CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761051Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	Original BLA
Application Number(s)	761051
Priority or Standard	Priority
Submit Date(s)	October 4, 2017
Received Date(s)	October 4, 2017
PDUFA Goal Date	June 4, 2018 (original PDUFA date) September 4, 2018 (extended PDUFA date)
Division/Office	Division of Hematology Products / OHOP
Review Completion Date	July 30, 2018
Established Name	Mogamulizumab-kpkc*
(Proposed) Trade Name	Poteligeo
Pharmacologic Class	CC chemokine receptor type 4 (CCR4) directed monoclonal antibody
Code name	KW0761
Applicant	Kyowa Kirin, Inc.
Formulation(s)	Intravenous; 20 mg/5 mL single-use vial
Dosing Regimen	1 mg/kg IV infusion over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle
Applicant Proposed Indication(s)/Population(s)	Treatment of cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy.

*The recommended established name is mogamulizumab-kpkc. Throughout the review, the term “mogamulizumab” was used for the established or nonproprietary name because the reviews were initiated prior to FDA acceptance of the suffix -kpkc.

Table of Contents

Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE=Office of Surveillance and Epidemiology
DEPI=Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
CDRH=Center for Devices and Radiological Health
COA=Clinical Outcomes Assessment

Glossary

ADCC	antibody-dependent cellular cytotoxicity
AESI	adverse event of special interest
Allo	allogeneic
ATL	adult T-cell leukemia/lymphoma
CCR4	CC chemokine receptor 4
COA	clinical outcomes assessment
CR	complete remission
CRF	case report form
CSR	clinical study report
CTCL	cutaneous T-cell lymphoma
DOR	duration of response
GVHD	graft-versus-host disease
HSCT	hematopoietic stem cell transplantation
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
INV	investigator
IR	information request
IRC	independent review committee
IRR	infusion-related reaction
ITT	intention-to-treat
mAb	monoclonal antibody
MF	mycosis fungoides
moga	mogamulizumab
NALT	new anti-lymphoma treatment
NE	not evaluable, not estimable
NHL	non-Hodgkin lymphoma
NME	new molecular entity
NRM	non-relapse mortality
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease, pharmacodynamics
PFS	progression-free survival
PFS-INV	progression-free survival per investigator
PFS-IRC	progression-free survival per IRC
PK	pharmacokinetics
PR	partial remission
PRO	patient reported outcome
PS	performance status

PT	preferred term
PTCL	peripheral T cell lymphoma
Q1, Q3	25^{th} percentile, 75^{th} percentile
QoL	quality of life
RDI	relative dose intensity
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SS	Sézary syndrome
SUR	safety update report
TE	treatment-emergent
TEAE	treatment-emergent adverse event

1 Executive Summary

1.1 Product Introduction

This review team recommends regular approval of mogamulizumab (POTELIGEO) for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy.

Mogamulizumab, a new molecular entity (NME), is a defucosylated, humanized IgG1 kappa monoclonal antibody that selectively binds to CC chemokine receptor 4 (CCR4), potentiating antibody-dependent cellular cytotoxicity and depletion of target cells. CCR4 is expressed by a subset of nonmalignant T cells, including regulatory T cells, and is overexpressed on the surface of cancer cells in the majority of patients with MF or SS. The recommended dose-schedule of mogamulizumab is 1 mg/kg as an intravenous infusion over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle, with treatment continued until disease progression or unacceptable toxicity.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The application contains sufficient evidence of effectiveness derived from a randomized clinical trial for mogamulizumab's intended use. The determination of efficacy is based on a multicenter, open-label, randomized, actively controlled phase 3 trial (Study 0761-010) in adult patients with MF or SS treated with at least one prior systemic therapy (median = 3). The trial randomized 372 patients with a 1:1 ratio to either a mogamulizumab or vorinostat arm. Investigator-assessed progression-free survival (PFS) was statistically significantly longer in the mogamulizumab arm (median 7.6 months; 95% CI: 5.6, 10.2) than in the vorinostat arm (median 3.1 months; 95% CI, 2.8, 4.0), with a hazard ratio (HR) of 0.53 (95% CI: 0.41, 0.69; 2-sided stratified log rank test $p<0.0001$). The PFS result according to an independent review committee (IRC) was supportive, with a HR (mogamulizumab/vorinostat) of 0.64 (95% CI: 0.50, 0.84). Sensitivity analyses of PFS confirmed the observed treatment effect of mogamulizumab. The confirmed objective response rate (ORR) per investigator was statistically significantly ($p<0.0001$) higher for mogamulizumab (28%) than for vorinostat (5%).

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Efficacy: Study 0761-010 provides adequate evidence of the efficacy of mogamulizumab for adults with MF or SS treated with at least one prior systemic therapy. This multicenter, open-label, randomized phase 3 trial in the intended population randomized 372 patients (55% having MF, 45% SS, and with a median of 3 prior systemic therapies) in a 1:1 ratio to either mogamulizumab at the recommended dose-schedule or vorinostat. Treatment continued until disease progression or unacceptable toxicity.

Mogamulizumab was associated with longer PFS and higher ORRs than vorinostat, meeting the trial's primary and first key secondary objective. For investigator-assessed PFS, the HR (mogamulizumab/vorinostat) was 0.53 (95% CI: 0.41, 0.69; 2-sided stratified log rank test p<0.0001) on intention-to-treat (ITT) analysis. The estimated median PFS was 7.6 months (95% CI: 5.6, 10.2) for the 186 patients randomized to mogamulizumab and 3.1 months (95% CI: 2.8, 4.0) for the 186 patients randomized to vorinostat, with an estimated median follow up of 13 months and 10 months, respectively. The results of the primary analysis were supported by blinded independent review, with a HR for PFS of 0.64 (95% CI: 0.50, 0.84). Results of sensitivity analyses of PFS confirmed the treatment effect of mogamulizumab.

The trial also demonstrated a statistically significantly improved ORR with mogamulizumab, based on global composite response criteria. The confirmed ORR per investigator was 28% with mogamulizumab compared to 5% ORR with vorinostat (p<0.0001).

Although greater improvement in PROs was reported with mogamulizumab compared to vorinostat, multiple limitations in the data (b) (4)

Safety: The safety evaluation is based on Study 0761-010. The median duration of randomized treatment was 5.6 months for mogamulizumab arm and 2.9 months for vorinostat. In the mogamulizumab arm, AEs reported in ≥ 20% included rash, infusion-related reaction (IRR), fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection (URTI). Other common AEs (in ≥10%) in this arm included skin infection, pyrexia, nausea, edema, thrombocytopenia, headache, constipation, mucositis, anemia, cough, and hypertension.

Randomized treatment with mogamulizumab carried a safety profile similar to crossover treatment after vorinostat. On pooled analysis of all 319 mogamulizumab recipients in this study, 35% had IRR; 25% had drug eruption; and 2% had reported use of systemic immunosuppressants for immune-mediated or possibly immune-mediated AEs.

In the literature, mogamulizumab prior to allogeneic HSCT has been associated with increased risks of severe acute graft-versus-host disease (GVHD), steroid-refractory GVHD, and nonrelapse mortality (NRM).

Overall benefit/risk assessment: In adult patients with relapsed or refractory MF or SS after at least one prior systemic therapy, the benefit/risk balance of mogamulizumab is acceptable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• SS and advanced MF tend to be chemotherapy resistant, are generally considered incurable, and are associated with reduced quality of life as well as shortened survival.	• SS and advanced MF are serious and life-threatening conditions.
Current Treatment Options	• Approved systemic therapies for CTCL include histone deacetylase inhibitors (vorinostat, romidepsin), bexarotene, brentuximab vedotin (in CD30+ subtypes), and methotrexate. Deep remissions are infrequent.	• More effective regimens are needed for MF/SS, particularly after failure of prior systemic therapy.
Benefit	• On ITT analysis of 372 patients with MF or SS after ≥ 1 prior systemic therapy (median 3), an open-label, randomized phase 3 trial (0761-010) demonstrated a statistically significantly prolonged PFS per investigator in recipients of mogamulizumab compared to vorinostat, with an estimated 47% reduction in the risk of progression or death. An analysis of PFS per IRC was supportive, with an estimated 36% reduction in this risk. • Based on global composite response criteria, the confirmed ORR per investigator was statistically significantly higher with mogamulizumab	• Based on PFS and response rate in a randomized, actively controlled trial, mogamulizumab has clinically meaningful activity in MF/SS after failure of prior systemic therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(28%) than vorinostat (5%).	
Risk and Risk Management	• In the mogamulizumab arm, the most common AEs (in ≥ 20%) were rash, IRR, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection. Other common AEs (in ≥10%) included skin infection, pyrexia, nausea, edema, thrombocytopenia, headache, constipation, mucositis, anemia, cough. and hypertension. • In the mogamulizumab arm, 36% had SAEs, most often involving infection; 18% discontinued treatment due to AEs, most often from drug eruption; and 2.2% had fatal AEs within 90 days of the last mogamulizumab dose. • In recipients of allo HSCT, pretransplantation mogamulizumab has been associated with increased risks of severe acute GVHD, steroid-refractory GVHD, and nonrelapse mortality.	• The safety profile of mogamulizumab is acceptable in the intended population. • Warnings and Precautions are warranted for IRRs, dermatologic toxicity, infection, autoimmune complications, and complications of allo HSCT after mogamulizumab. • The PI should describe the time course of drug eruption, provide guidelines for drug eruption and IRR, and recommend first-dose premedication. • A PMR is recommended to characterize the safety of allogeneic HSCT after mogamulizumab.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	Section 8.1.2 (Study Results)
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

{See appended electronic signature page}

Yvette Kasamon R. Angelo de Claro

2 Therapeutic Context

2.1 Analysis of Condition

MF and SS, the main types of cutaneous T-cell lymphoma (CTCL), comprise approximately 5% of non-Hodgkin lymphomas (NHLs). MF and SS are usually incurable and cause shortened survival as well as major morbidity. Prognosis varies widely and is related to clinical stage (Foss and

Girardi 2017; Agar et al 2010). MF primary presents in the skin, with potential involvement of nodes, blood, and viscera. Skin lesions may be localized or widespread, manifesting as patches or plaques, tumors (which may be disfiguring), erythroderma, and in ~10% of cases, large-cell transformation which is associated with a median overall survival (OS) of ~2 years. Patients with SS, a closely related, rare, and aggressive leukemic variant, have a median OS of ~3 years. In both diseases, pruritus is a leading symptom and can be debilitating. Skin exfoliation, 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 (Table 1). Skin-directed therapies are used for early-stage disease, whereas systemic therapies are used for refractory early-stage and advanced-stage disease (Foss and Girardi 2017; Tautinger et al 2017; Whittaker et al 2016).

2.2 Analysis of Current Treatment Options

Table 1 provides an overview of available systemic therapies for CTCL including MF/SS. Denileukin diftitox also received regular approval for (b) (4) but it is no longer marketed. With the exception of brentuximab vedotin, all of these drugs received regular approval on the basis of single-arm studies, with ORR determined primarily or solely in the skin compartment.

Total skin electron beam irradiation and phototherapy with psoralen and ultraviolet A (PUVA) are also widely used for CTCL requiring more than localized therapy. Drugs used off-label for CTCL include IFN-alpha and cytotoxic chemotherapy alone (e.g., liposomal doxorubicin) or in combination.

Table 1: Approved Systemic Therapies for CTCL

Drug (Year Approved)	Class	Indication	Pivotal Trial Design	Efficacy
Brentuximab vedotin (2017)	CD30 antibody-drug conjugate	Adults with primary cutaneous ALCL or CD30-expressing MF after prior systemic therapy	Randomized phase 3 (N=131): BV vs. physician choice of methotrexate or bexarotene	BV vs control: ORR4 56% vs 12%; CR 16% vs 2%; PFS HR 0.27 (95% CI, 0.17-0.43)
Romidepsin (2009)	HDAC inhibitor	CTCL after ≥ 1 systemic therapy	Two single-arm studies (N=167)	ORR 34 to 35%
Vorinostat (2006)	HDAC inhibitor	Cutaneous manifestations of CTCL after 2 systemic therapies	Two single-arm studies (N=107)	ORR 30% (all stages and ≥ IIB)
Bexarotene (1999)	Retinoid	Cutaneous manifestations of CTCL in patients refractory to ≥ 1 systemic therapy	Two single-arm, historically controlled studies (N=152) One postmarketing study (N=59)	ORR 30% to 38%
Methotrexate (1959)	Antimetabolite	Alone or in combination with other anticancer agents for advanced MF (CTCL)	Not in PI	ORR up to 50% as single agent

Source: FDA review
ALCL = anaplastic large cell lymphoma
Note: All have regular approval.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Mogamulizumab (also referred to as KW-0761) is an NME.

In Japan, mogamulizumab has approved indications in CCR4-positive adult T-cell leukemia/lymphoma (ATL) and in relapsed or refractory, CCR4-positive peripheral T-cell lymphoma (PTCL) and CTCL.

3.2 Summary of Presubmission/Submission Regulatory Activity

Mogamulizumab for T-cell lymphomas is investigated under IND 101843. Mogamulizumab was granted Orphan Drug Designation for the treatment of CTCL in 11/2010. Based on top-line results from a randomized phase 3 trial (0761-010), mogamulizumab was granted Breakthrough Therapy Designation in 8/2017 for the treatment of MF or SS after at least one prior systemic therapy.

A Type B pre-BLA meeting occurred 7/2017 regarding the CTCL indication, following Type B (3/2016, 10/2016) (b) (4)

During the BLA review, a major amendment was received 5/2/2018; refer to Section 4.2.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations

No significant issues arose on inspection of the Applicant and two clinical study sites.

4.2 Product Quality

The Office of Product Quality, CDER, recommends approval of BLA STN 761051 for Potoligeo (mogamulizumab) manufactured by Kyowa Kirin Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Potoligeo 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.

During the review of the application, multiple-item FDA-483 were issued for drug substance (DS) and drug product (DP) manufacturing facilities for mogamulizumab. The Applicant submitted additional information, including a major amendment dated 5/2/18 that extended the PDUFA date by 3 months. The final classification of acceptable (VAI) was made after satisfactory resolution of inspectional deficiencies for the DS and DP manufacturing sites. The application was recommended for approval from a facilities perspective.

Refer to Product Quality reviews (primary review and application technical lead review) for details.

4.3 Clinical Microbiology

The microbiology review teams determined that the drug substance and drug product were acceptable from a quality microbiology standpoint. Refer to Section 4.2 regarding the major amendment involving product quality.

4.4 Devices and Companion Diagnostic Issues

In conjunction with the Center for Devices and Radiological Health (CDRH) consultant, the clinical review team determined that a companion diagnostic for CCR4 expression is not required for safe and effective use of mogamulizumab in the intended population.

4.5 Clinical Outcomes Assessment (COA)

Supporting the impressions of the clinical and statistical reviewers, the COA consultants

(b) (4)

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Mogamulizumab (Poteligeo®, KW-0761) is a defucosylated humanized IgG1 monoclonal antibody (mAb) directed against human CC chemokine receptor 4 (CCR4). CCR4 is overexpressed on the surface of cancer cells in patients with T cell malignancies; mogamulizumab targets CCR4-expressing cells for lysis by antibody-dependent cellular cytotoxicity (ADCC).

The Applicant sought to evaluate the binding characteristics of mogamulizumab by surface plasmon resonance (SPR) and flow cytometry; mogamulizumab bound an immobilized CCR4 peptide, but an equilibrium dissociation constant (K_D) could not be determined. Mogamulizumab also bound immobilized FcγRIIIa, the Fc receptor essential for ADCC. Biotinylated mogamulizumab specifically bound peripheral lymphocytes from humans and cynomolgus monkeys, but not from dogs, rats, or mice. Likewise, the CCR4 amino acid sequence at the mogamulizumab binding region is identical in humans and cynomolgus monkeys, but differs in other species. The relative binding affinities of mogamulizumab between human and animal CCR4 were not evaluated.

In the presence of normal human peripheral blood mononuclear cells (PBMC), mogamulizumab mediated CCR4 expression-dependent ADCC lysis of CCR4 transfected cell lines and various human cancer cell lines; EC_{50} values could not be calculated due to the experimental design.

Mogamulizumab also mediated the lysis of adult T cell leukemia-lymphoma (ATL) patient-derived tumor cells in the presence of ATL patient-derived or normal human PBMCs; ADCC activity was lower using ATL patient-derived PBMCs versus normal human PBMCs. Observation of in vitro mogamulizumab-mediated ADCC lysis of ATL patient-derived tumor cells by ATL patient-derived PBMCs provided rationale for evaluating mogamulizumab in patients with ATL. Mogamulizumab also mediated ADCC activity in the presence of cynomolgus monkey PBMCs, suggesting mogamulizumab would be pharmacologically active in cynomolgus monkeys. Mogamulizumab did not mediate any appreciable complement-dependent cytotoxicity (CDC) activity. In the absence of effector cells mogamulizumab caused a modest decrease in cell surface CCR4 expression levels, although the mechanism of this phenomenon was not investigated.

The antitumor activity of mogamulizumab was evaluated in severe combined immunodeficiency (SCID) mouse xenograft models of CTCL and ATL. Once-weekly treatment with mogamulizumab (20 mg/kg) suppressed tumor growth without affecting body weight. Studies evaluating the antitumor activity of mogamulizumab in mice lacking natural killer (NK) cells were not conducted.

Toxicology studies were only conducted in cynomolgus monkeys due to the limited cross reactivity profile of mogamulizumab. The interpretation of these studies was hindered by the unknown relative binding affinities of mogamulizumab to human and cynomolgus monkey CCR4. Repeat-dose toxicity studies of up to 26 weeks in duration were conducted; these studies were conducted using the intravenous (IV) route, consistent with the intended clinical route of administration. In the 26-week study, mogamulizumab was administered IV at doses of 2.5, 10, or 40 mg/kg once weekly. Mogamulizumab was well-tolerated, and no adverse mogamulizumab-related changes were observed. Decreased CCR4-positive cell ratio and count were observed at all dose levels, consistent with the expected pharmacology of mogamulizumab. In the 4-week study, mogamulizumab was administered IV at doses of 0.05, 1.2, or 40 mg/kg once weekly, followed by a 3-month recovery period. No adverse mogamulizumab-related changes were observed; however, decreased levels of CCR4-positive and CD3-negative/CD16-postive (NK) cells were observed at all dose levels throughout the dosing period. Levels of both CCR4-positive and NK cells recovered by the end of the recovery period. Anti-mogamulizumab antibodies were common at the ≤1.2 mg/kg dose levels, which correlated with faster clearance and shorter half-life. The repeat-dose toxicity studies did not identify any potential target organs of toxicity. Safety pharmacology endpoints were incorporated into the repeat-dose toxicity studies, and there was no evidence of mogamulizumab-related effects on the cardiovascular, respiratory, renal, or central nervous systems.

Dermatologic adverse events (AE) were observed in humans that were not predicted by the repeat-dose toxicity studies in cynomolgus monkeys. The Applicant hypothesized immunological differences between young cynomolgus monkeys and older patients may have contributed to the unpredicted AEs observed in the clinic; a preliminary study determined

lymphocyte subset ratios were different in young and aged monkeys. An additional repeat-dose toxicity study was conducted to assess the incidence of dermal toxicity in ~20 year old cynomolgus monkeys. Mogamulizumab was administered IV once weekly at 10 mg/kg for 8 weeks, followed by a 4-week observation period. Mild erythema was observed in 2/4 monkeys following the second administration, resolved, and then recurred prior to or immediately after the fourth administration, and then resolved prior to the fifth administration without sequelae. The severity of the erythema was under-representative of the dermatologic AEs observed in some patients. Mogamulizumab was associated with changes in lymphocyte subsets; however, there were no differences in lymphocyte subsets between the monkeys with and without erythema.

In an embryo-fetal development study pregnant cynomolgus monkeys were administered mogamulizumab IV once weekly at 40 mg/kg (approximately 27 times the exposure in patients at the recommended dose, based on AUC) from the start of organogenesis until late 3rd trimester. No adverse mogamulizumab-related changes were observed in dams. Fetuses were delivered by cesarean; there was no mogamulizumab-related embryo-fetal lethality, teratogenicity, or fetal growth retardation. Significantly lower levels of CCR4-positive lymphocytes were observed in mogamulizumab-treated fetuses, consistent with the expected pharmacological activity of mogamulizumab. At the end of the study plasma exposure of mogamulizumab in the fetuses was ~60% that observed in the dams; this finding is consistent with the expected transfer of mogamulizumab across the placental barrier. The Poteligeo label states Poteligeo is not recommended during pregnancy or in women of childbearing potential not using contraception; contraception use is recommended in females of reproductive potential during treatment with Poteligeo and for at least 3 months following the last dose of Poteligeo. Antibodies may be excreted in human milk; (b) (4)

Fertility/early embryonic development and pre/postnatal development studies were not conducted as these studies are not required to support a marketing application for products intended to treat patients with advanced cancer. In repeat-dose toxicity studies no mogamulizumab-related adverse findings were observed in any male or female reproductive organs. In tissue cross-reactivity studies with human and cynomolgus monkey tissues, mogamulizumab did not bind any tissues from male or female reproductive organs.

The potential for mogamulizumab to elicit cytokine release or effect platelet function were evaluated in a series of in vitro studies. Experimental conditions may affect the results of cytokine release assays; therefore, three cytokine release assays were conducted under different conditions. Results of the cytokine release assays varied by the experimental conditions; mogamulizumab generally caused greater cytokine release (IL-6, TNF-α, and IFN-γ) in solid phase assays with isolated PBMCs. Platelet function assays were conducted with human and cynomolgus monkey platelets. Mogamulizumab did not bind to platelets, affect platelet aggregation, or affect platelet count under the conditions tested.

No carcinogenicity studies were conducted or are required to support a marketing application for the current indication. No genotoxicity studies were conducted or are required to support a marketing application for biotechnology-derived products such as mogamulizumab.

The nonclinical pharmacology and toxicology data submitted to this BLA are adequate to support the approval of mogamulizumab for the proposed indication.

5.2 Referenced NDAs, BLAs, DMFs

None

5.3 Pharmacology

Primary pharmacology

A. In vitro studies

The binding characteristics of mogamulizumab and the parental mouse antibody KM2160 were evaluated by SPR. Mogamulizumab and KM2160 bound a biotinylated CCR4 peptide (residues 12-29 of the CCR4 protein) similarly with an association rate constant (k_{on}) of 1.33-1.39x10^5 $(mol/L)^{-1}s^{-1}$; a dissociation rate constant (k_{off}) could not be determined, and thus an equilibrium dissociation constant (K_D) could not be calculated. No additional studies to determine the K_D were conducted. Similar binding between mogamulizumab and KM2160 indicate humanization and defucosylation did not alter CCR4 binding affinity. The relative binding affinities of mogamulizumab between human and animal CCR4 were not evaluated. Mogamulizumab bound FcγRIIIa, the Fc receptor essential for ADCC, with K_D values of 995 nM and 94.9 nM for the polymorphic variants 158-phenylalanine and 158-valine, respectively. The reactivity of biotinylated mogamulizumab to human, cynomolgus monkey, dog, rat, and mouse peripheral leukocytes was evaluated by flow cytometry. Biotinylated mogamulizumab specifically bound peripheral lymphocytes from humans and cynomolgus monkeys only; most the specific binding was in the CD4-positive subset. Similar binding in humans and cynomolgus monkeys is expected given the CCR4 amino acid sequence at the mogamulizumab binding region is identical in humans and cynomolgus monkeys. Biotinylated mogamulizumab did not bind peripheral lymphocytes from dogs, rats, or mice, or monocytes or granulocytes from any species tested. Together, these results suggest the cynomolgus monkey is the only relevant species for the nonclinical safety assessment of mogamulizumab.

The in vitro activity of mogamulizumab was evaluated in a series of cell-based assays. The CCR4-negative murine thymoma cell line EL4 was transfected with human CCR4 and expression was verified by flow cytometry. In the presence of effector cells (normal human PBMCs) mogamulizumab demonstrated CCR4 expression-dependent ADCC activity against transfected EL4 cells but not the parental EL4 cell line; the study design did not permit calculation of EC_{50} values. Various human cancer cell lines were also evaluated for endogenous levels of CCR4 by

flow cytometry; CCR4 expression levels generally correlated with susceptibility to ADCC mediated by mogamulizumab, but again EC_{50} values were not provided. In a parallel series of experiments mogamulizumab mediated ADCC using a human cancer cell line as target cells and cynomolgus monkey PBMCs as effector cells, suggesting mogamulizumab would be pharmacologically active in cynomolgus monkeys. Treatment of a CCR4-positive human cancer cell line with mogamulizumab in the absence of effector cells resulted in a ~20% decrease in CCR4 expression levels, although the mechanism of this phenomenon was not investigated. Fucosylated and defucosylated mogamulizumab were evaluated in a comparative ADCC assay confirming defucosylation conferred increased ADCC activity. Mogamulizumab did not mediate any appreciable CDC activity on human cancer cell lines at the concentrations tested (≤100 µg/mL) even in the presence of antibodies to neutralize complement regulatory proteins.

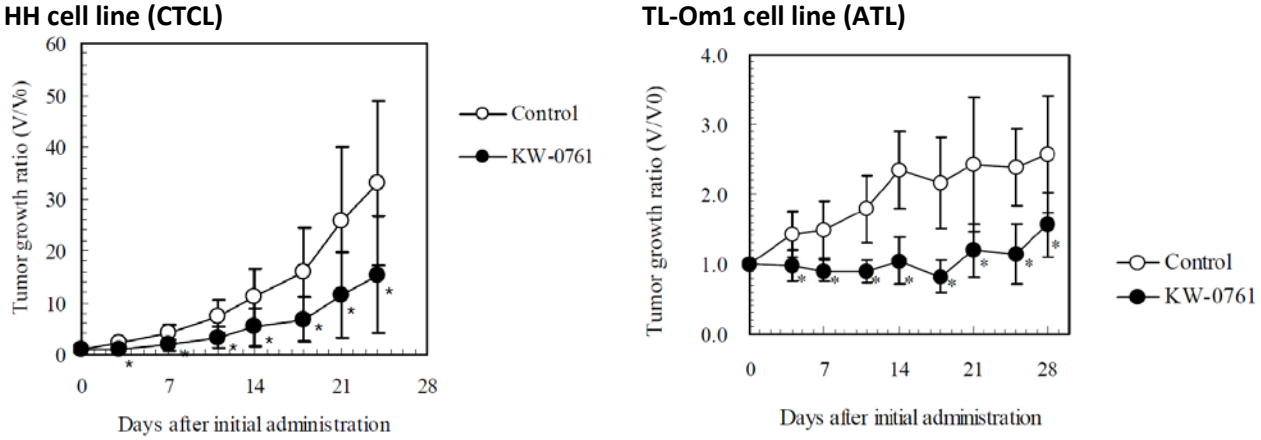
The activity of mogamulizumab was also evaluated using ATL patient-derived or normal human PBMCs as effector cells and ATL patient-derived tumor cells as target cells. Mogamulizumab demonstrated greater ADCC activity in the presence of normal human PBMCs, presumably due to the decreased number or dysfunction of patient-derived effector cells. Even though the activity was lower in the autologous setting, the observation of mogamulizumab-mediated ADCC activity against ATL patient-derived tumor cells provided rationale for evaluating mogamulizumab in patients with ATL.

B. In vivo studies

The antitumor activity of mogamulizumab was evaluated in mouse xenograft models of CTCL and ATL. Male SCID mice (Fox CHASE C.B-17/Icr-scidJcl) were subcutaneously injected with the human CTCL cell line HH or the ATL cell line TL-Om1. Once tumors formed mice were assigned to groups (n=10/group) to receive mogamulizumab (20 mg/kg) or saline administered IV once weekly for 4 weeks. Tumor volume and body weight were measured for up to 28 days. Treatment with mogamulizumab resulted in suppressed tumor growth in both mouse models (see Figure 1) with no significant effect on body weight (data not shown). Studies evaluating the antitumor activity of mogamulizumab in mice lacking NK cells were not conducted.

Figure 1: Effect of Mogamulizumab on Tumor Growth in Mouse Xenograft Models of CTCL and ATL

Figure excerpted from Applicant's submission



* P<0.05; tumor growth ratio (V/V_0): tumor volume on each day/tumor volume on Day 0.

Secondary Pharmacology

The potential for mogamulizumab to elicit cytokine release from human whole blood and isolated PBMCs was evaluated in a series of studies; each study was conducted under different conditions. Mogamulizumab generally caused greater cytokine release in solid phase assays with isolated PBMCs (see Table 2). The dissimilar study outcomes confirm the need to conduct cytokine release assays under more than one condition for a comprehensive hazard identification.

The first cytokine release study was a soluble phase assay and evaluated the release of TNF-α and IFN-γ from whole blood only; this study evaluated concentrations of mogamulizumab up to 10 µg/mL and only included a 4-hour incubation. Mogamulizumab caused the release of IFN-γ from the whole blood of 1/6 donors, and had no effect on TNF-α.

The second cytokine release study included a soluble phase assay using whole blood and a solid phase assay (dry coated) using isolated PBMCs; both formats evaluated the release of TNF-α, IFN-γ, and IL-6. The soluble phase assay evaluated concentrations of mogamulizumab up to 500 µg/mL for 24 hours while the solid phase assay evaluated concentrations of mogamulizumab up to 250 µg/mL for 48 hours. In both the soluble and solid phase assays mogamulizumab caused release of TNF-α, IFN-γ, and IL-6 from the whole blood and PBMCs of most donors; however, the magnitude of cytokine release was greater in the solid phase assay.

The third cytokine release study included a soluble phase assay using whole blood and a solid phase assay (wet coated) using isolated PBMCs; both formats evaluated the release of IFN-γ, IL-2, IL-6, and TNF-α. The soluble phase assay evaluated concentrations of mogamulizumab up to 50 µg/mL for 24 hours while the solid phase assay evaluated concentrations of mogamulizumab up to 10 µg/mL for 24 hours. In the soluble phase assay mogamulizumab caused minimal

release of TNF-α, IFN-γ, and IL-6 from the whole blood of most donors. In the solid phase assay mogamulizumab caused significant release of TNF-α, IFN-γ, and IL-6 from the PBMCs of all donors.

Table 2: Cytokine Release Assays: Summary of Results

Study #	Assay type	Cell type	Cytokine			
			IL-2	IL-6	TNF-α	IFN-γ
1	Soluble phase	Whole blood	Not tested	Not tested	No effect	Moderate effect, 1/6 donors
2	Soluble phase	Whole blood	Not tested	Moderate effect, 8/8 donors	Small effect, 8/8 donors	Small effect, 8/8 donors
	Solid phase (dry)	Isolated PBMCs	Not tested	Large effect, 8/8 donors	Large effect, 8/8 donors	Small effect, 7/8 donors
3	Soluble phase	Whole blood	No effect	Small effect, 5/6 donors	Small effect, 5/6 donors	Small effect, 6/6 donors
	Solid phase (wet)	Isolated PBMCs	No effect	Large effect, 6/6 donors	Large effect, 6/6 donors	Moderate effect, 6/6 donors

The potential effects of mogamulizumab on platelet function were evaluated in a series of studies. Biotinylated mogamulizumab did not bind to platelets in human or cynomolgus monkey peripheral blood (0.2-500 µg/mL) or affect platelet aggregation in human or cynomolgus monkey platelet rich plasma (0.2-2000 µg/mL). Treatment of human whole blood with mogamulizumab (10 and 100 µg/mL) did not affect platelet count.

