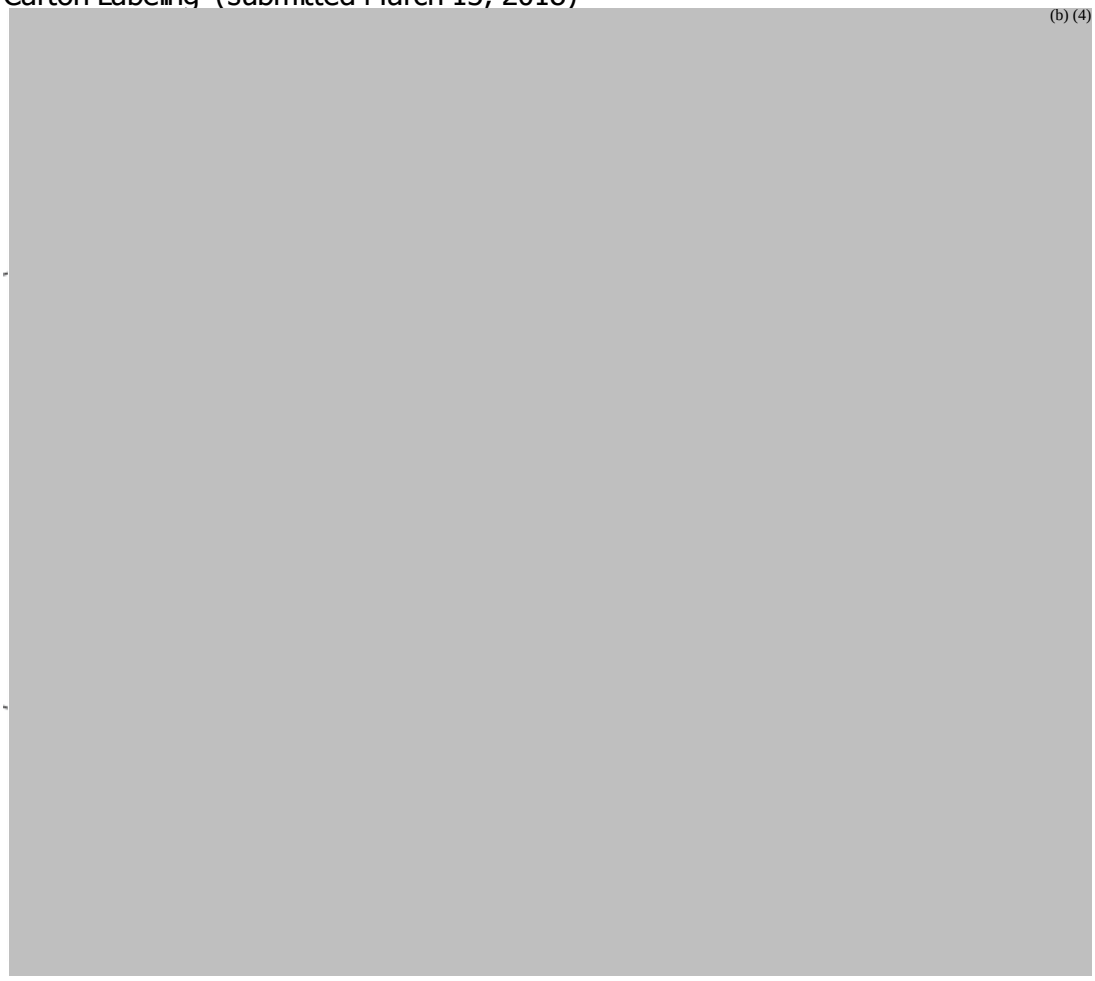
Patient Information (submitted March 13, 2018
\\cdsesub1\evsprod\bla761051\0053\m1\us\poteligeo--mogamulizumab--bla-761051-dmpp-opdp-ppi-mar-2018.docx)

Container Labels (submitted February 1, 2018)
(b) (4)

Carton Labeling (submitted March 13, 2018)

(b) (4)



Vicky Borders-Hemphill

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Jun Liu

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Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 22,
Silver Spring, MD 20993

Date: July 02, 2018
To: Administrative File, BLA 761051\0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OPQ/OPF/DMA
Endorsement: Reyes Candauchacon, Ph.D., Quality Assessment Lead, CDER/OPQ/OPF/DMA
Subject: Biological License Application (BLA)
US License: 2077
Applicant: Kyowa Kirin Pharmaceutical Development, Inc.
Facility: (b) (4)
Product: POTELIGEO® (Mogamulizumab) KW-0761
Dosage: Sterile, solution for intravenous infusion in a single use vial (4 mg/mL)
Indication: For the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy
Due Date: September 04, 2018

Recommendation for Approvability: The drug product section of this BLA, as amended, is recommended for approval from a product quality microbiology perspective.