Safety Pharmacology

No standalone safety pharmacology studies were conducted. Safety pharmacology endpoints were incorporated into the repeat-dose toxicity studies in male and female cynomolgus monkeys. No evidence of deleterious effects on the cardiovascular, respiratory, renal, or central nervous systems were observed in these studies.

5.4 ADME/PK

Type of Study	Major Findings
Distribution	
Tissue Distribution of [^{125}I]mogamulizumab after Single Intravenous Dose in Cynomolgus Monkeys /	A single dose of [^{125}I]mogamulizumab (1 mg/kg) was administered to male cynomolgus monkeys (n=3/group). Monkeys were sacrificed after 4, 24, or 336 hours. The distribution of radioactivity to the various tissues were evaluated.

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Study Report AE-6231-G</td><td>
Tissue distribution after a single dose of [^{125}I] mogamulizumab
<table>
<tr><th rowspan="2">Tissue/organ</th><th colspan="3">Ratio of tissue to plasma</th></tr>
<tr><th>4 hours</th><th>24 hours</th><th>336 hours</th></tr>
<tr><td>Plasma</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Blood</td><td>0.62</td><td>0.59</td><td>0.65</td></tr>
<tr><td>Spleen</td><td>0.22</td><td>0.19</td><td>0.26</td></tr>
<tr><td>Gall bladder</td><td>0.09</td><td>0.14</td><td>0.25</td></tr>
<tr><td>Lung</td><td>0.12</td><td>0.16</td><td>0.19</td></tr>
<tr><td>Thyroid</td><td>0.03</td><td>0.04</td><td>0.18</td></tr>
<tr><td>Urinary bladder</td><td>0.02</td><td>0.06</td><td>0.15</td></tr>
<tr><td>Liver</td><td>0.12</td><td>0.11</td><td>0.14</td></tr>
<tr><td>Kidney</td><td>0.12</td><td>0.12</td><td>0.14</td></tr>
<tr><td>Lymph node</td><td>0.07</td><td>0.11</td><td>0.14</td></tr>
<tr><td>Epididymis</td><td>0.04</td><td>0.13</td><td>0.13</td></tr>
<tr><td>Heart</td><td>0.07</td><td>0.11</td><td>0.12</td></tr>
<tr><td>Adrenal</td><td>0.1</td><td>0.11</td><td>0.12</td></tr>
<tr><td>Bone marrow</td><td>0.13</td><td>0.11</td><td>0.12</td></tr>
<tr><td>Prostate</td><td>0.05</td><td>0.12</td><td>0.11</td></tr>
<tr><td>Pituitary</td><td>0.05</td><td>0.06</td><td>0.1</td></tr>
<tr><td>Stomach</td><td>0.03</td><td>0.08</td><td>0.1</td></tr>
<tr><td>Submandibular gland</td><td>0.02</td><td>0.05</td><td>0.09</td></tr>
<tr><td>Testis</td><td>0.11</td><td>0.14</td><td>0.09</td></tr>
<tr><td>Small intestine</td><td>0.04</td><td>0.08</td><td>0.09</td></tr>
<tr><td>Skin</td><td>0.01</td><td>0.04</td><td>0.08</td></tr>
<tr><td>Large intestine</td><td>0.03</td><td>0.07</td><td>0.08</td></tr>
<tr><td>Aorta</td><td>0.02</td><td>0.03</td><td>0.06</td></tr>
<tr><td>Thymus</td><td>0.02</td><td>0.03</td><td>0.05</td></tr>
<tr><td>Pancreas</td><td>0.02</td><td>0.05</td><td>0.05</td></tr>
<tr><td>Eyeball</td><td>0.01</td><td>0.02</td><td>0.04</td></tr>
<tr><td>Fat</td><td>0.01</td><td>0.02</td><td>0.02</td></tr>
<tr><td>Skeletal muscle</td><td>0</td><td>0.01</td><td>0.02</td></tr>
<tr><td>Cerebrum</td><td>0.01</td><td>0.01</td><td>0.01</td></tr>
<tr><td>Cerebellum</td><td>0.01</td><td>0.01</td><td>0.01</td></tr>
</table>
</td></tr>
<tr><td>Metabolism</td><td>Metabolism studies were not conducted.</td></tr>
<tr><td>Excretion</td><td>Excretion studies were not conducted.</td></tr>
<tr><td>TK data from general toxicology studies</td><td></td></tr>
<tr><td>A 26-Week Repeated Intravenous Dose Toxicity Study of KW-0761 in Cynomolgus Monkeys / Study Report SBL303-139</td><td>
$t_{1/2}$: 6.77-20.9 days
Accumulation ($AUC_{0\text{-}7day}$ after the 26th cycle relative to that after the 1st cycle): significant accumulation (4.1-6.6x) at all dose levels.
Dose proportionality (based on $AUC_{0\text{-}7day}$): slightly less than or equal to dose proportional (0.64-1.05x) across the dosing range.
TK parameters after cycle 1
<table>
<tr><th colspan="2">Dose (mg/kg)</th><th>C_{max} (ng/mL)</th><th>$AUC_{0\text{-}7day}$ (ng·day/mL)</th><th>$t_{1/2}$ (day)</th></tr>
<tr><td rowspan="2">2.5</td><td>M</td><td>52180 ± 2360</td><td>172000 ± 12000</td><td>7.60 ± 2.51</td></tr>
<tr><td>F</td><td>50570 ± 10650</td><td>213000 ± 32000</td><td>6.77 ± 1.12</td></tr>
<tr><td rowspan="2">10</td><td>M</td><td>175800 ± 11000</td><td>678000 ± 39000</td><td>7.66 ± 3.52</td></tr>
<tr><td>F</td><td>139600 ± 18000</td><td>582000 ± 39000</td><td>12.3 ± 5.1</td></tr>
<tr><td rowspan="2">40</td><td>M</td><td>713700 ± 158000</td><td>2360000 ± 60000</td><td>6.86 ± 1.64</td></tr>
<tr><td>F</td><td>459500 ± 22400</td><td>1490000 ± 250000</td><td>6.95 ± 2.77</td></tr>
</table>
TK parameters after cycle 26
<table>
<tr><th colspan="2">Dose (mg/kg)</th><th>C_{max} (ng/mL)</th><th>$AUC_{0\text{-}7day}$ (ng·day/mL)</th><th>$t_{1/2}$ (day)</th><th>R</th></tr>
<tr><td rowspan="2">2.5</td><td>M</td><td>170900 ± 58800</td><td>936000 ± 369000</td><td>15.6 ± 4.0</td><td>5.4</td></tr>
<tr><td>F</td><td>166700*</td><td>874000*</td><td>19.2*</td><td>4.1*</td></tr>
<tr><td>10</td><td>M</td><td>714300 ± 97300</td><td>3950000 ± 520000</td><td>20.9 ± 13.7</td><td>5.8</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>F</td><td>468700 ± 26600</td><td>2510000 ± 230000</td><td>18.2 ± 5.2</td><td>4.3</td></tr>
<tr><td rowspan="2">40</td><td>M</td><td>2359000 ± 189000</td><td>12500000 ± 600000</td><td>14.1 ± 7.7</td><td>5.3</td></tr>
<tr><td>F</td><td>2236000 ± 694000</td><td>9780000 ± 3460000</td><td>15.6 ± 8.4</td><td>6.6</td></tr>
</table>
* Excludes data for animal with anti-mogamulizumab antibodies; R: accumulation ratio calculated as the ratio of $AUC_{0\text{-}7day}$ after the 26th cycle relative to the 1st cycle.
</td></tr>
<tr><td>TK data from reproductive toxicology studies</td><td></td></tr>
<tr><td>A Study for Effects of KW-0761 on Embryo-Fetal Development When Administered Weekly by Intravenous Administration to Pregnant Cynomolgus Monkeys / Study Report SBL303-049</td><td>
Mogamulizumab plasma exposure after first and last dose
<table>
<tr><th></th><th>$AUC_{0\text{-}7day}$ (ng·day/mL)*</th><th>Concentration 24 hours post dose (ng/mL)#</th></tr>
<tr><td>Dam</td><td>3849728.9</td><td>1700200.0</td></tr>
<tr><td>Fetus$</td><td>-</td><td>983340.0</td></tr>
<tr><td>Fetus to dam plasma exposure ratio</td><td>-</td><td>0.58</td></tr>
</table>
* After first dose; #after last dose; $sample taken from umbilical artery at time of cesarean.
No anti-mogamulizumab antibodies were detected in any maternal or fetal sample.
</td></tr>
</table>

5.5 Toxicology

5.5.1 General Toxicology

A 26-Week Repeated Intravenous Dose Toxicity Study of KW-0761 in Cynomolgus Monkeys / Study Report SBL303-139

Key Study Findings

- No adverse mogamulizumab-related changes were observed.
- Decreased $CCR4^+$ cell ratio and count were observed at all dose levels, consistent with the expected pharmacology of mogamulizumab.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 2.5, 10, or 40 mg/kg; test article was administered once weekly for 26 weeks
Route of administration:	IV (bolus)
Formulation/Vehicle:	3.68 mmol/L citric acid buffer solution containing 0.62% (w/v) sodium chloride
Species/Strain:	Monkey/cynomolgus
Number/Sex/Group:	3/sex/group
Age:	3 to 6 years old
Satellite groups/unique design:	No/No

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>None</td></tr>
<tr><td>Clinical signs</td><td>Unremarkable</td></tr>
<tr><td>Body weights</td><td>Unremarkable</td></tr>
<tr><td>Ophthalmoscopy</td><td>Unremarkable</td></tr>
<tr><td>ECG</td><td>Unremarkable</td></tr>
<tr><td>Hematology</td><td>Unremarkable</td></tr>
<tr><td>Clinical chemistry</td><td>Unremarkable</td></tr>
<tr><td>Urinalysis</td><td>Unremarkable</td></tr>
<tr><td>Gross pathology</td><td>Unremarkable</td></tr>
<tr><td>Organ weights</td><td>Unremarkable</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>Unremarkable</td></tr>
<tr><td>Peripheral blood immunophenotyping</td><td>There were no statistically significant differences in the percent or absolute number of $CD3^{-}CD16^{+}$ lymphocytes (NK cells).

A decrease in the ratio (see table below) and absolute number (data not shown) of $CCR4^{+}$ lymphocytes were observed.
% Mean difference in $CCR4^{+}$ cell ratio vs. concurrent control
<table>
<tr><th colspan="2" rowspan="2">Dose level</th><th colspan="7">Day</th></tr>
<tr><th>-8</th><th>28</th><th>56</th><th>84</th><th>119</th><th>147</th><th>182</th></tr>
<tr><td rowspan="2">2.5 mg/kg</td><td>M</td><td>-</td><td>-64%**</td><td>-64%**</td><td>-</td><td>-62%**</td><td>-62%**</td><td>-65%**</td></tr>
<tr><td>F</td><td>-</td><td>-63%**</td><td>-67%**</td><td>-61%**</td><td>-61%**</td><td>-58%**</td><td>-54%**</td></tr>
<tr><td rowspan="2">10 mg/kg</td><td>M</td><td>-</td><td>-62%**</td><td>-75%**</td><td>-77%*</td><td>-71%**</td><td>-53%**</td><td>-68%**</td></tr>
<tr><td>F</td><td>-</td><td>-72%**</td><td>-77%**</td><td>-79%**</td><td>-76%**</td><td>-75%**</td><td>-78%**</td></tr>
<tr><td rowspan="2">40 mg/kg</td><td>M</td><td>-</td><td>-55%**</td><td>-71%**</td><td>-</td><td>-61%**</td><td>-56%**</td><td>-65%**</td></tr>
<tr><td>F</td><td>-</td><td>-67%**</td><td>-72%**</td><td>-76%**</td><td>-80%**</td><td>-74%**</td><td>-77%**</td></tr>
<tr><td colspan="9">* P<0.05 , ** P<0.01</td></tr>
</table></td></tr>
<tr><td>ADA analysis</td><td>Anti-mogamulizumab antibodies were detected in 1 female at the 2.5 mg/kg dose level from Day 29 onwards.</td></tr>
<tr><td>KLH sensitization</td><td>A dose-dependent trend in decreased anti-KLH antibody titer (IgG, IgM) was observed in males and females; this trend was not statistically significant.</td></tr>
</table>

General Toxicology: Additional Studies

A 28-Day Repeated Dose Toxicity Study of KW-0761 Administered by Slow Intravenous Bolus Injection to Cynomolgus Monkeys / Study Report QUK00003

Mogamulizumab was administered IV once weekly at dose levels of 0, 0.05, 1.2, or 40 mg/kg for 4 weeks (4 doses) to cynomolgus monkeys (5/sex/group, including 2/sex/group to assess reversibility after a 3-month recovery period). No adverse mogamulizumab-related changes were observed. Decreased levels of $CCR4^{+}$ and $CD3^{-}CD16^{+}$ (NK) cells were observed at all dose levels by Day 2 and continued through Day 28; levels of both $CCR4^{+}$ and NK cells recovered by Day 130. Anti-mogamulizumab antibodies were detected in 10/10 monkeys at the 0.05 mg/kg dose level and in 4/10 monkeys at the 1.2 mg/kg dose level; presence of anti-mogamulizumab

antibodies correlated with faster clearance and shorter half-life. Humoral responses to challenge with KLH were unaffected by treatment with mogamulizumab.

5.5.2 Genetic Toxicology

Not conducted per ICH S6(R1).

5.5.3 Carcinogenicity

Not conducted per ICH S6(R1), S1, and S9.

5.5.4 Reproductive and Developmental Toxicology

Embryo-Fetal Development

A Study for Effects of KW-0761 on Embryo-Fetal Development When Administered Weekly by Intravenous Administration to Pregnant Cynomolgus Monkeys / Study Report SBL303-049

Key Study Findings

- No adverse mogamulizumab-related changes were observed in dams.
- No mogamulizumab-related embryo-fetal lethality, teratogenicity, or fetal growth retardation was observed.
- Mogamulizumab treatment was associated with significantly lower $CCR4^+$ lymphocyte ratio and count in dams and fetuses.
- The mean ratio of mogamulizumab concentration in fetuses to that in dams 24 hours after the last dose was 0.58.

Conducting laboratory and location:
(b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 or 40 mg/kg; test articles were administered once weekly for a total of 18 doses
Route of administration:	IV (bolus)
Formulation/Vehicle:	3.68 mmol/L citric acid buffer solution containing 0.62% (w/v) sodium chloride
Species/Strain:	Monkey/cynomolgus
Number/Sex/Group:	12/F/group
Satellite groups:	No
Study design:	Females were paired with males for 3 days, with the middle day designated as GD 0. Pregnancy was confirmed by ultrasound on GD 18. Test article was

	administered once weekly from GD 20 (start of organogenesis) to GD 139 (late third trimester), followed by cesarean on GD 140. Fetuses were euthanized prior to examination.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	Dams: none Embryos/fetuses: • Control: spontaneous abortion on GD 25 (1/12, 8.3%) • Mogamulizumab: spontaneous abortion on GD 106; fetal cardiac arrest on GD 100 (2/12, 16.7%)
Clinical signs	Dams: unremarkable
Body weights	Dams: unremarkable
Peripheral blood immunophenotyping	Dams and fetuses: at time of cesarean, significantly lower $CCR4^+$ lymphocyte ratio and count (see table below) were observed in the 40 mg/kg group relative to the control group. There were no differences between the ratio and absolute number of NK cells. **% Mean difference in $CCR4^+$ lymphocytes vs. concurrent control** Ratio / Absolute number Dams: -76.1%** / -67.6%** Fetuses: -62.9%** / -67.4%** ** P<0.01
Necropsy findings **Offspring**	Fetal cardiac arrest on GD 100: fetus and placenta were removed by cesarean; significant autolysis was observed which prevented complete examination. Torsion and stenosis of the umbilical cord were observed, which may have contributed to cardiac arrest. Death was considered unrelated to mogamulizumab. Spontaneous abortion on GD 106: fetus was of typical weight, and lack of maceration and autolysis suggested the fetus was alive immediately before abortion occurred. Suppurative and hemorrhagic placentitis with bacterial colonies was observed. Abortion was considered unrelated to mogamulizumab. Scheduled cesarean on GD 140: external, visceral, skeletal, hematology, and histopathology examinations did not identify any mogamulizumab-related changes.

5.5.5 Other Toxicology Studies

Assessment of Dermal Toxicity of Mogamulizumab in Aged Cynomolgus Monkeys / Study Report 14534

Key study findings:

- Mogamulizumab was associated with mild and reversible erythema in aged female cynomolgus monkeys, a finding that was not observed in previous toxicity studies in young cynomolgus monkeys.
- Mogamulizumab was associated with decreases in the ratio of Treg, CCR4$^+$ Treg, and effector Treg cells.

Conducting laboratory and location: (b) (4)

GLP compliance: No

The potential for mogamulizumab to cause dermatologic toxicity was evaluated in aged cynomolgus monkeys. A preliminary study determined the ratio of naïve Treg cells and effector Treg cells were significantly lower in aged monkeys compared to young monkeys. Mogamulizumab was administered IV once weekly at 10 mg/kg for 8 weeks (8 doses) to ~20-year old female cynomolgus monkeys (n=4), followed by a 4-week observation period; there was no control arm. Mild erythema was observed in two monkeys following the second administration; sites were biopsied or resolved prior to the third administration. Mild erythema recurred in both previously affected monkeys prior to or immediately after the fourth administration, and then resolved prior to the fifth administration. No subsequent dermal toxicities were observed. Mogamulizumab was associated with decreases in the ratio of Treg, CCR4$^+$ Treg, and effector Treg cells; however, there were no differences in lymphocyte subsets between the monkeys with and without erythema.

Cross-Reactivity Study of KM8761 (KW-0761) with Normal Human Tissues / Study Report IM1048

Key study findings:

- Mogamulizumab stained the membrane of lymphocytes in the peripheral blood smears, colon, esophagus, stomach, liver, lymph node, parathyroid, spleen, and tonsil.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

The cross-reactivity of biotinylated mogamulizumab was evaluated in a panel of normal human tissue cryosections at two concentrations (5 µg/mL and 25 µg/mL). Mogamulizumab stained the membrane of lymphocytes in the peripheral blood smears, colon, esophagus, stomach, liver,

lymph node, parathyroid, spleen, and tonsil; membranous staining of lymphocytes is consistent with the known expression pattern of CCR4. Mogamulizumab stained positive and negative control tissues as expected.

Cross-Reactivity Study of KM8761 (KW-0761) with Normal Cynomolgus Monkey Tissues / Study Report IM1049

Key study findings:

- Mogamulizumab stained the membrane of lymphocytes in the peripheral blood smears, colon, stomach, liver, lymph node, spleen, thymus, and tonsil.
- The staining patterns of mogamulizumab are comparable between humans and cynomolgus monkeys, indicating cynomolgus monkeys may be a relevant species for the nonclinical safety assessment of mogamulizumab.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

The cross-reactivity of biotinylated mogamulizumab was evaluated in a panel of cynomolgus monkey tissue cryosections at two concentrations (5 µg/mL and 25 µg/mL). Mogamulizumab stained the membrane of lymphocytes in the peripheral blood smears, colon, stomach, liver, lymph node, spleen, thymus, and tonsil. Mogamulizumab stained positive and negative control tissues as expected.

{See appended electronic signature page}

Michael Manning Christopher Sheth

6 Clinical Pharmacology

6.1 Executive Summary

The key review question focused on the appropriateness of the dose for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after systemic therapy.

The Office of Clinical Pharmacology has reviewed the information contained in BLA 761051. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Evidence of effectiveness	A randomized, open-label, active-controlled Phase III trial 0761-010 provides primary evidence. Exposure-response relationship for progression-free survival (PFS) and overall response rate (ORR) provides supportive evidence.
General dosing instructions	The recommended dose of POTELIGEO is 1 mg/kg administered as an intravenous infusion over at least 60 minutes. Administer on days 1, 8, 15, and 22 of the first 28-day cycle, followed by infusions on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity. Premedication, such as diphenhydramine and acetaminophen, is recommended for the first POTELIGEO infusion in all patients. POTELIGEO can be administered within (b) (4) 2 days of the scheduled dose. If a dose is missed (b) (4) and resume dosing schedule. Do not give POTELIGEO subcutaneously or by rapid intravenous administration.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose modification is needed for specific populations of age, sex, race, renal impairment, mild or moderate hepatic impairment, disease subtype (MF or SS), degree of CCR4 expression, or ECOG status. These factors were not found to be clinically significant covariates on effectiveness and safety.

There is no Post-Marketing Requirement (PMR) or Post-Marketing Commitment (PMC) from a clinical pharmacology perspective.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Mogamulizumab is a humanized IgG1 kappa monoclonal antibody. Mogamulizumab binds to CCR4, a G protein-coupled receptor for CC chemokines which is expressed on the surface of some cancer cells including T-cell malignancies, and involved in the trafficking of lymphocytes to various organs.

Following the administration of multiple doses of mogamulizumab every week or every 2 weeks in patients with T-cell malignancies, mogamulizumab concentrations increased proportionally with dose over the dose range of 0.01 to 1.0 mg/kg. Following repeated dosing of the approved recommended dosage, steady-state concentrations were reached after 8 doses (12 weeks), and the systemic accumulation was 1.6-fold. The geometric mean (% coefficient of variation, %CV) was 3.6 L (20.1%) for central volume of distribution (V_1), 17 days (65.5%) for terminal half-life ($t_{1/2}$), and 12 mL/h (83.7%) for clearance (CL).

Among 258 patients in Trial 0761-010 who were treated with POTELIGEO at the recommended dosage, 10 patients (3.9%) tested positive for treatment-emergent (treatment-induced or treatment-boosted) anti-drug antibodies (ADAs) by an electrochemiluminescent (ECL) assay. There were no positive neutralizing antibody responses. No discernible effect of ADAs on PK, efficacy or safety was detected.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposed a dose of mogamulizumab 1 mg/kg administered as an IV infusion over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle, followed by infusions on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity. Mogamulizumab at the proposed dosing regimen appears to be effective and has a manageable safety profile in adult patients (n = 186) with relapsed or refractory MF or SS after systemic therapy in Trial 0761-010. Although there was a correlation between body weight and exposure of mogamulizumab based on population pharmacokinetic (PK) analysis, the differences in exposure with body weight did not affect the safety or efficacy of mogamulizumab, thus supporting the use of body weight based dosing regimen.

Therapeutic Individualization

No therapeutic individualization for intrinsic or extrinsic factors is recommended by the population PK analysis. Although the effects of albumin, AST, mild to moderate hepatic impairment, and sex on CL, albumin on peripheral volume of distribution (V_2) and BSA on V_1 were found statistically significant in the population PK analysis, dose modification was not required as these factors were not found as a clinically significant covariate on effectiveness and safety. The population PK analysis also showed that other factors, e.g., age, race, renal impairment, disease subtype (MF or SS), degree of CCR4 expression, or ECOG status were not a significant covariate on PK parameters after adjusting dose by body weight.

Outstanding Issues

None.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

The summary of clinical pharmacology, pharmacokinetics and ADME information of mogamulizumab is listed below.

Pharmacology	
Mechanism of Action	Mogamulizumab is a humanized IgG1 kappa monoclonal antibody that binds to CCR4-expressing cells for ADCC resulting in depletion of the target cells.
Active Moieties	Mogamulizumab is the active moiety
QT Prolongation	Not evaluated. As a monoclonal antibody, mogamulizumab has low risk of QT interval prolongation.
General Information	
Bioanalysis	Mogamulizumab was measured using validated Enzyme Linked Immunosorbent Assay (ELISA) method.
Drug total exposure at steady state following the therapeutic dosing regimen	The mean ± SD was 21. 9 ± 6.2 µg/mL for C_{max} after the first dose (Cycle 1, Day 1) and 25.8 ± 9.6 µg/mL for C_{min} at steady state (Cycle 1, Day 28).
Minimal effective dose or exposure	1 mg/kg administered as an IV infusion over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle, followed by infusions on days 1 and 15 of each subsequent 28-day cycle.
Dose Proportionality	Mogamulizumab concentrations increased proportionally with dose over the dose range of 0.01 to 1.0 mg/kg (0.01 to 1 times the approved

	recommended dosage).
Accumulation	The accumulation ratio was 1.6-fold.
Variability	The %CV was 28.5% for C_{max} after the first dose (Cycle 1, Day 1) and 37.3% for C_{min} at steady state (Cycle 1, Day 28).
Immunogenicity	10/258 patients (3.9%) tested positive for treatment-emergent ADAs in Trial 0761-010. No positive neutralizing antibody responses. No discernible effect of ADAs on PK, efficacy or safety.
Distribution	
Volume of Distribution	The volume of distribution (%CV) was 3.6 L (20.1%).
Plasma Protein Binding	Not evaluated. As a monoclonal antibody with a molecular weight of 149 kDa, mogamulizumab is not expected to bind to plasma proteins.
Blood to Plasma Ratio	Not evaluated.
Substrate transporter	Not evaluated. As a monoclonal antibody, mogamulizumab is not expected to be a substrate of metabolic transporters.
Elimination	
Mean terminal elimination half-life	The half-life (CV%) was 17 days (65.5%).
Metabolism	
Primary metabolic pathway(s)	No evaluated. As a monoclonal antibody, mogamulizumab is expected to be degraded into low-molecular-weight peptides and amino acids *in vivo*.
Inhibitor/Inducer	Not evaluated.
Excretion	
Primary excretion pathways (% dose) ± SD	Not evaluated. As a monoclonal antibody, mogamulizumab is expected to be degraded into low-molecular-weight peptides and amino acids in vivo.

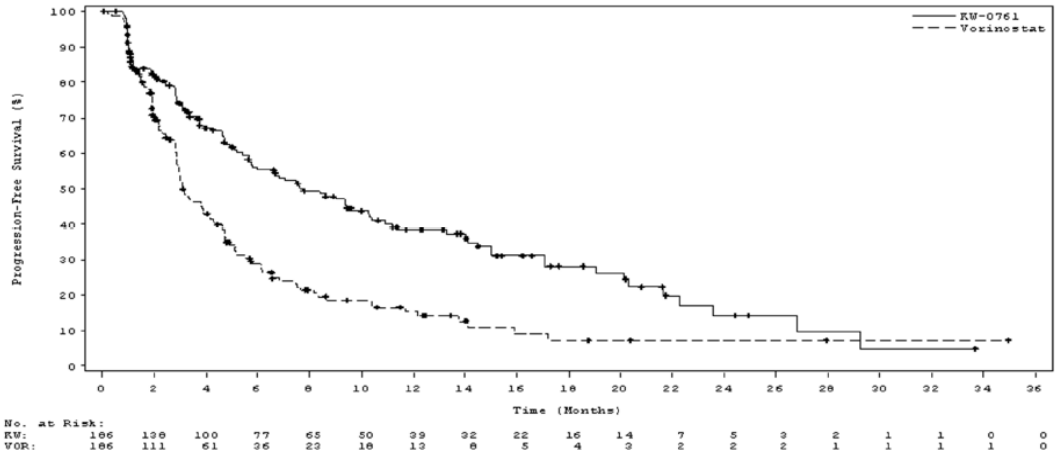
6.3.2 Clinical Pharmacology Questions

To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The proposed mogamulizumab dosing regimen had a longer PFS and a higher incidence of ORR with similar safety profile compared to vorinostat active control arm in adult patients with relapsed or refractory mycosis fungoides or Sézary syndrome after systemic therapy in Trial 0761-010.

Efficacy: Mogamulizumab demonstrated a longer PFS based on Investigator assessment, when compared to the vorinostat active control arm with a hazard ratio (HR) of 0.53 (95% CI: 0.41 - 0.69, 2-sided p<0.0001) in Trial 0761-010. The median PFS was 7.7 months (95% CI: 5. 7, 10.3) for mogamulizumab and 3.1 months (2.9, 4.1) for vorinostat. The Kaplan-Meier curves of PFS for mogamulizumab and vorinostat began to separate within the second treatment cycle and

the separation was maintained through approximately 28 months (**Figure 2**). The key secondary efficacy endpoint, confirmed ORR based on Investigator assessment, was also significantly higher for mogamulizumab (28.0%) than for vorinostat (4.8%) (risk difference = 23.1, p<0.0001).



KW=KW-0761 (mogamulizumab); VOR=vorinostat; + = censored.

Figure 2: Kaplan-Meier Curve of PFS for the ITT Population by Investigator's Assessment in Trial 0761-010.

Source: Clinical Study Report for Trial 0761-010, Figure 14.2.1.

Safety: The maximum tolerated dose (MTD) was not established up to 1.0 mg/kg every week for 4 weeks in the dose escalation Phase 1/2 Trial KW-0761-001. Mogamulizumab at the proposed dose regimen, appeared to be well tolerated and had generally comparable safety profile to vorinostat active control arm in the pooled safety population from Trial 0761-010 and all patients with CTCL from Trials 0761-001, 0761-004 and 0761-010 (**Table 3**). As compared to vorinostat, mogamulizumab had a slightly lower incidence of treatment-related any grade TEAEs, treatment-related Grade ≥3 TEAEs, treatment-related TEAEs leading to death, treatment-related TEAEs leading to study treatment discontinuation, except for treatment-related treatment-emergent SAEs.

Table 3: Overall Summary of Adverse Events in Trial 0761-010 and All Patients with CTCL (Pooled Safety Population)

AE Category	Number (%) of subjects			
	Study 0761-010			
	Randomized Treatment		Crossover	All Subjects with CTCL[a]
	Vorinostat (N=186)	KW-0761 1.0 mg/kg (N=184)	KW-0761 1.0 mg/kg (N=136)	KW-0761 (N=233)
Any TEAEs	185 (99.5)	179 (97.3)	127 (93.4)	227 (97.4)
Treatment-related TEAEs	178 (95.7)	156 (84.8)	99 (72.8)	196 (84.1)
NCI/CTCAE Grade 3, 4, or 5 TEAEs	85 (45.7)	78 (42.4)	47 (34.6)	95 (40.8)
Treatment-related NCI/CTCAE Grade 3, 4, or 5 TEAEs	65 (34.9)	47 (25.5)	21 (15.4)	56 (24.0)
TEAEs leading to death	9 (4.8)[b]	3 (1.6)	4 (2.9)[b]	7 (3.0)
Treatment-related TEAEs leading to death	3 (1.6)[b]	2 (1.1)	0	2 (0.9)
Treatment-emergent SAEs	46 (24.7)	69 (37.5)	36 (26.5)	82 (35.2)
Treatment-related treatment-emergent SAEs	30 (16.1)	36 (19.6)	14 (10.3)	39 (16.7)
TEAEs leading to study treatment discontinuation	43 (23.1)	35 (19.0)	30 (22.1)	42 (18.0)
Treatment-related TEAEs leading to study treatment discontinuation	40 (21.5)	25 (13.6)	23 (16.9)	29 (12.4)

Note: AEs that occurred beyond 90 days after the last dose of study treatment/after initiation of alternative therapy and were related to the randomized study treatment, or after start of mogamulizumab during crossover period and were related to vorinostat, are also included in the summary during randomized treatment period.

a: "All Subjects with CTCL" includes all subjects with CTCL treated with mogamulizumab in Studies KW 0761-001 and 0761-004, and subjects randomized to and treated with mogamulizumab in Study 0761-010. Subjects initially randomized to vorinostat and who crossed over to mogamulizumab in Study 0761-010 are not included in this pooled analysis.

b: Includes 1 subject with a TEAE with an outcome of death that occurred during the crossover period but ≤90 days after the last dose of vorinostat, and was considered related to vorinostat (not related to mogamulizumab).

AE=adverse event; CTCL=cutaneous T-cell lymphoma; N=number of subjects; NCI/CTCAE=National Cancer Institute/Common Terminology Criteria for Adverse Events; KW-0761=mogamulizumab; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Source: Clinical Study Report for Trial 0761-010, Table 12.2.1-1.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed mogamulizumab dose regimen is effective and appears to have a tolerable and manageable safety profile. The minimum mogamulizumab steady-state concentrations (25.8 ± 9.6 µg/mL) at the proposed dose regimen were greater than 10 µg/mL, where the maximum ADCC activity was observed in the *in vitro* studies using human cells (i.e.,

CD4+CD25+CCR4+ cells). The exposure-response (ER) relationships for efficacy and safety support the proposed dose regimen based on C_{min} after first dose of mogamulizumab ($C_{min,1st}$) and area under the plasma concentration-time curve over the dosing interval at steady state ($AUC_{0-\tau,SS}$) as summarized below. Refer to **Appendices 19.4.4** and **19.4.5** for more details on the ER analyses for both efficacy and safety.

ER relationship for Efficacy: The Kaplan-Meier analysis of the ER relationship for PFS (**Figure 3**) showed that there was no clear separation in PFS among the four quartiles according to $C_{min,1st}$ ($p = 0.97$) or $AUC_{0-\tau,SS}$ ($p = 0.21$).

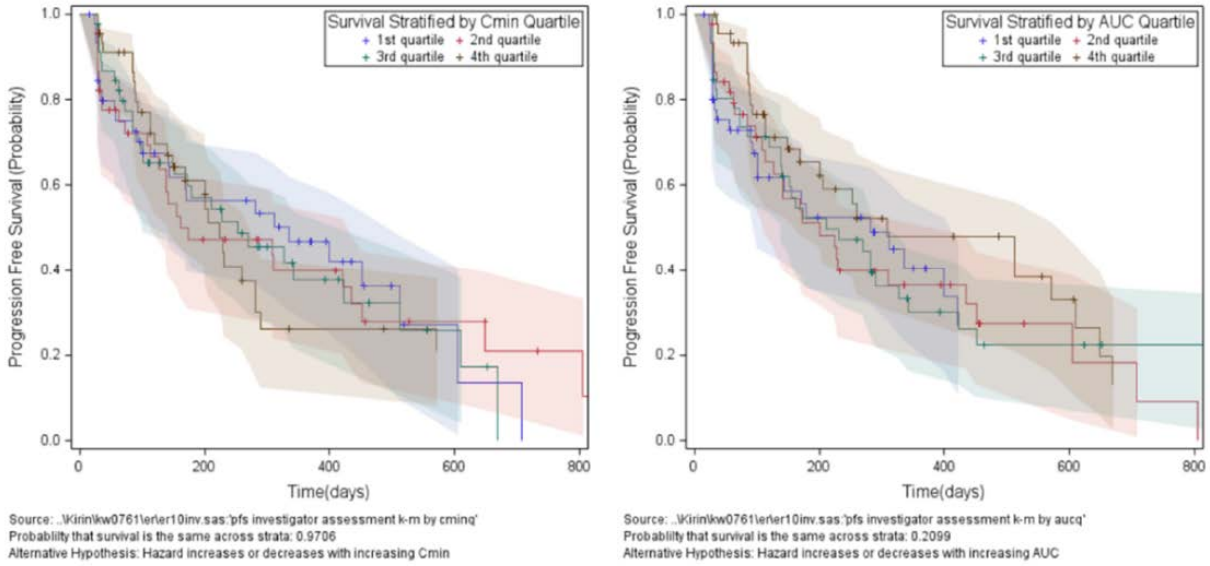


Figure 3: Kaplan-Meier analysis of Exposure-Response Relationships for PFS vs. $C_{min,1st}$ and $AUC_{0-\tau,SS}$ in Trial 0761-010

Source: Exposure-Response Report for Trial 0761-010, Figures 3 and 4.

ER relationship for Safety: The ER analysis for safety was conducted by comparing the safety profiles between four quartiles of mogamulizumab $AUC_{0-\tau,SS}$ in Trial 0761-010 to different safety endpoints. As shown in **Figure 4**, there was no notable ER relationship for most of the safety endpoints, e.g., injury, poisoning and procedural complications, general disorders and administration site conditions, infections and infestations, and gastrointestinal disorders, except an apparent trend for the incidence of skin and subcutaneous tissue disorders. However, the most frequently reported TEAEs regarding skin and subcutaneous tissue disorders were infusion-related reactions (33.2%) and drug eruption (23.9%). The majority of treatment-related infusion-related reactions and drug eruption were Grade 1 or 2, 4.4% of patients had Grade 3 treatment-related infusion-related reaction, 4.3% of patients had treatment-related Grade 3 drug eruption, and no patients had a Grade 4 or 5 treatment-related infusion-related reaction and drug eruption.

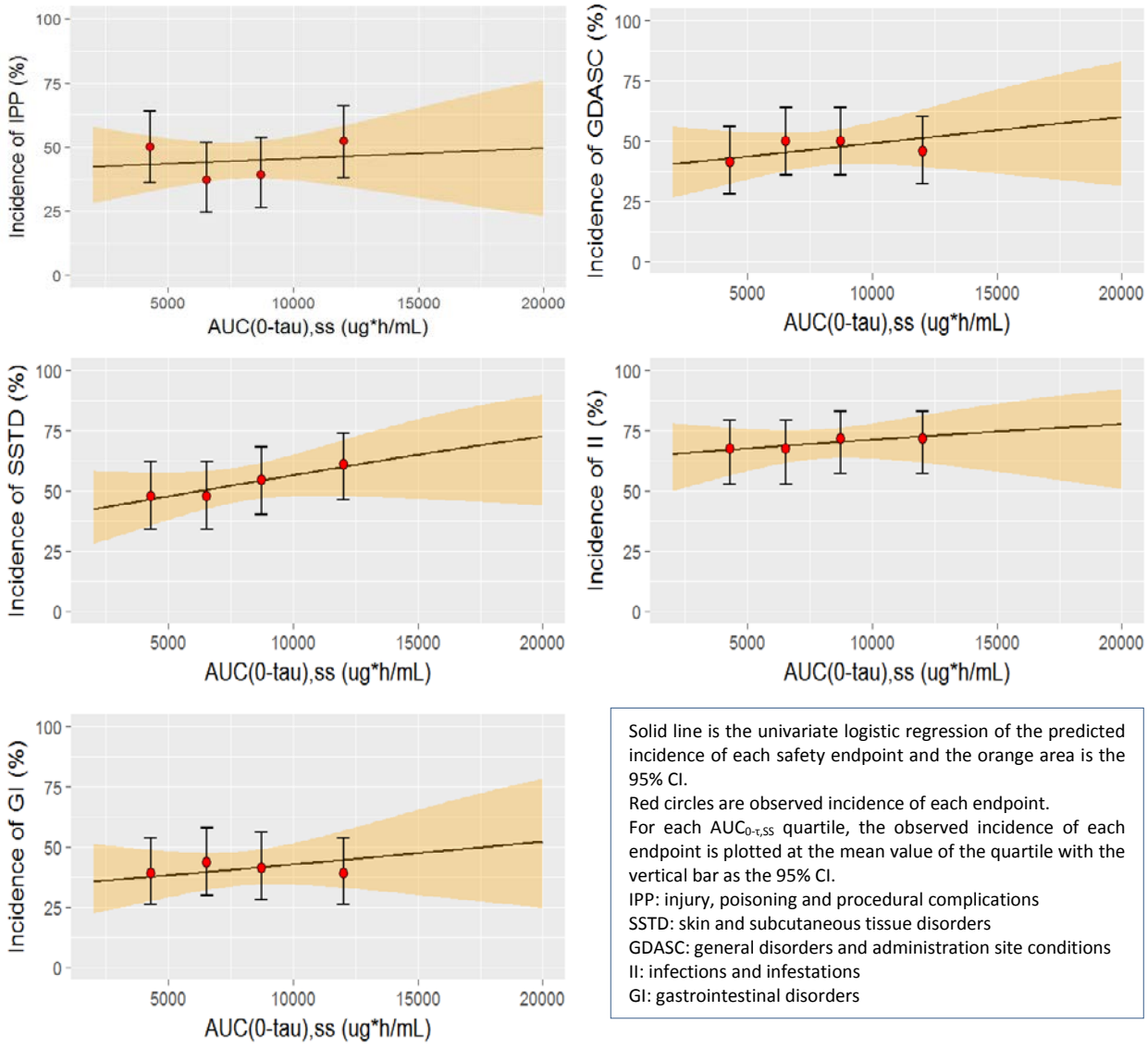


Figure 4: Exposure-Response Relationships for Safety Endpoints vs. Mogamulizumab $AUC_{(0-\tau),ss}$ in Trial 0761-010

Source: FDA reviewer's analysis based on dataset kw07.xpt from Trial 0761-010

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Population PK analysis (n = 444) showed that patient demographics such as, age (range: 22 - 101 years), body weight (36 - 150 kg), body mass index (16 - 47 kg/m^2), bilirubin (0.1 - 2.4 mg/dL), ALT (4 - 134 U/L), CRCL (26 - 216 mL/min), CCR4 Expression (1 - 100%), race (20% Japanese/69% non-Japanese/11% unknown), renal impairment (46% normal/35% mild/18% moderate/1% severe), clinical subtype (55% MF/45% SS), ADA status (3% positive/51% negative/46% unknown), ECOG status (54% Grade 0/39% Grade 1/7% Grade 2) and CCR4 expression status (78% positive/3% negative/19% unknown) were not found to have a clinically

meaningful influence on the PK parameters of mogamulizumab after adjusting dose by body weight. Albumin (1.7 - 5.2 g/dL), AST (8 - 199 U/L), hepatic impairment (18% mild/1% moderate), and gender (54% male/46% female) were found as statistically significant covariates on CL. Albumin (1.7 - 5.2 g/dL) also had an impact on V_2 and body surface area (1.2 - 2.7 m^2) was a significant predictor of V_1. Simulations were performed in 1000 virtual patients receiving 1 mg/kg mogamulizumab bi-weekly to evaluate the impact of identified covariates at 5th and 95th percentiles for each covariate distribution on PK parameters. The simulation results (**Table 4**) showed that the differences in mogamulizumab exposure ($C_{min,1st}$ and $AUC_{0-\tau,SS}$) are relative small, and are not expected to translate a statistically clinical meaningful difference in efficacy and safety given the observed flat ER relationships. Refer to **Appendix 19.4.3** for more details. Safety and effectiveness of mogamulizumab have not been established in pediatric patients and in pregnant or lactating women.

Table 4: Impact of Significant Covariates on Mogamulizumab Exposure

$AUC_{(0-\tau),ss}$ (mg·hr/L)	$C_{max,ss}$ (mg/L)	Description	Albumin (g/mL)	AST (U/L)	HI	Sex	$AUC_{(0-\tau),ss}$ %Reference	$C_{max,ss}$ %Reference
5217	10.1	Reference	4	24	Normal	Male	100%	100%
3193	5.1	Low albumin	3.05	24	Normal	Male	61%	51%
6718	14.1	High albumin	4.6	24	Normal	Male	129%	139%
6202	12.9	Low AST	4	13	Normal	Male	119%	127%
4010	6.8	High AST	4	61	Normal	Male	77%	67%
4576	8.4	Hepatic impairment	4	24	Mild to Moderate	Male	88%	83%
6793	14.6	Female	4	24	Normal	Female	130%	144%

HI: Hepatic Impairment

Source: Population PK Analysis Report Table 24.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Since mogamulizumab is administered by IV infusion, food-drug interactions are not anticipated or applicable. Drug-drug interactions are not expected based on the CYPs, other metabolizing enzymes, or transporters, as mogamulizumab is a monoclonal antibody. Therefore, no drug-drug interaction studies were conducted *in vitro* or *in vivo*.

{See appended electronic signature page}

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7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

Study 0761-010, summarized below, is the basis of the BLA.

Table 5: Primary and Supportive Clinical Trials

Trial	Population	Design	Regimen	Primary Endpoint	# Enrolled	Study status
Controlled studies to support efficacy and safety						
0761-010 (primary); NCT01728805	MF or SS after ≥ 1 systemic therapy	Phase 3, open-label, multicenter study randomizing 1:1 to moga vs vorinostat until PD; one-way cross-over	Moga 1.0 mg/kg IV on D1, 8, 15, and 22 of C1 and D1 and 15 of subsequent cycles	PFS-INV	372 (186 / arm)	Ongoing; enrollment complete (61 sites)
Supportive studies						
0761-001 (efficacy and safety); NCT01192984	CTCL and PTCL after ≥1 systemic therapy	Phase 1/2 dose-escalation, multicenter study	Phase 1 doses: 0.1, 0.3 and 1.0 mg/kg IV; phase 2 doses 1.0 mg/kg	Safety / MTD	42 (41 CTCL); 33 at 1.0 mg/kg (32 with MF/SS)	Completed

Source: Applicant's synopsis of studies, module 2.7.6

The BLA also included 5 single-arm studies conducted outside of the US (0761-0501, 0761-002, 0761-003, and 0761-004 in Japan, 0761-007 in Europe) involving T-cell malignancies other than CTCL (predominantly ATL and PTCL). The clinical reviewer did not, however, consider these data as supportive of efficacy because MF/SS is biologically distinct.

Reviewed data were provided electronically with the SDTM3.1.3 and Legacy data formats. All study datasets for study 0761-010 are available in the following location: \\CDSESUB1\evsprod\BLA761051\0001\m5\datasets\0761-010

7.2 Review Strategy

Study 0761-010 is the basis for the proposed indication and for the efficacy and safety assessments. The clinical reviewer evaluated data analysis datasets (Legacy format), clinical study reports (CSRs), the summary of clinical efficacy (SCE), summary of clinical safety (SCS), integrated summary of safety (ISS), individual patient narratives, the 120-day safety update report (SUR), numerous information requests (IRs), earlier submissions under mogamulizumab IND 101843, and relevant published literature. The strategy for safety review is described further in Section 8.2.1. The Statistical reviewer focused on efficacy assessment, through

assessing data quality, verifying the sponsor's results provided (in CSRs, SCE, ISE), conducted additional sensitivities and exploratory analyses to assess the robustness of the efficacy results.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study 0761-010

Title: Open-Label, Multi-Center, Randomized Study of Anti-CCR4 Monoclonal Antibody KW-0761 (Mogamulizumab) Versus Vorinostat in Subjects with Previously Treated Cutaneous T-Cell Lymphoma

ClinicalTrials.gov identifier: NCT01728805
First patient treatment date: 12/12/2012
Last patient's first dose: 1/29/2016
Data submission: all enrolled patients
Clinical cut-off dates for this submission:
12/31/2016 (efficacy)
6/15/2017 (primary safety data)
9/1/2017 (120-day SUR)

Trial Design
Study 0761-010 is a multicenter, open-label, randomized phase 3 study comparing mogamulizumab at the recommended dose-schedule vs. vorinostat 400 mg daily in 372 adults with MF/SS after at least one prior systemic therapy. The randomization ratio was 1:1, and randomization was stratified by disease type (MF vs. SS) and stage (IB/II vs. III/IV). One-way crossover from vorinostat to mogamulizumab was permitted in the case of disease progression (generally after a minimum of 2 cycles) or intolerable toxicity. Disease assessment was based on global composite response criteria which combine measures from each disease compartment (Olsen et al 2011).

Key Eligibility Criteria

- Stage IB through IV MF or SS, irrespective of CCR4 expression status, with failure of at least one systemic therapy
- No current large cell transformation
- Prior therapy
  - No prior allo HSCT; > 90 days since auto HSCT
  - > 4 weeks since systemic therapy and > 2 weeks since skin-directed therapy; however stable doses of systemic steroids (≤ 20 mg prednisone equivalent) and of low-to-medium potency topical steroids permitted (no change in preceding 4 weeks)
  - No prior vorinostat (apart from short exposure without PD or intolerable toxicity) or moga
- Age ≥ 18
- ECOG PS 0-1
- Evaluations

  - ANC ≥ 1500/µL (≥ 1000/µL if marrow involved)
  - Platelets ≥ 100,000/µL (≥ 75,000/µL if marrow involved)
  - Absolute CD4 ≥ 200/µL if prior alemtuzumab or anti-CD4 antibody
  - AST and ALT ≤ 2.5 x ULN (< 5.0 x ULN if liver involved), bilirubin ≤ 1.5 x ULN
  - CrCl > 50 mL/min or creatinine ≤ 1.5 x ULN
- Comorbidities
  - No active autoimmune disease or significant uncontrolled illness
  - No known HIV, HTLV-1, HBV, or HCV

Study Treatment: The mogamulizumab dose-schedule was 1 mg/kg i.v. over at least 60 minutes on days 1, 8, 15 and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent 28-day cycle. Vorinostat was dosed at 400 mg orally once daily, continuously in 28-day cycles. Treatment continued until disease progression or unacceptable toxicity.

Supportive Care: Prophylaxis for infection and IRRs was optional (see section on protocol amendments). Except for toxicity management, initiation or dose escalation of systemic or topical steroids was prohibited.

Guidelines for treatment-emergent drug rash:

- Grade 1: consider topical corticosteroids
- Grade ≥ 2: interrupt mogamulizumab and administer at least 2 weeks of topical corticosteroids. If rash improves to grade ≤ 1, mogamulizumab may be resumed. If rash recurs on rechallenge and is grade ≥ 3, permanently discontinue.

Evaluations: Refer to Appendix (Section 19.5) for the evaluation schedule. Responses required confirmation at two successive disease assessments, which included the modified Severity Weighted Assessment Tool (mSWAT), skin photographs, central flow cytometry, and CT.

Safety Reporting Period: The primary safety reporting window was until 90 days after last study drug or initiation of new anti-lymphoma therapy (NALT), whichever earlier. Subsequent AEs deemed related to the randomized study drug, or AEs occurring after crossover and deemed related to vorinostat, were included.

Study Endpoints

Primary endpoint: PFS-INV, defined as the time from randomization to documented progression, per consensus global response criteria (Olsen et al 2011) as assessed by the investigator, or death from any cause.

Key secondary endpoints:

ORR-INV (PR or CR per Global Composite Response Score, confirmed for ≥ 4 weeks)

Changes in quality of life (QoL) scores from baseline through 6-mo assessment, in order:
- Skindex-29 score
- FACT-G total score
- EQ-5D-3L index score

Other secondary endpoints included:
- PFS-IRC
- ORR-IRC
- Best overall response
- Duration of response (DOR)
- Time to response
- ORR after crossover
- Changes in Skindex-29, FACT-G, and EQ-5D-3L at other timepoints
- Changes in Pruritus Evaluation (Likert Scale, Itchy QoL).

Exploratory endpoints included OS, time to treatment failure, PFS after crossover to mogamulizumab vs. with vorinostat alone, safety

Statistical Analysis Plan

Primary efficacy population: all randomized patients

Primary analysis: The primary comparison of PFS with mogamulizumab vs. vorinostat was performed by intention-to-treat (ITT) analysis using a log-rank test stratified by disease type (MF or SS), disease stage (IB/II or III/ IV), and region (U.S., Japan, and rest of world). PFS measurements were censored at time of initiation of new anti-lymphoma therapy (including crossover) in the absence of progression of disease (PD). In addition, patients with clinical progression that did not meet formal PD criteria were censored at the time of clinical progression. The censoring rules were as the followings:

- In the event that a randomized patient withdraws from the study for any reason before documented progression, the time from the day of randomization to the last post-baseline tumor assessment from any compartment (skin, blood, bone marrow, lymph node, and viscera) will be used as a censored time point.
- For patients who are randomized to a treatment arm but have an unknown baseline assessment for a compartment, the PFS time will be censored at the randomization date if there is no post-baseline tumor assessment for that compartment or if there is any evidence of lymphoma in that compartment at post-baseline evaluation.
- For patients randomized to a treatment arm but withdrawing prior to the first post-baseline tumor assessment for any reason other than disease progression, the PFS time will be censored at the last documented visit.

- For patients who initiate a new anticancer therapy (including crossover to KW-0761) in the absence of a PFS event, the PFS time will be censored at the last tumor assessment (from any compartment) prior to the start of the new anticancer therapy.
- For patients not known to have died or have documented progression as of the end of the study, the PFS time will be censored at the date of the last post-baseline tumor assessment (from any compartment).

Assumptions and sample size determination: The study targeted a 50% improvement in median PFS from an assumed 169 days with vorinostat to 254 days. With an expected 24 month accrual and 12 month minimum follow-up time, with a total of 255 PFS events and a one sided type I error rate of 0.025, the expected power is 90%.

Timing of analyses: There was no formal interim analysis. The final primary analysis was to require 255 PFS events or a maximum of 24 month after the last randomized patient's first dose (1/29/2016). Based on ongoing blinded review of data, the Applicant reported that a total 241 PFS events had occurred as of 31 Dec 2016. With 90% of patients having discontinued randomized treatment and the remaining 10% having been followed for at least approximately 1 year, the Applicant chose to implement 31 Dec 2016 as an earlier than specified cut-off date, with the analysis having >85% power.

Sensitivity analyses: Three sensitivity analyses of PFS were originally planned during randomized treatment period based on the on-site Investigator's assessment and the ITT Set using the following definitions:

1) Sensitivity Analysis 1: PFS is defined as the time from the day of randomization to a treatment arm until documented progression defined in the primary analysis, or death due to any cause provided that death is not more than 8 weeks (56 days) after the last post-baseline tumor assessment or the last dose of study drug (if the patient did not have any postbaseline tumor assessment); Using this definition, the disease progression reported during the follow up period would not be considered as an event in the sensitivity analysis, but would be a censored value on the day of the last tumor assessment.

2) Sensitivity Analysis 2: PFS is defined as the time from the day of randomization to a treatment arm until the earliest date of documented progression defined in the primary analysis, or clinical progression at the end of the randomized treatment, or documented disease progression reported during the follow-up period, or death due to any cause; Using this definition, clinical progression noted at the end of the randomized treatment would be considered as an event in the sensitivity analysis.

3) Sensitivity Analysis 3: PFS is defined as the time from the day of randomization to a treatment arm until documented progression or death due to any cause. The date of documented disease progression will be the earliest date of disease progression in any compartment based on the Investigator's assessment per CTCL response criteria, which are

defined in the primary analysis, or disease progression reported during the follow-up period. For assessments where progression is reported by the investigator but is not confirmed by the IR, the progression date will be set to the last tumor assessment plus one day in the KW-0761 treatment arm and will be censored in the Vorinostat treatment arm; The same censoring rules as described in the primary analysis will be used for the sensitivity analyses.

In addition to the three sensitivity analyses, sensitivity analysis 4 is defined to consider death during safety follow-up.

4) Sensitivity Analysis 4: PFS is defined as the time from the day of randomization to a treatment arm until documented progression defined in the primary analysis, or death due to any cause if a death meets the following conditions:

For patients who had at least one post-baseline tumor assessment
• If the date corresponding to 56 days after the last post-baseline tumor assessment > the date corresponding to 90 days after the last dose of study drug: death until 56 days after the last post-baseline tumor assessment is included.
• if the date corresponding to 56 days after the last post-baseline tumor assessment is ≤ the date corresponding to 90 days after the last dose of study drug: death until 90 days after the last dose of study drug is included.

For patients who did not have any post-baseline tumor assessment
• death until 90 days after the last dose of study drug is included.

Analyses methods for the secondary endpoints:
ORR as assessed by the Investigator will be analyzed using Cochran-Mantel-Haenszel (CMH) test adjusted for disease type, disease stage, and region. Additional analyses may be performed adjusting for treatment and baseline characteristics.

The exact 95% CIs for ORR will be calculated for each treatment arm and for the difference in ORR between the two treatment arms.

The treatment differences in the mean change of Skindex-29 score from baseline across each planned timepoint (end of cycle 1, cycle 3, cycle 5) up to 6 months of assessments will be tested using a repeated measures mixed effects model with time, region, disease type, disease stage, treatment, and time-by-treatment interaction as factors and baseline score as a covariate. Restricted Maximum Likelihood (REML) method will be used. An unstructured covariance matrix will be employed to model the correlation among repeated measurements. Appropriate contrasts will be used to determine the difference between the Vorinostat treatment group and the KW-0761 treatment group across the end of Cycles 1, 3, and 5. In case of convergence problems, another variance-covariance structure will be considered. The selection of any of these structures will be determined after exploration of the observed correlation structure. Least squares (LS) means, corresponding standard errors, 95% two-sided CIs will be presented

for the within-group change for odd cycles. For the between-treatment group comparison, the difference in LS means, corresponding standard errors, 95% two-sided CIs, and two-sided p-value will also be derived from this ANCOVA model and presented for the odd cycles. This mixed-effects model will also be used to compare the treatment differences in the mean changes in Skindex-29 score from baseline to each scheduled time point at end of cycle 1, cycle 3, and cycle 5. In addition to the Skindex-29 score, a Skindex score based on a subset of Skindex questions may be analyzed in a similar fashion. Standard model diagnostics will be performed to assess the validity of the proposed ANCOVA model. These diagnostics will include an examination of the residuals for normality and homoscedasticity as well as testing for the significance of the treatment by baseline interaction term. If the residuals are not normally distributed, then the analysis will be carried out using Wilcoxon rank sum test instead. In addition to the analysis described above, summary statistics including n, mean, standard deviation, median, minimum, and maximum will be provided for Skindex-29 score at baseline and each scheduled time point and change in total score at each of these scheduled assessments for each treatment arm.

The same methods described above for the analysis of change in Skindex-29 score will be performed for the analysis of change from baseline for the ends of cycle 1,3, and 5 in FACTG total score and EQ-5D-3L index score.

Handling missing data for ORR:
Patients lacking valid data to assign a response status will be included in the denominator for response rate calculation based on the ITT Set, and they are considered non-responders.

Handling missing data for QoL:
Missing data for Skindex-29 and FACT-G will be handled according to the questionnaires' scoring guidelines. For Skindex-29, if responses to more than 25% of items are missing overall, the Skindex-29 score will be treated as missing. If any scale has more than 25% of the responses missing, the scale score is missing. The scale scores are the average of the non-missing items in a given scale. For FACT-G, if more than 50% of the items are responded for a subscale, the subscale scores will be prorated by multiplying the sum of the subscale by the number of items in the subscale and then dividing by the number of items responded. The total FACT-G score will be scored only if the overall item response rate is greater than 80%. For EQ-5D-3L, the EQ-5D index score will be treated as missing if not all five descriptors are responded.

Multiplicity control:
Comparisons of these four key secondary endpoints between the two treatment arms will be conducted using p-values that are adjusted to control the overall study-wise Type 1 error rate of 0.05. The four statistical tests that will be conducted are:
- ORR as assessed by the Investigator,
- Change in Skindex-29 score at through the 6-month assessment,
- Change in FACT-G total score at through the 6-month assessment, and
- Change in EQ-5D-3L index score at through the 6-month assessment.

Since these tests are not independent, the four key secondary tests will be conducted using the Sidak adjusted p-value method defined as $1-(1-p)^4$, where p is the original p-value of the individual test. These adjusted p-values will then be compared to .05 for each test.

Protocol Amendments
Of 8 amendments, the following are considered major:

Amendment	Notable changes
Amendment 2 (2/2013)	• Add DSMB • Changes to statistical analysis plan, including – Increase power of primary analysis to 90% – Change study's time-dependent stop to event-driven with maximum time provision – Reorder secondary and exploratory objectives to prioritize QoL comparisons • Exclude patients with large cell transformation • Allow patients with PD in one compartment to continue study drug for up to 8 weeks
Amendment 4 (11/2013)	• Enroll patients with limited prior exposure to vorinostat • Revise statistical methods for QoL testing
Amendment 5 (3/2014)	• Recommend premedication for first moga infusion in all patients • Reduce CT scanning from every 8 weeks to every 16 weeks after first year
Amendment 8 (1/2017)	• Include reporting of transplant information including AEs, based on publications about potentially increased complications of allo HSCT after moga

Source: FDA analysis

8.1.2 Study Results

Compliance with Good Clinical Practices
The Applicant stated the study was conducted in accordance with good clinical practices.

Financial Disclosure
Refer to the Appendix.

Table of Demographic Characteristics
Study 0761-010 randomized 186 patients to each treatment arm. In the ITT efficacy population (N = 372), the median age was 64 years, 58% were male, and 70% were white. Demographic characteristics were balanced between arms (Table 6).

Table 6: Demographics of Study 0761-010 ITT Efficacy Population (N = 372)

Parameter		MOGA (N = 186)		VORINOSTAT (N = 186)	
Age, y	Median (range)	63	(25 – 101)	65	(25 – 89)
	≥ 65	87	(47%)	97	(52%)
Sex	Male	109	(59%)	107	(58%)
Race	White	125	(67%)	135	(73%)
	Black	24	(13%)	13	(7%)
	Other or unknown	37	(20%)	38	(20%)
Region	US	98	(53%)	103	(55%)
	Europe	70	(38%)	70	(38%)
	Other	18	(10%)	13	(7%)
ECOG PS	0-1	184	(99%)	186	(100%)
	2	2	(1%)	0	(0%)

Source: CSR Table 11.2.1-1

Other Baseline Characteristics

Table 7 summarizes disease characteristics and prior therapies in the ITT efficacy population. In the mogamulizumab arm (N = 186), 56% of patients had MF, 44% SS. Similarly, in the vorinostat arm (N = 186), 53% had MF, 47% SS. At study baseline, 38% of patients overall had stage IB-II disease (11% stage IB), 10% stage III, 52% stage IV. Two-thirds of patients had blood and/or nodal involvement, whereas visceral involvement was rare.

This was in general a heavily pretreated patient population. The median number of prior systemic therapies was 3, with 18% having 1 prior therapy, 39% having 1-2 prior therapies, and 40% having ≥ 4.

The trial enrolled patients regardless of tumor CCR4 expression status. CCR4 expression status by skin biopsy immunohistochemistry (IHC) was missing in 82 (22%) of 372 patients due to unavailable biopsy or test failure (Table 7). Of the remaining 290 patients, all had CCR4 expression in ≥ 1% of lymphocytes, 280 (97%) had ≥ 10% expression and were considered "CCR4 positive" per protocol, and 10 (3%) had < 10% expression ("CCR4 negative"). The median CCR4 percentage on a continuous scale was 80%, with expression ranging from 1% to 100% of the lymphocytes (source: response to 1/2/2018 IR). In the mogamulizumab arm, baseline CCR4 expression status by IHC was available in 140 patients (75%), of whom all had CCR4 detected on ≥ 1% of lymphocytes on skin biopsy and 134 (72%) had CCR4 detected on ≥ 10% of the lymphocytes.