SUMMARY: Kyowa Kirin Pharmaceutical Development Inc. has submitted a new biologics license application, BLA 761051 to license the use of Mogamulizumab. Drug substance is manufactured at Kyowa Hakko Kirin Co., Ltd., Gunma, Japan and drug product is manufactured at (b) (4)
The application was submitted in eCTD format and included Module 1.1.2 - FDA form 356h, Module 1.2 - Cover letter, 1.14 – Labeling, Module 2 and Module 3.

INTRODUCTION:
Mogamulizumab drug product (DP) is manufactured by (b) (4)

This review covers the evaluation of the drug product aspects of the application from a product quality microbiology perspective.

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	October 04 2017	Original
0037	January 22, 2018	IR response
0046	February 20, 2018	IR response
0050	February 28, 2018	CCIT validation Protocol
0060	March 30, 2018	Amendment
0065	April 20, 2018	CCIT validation Results

0066	April 30, 2018	IR response
0071	June 29, 2018	IR response

ASSESSMENTS:

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

DP is a preservative-free, sterile, and clear to slightly opalescent, colorless solution presented at the concentration of 4 mg/mL in a single-use vial for intravenous (IV) administration. The 10-mL vial contains 5 mL deliverable volume of DP (20 mg). The composition of DP provided in Table 3.2.P.1.2.1-1 is reproduced below.

Table 3.2.P.1.2.1-1 Composition of Mogamulizumab Drug Product

Component	Function	Quality Standard	Concentration	Quantity per Vial[a]
Mogamulizumab	API	In-house[b]	4 mg/mL	20 mg
Citric Acid Monohydrate	(b) (4)	USP/Ph.Eur./JP	2.1 mmol/L[c]	2.2 mg[c]
Glycine		USP/Ph.Eur./JP	300 mmol/L	112.5 mg
Polysorbate 80		NF/Ph.Eur./JP	0.2 mg/mL	1 mg
Sodium Hydroxide		NF/Ph.Eur./JP	Adjust to pH 5.5	As required
Hydrochloric Acid		NF/Ph.Eur./JP	Adjust to pH 5.5	As required
Water for Injection (b) (4)		USP/Ph.Eur./JP	q.s. to 5 mL	q.s. to 5 mL

a: Quantified for deliverable quantity per vial. (b) (4)

(b) (4) (see Section 3.2.P.2.2.1.4)

b: Meets the Drug Substance (DS) specification (see Section 3.2.S.4.1)

c: Theoretical concentration or quantity calculated from the target protein concentration in the DP (4 mg/mL), (b) (4) (b) (4) (see Section 3.2.P.2.2.1.3.3.4). (b) (4) (b) (4)

API=Active Pharmaceutical Ingredient, USP=United States Pharmacopeia, NF=National Formulary, Ph.Eur.=European Pharmacopoeia, JP=Japanese Pharmacopoeia, q.s.=quantum sufficit.

Reviewer's comments: Section 2.2 Preparation and Administration of product label indicates DP diluted in 0.9% sodium chloride injection is either used immediately or stored at 2°- 8°C (36°F to 46°F) for no more than 4 hours from the time of preparation. The infusion solution is administrated for minimum of 60 minutes through an intravenous line containing a sterile, low protein binding, 0.22 micron in-line filter.

Satisfactory

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

Microbiological Attributes

(b) (4)

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Reyes Candau-Chacon

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Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: **6/4/2018**
To: Administrative File, **STN 761051/0**
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/Branch IV
Subject: New Biologic License Applications (BLA)
Applicant: Kyowa Kirin Pharmaceutical Development, Inc.
US License: **2077**
Facility: Kyowa Hakko Kirin Co., Ltd.
Gunma, Japan
FEI: 3007588904
Product: Mogamulizumab
Dosage: 4 mg/mL, intravenous infusion
Indications: Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy
PDUFA date: September 4, 2018

Recommendation: The drug substance part of this BLA is recommended for approval from quality microbiology perspective.

Review Summary

Kyowa Kirin has submitted this Biologics License Application (BLA) for mogamulizumab for the treatment of cutaneous T-cell lymphoma (CTCL). The drug substance (DS) is manufactured at Kyowa Hakko Kirin Co., Ltd., Gunma, Japan. The drug product (DP) is manufactured at (b) (4) The application contains CMC information in an eCTD format.

This review contains an assessment of the mogamulizumab drug substance section of the BLA from microbiology perspective. The amendments reviewed are provided in the table below:

Sequence number	Date	Description
0001	10/4/2017	Original BLA submission
0036	1/19/2018	Response to IR
0056	3/16/2018	Response to IR
0063	4/9/2018	Response to IR
0066	4/30/2018	Response to IR

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(b) (4)

Satisfactory

Conclusion

I. The drug substance part of this BLA is recommended for approval from quality microbiology perspective.

II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the OBP reviewer.

III. See Panorama for compliance status of the facilities.

Bo Chi

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Reyes Candau-Chacon

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