Clinical review comments:

- **This is the largest randomized, actively controlled trial conducted in CTCL.**
- **Study 0761-010 provides one of the largest sets of data available on CCR4 expression**

patterns in MF/SS. The performance characteristics of the validated CCR4 IHC assay in Study 0761-010 are reasonable; refer to the CDRH consult review.

- **On this reviewer's assessment, published data on CCR4 expression in MF/SS are limited compared to other T cell malignancies, and the MF/SS data are typically based on small and heterogeneous populations of patients (Remer et al 2014; Wu et al 2009). Refer to the Applicant's response to a 1/4/2018 IR for a synopsis of the CCR4 literature specifically in MF/SS.**
- **Although CCR4 is expressed in almost all cases of ATL, CCR4 expression in MF/SS, while frequent, appears less consistent in the literature. Several published studies have found less frequent CCR4 expression in earlier stage MF (Sugaya et al 2015). Cross-study comparisons are limited by the variable CCR4 detection methods, by patient heterogeneity, and by sample size. However, in the present study, all 290 evaluable patients had detectable CCR4 expression by skin biopsy. Given this and the fact that Study 0761-010 enrolled patients regardless of CCR4 status, an indication that is not restricted to CCR4-expressing disease is justifiable.**
- **The protocol-specified threshold for "positive" CCR4 expression (≥ 10% of lymphocytes) has been used in the CTCL literature and serves to reduce false-positive results. It is not based on any predictive correlation associated with a <10% versus ≥ 10% expression level (source: response to 1/2/2018 IR).**

Table 7: Disease Characteristics of ITT Efficacy Population (N = 372)

Parameter		MOGA (N = 186)		VORINOSTAT (N = 186)	
Diagnosis	MF	105	(56%)	99	(53%)
	SS	81	(44%)	87	(47%)
CCR4 expression status by IHC [a]	≥ 1% lymphs	140	(75%)	150	(81%)
	≥ 10% lymphs (positive)	134	(72%)	146	(78%)
	< 10% lymphs (neg)	6	(3%)	4	(2%)
	Not done or test failure	46	(25%)	36	(19%)
# of prior systemic regimens	Median (range)	3	(1 – 18)	3	(0 – 14) [b]
	1	28	(15%)	40	(22%)
	2	40	(21%)	38	(20%)
	3	40	(21%)	37	(20%)
	≥ 4	78	(42%)	70	(38%)
	≥ 6	44	(24%)	31	(17%)
Months since diagnosis	Median (range)	41	(1 – 362)	35	(1 – 306)
Current clinical stage	IB	14	(8%)	27	(15%)
	II (A, B)	53	(28%)	45	(24%)
	III (A, B)	22	(12%)	16	(9%)

Table 7: Disease Characteristics of ITT Efficacy Population (N = 372)

Parameter		MOGA (N = 186)		VORINOSTAT (N = 186)	
	IV (A1, A2, B)	96	(52%)	98	(53%)
Stage for stratification	IB or II	68	(37%)	72	(39%)
	III or IV	118	(63%)	114	(61%)
Current disease sites	Blood	122	(66%)	122	(66%)
	Nodes	124	(67%)	122	(66%)
	Viscera	3	(2%)	3	(2%)
	Skin	186	(100%)	186	(100%)
Skin-directed therapy	Radiotherapy	55	(30%)	52	(28%)
	PUVA	80	(43%)	63	(34%)
Systemic therapy	Bexarotene	197	(58%)	110	(59%)
	IFN-α	81	(44%)	94	(51%)
	Methotrexate	69	(37%)	73	(39%)
	ECP	71	(38%)	65	(35%)
	Romidepsin	45	(24%)	32	(17%)
	Nitrogen mustard	28	(15%)	40	(22%)
	Pralatrexate	14	(8%)	13	(7%)
	Liposomal doxorubicin	23	(12%)	19	(10%)
	Vorinostat	2 [c]	(1%)	0	(0%)
Response to last systemic therapy	≥ PR	62	(33%)	69	(37%)
	No response	105	(56%)	99	(53%)
	Unknown	19	(10%)	18	(10%)

Source: CSR Table 11.2.2-1 and 11.2.3-1 except as noted

ECP, extracorporeal photopheresis; PUVA, psoralen + ultraviolet light A

[a] Per (b) (4) CCR4 IHC assay. The % positivity was to be determined first using % of neoplastic cells; if neoplastic and nonneoplastic cells were not easily distinguishable, % of total lymphocytes was to be used.

[b] 1 patient had no prior systemic therapies.

[c] Source: response to 1/2/18 IR.

Patient Treatment and Disposition

Treatment and disposition of the efficacy population are presented in Table 8. For the safety population, refer to Section 8.2.2.

Table 8: Treatment and Disposition of Efficacy Population

Parameter		MOGA (N = 184 treated, from 186)		VORINOSTAT (N = 186)	
Exposure to Randomized Treatment					
Received study drug	Yes	184		186	
Tx duration, months	Median	5.6		2.8	
	Range	0.0 – 45.3		0.1 – 34.8	
	Q1, Q3	2.3, 11.5		1.6, 5.6	
Cycles initiated [a]	Median	6 [b]		3	
	Range	1 – 45		1 – 36	
	Q1, Q3	3, 12		2, 6	
Relative dose intensity (RDI)	Mean	94%		89% [c]	
	≥ 90%	142	(77%)	_	
	≥ 80%	172	(93%)	_	
Patients on tx by month	≥ 2 mo	143	(78%)	113	(61%)
	≥ 3 mo	120	(65%)	82	(44%)
	≥ 6 mo	90	(49%)	41	(22%)
	≥ 12 mo	43	(23%)	19	(10%)
	≥ 24 mo	9	(5%)	4	(2%)
Disposition, Including Crossover Treatment					
Status of randomized tx	Ongoing	27	(15%)	10	(5%)
	Discontinued	157	(85%)	176	(95%)
Reason randomized tx stopped	PD	98/157	(62%)	127/176	(72%)
	Per pt or physician	22	(14%)	5	(3%)
	AE or intolerance	28	(18%)	32	(18%)
	Death	2	(1%)	2	(1%)
	Other	7	(4%)	10	(6%)
Crossover to moga	Yes	N/A		136	(73%)
Reason	Inefficacy			109	(80%)
	Intolerance			27	(20%)
Crossover tx given	Yes	NA		133	(72%)
Vorinostat exposure before crossover, months	Median	N/A		2.4	
	Range			0.5, 23.0	
	Q1, Q3			1.6, 4.6	
Moga cycles initiated after	Median	N/A		7	

Table 8: Treatment and Disposition of Efficacy Population

Parameter		MOGA (N = 184 treated, from 186)		VORINOSTAT (N = 186)	
crossover	Range			1 – 46	
	Q1, Q3			3, 12	

Source: FDA clinical reviewer except where noted.

Tx, treatment; NR, not reported.

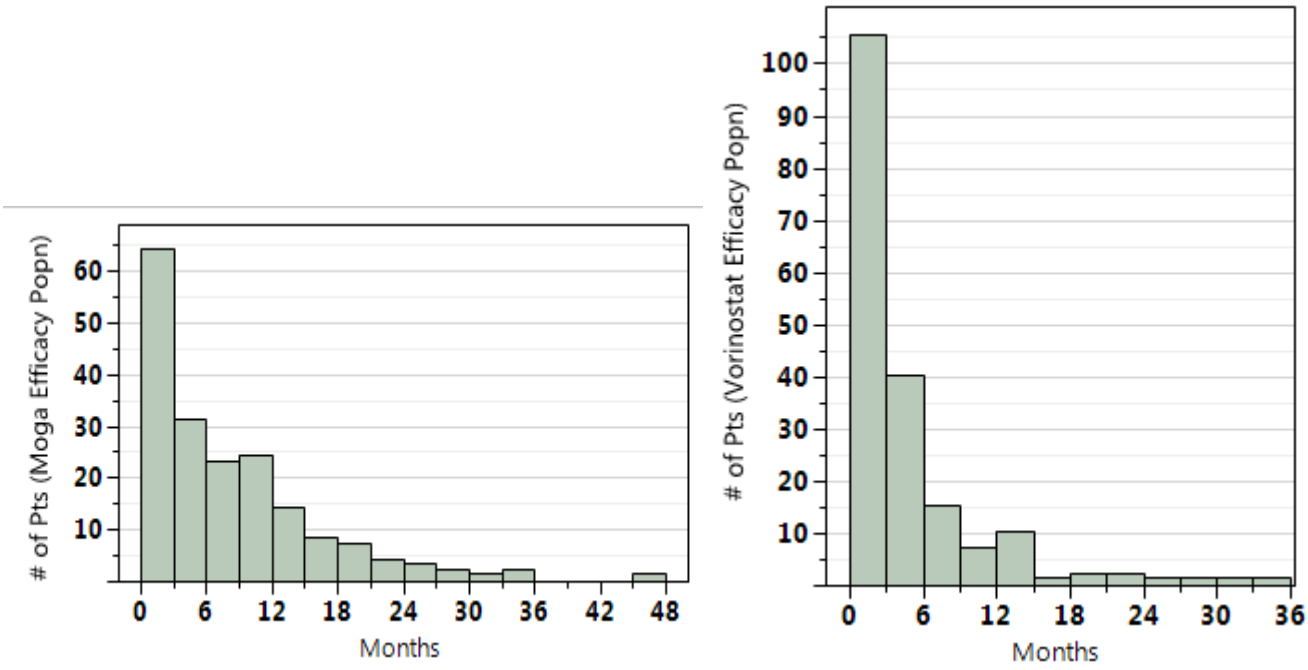
Data cut-off, 12/2016

[a] Cycle length is 28 days for either arm.

[b] Median 14 infusions (range, 1 – 90)

[c] Source: CSR Table 12.1.101

Figure 5: Duration of Randomized Treatment in Efficacy Population



Source: FDA clinical reviewer

Clinical review comments:

- **Particularly among patients with PD on vorinostat, the generally short exposure to vorinostat prior to crossover raises substantial concern for bias. It often takes several months to achieve an objective response to vorinostat, yet ~40% of patients on the**

0761-010 vorinostat arm completed < 2 months of treatment. This early crossover, and thus inadequate exposure to the control treatment, potentially biases the efficacy results in favor of the experimental arm. In a pivotal trial of vorinostat in relapsed/refractory CTCL, for example, the median time to response was ~2 months, but ranged from ~1 month to > 5 months. In the other pivotal trial in CTCL, the median time to response was 2.7 months. Early crossover might also explain, in part, the much lower response rates with vorinostat in Study 0761-010 than in the literature; namely, had vorinostat been continued for longer, ORR might have improved.

Protocol Violations/Deviations

Over 21% of patients had use of prohibited medications reported during randomized treatment, mostly involving topical steroids. Approximately one-quarter of the efficacy population (98 patients; 47 on vorinostat, 51 on mogamulizumab) did not discontinue high-potency topical steroids or oral steroids at study entry and/or received prohibited steroids during randomized treatment (source: CSR Section 10.2). A post-hoc analysis of PFS-INV excluding these 98 patients and an additional patient without prior systemic therapy (on the vorinostat arm) was reportedly consistent with the primary PFS analysis (CSR Sections 10.2 and 11.4.1.3).

By the efficacy cut-off date, 6 patients approved for crossover from vorinostat to mogamulizumab based on PD did not meet the protocol-specified, formal criteria for PD in retrospect. All had worsening disease and/or symptoms at the time of crossover.

Clinical review comment:

- **Because steroid use deviations occurred with similar frequency in the two arms, the deviations are unlikely to impact the overall conclusions about efficacy.**

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Of concomitant medications taken by ≥ 20% of patients in either arm, the use of specific types of medication was generally comparable between arms. Exceptions included a higher percentage of the mogamulizumab arm receiving anti-infective agents and glucocorticoids (source: CSR Section 11.2.4).

The investigator-reported noncompliance with dosing for vorinostat was 18% (source: CSR Section 11.3).

Clinical review comment:

- **The reported mean RDI of vorinostat was reasonable (89%). It is unlikely that compliance issues contributed significantly to the markedly poor performance of the vorinostat arm in Study 0761-010 relative to registrational and other published studies**

of vorinostat. In this reviewer's opinion, the more stringent response criteria used in 0761-010, coupled with potentially insufficient duration of exposure to vorinostat s (which raises the question of bias), are leading considerations.

Data Quality and Integrity
The quality and integrity of the clinical data appeared acceptable.

Efficacy Results – Primary Endpoint
For the primary analysis, PFS was defined as the time from the day of randomization until documented progression in any compartment per consensus response criteria assessed by the investigators, or documented disease progression reported during the follow-up period (prior to the start of alternative CTCL therapy), or death due to any cause. In the primary efficacy analysis, patients with clinical progression not meeting formal PD criteria were censored at the last tumor assessment of crossover or end of treatment.

At the time of efficacy data cut-off (31 Dec 2016), a total of 241 PFS events had been observed based on Investigator's assessment: 110 (59.1% of patients) in the mogamulizumab group and 131 (70.4%) in the vorinostat group. For patients without progression who were continuing to receive randomized treatment as of the cut-off date, PFS was censored at the date of the last tumor assessment prior to data cut-off.

Statistical review comment:

- **The PFS results in the CSR were verified using the submitted analysis dataset. However, the Applicant has used 30 days per month for the analysis, rather than FDA's common use of 30.4375 (365.25/12) days per month. All PFS calculations in this review use the 30.4375 days/month conversion. The recalculated PFS (INV and IRC) results are given in the below paragraph, Table 9 and Figure 6.**

The results of Study 0761-010 show that treatment with mogamulizumab was associated with a statistically significant improvement in PFS compared to vorinostat with a HR (moga/vorinostat) of 0.53 (95% CI: 0.41, 0.69), and with a 2-sided p<0.0001 (stratified log rank test). The estimated median PFS was 7.6 months (95% CI: 5.6, 10.2) for mogamulizumab and 3.1 months (2.8, 4.0) for vorinostat. At 6, 12, and 18 months after the start of randomized treatment, the PFS probability was consistently higher for mogamulizumab (55.3%, 38.3%, and 28.0%, respectively) compared to vorinostat (28.8%, 15.3%, and 7.2%, respectively).

Table 9: Summary of PFS-INV (ITT population)

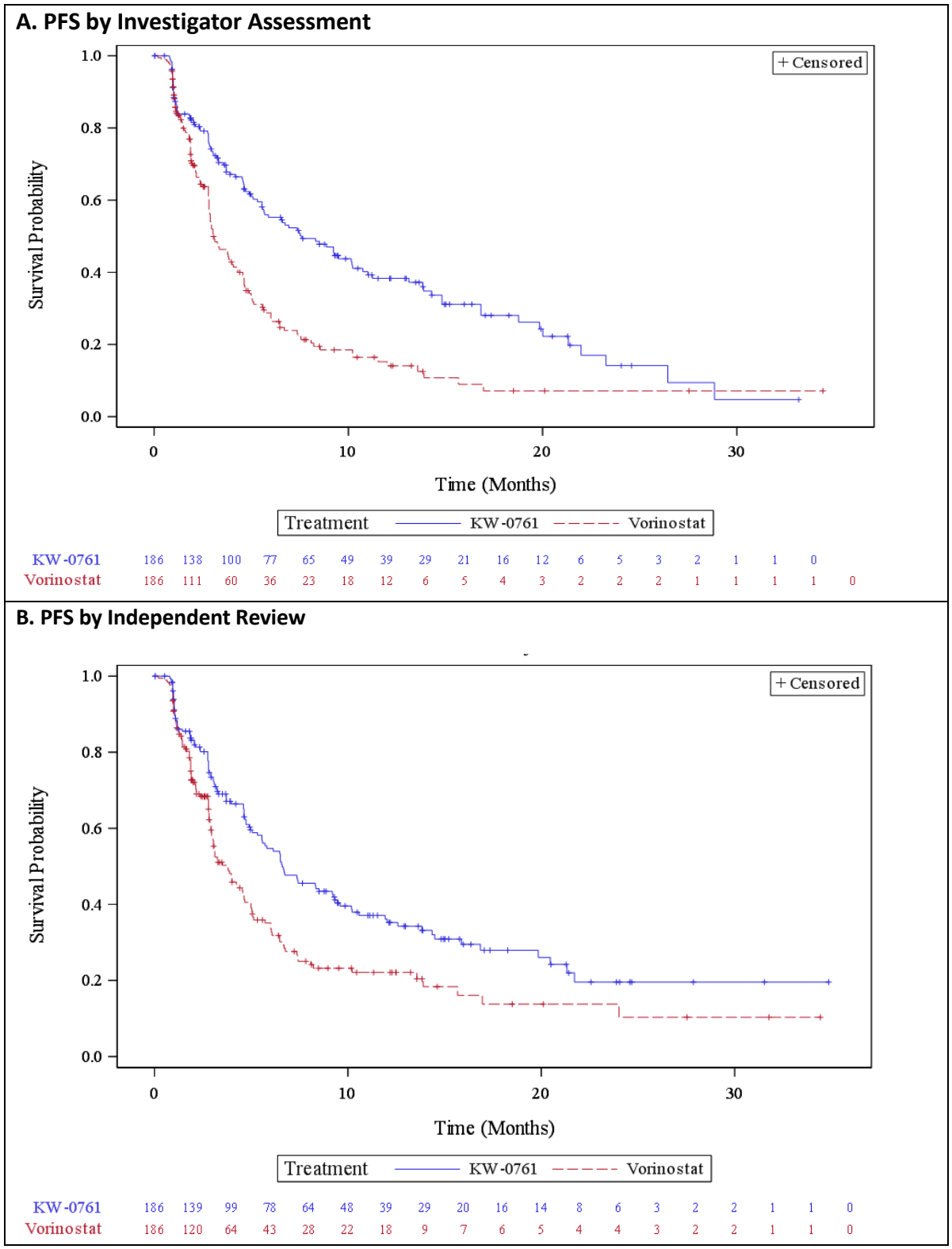
	Mogamulizumab N=186	**Vorinostat N=186**
Number of Patients with PFS Event (n, %)	110 (59.1)	131 (70.4)
Earliest Contributing Event:		
Progressive disease	104 (55.9)	128 (68.8)
Death	6 (3.2)	3 (1.6)
Number of Patients Censored (n, %)	76 (40.9)	55 (29.6)
Progression-free Survival (Months) [a]		
Median (95% CI)	7.6 (5.6, 10.2)	3.1 (2.8, 4.0)
Median follow up (95% CI) for PFS	13.0 (10.5, 15.2)	10.4 (7.7, 13.2)
Comparison (Mogamulizumab vs Vorinostat) [b]		
Hazard ratio (95% CI)	0.53 (0.41, 0.69)	
Log rank p-value	<.0001	
Rate (%) of Being Alive without Progression for at Least		
6 months (95% CI)	55.3 (47.5, 63.0)	28.8 (21.3, 36.2)
12 months (95% CI)	38.3 (30.1, 46.4)	14.1 (7.7, 20.4)
18 months (95% CI)	28.0 (19.4, 36.6)	7.2 (1.3, 13.0)

Source: FDA statistical reviewer

a Kaplan-Meier estimate. 95% CIs are obtained from SAS proc life test using log-log transformation.

b Hazard ratio and 95% CI are based on Cox proportional hazards model with treatment, disease type, disease stage, and region as covariates. P-value (two-sided) was obtained from a stratified log rank test (one-sided test at 0.025 level or equivalently two-sided test at 0.05 level) with disease type, disease stage, and region as stratification factors, using SAS proc life test.

Figure 6: Kaplan-Meier Curves of PFS (ITT Analysis)



Source: FDA statistical reviewer

***Statistical review comments*:**

- **Notably 76 (41%) patients in the mogamulizumab arm were censored in the analysis of PFS-INV, among which 36 (47% of 76) patients were censored before 6 months since randomization. Because of the large amount of early censoring, the estimation of survival distribution including PFS rates at 6, 12, 18 months and median PFS may not be reliable.**

As shown in Table 10, the majority of censored observations for PFS were due to discontinuing randomized treatment without documented disease progression per CTCL response criteria. The percentage of patients who were censored due to discontinuation for AE or intolerance was higher for the vorinostat group than for the mogamulizumab group, while the percentage of patients who were censored due to discontinuation for clinical progression was similar for the two treatment groups.

FDA issued an IR on January 31, 2018 and two follow-up IRs on February 16, 2018 and February 20, 2018, for the Applicant to provide the numbers of patients who were censored by reasons (e.g. loss to follow up, AE), by time (before 6 month and after 6 month), and by treatment. Table 10 summarizes the Applicant's response.

Table 10 Summary of Reasons for Censoring by Treatment Arms

Reason for censoring	Mogamulizumab n (%)[a]	Vorinostat n (%)[a]
Total number of censored observations	76 (100)	55 (100)
Clinical PD [b]	16 (21.1)	10 (18.2)
Ongoing randomized treatment	16 (21.1)	7 (12.7)
AE/intolerance	14 (18.4)	25 (45.5)
Withdrew consent	9 (11.8)	3 (5.5)
Investigator decision	7 (9.2)	0
Other	5 (6.6)	7 (12.7)
Withdrawal prior to first post-baseline assessment	3 (3.9)	2 (3.6)
New anti-cancer therapy	3 (3.9)	0
No baseline assessment nor no post-baseline assessment	2 (2.6)	0
Protocol noncompliance	1 (1.3)	0
Lost to follow-up	0 (0.0)	1 (1.8)

Source: Response to IR.
a Percentage is calculated based on number of patients with censored observation.
b Patients with disease progression that did not meet criteria for PD based on CTCL response criteria. CRF for crossover only captured progression. Patients who crossed over to mogamulizumab without progression documented in a compartment per CTCL response criteria were assessed by the Applicant as clinical progression.

Since Table 10 shows imbalanced censoring between two treatment arms, which raised the concern of potential premature censoring and informative censoring, FDA conducted additional sensitivity analyses (see Table 13). These additional sensitivity analyses support the efficacy of mogamulizumab and show that mogamulizumab is associated with prolonged PFS compared to vorinostat with HRs ranging from 0.53 to 0.74.

Clinical review comment:

- **Although the difference in PFS with mogamulizumab vs. vorinostat is statistically significant, the actual difference in median PFS is modest.**

Efficacy Results – Secondary and Other Relevant Endpoints, Excluding PROs

A. Response Rate

Overall objective response rate (ORR) as assessed by the Investigators for the ITT Set was a key secondary efficacy endpoint. ORR was defined as the proportion of patients who had a confirmed CR or PR, defined as documented CR or PR per Global Composite Response Score that was confirmed by a subsequent observation at least 4 weeks later.

As shown in Table 11, confirmed ORR based on Investigator assessment was significantly higher for mogamulizumab (28.0%) than for vorinostat (4.8%). The p-value is < 0.0001 using Cochran-Mantel-Haenszel test adjusting for disease type, disease stage, and region.

Table 11: Confirmed Response Rates per Investigator During Randomized Treatment (ITT)

	Mogamulizumab N=186	**Vorinostat N=186**
Overall Response in All Patients		
Overall Response Rate (confirmed CR + PR) (n, %)	52 (28.0)	9 (4.8)
95% CI [a]	(21.6, 35.0)	(2.2, 9.0)
Risk Diff, moga – vorinostat (95% CI) [a]	23.1 (12.8, 33.1)	
P-value [b]	<.0001	
Adjusted P-value [b]	<.0001	
Confirmed Best Overall Response		
CR, n (%)	4 (2)	0 (0)
95% CI	(1, 5)	(0, 2)
PR, n (%)	47 (25)	9 (5)
95% CI	(20, 33)	(2, 9)
Response by Compartment (Confirmed CR + PR) [c]		
Blood	n=124	n=125
Response rate, n (%)	83 (67)	23 (18)
95% CI	(58, 75)	(12, 26)

Table 11: Confirmed Response Rates per Investigator During Randomized Treatment (ITT)

	Mogamulizumab N=186	Vorinostat N=186
Skin	n=186	n=186
Response rate, n (%)	78 (42)	29 (16)
95% CI	(35, 49)	(11, 22)
Lymph nodes	n=136	n=133
Response rate, n (%)	21 (15)	5 (4)
95% CI	(10, 23)	(1, 9)
Viscera	n=6	n=4
Response rate, n (%)	0 (0)	0 (0)
95% CI	(0, 46)	(0, 60)
Response by Histology		
Patients with MF	n=99	n=105
Overall Response Rate (confirmed CR + PR) (n, %)	22 (21.0)	7 (7.1)
95% CI	(13.6, 30.0)	(2.9, 14.0)
Risk Diff (95% CI)	13.9 (0.1, 27.4)	
Patients with SS	n=87	n=81
Overall Response Rate (confirmed CR + PR) (n, %)	30 (37.0)	2 (2.3)
95% CI[a]	(26.6, 48.5)	(0.3, 8.1)
Risk Diff (95% CI)	34.7 (19.9, 48.4)	

Source: FDA statistical reviewer
Note: Overall response rate is based on Global Composite Response score.
a Exact 95% CIs.
b P-value was obtained from Cochran-Mantel-Haenszel test adjusting for disease type, disease stage, and region. Adjusted P-value was calculated using Sidak method.
c Responses in blood and skin must have persisted for at least 4 weeks to be considered confirmed and were evaluated every 4 weeks for the first year. Responses in lymph nodes, visceral disease and overall were evaluated every 8 weeks for the first year.

Clinical review comments:

- **ORR by IRC (a secondary objective) was consistent with ORR-INV, favoring mogamulizumab. Response rates overall and by disease compartment, according to the IRC, are provided in the Appendix (Table 51). The confirmed ORR-IRC was 23% (17, 30) with mogamulizumab and 4% (2, 8) with vorinostat. Although the Applicant reported p values, the p values are nominal.**
- **There were few CRs with mogamulizumab.**
- **After crossover to mogamulizumab, the ORR-INV by ITT analysis was 30% (23, 39), with 41/136 confirmed responses, 50 non-responders, and 36 patients not assessable (source: CSR Table 11.4.2.-7).** (b) (4)

(b) (4) **the potential carryover effect of prior vorinostat (20% crossed over due to intolerance to vorinostat rather than disease progression).**

Response by compartment and by histology

As summarized in Table 11, mogamulizumab was associated with higher investigator-assessed response rates than vorinostat in the 3 main disease compartments (blood, skin, lymph node) and in both disease types (SS and MF).

Clinical review comments:

- **The activity of mogamulizumab appears greater in the blood and skin than in lymph nodes.**
- **Among the few patients with visceral involvement at baseline (6 randomized to mogamulizumab, 4 to vorinostat) there were no confirmed responses in the viscera in either treatment arm.**

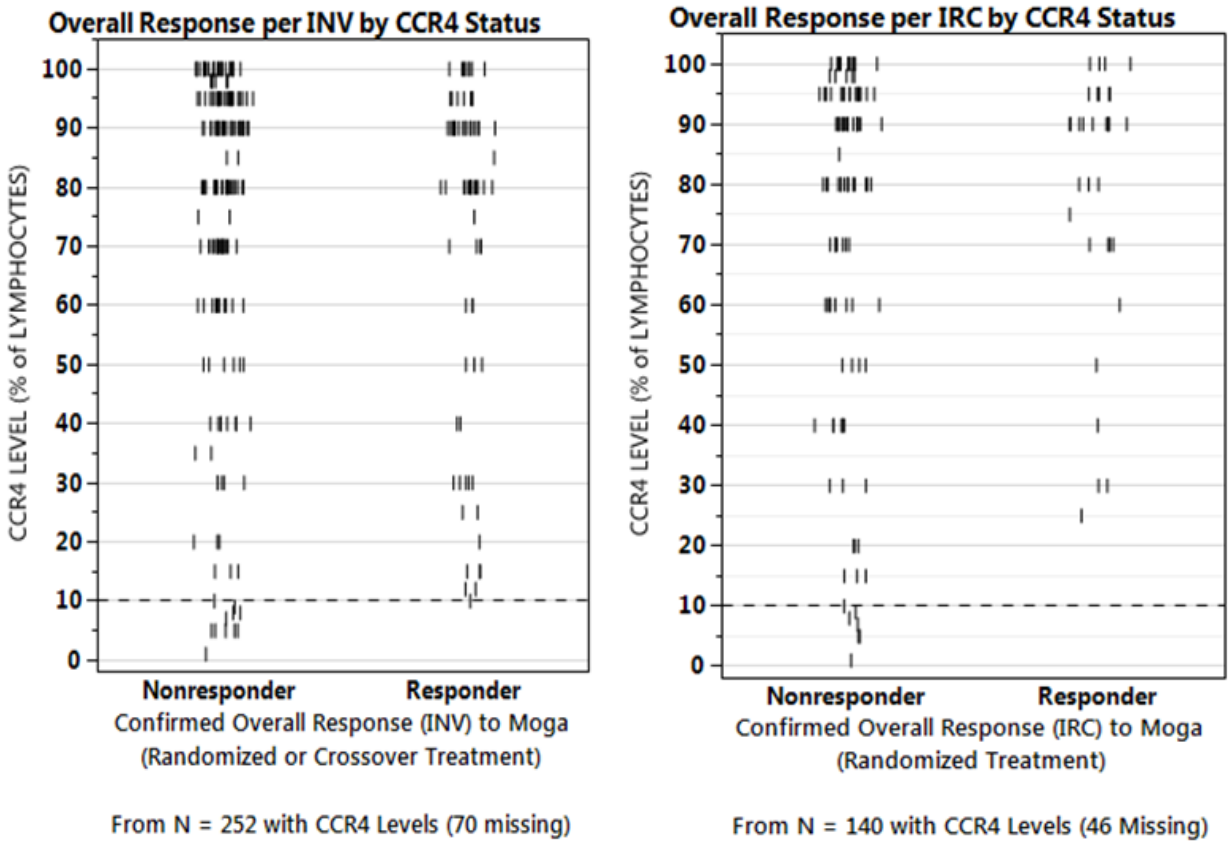
Response by CCR4 expression status

The FDA clinical reviewer conducted an exploratory analysis of confirmed overall response to mogamulizumab according to tumor CCR4 status by IHC (Figure 7). The minimum CCR4 expression level associated with confirmed overall response was 10% (response per investigator, in recipients of randomized + crossover treatment) and 25% (response per IRC, in recipients of randomized treatment). The large amount of missing CCR4 data limited the analysis.

In the 6 mogamulizumab recipients with <10% CCR4 expression, two patients had compartmental responses, both in the skin:

- A patient randomized to mogamulizumab (ID 302-0002, CCR4 7%) had skin PR by investigator-assessed SWAT on D56 and D84, and PR by IRC-assessed SWAT on D56.
- A patient upon crossover to mogamulizumab (ID 128-0006, CCR4 5%) had skin PR by investigator-assessed SWAT on D50 and D78, without independent review.

Figure 7: Response to Mogamulizumab According to CCR4 Status



Source: FDA clinical reviewer

B. PFS by IRC

Analyses of PFS-IRC (a secondary endpoint) during the randomized treatment period were performed. Results are presented in Table 12. The estimated median PFS by independent review was 6.6 months (5.6, 9.2) for mogamulizumab vs. 3.8 months (3.0, 4.6) for vorinostat (HR = 0.64; 95% CI: 0.50, 0.84; p<0.001). Thus, the conclusion of significant efficacy of mogamulizumab is consistent with that of the primary analysis.

Table 12: Summary of PFS Based on Independent Review (Intent-to-Treat Set)

	Moga N=186	Vorinostat N=186
Number of Patients with PFS Event (n, %)	110 (59.1)	122 (65.6)
Earliest Contributing Event:		
Progressive disease	108 (58.1)	118 (63.4)
Death	2 (1.1)	4 (2.2)
Number of Patients Censored (n, %)	76 (40.9)	64 (34.4)
Progression-free Survival (Months)[a, b]		
Median (95% CI)	6.6 (5.6, 9.2)	3.8 (3.0, 4.6)
Median follow up (95% CI) for PFS	13.8 (11.3, 15.8	10.2 (7.8, 12.5)
Comparison (Mogamulizumab vs Vorinostat)[c]		
HR (Moga/Vorinostat)(95% CI)[c]	0.64 (0.50, 0.84)	
Log rank p-value	0.0007	
Rate (%) of Being Alive without Progression for at Least [a]		
6 months (95% CI)	54.7 (46.9, 62.5)	35.1 (27.3, 42.9)
12 months (95% CI)	36.2 (28.3, 44.0)	22.1 (14.9, 29.3)
18 months (95% CI)	27.9 (19.7, 36.2)	13.8 (5.8, 21.7)

Source: FDA statistical reviewer
a Kaplan-Meier estimate.
b 95% CIs are obtained from SAS proc life test using log-log transformation.
c Hazard ratio and 95% CI are based on Cox proportional hazards model with treatment, disease type, disease stage, and region as covariates. P-value (two-sided) was obtained from a stratified log rank test (one-sided test at 0.025 level or equivalently two-sided test at 0.05 level) with disease type, disease stage, and region as stratification factors.

Clinical review comments:

- **The estimated treatment effect is smaller by independent review (HR for PFS = 0.64) than by investigator (HR = 0.53). Because this is an open-label trial and response assessment in the skin is particularly susceptible to bias, PFS per independent review, rather than PFS per investigator, is the main basis for my regulatory recommendation.**
- **I disagree with the Applicant's assessment that the efficacy data are mature. There is a large amount of early censoring for PFS and DOR on the mogamulizumab arm that raises concern for substantial informed censoring. This is driven to a large extent by censoring for clinical progression in the primary PFS analysis. Because of the relatively short follow-up (mainly a function of early censoring), the estimates of median PFS and DOR may also be unstable.**

C. PFS Sensitivity Analyses

To assess the robustness of the primary results, the Applicant conducted four pre-specified analyses and one additional sensitivity analysis. To assess potential impact of premature censoring and potential informed censoring, the FDA reviewer conducted six additional sensitivity analyses. The results of these sensitivity analyses are given in Table 13. Across all sensitivity analyses of PFS, the results favored mogamulizumab. The HR ranged from 0.53, which equaled the HR in the primary analysis, to 0.74.

Table 13: Sensitivity Analyses of PFS

	HR (moga/ vorinostat)	95% CI	p-value
Sensitivity analyses conducted by Applicant [a]			
Primary Analysis (PFS-INV – ITT)[b]	0.53	(0.41, 0.69)	<.0001
Secondary Analysis (PFS by Independent Review – ITT)	0.64	(0.50, 0.84)	<.0001
Secondary Analysis (PFS-INV – Efficacy Evaluable Set [c])	0.51	(0.37, 0.69)	<.0001
Sensitivity analysis 1 (PFS-INV – PD reported during follow-up period not considered an event, censored on last tumor assessment date – ITT)	0.52	(0.40, 0.68)	<.0001
Sensitivity analysis 2 (PFS-INV – Clinical progression at end of randomized treatment period considered an event – ITT)	0.61	(0.47, 0.78)	<.0001
Sensitivity analysis 3 (PFS-INV – worst case with earliest date of PD in any compartment or death due to any cause – ITT)	0.72	(0.54, 0.96)	0.0148
Sensitivity analysis 4 (PFS-INV – Death events meeting the specified conditions are included – ITT)	0.52	(0.40, 0.68)	<.0001
Sensitivity analysis 5 (PFS-INV – Patients with specific protocol deviations are excluded)	0.63	(0.46, 0.86)	<.0001
Additional sensitivity analyses by FDA reviewer			
1. set to event if censoring <6 months from randomization for both arms	0.58	0.46, 0.72	<.0001
2. set to event if censoring <6 months from randomization for moga arm only	0.74	0.58, 0.94	0.0117
3. set to event if censoring occurred >90 days from data cutoff date (12/31/16) for both arms [b]	0.53	0.41, 0.69	<.0001
4. set to event if censoring occurred >90 days from data cutoff date (12/31/16) for moga arm only [b]	0.53	0.41, 0.69	<.0001
5. set clinical progression to event for both arms	0.57	0.44, 0.73	<.0001
6. set clinical progression, withdrawal of consent, Investigator Decision, and new anti-cancer therapy to event for both arms	0.64	0.51, 0.82	0.0003

a Source: Clinical overview, Table 2.5.4.5-1. Please refer to Section 1.1.1 for more details on the censoring rules.
b These two sensitivity analyses sets appear the same as the primary analysis.
c Efficacy Evaluable set includes all patients who received at least one dose and who have baseline tumor assessment and at least one post-baseline assessment for response.

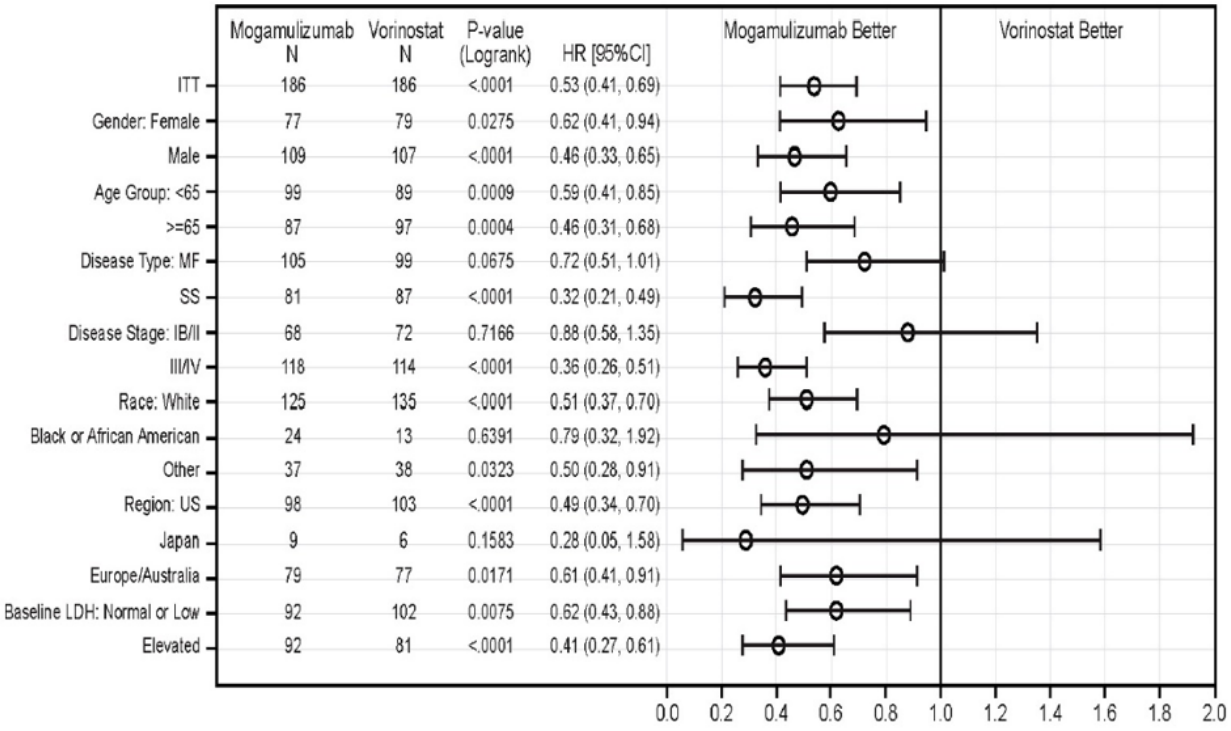
Clinical review comment:

- **Because the primary PFS analysis censored clinical progression, thereby promoting informed censoring, PFS sensitivity analysis #2 (treating clinical progression as an event) is the most important sensitivity analysis in this reviewer's opinion.**

D. PFS Subgroup Analyses

Subgroup analyses of PFS including by age group, gender, disease stage, and disease type were performed. Figure 8 presents summaries of the analyses. Across these analyses, the direction of the treatment effect was consistent, with the results favoring mogamulizumab.

Figure 8: Subgroup Analysis: Forest Plots of HR for PFS-INV (ITT)



Source: Clinical overview, Figure 2.5.4.5-2

***Clinical review comment*:**

- **For PFS-INV in patients with early stage (IB/II) disease, the upper bound of the 95% CI for the HR is 1.35. However, it would be incorrect to include that patients with earlier stage disease do not benefit from mogamulizumab, as the patient numbers are limited, and the trial was not designed to detect differences according to stage.**

E. Duration of Response

DOR is assessed for patients with confirmed CR or PR, and is defined as time from first objective response to date of objectively documented PD or death. In this analysis, patients

who did not have PD as of data cut-off were censored at the day of their last tumor assessment (from any compartment).

As shown in Table 14, based on Investigator's assessment, the estimated median DOR for confirmed responders was 13.9 months (95% CI: 9.3, 18.9) for mogamulizumab and 9.0 months (95% CI: 4.6, -) for vorinostat. Based on IRC, the estimated median DOR for the mogamulizumab group was 15.8 months.

Table 14: Duration of Response with Randomized Treatment

	Mogamulizumab N=186	**Vorinostat N=186**
By Investigator Assessment		
Number of Patients with Confirmed CR or PR	N=52	N=9
Patients with PD or Death (n, %)	26 (50)	4 (44)
Patients Censored (n, %)	26 (50)	5 (56)
Duration of Response (95% CI)(months) [a]		
Median	13.9 (9.3, 18.9)	9.0 (4.6, –)
Median follow up for DOR	12.5 (10.1, 15.7)	9.2 (3.3, 9.5)
By Independent Review		
Number of Patients with Confirmed CR or PR	N=43	N=7
Patients with PD or Death (n, %)	16 (37)	1 (14)
Patients Censored (n, %)	27 (63)	6 (86)
Duration of Response (95% CI) (months) [a]		
Median	15.8 (11. 6, –)	– (6.8, –)
Median follow up for DOR	11.1 (10.1, 12.9)	11.5 (4.6, 12.2)

Source: FDA statistical reviewer

[a] Kaplan-Meier estimates

– = not estimable

Clinical review comment:

- **There is a large amount of early censoring for DOR, as with PFS, on the mogamulizumab arm.**

F. Overall Survival

OS was defined as the time from the date of randomization until the date of death due to any cause. Patients who are still alive at the end of the survival follow-up period or are lost to follow-up at the time of analysis were censored on the last date the patient is known to be alive. In the as-randomized analysis (ITT analysis), OS data were compared between two arms as randomized regardless of the crossover. The rank preserving structural failure time (RPSFT) modeling and inverse probability censoring weighting (IPCW) methods was used to correct for impact due to crossover. Table 15 below summarized those analyses for OS.

Table 15: Summary of OS as an Exploratory Endpoint

Adjustment for Crossover	HR	95% CI
As randomized [a, #]	0.93	(0.61, 1.43)
Censoring at crossover [b]	0.71	(0.41, 1.24)
Rank Preserving Structural Failure Time Modeling[c]	0.74	(0.48, 1.14)
Inverse Probability Censoring Weighting Method [d]	0.51	(0.17, 2.91)

Source: Applicant's clinical overview Table 2.5.4.5-5

[a] Crossed over analyzed as randomized with no adjustment (p-value and CI by log-rank and Cox model with covariates Stage, Type, and Region).

[b] Crossed over censored at time crossover occurred (p-value and CI by log-rank and Cox model with covariates Stage, Type, and Region).

[c] p-value and 95% CI by log-rank and Cox model with covariates Stage, Type, and Region.

[d] 95% CI was based on 10000 bootstrap samples with logistic models for the weight calculation, including terms of baseline ECOG score, age group, sex, Stage, Type, Region, time dependent disease progression status and number of adverse events.

*Statistical reviewer's note:* 87 deaths (47 from mogamulizumab arm and 40 from vorinostat arm) occurred in the study.

Statistical review comment:

The results of the exploratory analyses that adjusted for crossover, appeared more favorable than the results of ITT analysis of OS, which was not expected to be statistically significant since most patients from the control arm received of mogamulizumab. The results from these exploratory analyses generally provide support to the benefit of mogamulizumab. However, none of these analyses was statistically significant.

***Clinical review comment*:**

- **The OS data are immature. No formal statistical comparisons between arms should be conducted as OS was an exploratory endpoint. For these reasons, no meaningful conclusions can be drawn from the current OS data.**
- **I disagree with concluding that, after adjusting for crossover, there is suggestion of a potential survival advantage with mogamulizumab. The data are immature, and the 95% CIs for the HR for OS are broad. Particularly with the IPCW method, a survival disadvantage with mogamulizumab cannot be excluded.**

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Cross-sectional Analysis of PRO Outcomes

The three key secondary QoL assessments were performed using the Skindex-29, FACT-G and

EQ-5D-3L.

The Skindex-29 is a validated instrument to measure the effect of skin disease on HRQoL. It is composed of 29 items assessing 3 domains: emotions, symptoms, and functioning. The items are scored on a 5-point Likert-type scale ("never," "rarely," "sometimes," "often," or "all the time"). Responses to each item are transformed to a linear scale of 100 (where 0 equals "never", 25 equals "rarely," 50 equals "sometimes," 75 equals "often," and 100 equals "all the time") for scale score calculation. A scale score is the mean of a patient's responses to the items in a given scale and the composite Skindex-29 score is calculated as the average of the 3 scale scores to measure the overall impact on QoL. Higher scores indicate a higher impact of skin disease.

The FACT-G is a validated instrument for assessing HRQoL in patients with cancer. The FACT-G consists of 27 items in the following 4 domains: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. The total FACT-G score is obtained by summing individual subscale scores. Response scores on negatively-phrased questions are reversed before summing. Higher scores for the scales and subscales indicate better QoL.

The EQ-5D-3L generic QoL questionnaire is comprised of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain or Discomfort, and Anxiety or Depression. Each dimension has 3 levels: (1) no problem; (2) some problem; or (3) extreme problem. Thus, the final scoring consists of 243 possible combinations or health states. The utility value for each state is assigned based on a set of preference weights (tariffs) elicited from the general population.

Table 16 summarizes the mean change scores of the QoL assessments from baseline across 6-month (Cycle 7) assessment.

Table 16: Mean Change in Scores from Baseline through 6 Months

	Diff. in mean change from baseline across 6-month assessment (=Cycle 7)	95% CI
Skindex-29 Total Score	-6.7	(-10.14, -3.19)
Skindex-29 Emotional Scale Score	-6.8	(-10.64, -2.94)
Skindex-29 Functional Scale Score	-6.6	(-10.32, -2.86)
Skindex-29 Symptoms Scale Score	-5.8	(-9.86, -1.81)
FACT-G Total Score	6.9	(4.33, 9.47)
EQ-5D-3L Index Score	0.03	(0.01, 0.06)

Source: FDA statistical reviewer

The following three line graphs present group means with 95% CI of the three key secondary QoL scores by treatment arms (source: FDA analyses).

Figure 9: Mean Skindex-29 Total Score by Treatment Arm

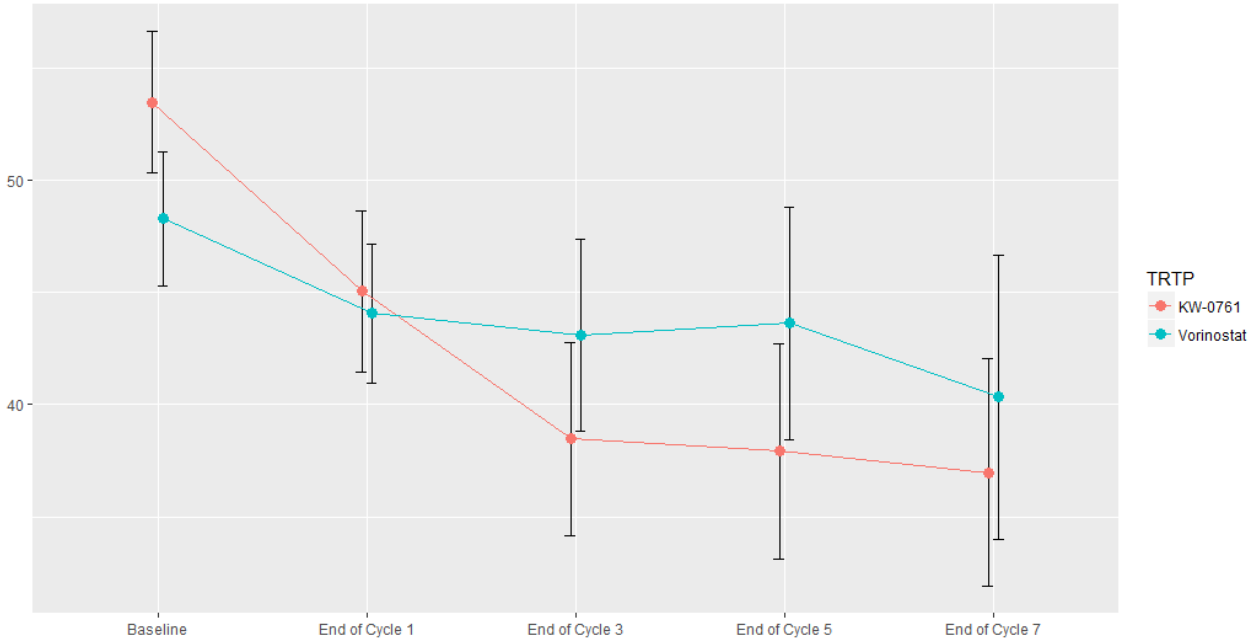


Figure 10: Mean FACT-G Total Score

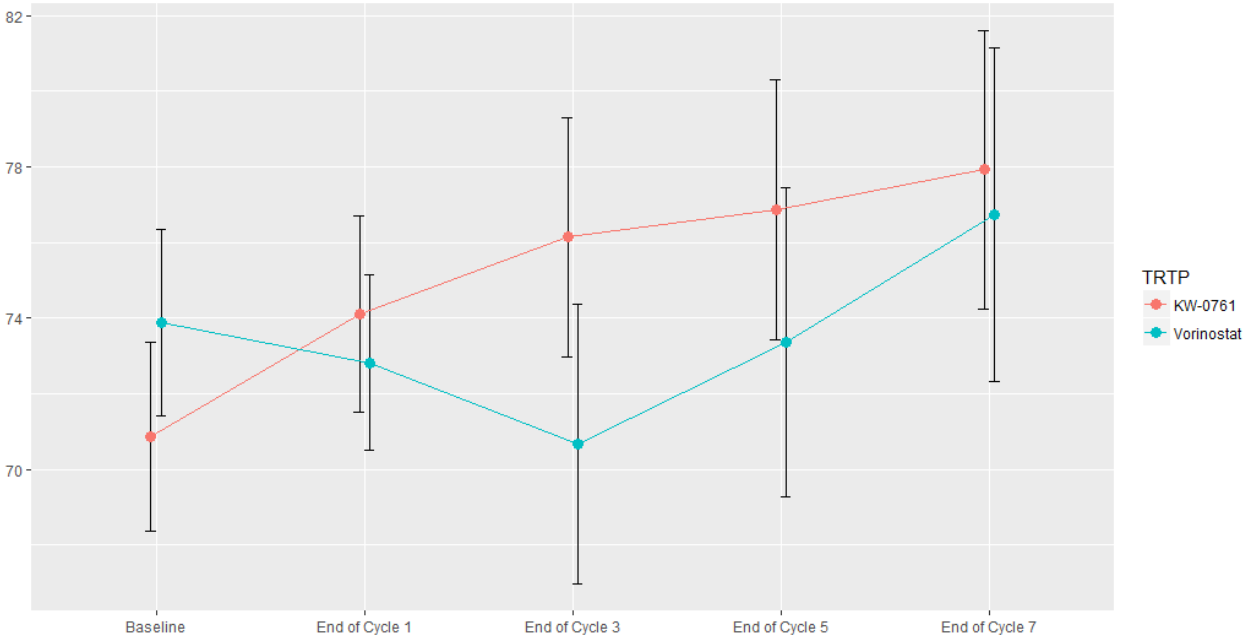
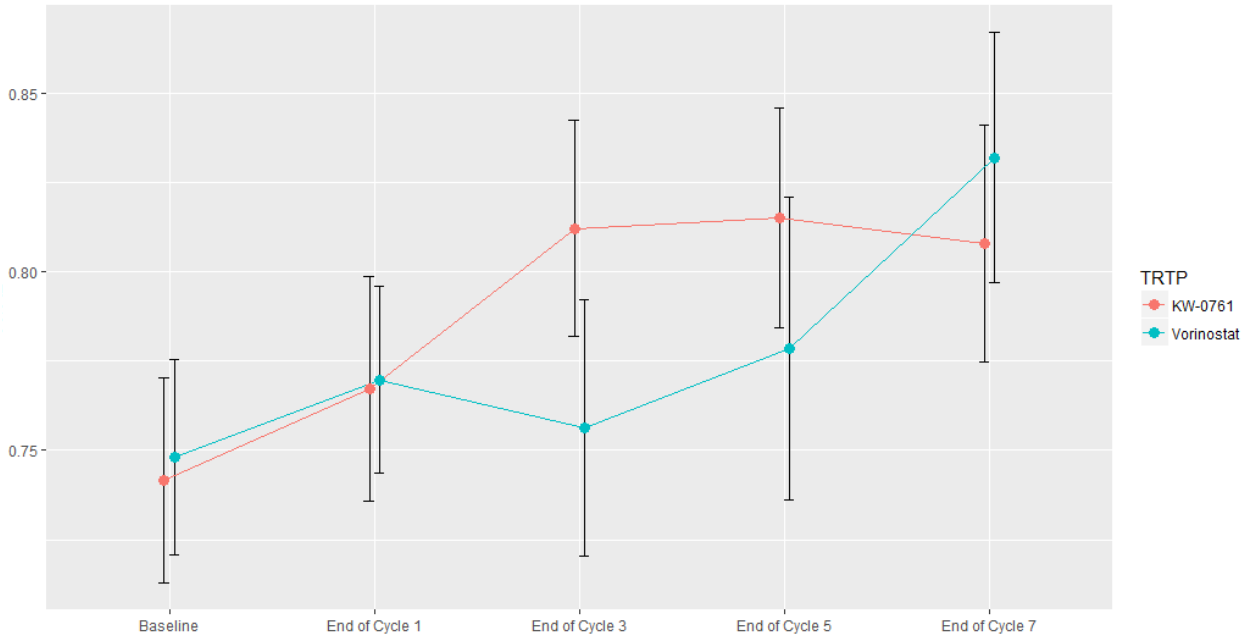


Figure 11: Mean EQ-5D-3L Index Score



Source for above 3 figures: FDA statistical reviewer

Longitudinal Analysis of PRO Outcomes

The three line graphs below present means changes from baselines with 95% CI of the three key secondary QoL scores by treatment arm (FDA analysis).

Figure 12: Mean Change of Skindex-29 Total Score

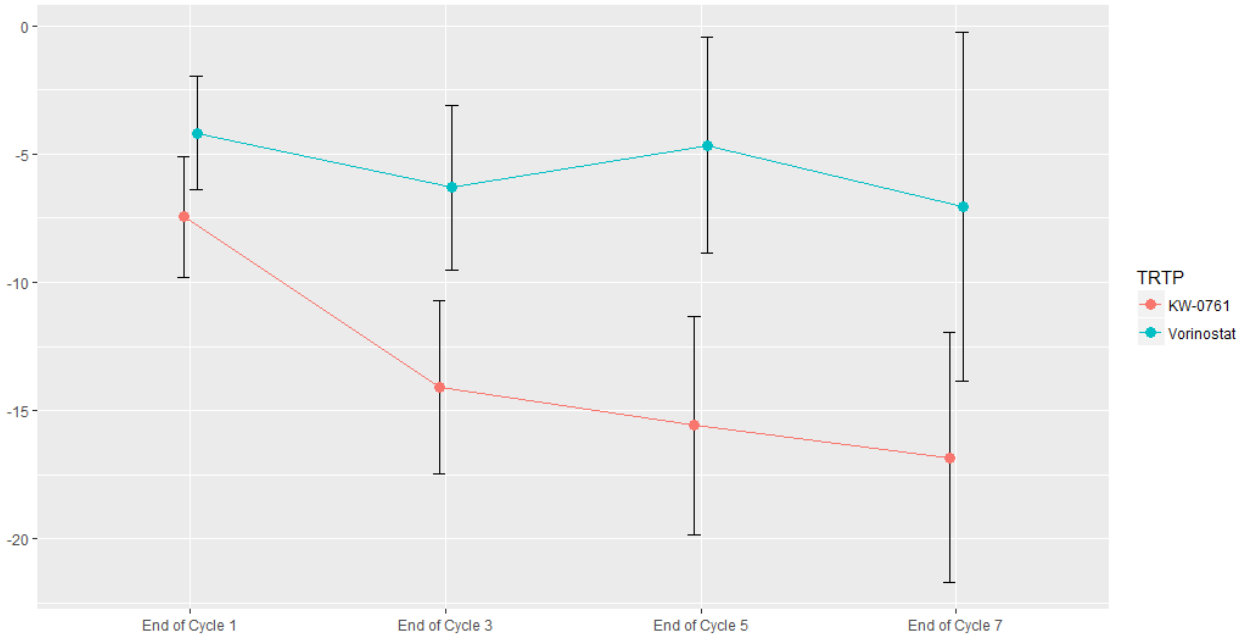


Figure 13: Mean Change in FACT-G Total Score

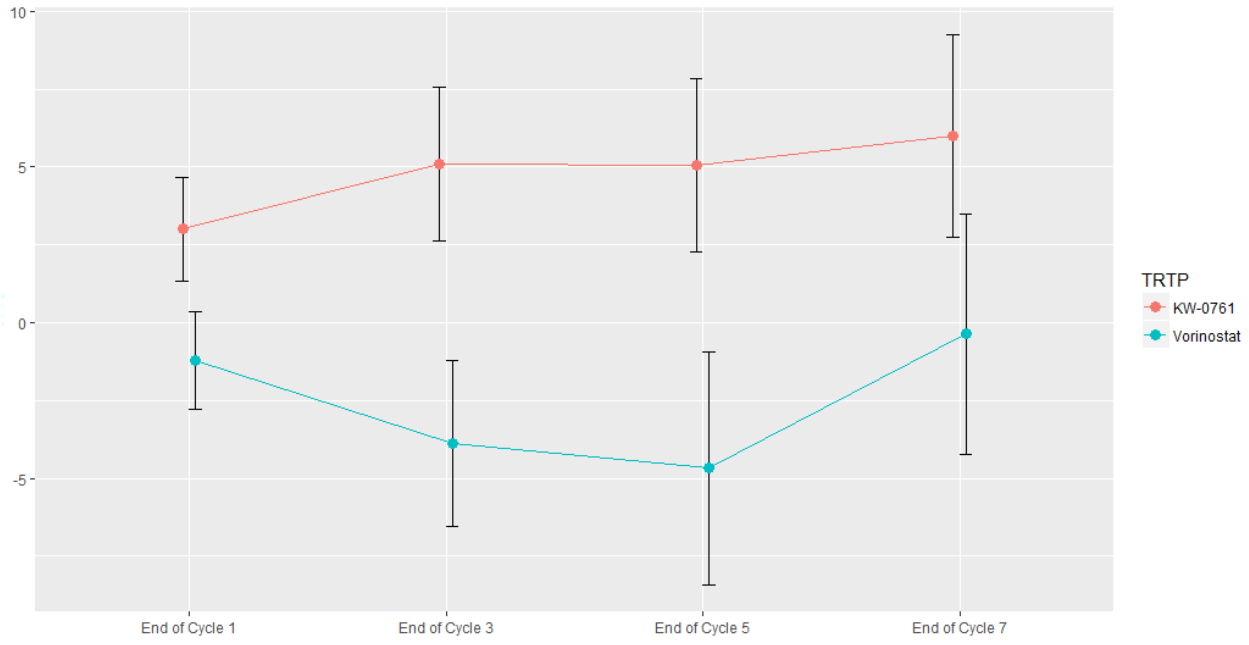
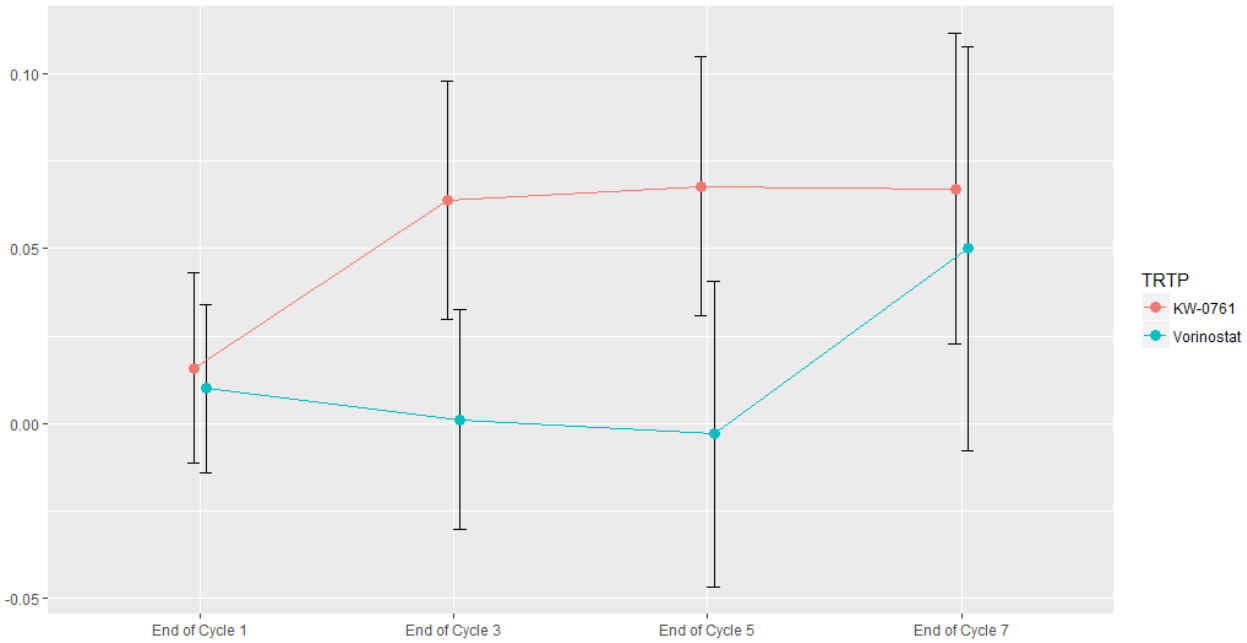


Figure 14: Mean Change in EQ-5D-3L Index Score



Source for above 3 figures: FDA statistical reviewer

***Statistical reviewer's comments*:**

- **The results in Table 16 and the figures above suggest a benefit of mogamulizumab compared to vorinostat to variable degrees with different QoL assessments. However, there are concerns with missing data. Table 17 presents the completion rate of Skindex-29 total score, FACT-G total score, and EQ-5D-3L index score.**

Table 17: Cumulative Completion Rate of QoL Assessments at Selected Cycles

	Mogamulizumab (N=186)	Vorinostat (N=186)	Total (N=372)
Skindex-29 total score			
Baseline	173	179	352
Cycle 1	163	171	334
Cycle 3	121	98	219
Cycle 5	100	60	160
Cycle 7	84	41	125
FACT-G total score			
Baseline	177	184	361
Cycle 1	168	172	340
Cycle 3	123	99	222
Cycle 5	101	61	162
Cycle 7	84	41	125
EQ-5D-3L index score			
Baseline			366
Cycle 1	167	174	341
Cycle 3	123	100	223
Cycle 5	101	60	161
Cycle 7	84	41	125

Source: FDA statistical reviewer

Therefore, the statistical and COA review teams requested the Applicant to assess how the missing data impact their conclusions and to provide:
a. The number of patients who did not record the Skindex-29 total score at cycle 3 by reason (e.g., AE, death, loss to follow up, clinical progression, missed assessment, crossover) and by treatment.
b. For crossover patients, whether the Skindex-29 total scores were assessed at cycle 3 if the crossover occurred before cycle 3, and if so, to clarify whether the analyses included these measurements in the control arm.
c. Further information to understand the rationale for the missingness.

Table 18 and Table 19 summarize the Applicant's response to this IR.

Table 18: Availability of PRO Measurements at Cycle 3 (Including Reasons for Missing Data)

Skindex-29 Total Score		
Available Data	**Mogamulizumab**	**Vorinostat**
Yes	121 (65.76%)	98 (52.69%)
No (Reason Provided Below)	63 (34.24%)	88 (47.31%)
Progressive disease - clinical	10 (15.87%)	5 (5.68%)
Progressive disease per CTCL response	26 (41.27%)	5 (5.68%)
Adverse event	6 (9.52%)	4 (4.55%)
Crossover due to intolerance	N/A	12 (13.64%)
Crossover due to progression	N/A	46 (52.27%)
Investigator decision	2 (3.17%)	0 (0.00%)
Withdrawal of consent	7 (11.11%)	3 (3.41%)
Death	2 (3.17%)	1 (1.14%)
Other	1 (1.59%)	4 (4.55%)
Missing	9 (14.29%)	8 (9.09%)
FACT-G Total Score		
Available Data	Mogamulizumab	Vorinostat
Yes	123 (66.85%)	99 (53.23%)
No (Reason Provided Below)	61 (33.15%)	87 (46.77%)
Progressive disease - clinical	10 (16.39%)	5 (5.75%)
Progressive disease per CTCL response	26 (42.62%)	5 (5.75%)
Adverse event	6 (9.84%)	4 (4.60%)
Crossover due to intolerance	N/A	12 (13.79%)
Crossover due to progression	N/A	47 (54.02%)
Investigator decision	2 (3.28%)	0 (0.00%)
Withdrawal of consent	7 (11.48%)	3 (3.45%)
Death	2 (3.28%)	1 (1.15%)
Other	1 (1.64%)	4 (4.60%)
Missing	7 (11.48%)	6 (6.90%)
EQ-5D-3L Index Score		
Available Data	Mogamulizumab	Vorinostat
Yes	123 (67.21%)	100 (53.76%)
No (Reason Provided Below)	60 (32.79%)	86 (46.24%)
Progressive disease - clinical	10 (16.67%)	5 (5.81%)
Progressive disease per CTCL response	26 (43.33%)	5 (5.81%)
Adverse event	6 (10.00%)	4 (4.65%)
Crossover due to intolerance	N/A	12 (13.95%)
Crossover due to progression	N/A	47 (54.65%)
Investigator decision	1 (1.67%)	0 (0.00%)
Withdrawal of consent	7 (11.67%)	3 (3.49%)
Death	2 (3.33%)	1 (1.16%)
Other	1 (1.67%)	4 (4.65%)
Missing	7 (11.67%)	5 (5.81%)

Source: Applicant's response to FDA IR #31.

Table 19: Availability of PRO Measurements at Cycle 5 (Including Reasons for Missing Data)

Skindex-29 Total Score		
Available Data	**Mogamulizumab**	**Vorinostat**
Yes	100 (54.35%)	60 (32.26%)
No (Reason Provided Below)	84 (45.65%)	126 (67.74%)
Progressive disease - clinical	15 (17.86%)	6 (4.76%)
Progressive disease per CTCL response	39 (46.43%)	9 (7.14%)
Adverse event	10 (11.90%)	4 (3.17%)
Crossover due to intolerance	N/A	21 (16.67%)
Crossover due to progression	N/A	72 (57.14%)
Investigator decision	3 (3.57%)	0 (0.00%)
Withdrawal of consent	8 (9.52%)	4 (3.17%)
Death	2 (2.38%)	2 (1.59%)
Other	2 (2.38%)	6 (4.76%)
Missing	5 (5.95%)	2 (1.59%)
FACT-G Total Score		
Available Data	Mogamulizumab	Vorinostat
Yes	101 (54.89%)	61 (32.80%)
No (Reason Provided Below)	83 (45.11%)	125 (67.20%)
Progressive disease - clinical	15 (18.07%)	6 (4.80%)
Progressive disease per CTCL response	39 (46.99%)	9 (7.20%)
Adverse event	10 (12.05%)	4 (3.20%)
Crossover due to intolerance	N/A	21 (16.80%)
Crossover due to progression	N/A	72 (57.60%)
Investigator decision	3 (3.61%)	0 (0.00%)
Withdrawal of consent	8 (9.64%)	4 (3.20%)
Death	2 (2.41%)	2 (1.60%)
Other	2 (2.41%)	6 (4.80%)
Missing	4 (4.82%)	1 (0.80%)
EQ-5D-3L Index Score		
Available Data	Mogamulizumab	Vorinostat
Yes	101 (55.19%)	60 (32.26%)
No (Reason Provided Below)	82 (44.81%)	126 (67.74%)
Progressive disease - clinical	15 (18.29%)	6 (4.76%)
Progressive disease per CTCL response	39 (47.56%)	9 (7.14%)
Adverse event	10 (12.20%)	4 (3.17%)
Crossover due to intolerance	N/A	21 (16.67%)
Crossover due to progression	N/A	72 (57.14%)
Investigator decision	2 (2.44%)	0 (0.00%)
Withdrawal of consent	8 (9.76%)	4 (3.17%)
Death	2 (2.44%)	2 (1.59%)
Other	2 (2.44%)	6 (4.76%)
Missing	4 (4.88%)	2 (1.59%)

Source: Applicant's response to FDA IR #31.

***Statistical Review Comments*:**

- **It appears most of the missing data were missing by study design (i.e., death, AE, or progression of disease). Below Table 20 provides quality of completion results excluding the**

missing data by study design. The results indicate high levels of study compliance (>90%) which are consistent for all measures throughout the course of the study.

Table 20: Available and Missing Data at the Specified Time Points Among Patients in the CSP

Visit	Patients with Available Data[1] N (%)	Patients Missing All Data[1] N (%)
Skindex - 29[2]		
Baseline	352 (95.1)	18 (4.9)
Cycle 1	334 (95.4)	16 (4.6)
Cycle 3	219 (92.4)	18 (4.9)
Cycle 5	160 (95.8)	7 (4.2)
Cycle 7	125 (97.7)	3 (2.3)
FACT-G[3]		
Baseline	366 (98.9)	4 (1.1)
Cycle 1	345 (98.6)	5 (1.4)
Cycle 3	223 (94.1)	14 (5.9)
Cycle 5	162 (97.0)	5 (3.0)
Cycle 7	126 (98.4)	2 (1.6)
EQ-5D-3L[4]		
Baseline	366 (98.9)	4 (1.1)
Cycle 1	343 (98.0)	7 (2.0)
Cycle 3	223 (94.1)	14 (5.9)
Cycle 5	162 (97.0)	5 (3.0)
Cycle 7	126 (98.4)	2 (1.6)

Source: the Applicant's QoL Report Table 3
Abbreviation: CSP = cross-sectional population; EQ-5D-3L = European Quality of Life 5 dimensions 3 levels; FACT-G = Functional Assessment of Cancer Therapy-General; HUI = Health Utility Index; QoL = quality of life.
Of note: the total percentage was based on the number of patients who completed/had missing data divided by the total number
of patients ongoing at the time of data collection.
[1]The CSP population consisted of patients who had survived and maintained in the study into the Day 1 of each visit and had available QoL data for that visit.
[2]Patients were administered the Skindex-29 instrument at Baseline, and on Day 1 of every other treatment visit. The instrument includes 29 items assessing 3 domains: emotions, symptoms, and functioning. The items are scored on a 5-point Likert-type scale (never, rarely, sometimes, often, all the time). Responses to each item are transformed to a linear scale of 100 (never = 0, rarely = 25, sometimes = 50, often = 75, all the time = 100) for the purpose of scale score calculation. A scale score was the mean of a patient's responses to the items in a given scale and the composite Skindex-29 score was calculated as the average of the 3 scale scores to measure the overall impact on QoL. Higher scores indicate a higher impact of skin disease.
[3]Patients were administered the FACT-G instrument at Baseline, and on Day 1 of every other treatment visit. The instrument includes 27 items in the following 4 domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. The total FACT-G score is obtained by summing individual subscale scores. Response scores on negatively-phrased questions are reversed

before summing. Higher scores for the scales and subscales indicate better QoL.
[4]Patients were administered the EQ-5D-3L instrument at Baseline, and on Day 1 of every other treatment visit. The instrument includes 5 items which address the domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Items in questionnaire use the patient rating of 1 to 3, where 1 = "no problems" and 3 = "extreme problems." The scores of the 5 health state domains are scored into a single HUI. The EQ-VAS measures current health status from 0 to 100 where 0 is given the verbal label "worst imaginable health state" and 100 is given the label "best imaginable health state."

Clinical and statistical review comments:

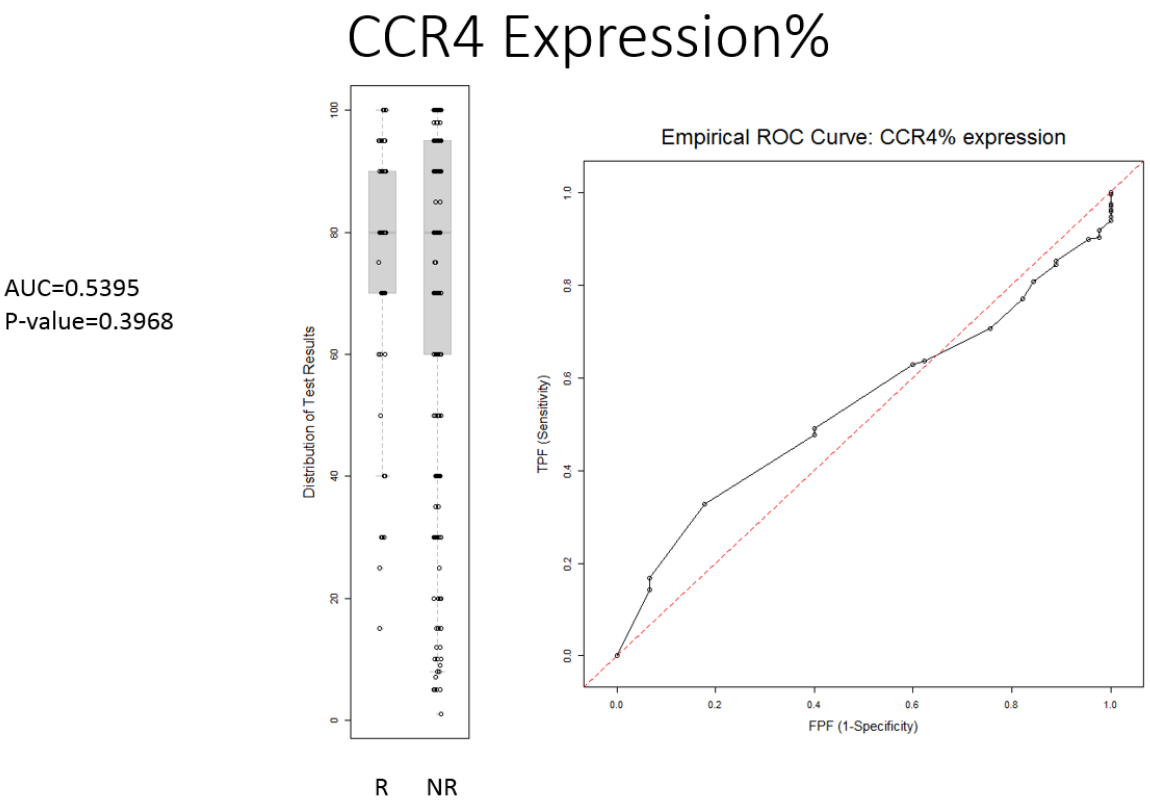
- **Due mainly to the large amount of missing data, including missing data by design (due to death, AE, disease progression) even at earlier time points, the Agency has concerns regarding the interpretability and meaningfulness of the PRO data. There are also limitations with the choice of QoL instrument.** (b) (4) **Refer to the COA consult for additional evaluations.**
- **The Skindex-29 scale is susceptible to recall error (past 4 weeks) and informs the frequency but not severity of symptoms** (b) (4)

Additional Analyses Conducted on the Individual Trial

ROC Curve for CCR4 Expression

As mogamulizumab targets cells expressing CCR4, the Applicant investigated whether testing patients prior to treatment for CCR4 expression status correlated with clinical activity as exhibited by a significant increase in PFS-INV within the mogamulizumab arm as compared to the vorinostat arm. The baseline CCR4 status of patient samples from this trial were analyzed using a preplanned analysis at the completion of the trial employing the CCR4 assay with a 10% cutoff for CCR4 expression status (i.e., CCR4 percent positive malignant lymphocytes ≥ 10% versus < 10%). The statistical review team conducted the analysis to explore the optimal cutoff for CCR4 expression status (Figure 15).

Figure 15: ROC Curve for CCR4 Expression



Source: FDA statistical reviewers

Statistical review comments:

1. The left-hand graph in the figure displays the distribution of CCR4 expression% by responder vs non-responder. It appears that there are fewer patients in the responder group than that in the non-responder group. The shadow box of each group represents its median and 25%-75% quartile. The medians of CCR4 expression% for the responder and the non-responder group were both 80%.
2. The right-hand graph in the figure is the ROC plot for using CCR4 classifier as a binary classifier, which indicates that classification accuracy of CCR4 is similar with random guess.
3. The two numbers on the left hand of the figure. AUC is a number to represent the performance of the binary classifier, CCR4. The AUC for this CCR4 is close to 0.5, which tells us that the CCR4 classification accuracy is not better than random guess.
4. In addition, is equivalent to the probability that the classifier will rank a randomly chosen positive instance higher than a randomly chosen negative instance. The p-value from Wilcox Rank Sum test shows that the probability that the CCR4 ranked a randomly chosen positive instance is not different from that ranked a randomly chosen negative instance.

8.1.3 Assessment of Efficacy Across Trials

KW-0761-US-001, a 42-patient, phase 1/2 dose-escalation trial of mogamulizumab, included 32 patients with MF/SS treated at the 1.0 mg/kg dose level (Table 5). Efficacy, based on ORR-INV per global composite response criteria, was consistent with that observed in Study 0761-010. Of the 38 patients with MF/SS evaluated for efficacy (median 5 prior systemic therapies), the reported ORR with all dose levels combined was 37% (8% CR, 29% PR). By histology, ORR was 47% in SS and 29% in MF (source: KW-0761-US-001 CSR).

8.1.4 Integrated Assessment of Effectiveness

In adult patients with MF or SS treated with at least one prior systemic therapy, Study 0761-010 (a randomized, open-label, actively controlled trial) demonstrated that mogamulizumab at the recommended dose-schedule resulted in a statistically significant improvement in PFS compared to vorinostat. This was in general a poor-risk patient population; in the 372 patients combined (55% having MF, 45% SS), the median number of prior systemic therapies was 3, 40% of patients had ≥ 4 prior systemic therapies, and 52% had stage IV disease.

For investigator-assessed PFS (the primary study endpoint), the HR (mogamulizumab/vorinostat) was 0.53 (95% CI: 0.41, 0.69; 2-sided stratified log rank test $p<0.0001$) on ITT analysis. The estimated median PFS was 7.6 months (95% CI: 5.6, 10.2) for the 186 patients randomized to mogamulizumab and 3.1 months (2.8, 4.0) for the 186 patients randomized to vorinostat, with an estimated median follow up of 13 months and 10 months, respectively.

The results of the primary analysis were supported by blinded independent review, with a HR for PFS of 0.64 (95% CI: 0.50, 0.84). The estimated median PFS was 6.6 months (95% CI: 5.6, 9.2) for mogamulizumab and 3.8 months (95% CI: 3.0, 4.6) for vorinostat. Results of sensitivity analyses of PFS confirm the treatment effect of mogamulizumab.

Notably, although there was a statistically significant difference in the HR for PFS-INV in the mogamulizumab vs. vorinostat arms, the difference in estimated median PFS was modest (on the order of several months). However, in patients with relapsed or refractory disease after prior systemic therapy, the observed difference can be clinically meaningful.

The trial also demonstrated improvement in ORR with mogamulizumab, using global composite response criteria. The confirmed ORR per investigator was 28% with mogamulizumab compared to 5% ORR with vorinostat ($p<0.0001$). The responses to mogamulizumab were higher in blood and skin than in lymph nodes and viscera. A similar ORR to mogamulizumab was reported in Study 0761-US-001.

The poor performance of the control arm is notable. There is a disconnect between the low response rate (5%) with vorinostat in Study 0761-010 vs. the ~30% response rate to vorinostat historically (Table 1). Cross-study comparisons are limited in part by patient heterogeneity and differences in response criteria. The discrepancies may be attributable in part to the more stringent response criteria in 0761-010 (global composite response criteria with confirmation ≥ 4 weeks later) than in prior studies with vorinostat (skin-limited response criteria without a minimum required duration of response). Another possible factor is inadequate exposure to vorinostat in 0761-010; the median vorinostat exposure was only ~2 cycles prior to crossover to mogamulizumab, which occurred in >70% of patients randomized to vorinostat.

Although Study 0761-010 suggests more symptom/function improvement with mogamulizumab than vorinostat, as measured by the Skindex-29 total score, the FACT-G total score, and EQ-5D-3L index score, no asserted conclusions can be made on improvement of PRO outcomes due to the large amount of missing data including at earlier time points; inconsistent results with 1 positive and 2 negative findings depending on the scale; and limitations of the QoL instruments.

In conclusion, in Study 0761-010, a large, international, randomized controlled trial that used stringent global response assessment criteria, mogamulizumab was found to be superior to an established standard of care in the treatment of MF/SS with statistically significant increases in PFS (primary endpoint) and ORR (key secondary endpoint). The study results show some differences favoring mogamulizumab in PRO measures (key secondary endpoints) of symptom control and functional status. However, no asserted conclusions can be drawn due to the large portion of missing data and limitations of the QoL instruments. The efficacy outcomes with mogamulizumab in this trial suggest a positive effect for its use in adult patients with relapsed or refractory MF or SS after at least one prior systemic therapy.

The Applicant proposed a broader indication for mogamulizumab, namely for the treatment of CTCL after prior systemic therapy. Because Study 0761-010 was restricted to adults with MF and SS, there are no submitted data to support the use of mogamulizumab in other types of CTCL, such as the primary cutaneous CD30+ lymphoproliferative disorders. For clarity and to avoid postremission (maintenance) use of mogamulizumab, the clinical team recommends to specify that mogamulizumab is for relapsed or refractory MF or SS after at least one prior systemic therapy. This is in alignment with the 0761-010 entry criteria.

Restricting the indication to CCR4-expressing disease would be reasonable as CCR4 expression in MF/SS, while frequent, is heterogeneous, there is a paucity of data in cases of “low” CCR4 expression (defined in this protocol as < 10%), and there are no data available in cases of undetectable CCR4 expression. However, the trial enrolled patients regardless of CCR4 expression status, the 290/372 cases with available CCR4 data all had detectable CCR4 expression (by IHC of skin biopsies), and the minimum CCR4 expression level for mogamulizumab activity is not defined. Therefore, the clinical review team recommends to not

restrict the indication to CCR4-expressing disease and to instead describe the CCR4 expression data in the efficacy section of the PI.

The recommended dose-schedule of mogamulizumab is 1 mg/kg as an intravenous infusion over at least 60 minutes on days 1, 8, 15 and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent 28-day cycle, with treatment continued until disease progression or unacceptable toxicity.

8.2 Review of Safety

8.2.1 Safety Review Approach

The primary safety analysis considers all-causality treatment-emergent AEs (TEAEs) in recipients of any study drug on Study 0761-010. TEAEs were defined as AEs that are new or worsened from baseline grade or are unknown to have worsened from baseline. AEs indicating PD were discounted from the safety analysis. For Study 0761-010, the primary safety reporting window was until 90 days after last study drug or initiation of NALT, whichever earlier. Use of investigator attribution (b) (4) substantially underestimated the potential risks and thus was not considered in this safety review.

The Applicant reported AEs using single MedDRA preferred terms (PTs). For increased sensitivity, FDA instead used a combination of ungrouped and custom grouped PTs, as defined in the Appendix. Unless otherwise noted, all presented analyses use the FDA grouping. For increased sensitivity, in contrast to the Applicant, FDA also combined PTs involving more than one system organ class (SOC) under the most frequently affect SOC.

The clinical reviewer used JMP 13, supplemented by the MedDRA Adverse Event Diagnosis Tool, to conduct safety analyses using the data analysis datasets.

8.2.2 Review of the Safety Database

Overall Exposure
The number of patients exposed to study treatment was adequate for safety review, as summarized below.

Table 21: Size of Safety Populations in Study 0761-010

		Study 0761-010 safety population (N = 370)
Mogamulizumab	Randomized treatment	184
	Crossover from vorinostat	135 [a]
	Pooled (randomized + crossover)	319
Vorinostat	Randomized treatment	186

[a] 135 / 138 patients treated after crossover

Exposure is summarized in Table 22 and Figure 16. The median duration of randomized treatment was 2-fold longer in the mogamulizumab arm. Notably, 39% of the vorinostat arm had < 2.0 months of study treatment, compared to 22% of the mogamulizumab arm. Most patients on vorinostat (74%) crossed over to moga, typically due to inefficacy (80%), after a median exposure to vorinostat of 2.5 months (source: FDA analysis). The median exposure to mogamulizumab was similar during randomized treatment (6 cycles) and crossover (7 cycles).

Table 22: Exposure to Study Treatment (0761-010)

Parameter		MOGA (N = 184)		VORINOSTAT (N = 186)	
Exposure (Randomized Treatment)					
Tx duration, months	Median	5.6		2.8	
	Range	0.0 – 50.4		0.1 – 38.2	
	Q1, Q3	2.3, 11.5		1.6, 5.6	
Cycles initiated [a]	Median	6 [b]		3	
	Range	1 – 51		1 – 38	
	Q1, Q3	3, 13		2, 6	
Relative dose intensity	Mean	94%		89%	
	≥ 90%	142	(77%)	_	
	≥ 80%	172	(93%)	_	
Patients on tx by month	≥ 2 mo	143	(78%)	112	(60%)
	≥ 3 mo	120	(65%)	81	(44%)
	≥ 6 mo	89	(48%)	41	(22%)
	≥ 12 mo	43	(23%)	20	(11%)
	≥ 24 mo	12	(7%)	5	(3%)
Action Due to AE (Randomized Treatment)					
Treatment withdrawn		34	(18%)		
Dose interrupted		81	(44%)		
Exposure (Crossover)					

Table 22: Exposure to Study Treatment (0761-010)

Parameter		MOGA (N = 184)		VORINOSTAT (N = 186)	
Crossover to moga	Yes	N/A		138 [c]	(74%)
	Due to inefficacy [d]			111	(80%)
	Due to intolerance			27	(20%)
Vorinostat exposure before crossover, months	Median	N/A		2.5	
	Range			0.5 – 36.1	
	Q1, Q3			1.6, 4.6	
Moga cycles initiated after crossover [c]	Median	N/A		7	
	Range			1 – 52	
	Q1, Q3			3, 13	

Source: FDA analysis

a Cycle length is 28 days for either arm.

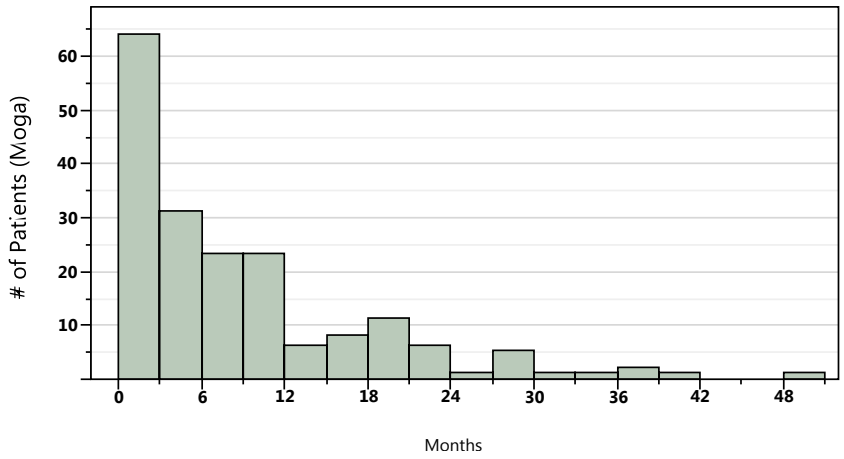
b Median 14 infusions (range, 1 – 100)

c 135 treated after crossover

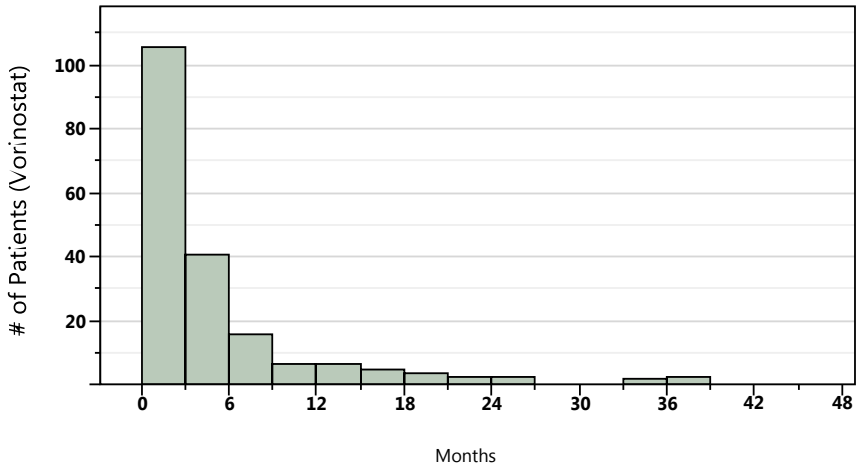
d Includes 6 patients with clinical progression not meeting formal PD criteria (source: CSR Table 4.1.2)

Figure 16: Distribution of Exposure to Study Treatment (Safety Population)

Mogamulizumab Exposure During Randomized Treatment (N = 184)



Vorinostat Exposure (N = 186)



Source: FDA analysis

Of the 370 treated patients in Study 07610-010, 30 (8%) remained on randomized treatment as of the 6/2017 cutoff (mogamulizumab, 22 patients or 12%; vorinostat, 8 patients or 4%). In the vorinostat arm, of the 138/186 patients (74%) who crossed over to mogamulizumab, 25 (18%) remained on treatment.

Relevant Characteristics of the Safety Population

The baseline characteristics of the primary safety population (Table 23) are virtually identical to those of the primary efficacy population.

Table 23: Baseline Characteristics of Primary Safety Population (N = 370)

Parameter		MOGA (N = 184)		VORINOSTAT (N = 186)	
Age, y	Median (range)	63	(25 – 101)	65	(25 – 89)
	≥ 65	85	(46%)	97	(52%)
Sex	Male	107	(58%)	107	(58%)
Race	White	124	(67%)	135	(73%)
	Black	24	(13%)	13	(7%)
	Asian	12	(7%)	7	(4%)
	Other	24	(13%)	31	(17%)
Region	US	97	(53%)	103	(55%)
	Japan	9	(5%)	6	(3%)
	Other	78	(42%)	77	(41%)
ECOG PS	0-1	182	(99%)	186	(100%)
	2	2	(1%)	0	(0%)
Diagnosis	MF	105	(57%)	99	(53%)
	SS	79	(43%)	87	(47%)
# Systemic therapies	Median (range)	3	(1 – 18)	3	(0 – 14)
	1	28	(15%)	40	(22%)
	2	39	(21%)	38	(20%)
	3	39	(21%)	37	(20%)
	≥ 4	78	(42%)	70	(38%)

Source: CSR Table 14.1.2.2

Review comment:

- **Because of the longer exposure to mogamulizumab, AEs in general are expected to be increased compared to the vorinostat arm. This can make characterization of the relative AE profiles challenging. Exposure-adjusted safety analyses could be considered, but would not affect regulatory decisions or the clinical review team's recommended labeling.**

Adequacy of the Safety Database

The safety database was adequate for review. Inadequacies were addressed through multiple information requests.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events
AEs were graded in using National Cancer Institute CTCAE version 4 and were classified using MedDRA terminology. Mapping of verbatim terms to MedDRA PTs appeared acceptable.

As mentioned in Section 8.2, the Applicant's safety analyses used ungrouped PTs, whereas FDA created a customized grouping of PTs (b) (4)

(b) (4)

Routine Clinical Tests
The schedule of routine clinical testing was adequate for safety evaluation.

8.2.4 Safety Results

8.2.4.1 Deaths
In Study 0761-010, fatal AEs within 90 days of the last mogamulizumab dose occurred in 2.2% (7/319) of patients as of the safety update report, based on FDA adjudication (Table 24).

Table 24: Non-PD Deaths within 90 Days of Last Study Treatment

Any mogamulizumab (N = 319)	
Total [a]	**7 (2.2%)**
Infection	2
Polymyositis and secondary pneumonia	1
Acute hypoxemia and arrhythmia; preceding sepsis	1
Hypoalbuminemia, anorexia, general decline; preceding sepsis and large protein loss of unclear etiology	1
Gastrointestinal hemorrhage	1
Pulmonary embolism	1
Vorinostat without crossover (N = 51)	
Total	**7 (13.7%)**
Infection	5
Pulmonary embolism	1
Cause unclear	1

Source: FDA analysis
Data cutoff date: 9/1/2017 (SUR)
a 4 death after randomized treatment, 3 after crossover.

8.2.4.2 Serious Adverse Events
SAEs, regardless of causality and excluding disease progression/MF, were reported in 36% of the moga randomized arm and 24% of the vorinostat arm. Table 25 provides a breakdown of

SAEs according to SOC and PT, excluding the crossover period. The mogamulizumab arm had a ≥ 2% but ≤ 5% higher reported incidence of:

- SAEs in SOCs involving infections, general disorders/administration site conditions, and injury/poisoning/procedural complications.
- SAEs with a PT or grouped PT of pneumonia, pyrexia, and hepatitis.

In patients randomized to mogamulizumab, 64% of patients had at least one infection-related AE, and 16% of patients had at least one SAE in the infection SOC. Infections are reviewed further in Section 8.2.5. SAEs after crossover to mogamulizumab are summarized in Table 28.

SAEs reported in > 2% of patients randomized to mogamulizumab were pneumonia (5%), sepsis (4%), pyrexia (4%) and skin infection (3%); other SAEs, each reported in 2%, included hepatitis, pneumonitis, rash, IRR, lower respiratory tract infection, and renal insufficiency.

Table 25: SAEs with Randomized Treatment

Event	Randomized Treatment			
	MOGA (N = 184)		VORINOSTAT (N = 186)	
	n	%	n	%
Age grade ≥ 3 AE	79	43%	86	46%
Age grade ≥ 4 AE	13	7%	15	8%
Any SAE	66	**36%**	45	24%
SAE by System Organ Class				
Infections, infestations	30	**16%**	20	11%
General disorders, administration site conditions	11	**6%**	7	4%
Respiratory, thoracic, mediastinal	9	5%	5	3%
Injury, poisoning, procedural	7	**4%**	2	1%
Neoplasms	5	3%	2	1%
Metabolism and nutrition	6	3%	4	2%
Musculoskeletal, connective tissue	6	3%	3	2%
Gastrointestinal	3	2%	8	4%
Blood and lymphatic system	1	1%	5	3%
Cardiac	4	2%	2	1%
Skin and subcutaneous tissue	4	2%	3	2%
Vascular	4	2%	1	1%
Nervous system	3	2%	2	1%
Renal and urinary	3	2%	3	2%
SAE by Preferred Term or Grouped Preferred Term				
Pneumonia	9	5%	3	2%
Pyrexia	8	4%	1	1%
Sepsis	8	4%	7	4%
Skin infection	6	3%	9	5%
Hepatitis	4	2%	0	0%
Lower respiratory tract infection	4	2%	1	1%
Hypercalcemia	3	2%	0	0%
Infusion related reaction	3	2%	0	0%
Pneumonitis	3	2%	0	0%
Rash	3	2%	1	1%
Renal insufficiency	3	2%	3	2%
Thrombosis or thromboembolism	2	1%	5	3%
Musculoskeletal pain	1	1%	3	2%
Fatigue	0	0%	3	2%

Source: FDA analysis
Data cut: 6/2017

Table 25: SAEs with Randomized Treatment

Event	Randomized Treatment			
	MOGA (N = 184)		VORINOSTAT (N = 186)	
	n	%	n	%

Includes all-cause events reported up to 90 days after last dose of randomized treatment and selected events afterwards. Excludes events reported during crossover.

Bolded categories are involved ≥ 2.0% more in the moga arm.

8.2.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

During randomized treatment, 18% of patients discontinued mogamulizumab due to AEs. The leading cause was rash or drug eruption (7.1%), followed by infection (source: FDA analysis).

8.2.4.4 Significant Adverse Events

Refer to Section 8.2.5 for discussion of the following significant AEs: infection, drug eruption, IRR, autoimmune disease, and potential complications of allogeneic HSCT.

Tumor lysis syndrome (TLS): [redacted] (b) (4) On FDA analysis, grade ≥ 3 hyperuricemia occurred more often with randomized mogamulizumab treatment (29%) than vorinostat (11%), as did grade 4 hyperuricemia and any-grade hyperuricemia reported as an AE (Section 8.2.4.6). However, in the AE dataset, of the 319 recipients of mogamulizumab during either randomized or crossover treatment, only two (< 1%) had TLS reported as an AE, raising the possibility of underreporting. In response to an IR to evaluate the TLS rate based on CRF review, the Applicant identified TLS in 1.6% of mogamulizumab recipients in Study 0761-010 (source: response to 11/24/17 IR).

Cardiac complications: [redacted] (b) (4) citing 3 cases across all mogamulizumab trials, as does the ISS (Section 5.4.5). However, FDA analysis of the AE dataset using grouped PTs identified 8 cardiac AEs in Study 0761-010 alone: cardiac failure (grouped term) in 3/319 recipients of mogamulizumab and myocardial ischemia (angina pectoris) or infarction in 5.

Review comment:

- **Based on the submitted data, TLS and cardiac complications after mogamulizumab** [redacted] (b) (4)

8.2.4.5 Treatment Emergent Adverse Events and Adverse Reactions

A. TEAEs with Randomized Treatment

Refer to Section 8.2.5 for discussion of the following significant AEs: infection, drug eruption, IRR, complications of allogeneic HSCT after mogamulizumab, and autoimmune complications. FDA grouping of PTs is defined in the Appendix.

During the randomized treatment period, common (≥ 10%) all-grade AEs reported ≥ 2% more with mogamulizumab than vorinostat were rash, IRR, URTI, skin infection, musculoskeletal pain, pyrexia, and mucositis (Table 26). The mogamulizumab arm had ≥ 2% but < 5% more grade ≥ 3 rash and grade ≥ 3 pneumonia.

Table 26: AEs Reported in ≥ 5% of Safety Population and ≥ 2% More with Mogamulizumab

SOC or main SOC and PT [a]	MOGA (N = 184)				VORINOSTAT (N = 186)			
	All grades		Grade ≥ 3		All grades		Grade ≥ 3	
	n	%	n	%	n	%	n	%
Skin, subcutaneous tissue								
Rash (including drug eruption)	64	35%	9	5%	20	11%	3	2%
Drug eruption (flagged)	45	24%	9	5% [b]	1	< 1%	0	0%
Hypersensitivity	11	6%	2	1%	3	2%	0	0%
Injury, poisoning, procedural								
IRR	61	33%	3	2%	0	0%	0	0%
Fall	11	6%	2	1%	3	2%	0	0%
Infections, infestations								
URTI	40	22%	0	0%	29	16%	2	1%
Skin infection	35	19%	5	3%	25	13%	7	4%
Candidiasis	16	9%	0	0%	6	3%	0	0%
Folliculitis	14	8%	0	0%	4	2%	1	1%
Pneumonia	11	6%	9	5%	3	2%	3	2%
Otitis	9	5%	0	0%	4	2%	0	0%
Herpesvirus infection	9	5%	3	2%	3	2%	0	0%
Musculoskeletal, connective tissue								
Musculoskeletal pain	40	22%	1	1%	31	17%	5	3%
General disorders, administration site								
Pyrexia	31	17%	1	1%	12	6%	0	0%
Gastrointestinal								
Mucositis	22	12%	2	1%	11	6%	0	0%

Table 26: AEs Reported in ≥ 5% of Safety Population and ≥ 2% More with Mogamulizumab

SOC or main SOC and PT [a]	MOGA (N = 184)				VORINOSTAT (N = 186)			
	All grades		Grade ≥ 3		All grades		Grade ≥ 3	
	n	%	n	%	n	%	n	%
Investigations								
Hyperuricemia	14	8%	0	0%	5	3%	1	1%
Weight increase	14	8%	1	1%	2	1%	0	0%
Hypomagnesemia	11	6%	0	0%	4	2%	0	0%
Psychiatric								
Depression	13	7%	2	1%	6	3%	0	0%
Cardiac								
Arrhythmia	9	5%	2	1%	5	3%	0	0%
Eye disorders								
Conjunctivitis	9	5%	0	0%	2	1%	0	0%

[a] Includes grouped terms

[b] All reported as grade 3.

Source: FDA analysis

Bolded terms indicate ≥ 2.0% more Grade ≥ 3 AEs in the moga arm.

Other common AEs associated with mogamulizumab, regardless of incidence relative to the vorinostat, included (per Table 26 and Table 27):

- General disorders: fatigue (31%), edema (16%)
- Gastrointestinal disorders: diarrhea (27%), nausea (16%), constipation (13%)
- Blood and lymphatic system disorders: thrombocytopenia (14%), anemia (12%)
- Nervous system disorders: headache (14%)
- Vascular disorders: hypertension (10%)
- Respiratory disorders**:** cough (11%)

Review comments:

- (b) (4) **Use of grouped PTs is preferable for more sensitive and informative labeling.**
- (b) (4)

In both treatment arms, AEs reported in ≥ 20% included fatigue and diarrhea. With mogamulizumab, other AEs reported in ≥ 20% were, in addition to IRR, rash, musculoskeletal

pain, and URTI. In contrast, with vorinostat, the other AEs reported in ≥ 20% were nausea, thrombocytopenia, renal insufficiency, and decreased appetite (Table 27).

Table 27: Comparison of AEs Reported in ≥ 10% of Either Arm

PT or Grouped PT	MOGA (N = 184)		VORINOSTAT (N = 186)	
	All grades		All grades	
	n	%	n	%
Rash	64	35%	20	11%
IRR	61	33%	0	0%
Fatigue	57	31%	93	50%
Diarrhea	50	27%	119	64%
Musculoskeletal pain	40	22%	31	17%
URTI	40	22%	29	16%
Skin infection	35	19%	25	13%
Pyrexia	31	17%	12	6%
Nausea	30	16%	78	42%
Edema	30	16%	29	16%
Thrombocytopenia	25	14%	77	41%
Headache	25	14%	27	15%
Constipation	23	13%	34	18%
Mucositis	22	12%	11	6%
Anemia	22	12%	26	14%
Cough	21	11%	20	11%
Hypertension	18	10%	27	15%
Renal insufficiency	16	9%	74	40%
Hyperglycemia	16	9%	24	13%
Xerosis	15	8%	30	16%
Dizziness	15	8%	20	11%
Decreased appetite	14	8%	45	24%
Alopecia	13	7%	35	19%
Vomiting	12	7%	24	13%
Weight decreased	11	6%	32	17%
Abdominal pain	10	5%	34	18%
Muscle spasms	9	5%	30	16%
Dysgeusia	7	4%	54	29%

Source: FDA analysis
Excludes AEs reported during crossover treatment with moga.
Bolded terms occur ≥ 2.0% more in the moga arm.

Review comment:

- **Because mogamulizumab is a NME and in a different drug class than vorinostat, the PI should describe not only the AEs occurring more often with mogamulizumab, but all**

common AEs associated with mogamulizumab. Otherwise, there is a considerable amount of safety data that is not communicated (Table 27).

B. TEAEs in Crossover and Pooled Analyses

AEs and SAEs after crossover to mogamulizumab

In the crossover period (N = 135), the median exposure to mogamulizumab was 7 cycles (source: FDA analysis). During crossover treatment, grade ≥ 3 AEs were reported in 37% and SAEs in 29% of mogamulizumab recipients. Compared to the randomized mogamulizumab arm, the crossover arm had similar reported rates of grade ≥ 3 AEs (37% with crossover vs. 43% with randomized mogamulizumab treatment), grade ≥ 4 AEs (5% vs. 7%), and SAEs (29% vs. 36%). The overall patterns of SAEs and all-grade AEs were also similar (Table 28). Whether mogamulizumab was the initial or subsequent study treatment,

- SAEs most often involved the SOCs of infection and general/administration site conditions (10% and 6%, respectively, in both cases).
- Any-grade AEs most often involved rash and IRR (>30% in both cases).

Table 28: AEs and SAEs After Crossover to Mogamulizumab

Event	CROSSOVER TO MOGA (N = 135)	
	n	%
Any grade ≥ 3 AE	50	37%
Any grade ≥ 4 AE	7	5%
Any SAE	39	29%
SAE by SOC in ≥ 2%		
Infections, infestations	13	10%
General, administration site	8	6%
Injury, poisoning, procedural	6	4%
Neoplasms	6	4%
Gastrointestinal	5	4%
Hepatobiliary	4	3%
Cardiac	3	2%
Musculoskeletal, connective tissue	3	2%
SAE by PT in ≥ 2%		
IRR	4	3%
Skin infection	3	2%
Hepatitis	3	2%
Chest pain	3	2%
Nonmelanoma skin cancer	3	2%

Table 28: AEs and SAEs After Crossover to Mogamulizumab

Event	CROSSOVER TO MOGA (N = 135)	
	n	%
Any-grade AEs in >10% by PT or Grouped PT [a]		
IRR	51	38%
Rash, including drug eruption	52	39%
Drug eruption (flagged) [b]	35	26%
Musculoskeletal pain	28	21%
URTI	25	19%
Fatigue	24	18%
Skin infection	23	18%
Diarrhea	23	18%
Hepatitis [c]	16	12%
Mucositis	16	12%
Edema	16	12%
Headache	16	12%
Pyrexia	16	12%

Source: FDA analysis
[a] AEs involved in 10% were thrombocytopenia, constipation, abdominal pain, arthralgia, and folliculitis.
[b] 5 patients (4%) grade 3.
[c] In the randomized moga arm, 13/184 (7%) patients had an AE of hepatitis, with 2% (3/184) having grade ≥ 3 hepatitis.

8.2.4.6 Laboratory Findings

Table 29 below summarizes common (≥ 10% of either arm) TE laboratory abnormalities in the 0710-01 safety population, excluding the crossover period. In reporting TE laboratory abnormalities, a change from grade 3 at baseline to grade 4 was included in the "grade 3-4" column, as was a change from grade ≤ 2 at baseline to grade ≥ 3.

In both arms, most detected treatment-emergent (TE) laboratory abnormalities were grade 1-2. Of the common (≥ 10%) identified any-grade TE laboratory abnormalities, the following occurred ≥ 2.0% more in the mogamulizumab arm: Absolute CD4 count decrease, anemia, leukopenia, lymphopenia, hypoalbuminemia, hypocalcemia, hyperuricemia, hypophosphatemia, hypomagnesemia, hypoglycemia, and hypercalcemia.

Of the grade 3-4 abnormalities, most were grade 3 in both arms. Of the grade 3-4 TE laboratory abnormalities detected in ≥ 5% of either arm, the mogamulizumab arm had ≥ 2% more grade 3-4 hyperuricemia (29%, vs. 11% with vorinostat) and grade 3-4 lymphopenia (16% vs. 12%) including grade 3-4 CD4 lymphopenia (43% vs. 8%). The analysis of CD4 lymphopenia is limited

by missing data in the majority of the overall safety population (Table 29). The only grade 4 TE abnormalities detected ≥ 2% more in the mogamulizumab arm were lymphopenia (5% grade 4, vs. 1% with vorinostat) and hyperuricemia (6% vs. 3%).

Table 29: Common (≥ 10%) TE Laboratory Abnormalities (Randomized Treatment)

Parameter [a]	MOGAMULIZUMAB (N = 184)						VORINOSTAT (N = 186)					
	Any grade		G 3-4		G 4		Any grade		G 3-4		G 4	
	n	%	n	%	n	%	n	%	n	%	n	%
HEMATOLOGY												
CD4 count decrease [b]	62	63%	43	43% [c]	10	1%	6	17%	3	8%	1	< 1%
Anemia	64	35%	3	2%	0	0%	78	42%	4	2%	0	0%
Leukopenia	61	33%	4	2%	2	1%	38	20%	3	2%	0	0%
Lymphopenia	57	31%	29	16% [c]	9	5% [c]	22	12%	7	4%	2	1%
Thrombocytopenia	53	29%	0	0%	0	0%	124	67%	13	7%	4	2%
Neutropenia	18	10%	3	2%	1	< 1%	25	13%	6	3%	1	< 1%
CHEMISTRY												
Hyperglycemia	120	65%	8	4%	0	0%	127	68%	19	10%	0	0%
Hypoalbuminemia	62	34%	3	2%	0	0%	50	27%	4	2%	0	0%
Hypocalcemia	56	30%	5	3%	3	2%	37	20%	3	2%	2	1%
Hyperuricemia	54	29%	54	29% [c]	11	6% [c]	20	11%	20	11%	6	3%
Hypophosphatemia	48	26%	10	5%	2	1%	44	24%	9	5%	1	< 1%
AST increased	46	25%	3	2%	0	0%	54	29%	2	1%	0	0%
ALT increased	34	18%	2	1%	0	0%	39	21%	1	< 1%	0	0%
Creatinine increase	34	18%	1	< 1%	1	< 1%	120	65%	1	< 1%	1	< 1%
Alk phos increased	31	17%	0	0%	0	0%	32	17%	2	1%	0	0%
Hypomagnesemia	31	17%	1	< 1%	0	0%	15	8%	1	< 1%	1	< 1%
Hypoglycemia	24	13%	0	0%	0	0%	15	8%	1	< 1%	1	< 1%
Hypercalcemia	22	12%	1	< 1%	0	0%	15	8%	1	< 1%	0	0%
Bilirubin increased	16	9%	0	0%	0	0%	35	19%	1	< 1%	0	0%
Hypermagnesemia	14	8%	1	< 1%	0	0%	49	26%	4	2%	0	0%

Table 29: Common (≥ 10%) TE Laboratory Abnormalities (Randomized Treatment)

Parameter [a]	MOGAMULIZUMAB (N = 184)						VORINOSTAT (N = 186)					
	Any grade		G 3-4		G 4		Any grade		G 3-4		G 4	
	n	%	n	%	n	%	n	%	n	%	n	%

Source: FDA analysis

Represents all-cause laboratory abnormalities that are new, worsened from baseline, or unknown if worsened, during and up to at least 90 days post treatment, if ≥ 2.0% more in moga arm for any grade or grade ≥ 3 abnormalities.

[a] **Bolded labs** have ≥ 2% higher incidence of any-grade abnormalities in the moga arm

[b] Denominator (# of patients with ≥ 1 post-treatment measurement): moga 99, vorinostat 36

[c] ≥ 2% higher in moga arm

For patients who crossed over from vorinostat to mogamulizumab, the Applicant reported that shifts from grade < 3 to grade ≥ 3 laboratory values occurred with similar frequency during the crossover portion as during randomized treatment with mogamulizumab (source: CSR Section 12.4.2.1.1).

Review comments:

- **Because of the substantially longer exposure to randomized study treatment in the mogamulizumab arm, the overall higher incidence of AEs and TE laboratory abnormalities is not unexpected.**
- **The CSR reports shifts from grade ≤ 2 to grade ≥ 3 labs. This misses TE shifts from grade ≤ 1 to grade 1 or 2, as well as shifts from grade 3 to grade 4.**
- **TE CD4 lymphopenia was evaluable in only 54% (99/184) of the mogamulizumab arm and 19% (36/186) of vorinostat arm, thereby limiting the precision of the estimates.**
- **Hyperuricemia is a leading treatment-emergent abnormality in the mogamulizumab arm. However, the preferred term of "tumor lysis syndrome" was reported rarely as an AE (< 1%). Refer to Section 8.2.4.4 for further discussion.**

Hy's law screen: Among the 319 mogamulizumab recipients combined, hepatitis was a reported AE in 8% (25/319) and an SAE in 2% (6/319; Table 25 and Table 28). The Applicant conducted a Hy's law screen (bili ≥ 2 x ULN, alk phos < 2 x ULN, and ALT > 3 x ULN, with 0-14 days between ALT and bilirubin peak) and did not identify confirmed Hy's law cases in recipients of mogamulizumab. One case was identified on the vorinostat arm (source: response to 11/24/2017 and 12/18/2017 IRs).

8.2.4.7 Vital Signs

The Applicant identified no overall trends for significant changes in vital signs during randomized treatment with mogamulizumab or vorinostat (source: CSR Section 12.5).

8.2.4.8 Electrocardiograms

Not evaluated comprehensively in this study.

8.2.4.8 QT

Refer to Section 6.3.

8.2.4.9 Immunogenicity

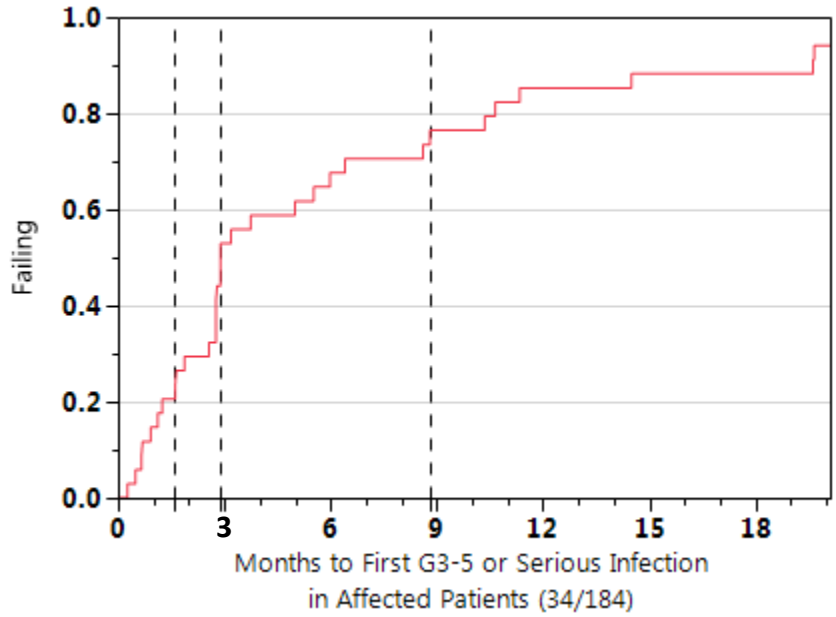
Refer to Section 6.3.

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Infection

In Study 0761-010, 18% of patients randomized to mogamulizumab (34/184) had grade ≥ 3 infection or an infection-related SAE. Infection-related SAEs in ≥ 2% included pneumonia (5%), sepsis (4%), skin infection (3%), and lower respiratory tract infection (2%), per Section 8.2.4.2. The time to grade ≥ 3 or serious infection or the first such infection, among affected patients, is shown in Figure 17. The median time to event or first event was 2.9 months (Q1 - Q3: 1.6 – 8.8 months).

Figure 17: Time to Grade ≥ 3 or Serious Infection in Mogamulizumab Arm



Source: FDA analysis

The Applicant reported that exposure-adjusted incidence of infection AEs, based on the infection SOC, were numerically lower in the mogamulizumab arm than the vorinostat arm (source: SCS Section 2.7.4.2).

Review comment:

- **Because infection is common in patients with CTCL, it is difficult to determine to what degree the treatment regimen vs. the underlying disease contributes to these infection rates. Nevertheless, a Warning and Precaution on infection is justifiable in in the mogamulizumab PI.**

8.2.5.2 Drug Eruption

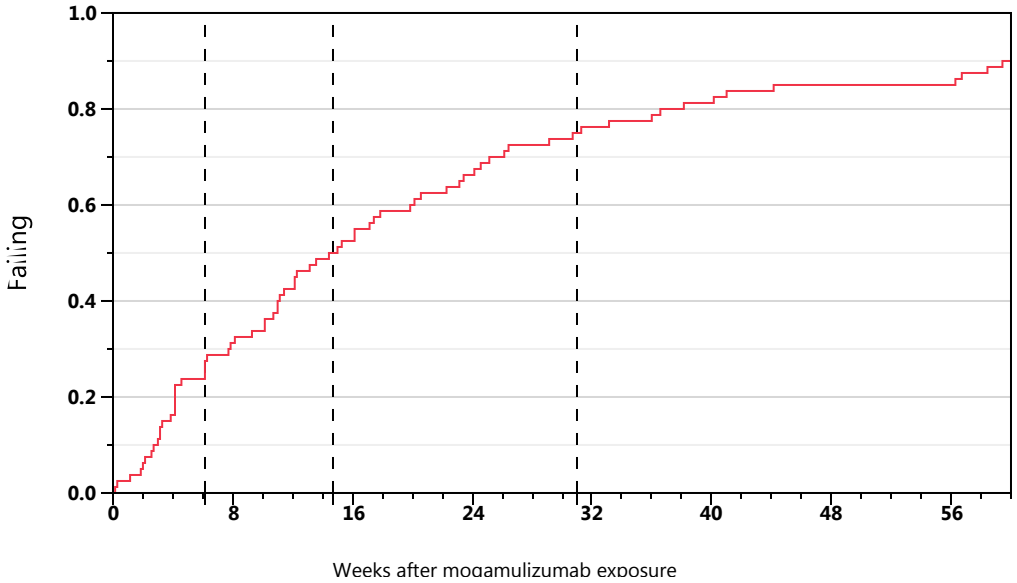
Rash (drug eruption) is one of the most common adverse reactions (ARs) associated with mogamulizumab. Fatal or life-threatening skin toxicity, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported infrequently. Of 528 recipients

of mogamulizumab in clinical trials, grade 3 skin ARs were reported in 3.6%, grade 4 skin ARs in < 1%, and SJS in < 1% (source: response to 1/4/2018 IR and labeling IRs).

In Study 0761-010, on FDA pooled analysis, 25% (80/319) of mogamulizumab recipients had a reported AE of drug eruption, including 25% (34/135) of patients after crossover from vorinostat. The maximum grade was grade 1 in 32 patients (40%), grade 2 in 34 patients (43%), and grade 3 in 14 patients (18%). Protocol-specified management included topical steroids with or without interruption of mogamulizumab. Among the 80 patients, drug eruption resulted in interruption of mogamulizumab in 26% and permanent cessation in 33%.

The onset of drug eruption is variable, and the affected areas and appearance vary. In Study 0761-010, the median time to onset was 15 weeks (Q1, Q3: 6.1, 31.0 weeks), with 25% of cases occurring after 31 weeks (Figure 18). The more common presentations reported included papular or maculopapular rash, lichenoid, spongiotic, or granulomatous dermatitis, and mobiliform rash. Other presentations included scaly plaques, pustular eruption, folliculitis, non-specific dermatitis, and psoriasiform dermatitis (source: response to 1/4/18 IR).

Figure 18: Time to Drug Eruption in Mogamulizumab Recipients (N = 80 from 319)



Source: FDA analysis

Clinical review comments:

- **The PI should describe the variable time course of mogamulizumab drug eruption and advise monitoring for dermatologic toxicity throughout the treatment course.**
- **The protocol specified that grade ≥ 2 rash (and grade 1 rash prior to topical steroid treatment) be biopsied, in part to help distinguish drug eruption from relapse. Failure to correctly distinguish drug eruption from relapse could affect PFS estimates.**

8.2.5.3 Infusion-Related Reactions

Of 319 mogamulizumab recipients in Study 0761-010, 112 (35%) had IRR as a preferred term, including 51/135 (38%) patients after crossover. More than 90% of patients with IRR (102; 91%) developed IRR with the first infusion, with subsequent new-onset IRRs being limited to 1 or 2 cases per infusion (source: FDA analysis).

Most cases (103 patients; 92%) were grade 1-2; the maximum grade was grade 1 in 52 patients (46%), grade 2 in 51 patients (46 %), and grade 3 in 9 patients (8%). IRR resulted in dose interruption in 25 / 112 patients (22%) and drug withdrawal in 4 patients (4%). Fatal and life-threatening IRRs have been reported in other recipients of mogamulizumab.

Beginning with protocol amendment 5, premedication (acetaminophen and diphenhydramine) for the first mogamulizumab infusion was recommended for all patients. In all recipients of mogamulizumab combined (N = 319), the incidence of IRR was numerically lower in those given premedication (32%, vs 42% without premedication). However, the observations are based upon small numbers and driven by the higher percentage of grade 2 reactions in the no-premedication group (Table 30).

Table 30: Incidence of IRR With and Without Premedication (Study 0761-010)

Subjects with Infusion-Related Reaction	Subjects without Premedication N=96	Subjects with Premedication N=223	Total N=319
Total, n (%)[a]	40 (41.7)	72 (32.3)	112 (35.1)
Grade 1, n (%)	16 (16.7)	38 (17.0)	54 (16.9)
Grade 2, n (%)	23 (24.0)	26 (11.7)	49 (15.4)
Grade 3, n (%)	1 (1.0)	8 (3.6)	9 (2.8)

[a] Percentages within each group were calculated using as denominator total number of subjects per group. The denominators for subjects without premedication, subjects with premedication and total number of subjects were 96, 223 and 319, respectively.

Source: Response to 1/4/18 IR

Review comment

- (b) (4) **based on Table 30, there may be a benefit to premedication. Therefore, this reviewer recommends to include premedication in the dosage and administration instructions.**

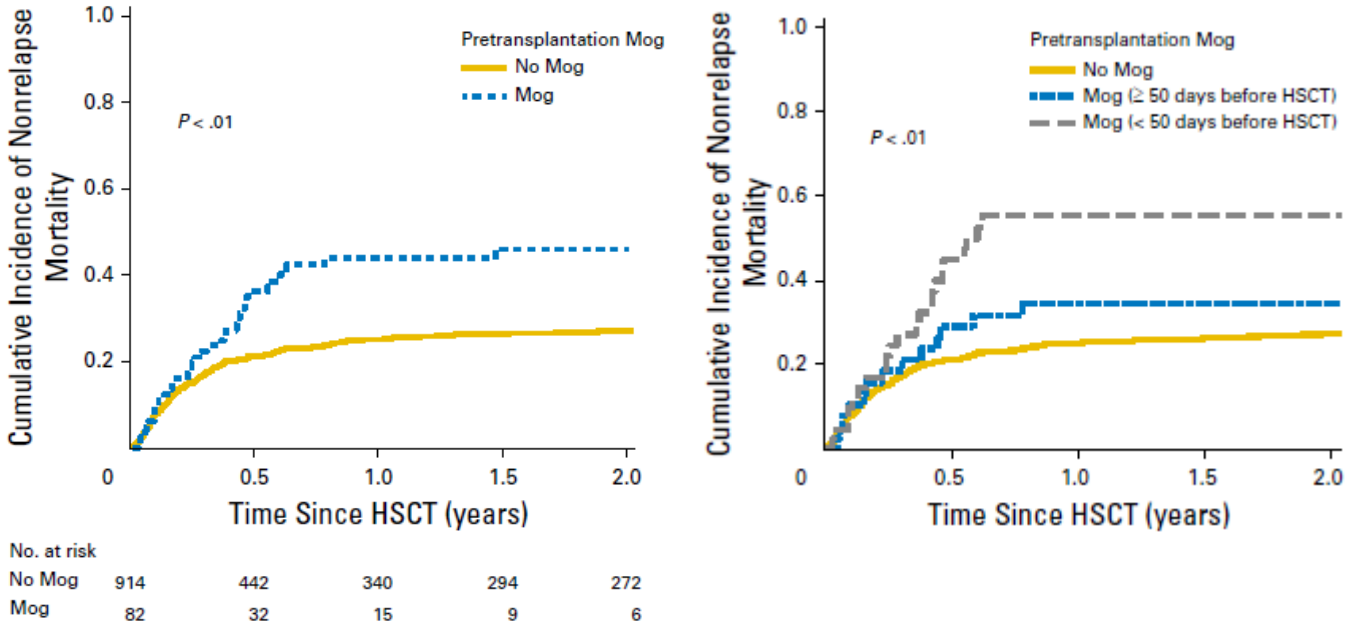
8.2.5.4 Complications of Allogeneic HSCT after Mogamulizumab

In several retrospective studies or case series, exposure to mogamulizumab before allogeneic (allo) HSCT has been associated with increased risks of transplant complications, including higher risks of severe acute GVHD, steroid-refractory GVHD, and death (Fuji et al 2016, Inoue et al 2016; Sugio et al 2016). For example, through invited hospital surveys on patients with ATLL (99/232 invited hospitals participated), Fuji et al (2016) evaluated the impact of pretransplantation mogamulizumab on allo HSCT outcomes. Pretransplantation

mogamulizumab was associated with higher risks of severe acute GVHD, steroid-refractory GVHD, and death (Figure 19 and Table 31). A shorter interval between the last mogamulizumab dose and allo HSCT has been associated with a higher risk of transplant complications (Table 31 from Fuji et al 2016; Sugio et al 2016).

These observations are plausible, because mogamulizumab could target CCR4+ T regulatory cells (both host- and donor- derived) and Th2 cells, disrupting immune tolerance. In the allo transplant setting, T-regulatory cells mitigate severe acute GVHD (Hoffmann et al 2002), and impaired reconstitution of T-regulatory cells has been associated with development of GVHD, including chronic GVHD.

Figure 19: NRM According to Mogamulizumab Exposure in Patients with ATLL



Source: Fuji et al 2016, figures 1 and 2.
Note: This is a retrospective, questionnaire-based analysis.

Table 31: Allogeneic HSCT Toxicities According to Mogamulizumab Exposure

	No moga pretransplantation (N = 914)	Moga pretransplantation (N = 82)	Multivariable analysis: HR (moga/no moga) with 95% CI
Grade II-IV aGVHD	381 (44%)	47 (58%)	1.71 (1.02 – 2.86)
Grade III-IV aGVHD	150 (17%)	25 (31%)	2.04 (1.15 – 3.64)
Steroid-refractory aGVHD [a]	80/341 (23%)	23/47 (49%)	--
NRM	1-y 25% (22 – 28)	1-y 44% (33 – 54)	1.93 (1.29, 2.88)
Moga ≥ 50 d prior (n = 38)			1.58 (0.86, 2.91)
Moga < 50 d prior (n = 42)			2.26 (1.40, 3.66)

Source: Fuji et al 2016

[a] Among patients who received systemic steroids for GVHD. Univariate p < 0.01

Review comments:

- **The published data on allo HSCT outcomes after mogamulizumab have multiple limitations, such as their retrospective nature, heterogeneity in patient, disease, and transplant characteristics, variability in mogamulizumab timing and exposure, and particularly in the series by Fuji et al (2016), possible reporting bias. Although the findings are not definitive, the safety signals are consistent and biologically plausible.**
- **The Applicant submitted allo transplant datasets for recipients of prior mogamulizumab across studies (32 with CTCL, 8 with other T-cell malignancies) as part of an ongoing query. However, the datasets were rudimentary, lacked multiple key data elements including cause of death, and had errors including in GVHD grading, precluding safety analysis. Further characterization of allo HSCT complications in recipients of mogamulizumab is warranted, and this is the basis of the recommended safety PMR described in Section 13.**
- **In the Warnings and Precaution section on allo HSCT, the proposed PI stated** (b) (4) [redacted] **Such statements are misleading.**
- **In this reviewer's opinion, there is also biologic plausibility for severe GVHD should mogamulizumab be given after allo HSCT. A Tracked Safety Issue and/or expansion of the Warning and Precaution to include posttransplantation mogamulizumab may become indicated.**

8.2.5.5 Autoimmune Complications

Reduction of CCR4+ T-regulatory cells might potentiate autoimmune disease**.** By targeting CCR4-expressing T-regulatory cells (Ni et al 2014), mogamulizumab at least theoretically could cause immune-mediated adverse events (IMAEs). Based on biologic plausibility and the identification of several grade ≥ 3 IMAEs in Study 0761-010, FDA requested that the Applicant analyze IMAEs or potential IMAEs, regardless of attribution, in all mogamulizumab recipients on this study (see 12/7/2017 response to the IR dated 11/24/2017). The identified cases included

myositis, hepatitis, and a variant of Guillain-Barré syndrome, as summarized in Table 32. Resultant use of systemic immunosuppressants was reported in these 6/319 (1.9%) mogamulizumab recipients. Treatment-emergent hypothyroidism (grade 1 or 2) was additionally identified in 1.3% of mogamulizumab recipients and managed with observation or levothyroxine.

Table 32: IMAEs or Possible IMAEs after Mogamulizumab (from N of 319)

Patient ID	Category	Approximate onset after start of moga	Description	Comments
0761-010-(b) (6) [a]	Hepatitis, Polymyositis	4.5 mo	G3 acute hepatitis, followed ~1 mo later by rapidly progressive, fatal polymyositis	Death from polymyositis and pneumococcal pneumonia. Liver biopsy had shown a mixed lymphocytic infiltrate.
0761-010-(b) (6) [a]	Guillain-Barré variant	6.5 mo	G3 Miller-Fisher syndrome with subsequent transaminitis and muscle weakness	Death from respiratory failure and pneumonia, in setting of ongoing neurologic syndrome.
0761-010-(b) (6) [a]	Myositis, Myocarditis	5 mo	G3 myositis, G3 myocarditis	Initial myositis, elevated troponin, transaminitis; scattered necrosis on muscle biopsy. After taper of IS, represented with g3 myocarditis; cardiac biopsy showed lymphocytic myocarditis
0761-010-(b) (6) [a]	Hepatitis	2 y	G4 autoimmune hepatitis	Resolved with immunosuppressive therapy
0761-010-(b) (6) [b]	Pneumonitis	10 mo	G3 pneumonitis	Etiology (infectious vs. immune) unclear; treated for both with recovery in 8 days.
0761-010-(b) (6) [b]	Polymyalgia rheumatica (PMR)	7 mo	G2 PMR, followed by unspecified myopathy	PMR managed with systemic steroids. Data on subsequent myopathy not provided.

Source: FDA analysis and response to 11/24/2017 and 3/7/2018 IRs.
Data cutoff date: 9/1/2017 (SUR)
IS = immunosuppression
[a] Probable or definite IMAE per FDA adjudication
[b] Possible IMAE

Review comments:

- **Because IMAEs appear not to have been systematically monitored on Study 0761-010 apart from TSH monitoring, this reviewer suspects that the incidence of autoimmune complications after mogamulizumab is underestimated. This includes endocrine events, which need not be treated with systemic immunosuppression to qualify as IMAEs. The Applicant, however, did not view hypothyroidism as a potential**

autoimmune complication because "none of the events was managed by autoimmune therapy, such as steroids" (source: response to 12/18/2017 IR).

- **In this reviewer's opinion, the Applicant understates the risk of autoimmune complications with mogamulizumab, citing preceding viral infection as an alternative explanation for several of the grade ≥ 3 cases and stating that the g 4 autoimmune hepatitis is unrelated to mogamulizumab due to its late onset (source: response to 11/24/2017 IR and 3/7/2018 IRs). The proposed PI does not mention autoimmune complications after mogamulizumab outside of the allogeneic HSCT setting, and the most recent investigator brochure lacks a dedicated section on IMAEs. However, based on clinical data and biological plausibility, a Warning and Precaution on autoimmune complications is warranted.**

8.2.6 COA Analyses Informing Safety/Tolerability

None

8.2.7 Safety Analyses by Demographic Subgroups

Approximately half of the patients (182; 49%) in the primary safety population were aged ≥ 65. SAE rates according to age and sex are summarized in Table 33. There are insufficient data to evaluate safety differences according to race. In both arms, rates of grade ≥ 3 and serious AEs during randomized treatment were numerically higher, by approximately 5%, in patients aged ≥ 65 compared to < 65. In all recipients of mogamulizumab (randomized + crossover), rates of grade ≥ 3 and serious AEs were likewise numerically higher, by 7 to 10%, in patients aged ≥ 65.

Table 33: Safety According to Age and Sex (Study 0761-010)

Parameter			Pooled Analysis		Randomized Treatment			
			MOGA (N = 319)		MOGA (N = 184)		VORINOSTAT (N = 186)	
Age	Distribution	≥ 65	162	(51%)	85	(46%)	97	(52%)
		< 65	157	(49%)	99	(54%)	89	(48%)
	Any SAE	≥ 65	59	**(36%)**	32	**(38%)**	26	**(27%)**
		< 65	46	(29%)	34	(34%)	19	(21%)
	Grade ≥ 3 AE	≥ 65	73	**(45%)**	39	**(46%)**	50	**(52%)**
		< 65	56	(36%)	40	(40%)	36	(40%)
Sex	Distribution	Male	183	(57%)	107	(58%)	107	(58%)
		Female	136	(43%)	77	(42%)	79	(42%)
	Any SAE	Male	56	(31%)	38	(36%)	21	(20%)
		Female	49	**(36%)**	28	(36%)	24	**(30%)**

Source: FDA analysis

Bolded percentages are ≥ 2% higher in patients aged ≥ 65 vs. < 65 or in females vs. males.

8.2.8 Specific Safety Studies/Clinical Trials

None.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development
Refer to Section 5.5.3.

Human Reproduction and Pregnancy
Refer to Section 5.5.4.

Pediatrics and Assessment of Effects on Growth
Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Not applicable.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
Hepatitis B virus reactivation and stress cardiomyopathy have been reported postmarketing. Refer to Section 8.2.5.4 for concerns regarding safety of allogeneic HSCT after mogamulizumab.

Expectations on Safety in the Postmarket Setting
Because recipients of the marketed drug might not have met eligibility criteria for the study supporting BLA approval, AEs may occur with higher incidence and severity in the postmarket setting. New safety signals might also emerge with larger numbers of patients exposed.

8.2.11 Integrated Assessment of Safety

In adults with relapsed or refractory MF or SS after at least one prior systemic therapy, mogamulizumab carries an acceptable safety profile. The safety evaluation is based on Study 0761-010, a multicenter, randomized, open-label clinical trial that compared mogamulizumab and vorinostat in the intended population. Mogamulizumab was administered at the recommended dose-schedule (1 mg/kg intravenously over at least 60 minutes on days 1, 8, 15 and 22 of the first 28-day cycle and on days 1 and 15 of subsequent cycles) with optional first-dose premedication. Vorinostat was standardly dosed (400 mg orally once daily, continuously in 28-day cycles). Treatment continued until unacceptable toxicity or progressive disease. The trial excluded patients with active autoimmune disease, autologous HSCT within 90 days, or prior allogeneic HSCT.

The median age overall was 64 years, 58% were male, 70% were white, and 99% had an ECOG performance status of 0 or 1. The median number of prior systemic therapies was 3.
Of the 370 patients treated (55% with MF, 45% with SS), 184 received mogamulizumab as randomized treatment and 186 received vorinostat. In the vorinostat arm, 135 patients (73%) subsequently crossed over to mogamulizumab for a total of 319 mogamulizumab recipients.

The primary safety analysis considered all-cause TEAEs associated with randomized treatment. The median duration of randomized treatment was 2-fold longer in the mogamulizumab arm (5.6 months) than in the vorinostat arm (2.9 months). In both arms, AEs reported in ≥ 20% included fatigue and diarrhea. With vorinostat, the other AEs reported in ≥ 20% were nausea, thrombocytopenia, renal insufficiency, and decreased appetite. With mogamulizumab, the other AEs reported in ≥ 20% were rash, IRR, musculoskeletal pain, and URTI. Other common ARs (in ≥10%) in the mogamulizumab arm included skin infection, pyrexia, nausea, edema, thrombocytopenia, headache, constipation, mucositis, anemia, cough, and hypertension. Grade 4 treatment-emergent laboratory abnormalities observed in ≥ 1% of the mogamulizumab arm included lymphopenia (5%), leukopenia (1%), and hypophosphatemia (1%).

Randomized treatment with mogamulizumab carried a safety profile similar to crossover treatment. On pooled analysis of the 319 mogamulizumab recipients,

- 35% had IRR
- 25% had a reported AE of drug eruption, with 40% of the cases being maximum grade o1, 43% grade 2, 18% grade 3. Grade ≥ 4 skin toxicity, including SJS/TEN, has been reported in other mogamulizumab studies and/or postmarketing.
- 1.9% had reported use of systemic immunosuppressants for immune-mediated or possibly immune-mediated AEs, which included myositis, myocarditis, hepatitis, and a variant of Guillain-Barré syndrome.

Warnings and Precautions are recommended for IRRs, dermatologic toxicity, infection, autoimmune complications, and complications of allo HSCT after mogamulizumab. In the literature, mogamulizumab prior to allogeneic HSCT has been associated with increased risks of severe acute GVHD, steroid-refractory GVHD, and nonrelapse mortality. A PMR is recommended to further characterize the safety of allogeneic HSCT (b) (4)

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The submitted clinical data from Study 0761-010 show that there was a statistically significant improvement in PFS and ORR with mogamulizumab compared to vorinostat. The PRO data, which the Applicant views as showing a meaningful benefit with mogamulizumab compared to vorinostat, have multiple limitations. From a statistical point of view, the study achieved the primary objective and one of the key secondary objectives (ORR). These results support an indication in patients with MF/SS who have received at least one prior systemic therapy.

8.4 Conclusions and Recommendations

The randomized clinical trial of mogamulizumab versus vorinostat demonstrated that use of mogamulizumab in patients with MF or SS who have received at least one prior systemic therapy resulted in a longer PFS and higher ORR rate compared to vorinostat. However, no asserted conclusions can be made on improvement of PROs with mogamulizumab due to the large amount of missing data (including at earlier time points), inconsistent results, and the limitations of the QoL instruments used.

{See appended electronic signature page}

Haiyan Chen

Lei Nie/Jingjing Ye

{See appended electronic signature page}

Yvette Kasamon

R. Angelo de Claro

9 Advisory Committee Meeting and Other External Consultations

Mogamulizumab was not presented to the Oncologic Drug Advisory Committee or other external consultants because the application did not raise significant efficacy or safety issues for the proposed indication.

10 Pediatrics

Not applicable for the proposed indication. The application does not trigger PREA, as mogamulizumab is an NME with orphan designation.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

The following are recommendations for the mogamulizumab (POTELIGEO) PI based on this review.

Table 34: Summary of Significant Labeling Changes

Section	Proposed Labeling	Recommended Labeling
Indication	• POTELIGEO is a CC chemokine receptor type 4 (CCR4 (b) (4) monoclonal antibody indicated for the treatment of (b) (4)	• POTELIGEO is a chemokine receptor type 4 (CCR4) directed monoclonal antibody indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy. (Revised to reflect the population studied)
Dosage and Administration	• No mention of IRR prophylaxis	• Recommend first-dose IRR prophylaxis for all patients.
Warnings and Precautions	• W and P for dermatologic reactions, infusion-related reactions, infections, complications of allogeneic HSCT, (b) (4)	• Add W and P for autoimmune complications, given the safety signal and its biologic plausibility. • (b) (4)
Warnings and Precautions, Adverse Reactions	• (b) (4)	• Pool mogamulizumab safety data from randomized + crossover treatment for more sensitive labeling.
Adverse Reactions	• (b) (4)	• (b) (4)

Table 34: Summary of Significant Labeling Changes

Section	Proposed Labeling	Recommended Labeling
	• (b) (4)	(b) (4) . • To inform safety, include common ARs with mogamulizumab regardless of incidence relative to vorinostat. • Present ARs using grouped PTs for more sensitive and informative labeling.
Clinical Studies	• Provides PFS per investigator only • (b) (4) •	• Add PFS per independent review, as this informed the regulatory decision. • (b) (4) • Present p-values only for prespecified comparisons.
Clinical Studies	• (b) (4)	• (b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team does not recommend a REMS. Based on the risk/benefit profile of mogamulizumab, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

13 Postmarketing Requirements and Commitments

The clinical review team recommends the following postmarketing requirement under the Food and Drug Administration Amendments Act. Refer to the action letter for final wording and milestone dates.

PMR: Characterize complications after allogeneic hematopoietic stem cell transplantation (HSCT) following mogamulizumab in at least 50 patients with hematologic malignancies (at least 40 with cutaneous T-cell lymphoma), of whom at least two-thirds received mogamulizumab as the last regimen prior to HSCT. Evaluate toxicities at least through transplant Day 180, and

include details of prior mogamulizumab treatment and the transplant regimen. Characterize toxicities including grade II-IV acute graft-versus-host disease (GVHD), severe (grade III-IV) acute GVHD, steroid-refractory acute GVHD, grade 4, potentially immune-mediated adverse events, graft failure, hepatic veno-occlusive disease, critical illness, and non-relapse mortality and the cause. The study may characterize toxicities prospectively, or through a combination of prospective and retrospective data analysis. Utilize registry data (for example the Center for International Blood and Marrow Transplantation Research registry) to inform the analysis.

Rationale: There is a strong signal in the literature that recipients of pretransplantation mogamulizumab have increased risks of severe acute GVHD, steroid-refractory GVHD, and nonrelapse mortality. These apparent risks have a biological rationale, in that mogamulizumab can deplete CCR4-expressing T regulatory cells and disrupt immune tolerance. With approval of mogamulizumab, its use as a potential bridge to allogeneic HSCT will almost certainly increase. The safety of allogeneic HSCT after mogamulizumab requires further characterization; however there are insufficient data in the BLA to permit safety analysis.

Milestone dates:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	1/2019
Interim Report Submission:	7/2021
Study Completion:	2/2024
Final Report Submission:	8/2024

14 Division Director (DHOT)

{See appended electronic signature page}

John Leighton, PhD

15 Division Director (OCP)

{See appended electronic signature page}

Nam Atiqur Rahman, PhD

16 Division Director (OB)

{See appended electronic signature page}

Rajeshwari Sridhara, PhD

17 Division Director (Clinical)

I concur with the review team's recommendations for the approval of mogamulizumab, a defucosylated, humanized IgG1 kappa monoclonal antibody that selectively binds to chemokine receptor 4, for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy.
The recommended dose-schedule of mogamulizumab is 1 mg/kg as an intravenous infusion over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle. The efficacy and safety were demonstrated in a multicenter, open-label, randomized phase 3 trial comparing mogamulizumab with vorinostat. Trial results demonstrated that mogamulizumab was associated with longer PFS and higher overall response rates than vorinostat. Adverse events reported in ≥ 20% of patients included rash, infusion-related reaction (IRR), fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection. The primary reviewer found a published report of use of mogamulizumab prior to allogeneic HSCT and noted its use has been associated with increased risks of severe acute graft-versus-host disease (GVHD), steroid-refractory GVHD, and nonrelapse mortality. The labeling contains Warnings and Precautions for IRRs, dermatologic toxicity, infection, autoimmune complications, and complications of allo HSCT after mogamulizumab.

{See appended electronic signature page}

Ann T. Farrell, M.D.

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit of mogamulizumab-kpkc was also assessed by Drs. Farrell, de Claro and Kasamon, and I concur with their recommendation to approve this drug. My signature below represents an approval recommendation for the clinical portion of this application under the OCE. My signature below also represents the approval decision of this application under CDER.

{See appended electronic signature page}

Richard Pazdur, M.D.

19 Appendices

19.1 References

Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol* 2010;28(31):4730-4739.

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19.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): 0761-010

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 762		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

19.3 Nonclinical Pharmacology/Toxicology

No additional nonclinical data reviewed.

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1 Summary of Bioanalytical Method Validation and Performance

Bioanalytical Method for Detection of Mogamulizumab

Bioanalytical methods for the quantitative determination of mogamulizumab in human plasma and serum were developed and validated using an enzyme-linked immunosorbent assay (ELISA). The ELISA method for determination of mogamulizumab in plasma was validated at (b) (4) to support Japanese based clinical trials (0761-0501, 0761-002, 0761-003, and 0761-004) and at (b) (4) to support trials (KW-0761-001, 0761-009, and 0761-010) outside of Japan. However, following analysis of the plasma samples from Trial KW-0761-001, incurred sample re-analysis (ISR) criteria (i.e., at least two-thirds of the ISR results must be within 30% of the original results) were not met for the analytical method at (b) (4) validated by Study 08-8454. The reason for the failure to meet ISR criteria could not be elucidated and thus the mogamulizumab plasma concentrations from Trial KW-0761-001 were considered unreliable and the PK results have not been utilized to support the determination of mogamulizumab concentrations in this application. The analytical method for the determination of mogamulizumab concentrations was subsequently modified by changing the composition of buffer, the calibration range and the matrix from plasma to serum, and the modified method was validated in Study 12-8496. Validation parameters of ELSIA methods (**Table 35**) at (b) (4) Studies 37-K-083 and 37-K-085) and (b) (4) Study 12-8496) met acceptance criteria of the US FDA Guidance for Industry "Bioanalytical Method Validation (May 2001)", demonstrating the adequacy of analytical method for the determination of mogamulizumab in human plasma and serum samples. The equivalence of the plasma and serum assays (Studies 37-K-083, 12-8496 and 15-8480) for the determination of mogamulizumab concentration was tested and confirmed in Study 0761-PS1, since the difference in the mogamulizumab concentration between the plasma and serum samples at the low and high concentrations met acceptable criteria (± 30%).

Table 35: Summary of Analytical Methods for the Determination of Mogamulizumab Concentration

Analytical Facility	(b) (4)		
Validation study	**37-K-083, 37-K-085**	**08-8448**	**12-8496**
Matrix	**Plasma**	**Plasma**	**Serum**
Quantification Range (ng/mL)	5 to 200	10 to 200	12.5 to 800
Intra-day Reproducibility			
Accuracy (%RE)	−10.0 to 10.9	−24.2 to −8.8	−14.3 to −6.4
Precision (%CV)	3.3 to 23.8	1.1 to 16.4	1.7 to 9.0
Inter-day Reproducibility			
Accuracy (%RE)	−5.2 to 10.4	1.0 to 5.0	−12.0 to −3.2
Precision (%CV)	12.5 to 24.3	15.7 to 20.9	5.2 to 10.3
Stability			
RT	24 hours	2 hours[a]	19.7 hours
4°C	7 days	Not Done	Not Done
−20°C	NA	1 month[a]	18 months
−80°C	24 months	1 month[a, b]	24 months
Freeze-Thaw	6 cycles	6 cycles[a]	8 cycles
Clinical studies in which method was used	0761-0501, 0761-002, 0761-003, 0761-004	KW-0761-001	0761-009, 0761-010

RT=Room temperature
a: Data from Study KHK0087
b: Set temperature is −70°C

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2.7.1.2.1-1

Bioanalytical Method for Detection of CCR4 Expression

The fully automated immunohistochemistry (IHC) assay (b) (4) CCR4 (KM2160) CDx Assay) using (b) (4) anti-CCR4 (KM2160) mouse monoclonal primary antibody on the BenchMark series of instruments with the OptiView DAB IHC Detection Kit was developed and validated for the determination of CCR4 expression in human tissue. Evaluated validation parameters (**Table 36**) included precision, robustness (acceptable staining on inter-batch, -operator, -platform), specificity, and stability of slides met acceptance criteria of the FDA's "Guidance for Submission of Immunohistochemistry Applications to the FDA" recommendations, demonstrating the adequacy of analytical method for the determination of CCR4 expression in patients' tissues.

Table 36: (b) (4) CCR4 IHC Method Performance Characteristics

Parameter	Study	Result
Specificity	Immunoreactivity	99.3% (133/134 cores; 32 different normal tissue types and 47 different tumor tissue types.) with no crossreactivity 100% with no background that interfered with slide interpretation
	Peptide Inhibition	CCR4 peptide (CCR4 28 amino acids; NPTDIADTTLDESIYSNYYLYESIPKPC) reduces signal in a dose dependent fashion.
Robustness and Precision	IntraPlatform	Concordant results of three BenchMark ULTRAs: OPA: 97.6% (95% confidence interval: 91.7-99.3%) PPA: 97.6% (95% CI: 87.7-99.6%) NPA: 97.6% (95% CI: 87.7-99.6%)
	IntraDay	Concordant results: OPA: 100.0% (94.8-100.0%) PPA: 100.0% (90.1-100.0%) NPA: 100.0% (90.1-100.0%)
	InterDay	Concordant results: OPA: 100.0% (95% CI: 97.3-100.0%) PPA: 100.0% (95% CI: 94.8-100.0%) NPA: 100.0% (95% CI: 94.7-100.0%)
	Intra-Reader Precision	Concordant results: APA: 98.6% (95% CI: 97.2-99.7%) ANA: 98.6% (95% CI: 97.1-99.7%)
	Inter-Reader Precision	Concordant results: Round 1: APA: 96.6% (95% CI: 93.1-99.3%) ANA: 96.5% (95% CI: 93.0-99.3%) Round 2: APA: 96.0% (95% CI: 92.3-98.7%) ANA: 95.9% (95% CI: 92.0-98.7%)
Stability (Antibody)	Accelerated Stability	Data from three lots tested support a predicated dating of 24 months stability

OPA: overall percent agreement, PPA: positive percent agreement, NPA: negative percent agreement, APA: average positive agreement, ANA: average negative agreement

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2.7.1.2.3.1.2-1

Bioanalytical Methods for Detection of Anti-Product Binding AND Neutralizing Antibodies

Bioanalytical methods for the detection of ADA in human plasma and serum using an ELISA and an electrochemiluminescence immunoassay (ECLA) were developed and validated. An assay for the detection of anti-product neutralizing antibodies (APNA) using ECLA was also developed and validated in the course of the clinical development program for mogamulizumab (**Table 37**).

Table 37: Bioanalytical Methods for Measuring Anti-Product Binding and Neutralizing Antibodies

		Anti-mogamulizumab Binding Antibodies		Anti-mogamulizumab Neutralizing Antibodies	
Study No. (Region)	**Sample Type (Matrix)**	**Bioanalytical Method (Lab)**	**Validation Study No.**	**Bioanalytical Method (Lab)**	**Validation Study No.**
0761-0501 (Japan)	Plasma	ELISA (b) (4)	37-K-084	Not Done*	Not Applicable
0761-002 (Japan)	Plasma	ELISA	37-K-084	Not Done*	Not Applicable
0761-003 (Japan)	Plasma	ELISA ECLA	37-K-084 P11-29202	ECLA (b) (4)	P11-29203
0761-004 (Japan)	Plasma	ELISA ECLA	37-K-084 P11-29202	ECLA	P11-29203
KW-0761-001 (US)	Plasma	ECLA	10/065-020	ECLA	08/065-011 10/065-021
KW-0761-002 (US)	Plasma	ECLA	10/065-020	ECLA	08/065-011 10/065-021
0761-007 (EU)	Serum	ECLA	P11-29202 P14-29210	ECLA	P11-29203 P14-29210
0761-009 (US, Caribbean, EU, and South America)	Serum	ECLA	P11-29202 P14-29210	ECLA	P11-29203 P14-29210
0761-010 (US, EU, Japan, and Australia)	Serum	ECLA	P11-29202 P14-29210	ECLA	P11-29203 P14-29210

EU=European Union; (b) (4) US=United States

*The method was not developed.

Source: Integrated Summary of Immunogenicity, Table 6.1-1

A. Detection of ADAs

Initially ADAs in plasma were determined by ELISA for all 4 clinical trials (0761-0501, 0761-002, 0761-003 and 0761-004) conducted in Japan. A new method was then developed and validated using ECLA (Study P11-29202) with improved sensitivity for the detection of ADAs in human plasma and serum at (b) (4) A partial validation was performed to determine the ADA titers at (b) (4) to support clinical Trials 0761-007, 0761-009 and 0761-010. All validation parameters, e.g., selectivity, calibration curves, precision, accuracy, quantification range, storage stability, and prozone effect for ELISA (**Table 38**) and ECLA (**Table 39**) methods, met the acceptance criteria of the US FDA Guidance for Industry "Bioanalytical Method Validation (May 2001)", demonstrating that the analytical methods are suitable for the assay of ADAs in human plasma and serum samples.

Table 38: Summary of Analytical Methods for the Detection of Anti-Drug Antibodies in Human Plasma by ELISA

Analyte	Anti-mogamulizumab antibody
Analytical Facility	(b) (4)
Validation study	**37-K-084**
Matrix	**Plasma**
Quantification Range	5-200 ng/mL
Intra-day Reproducibility	
Accuracy (%RE)	3.1 to 8.8
Precision (%CV)	1.6 to 10.1
Inter-day Reproducibility	
Accuracy (%RE)	2.2 to 8.6
Precision (%CV)	−6.8 to 6.3
Stability at RT (positive control)	4 hours
Clinical studies in which method was used	0761-0501, 0761-002, 0761-003, 0761-004

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2.7.1.2.2-1

Table 39: Summary of Analytical Methods for the Detection of Anti-Drug Antibodies in Human Plasma and Serum by ECLA

Assay	Analytical Facility	(b) (4)	(b) (4)	
	Validation study	**10/065-020**	**P11-29202**	**P11-29202[a]**
	Matrix	**Plasma**	**Serum**	**Plasma**
Screening	Sensitivity	<50 ng/mL	19.4 ng/mL	18.1 ng/mL
	Precision (%CV)			
	Intra-assay	3 to 8	2.9 to 6.8	
	Inter-assay	11 to 13	6.2 to 7.2	
	Drug interference (200 ng/mL of PC)	Tolerates up to 51.2 µg/mL of KW-0761	Tolerates up to 16 µg/mL of KW-0761	
Confirmatory	Sensitivity	<50 ng/mL	2.5-100 ng/mL	
	Precision (%CV)			
	Intra-assay	4 to 5	0.2 to 3.8	
	Inter-assay	8 to 17	0.5 to 4.8	

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2.7.1.2.2-1

B. Detection of APNAs

The developed and validated bioanalytical method (Study P11-29203) using ECLA for the detection of APNAs in human plasma and serum at (b) (4) also met the acceptance criteria of the US FDA Guidance for Industry "Bioanalytical Method Validation (May 2001)", demonstrating that the analytical methods are suitable for the assay of APNAs in human plasma and serum samples (**Table 40**).

Table 40: Summary of Analytical Methods for the Detection of Anti-Product Neutralizing Antibodies in Human Plasma and Serum by ECLA

Assay	Analytical Facility	(b) (4)	(b) (4)	
	Validation study	**08/065-011**	**P11-29203**	**P11-29203** [a]
	Matrix	**Serum**	**Serum**	**Plasma**
Screening	Sensitivity	0.806 µg/mL	1.08 µg/mL	1.09 µg/mL
	Precision (%CV)			
	Intra-assay	6 to 19	3.7 to 4.7	
	Inter-assay	19	13.5	
	Drug interference	Tolerates up to 0.5 µg/mL of KW-0761 (2 µg/mL of PC)	Tolerates up to 0.125 µg/mL of KW-0761 (4 µg/mL of PC)	
Confirmatory	Precision (%CV)			
	Intra-assay	4 to 8	2.3 to 1.7	
	Inter-assay	17 to 14	9.0 to 16.0	

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2.7.1.2.2-1

19.4.2 Clinical PK and Immunogenicity Assessments

PK Assessment

The PK of mogamulizumab was characterized by non-compartmental analysis (NCA) based on intensive PK data from single- and multiple-dose trials (Trial 0761-0501 and Trial 0761-002) in Japanese patients with CCR4-positive relapsed ATL or PTCL.

In Trial 0761-0501, Patients (n = 16) were administered with mogamulizumab by iv infusion weekly for 4 weeks at doses of 0.01, 0.1, 0.5 and 1.0 mg/kg. The mean PK profiles and the PK parameters of mogamulizumab based on NCA are shown in **Figure 20** and **Table 41**, respectively. C_{max} and C_{min} increased with repeated doses of mogamulizumab. The mean accumulation ratio for $AUC_{0\text{-}7\ days}$ after the 4^{th} dose was 2.2 to 3.5.

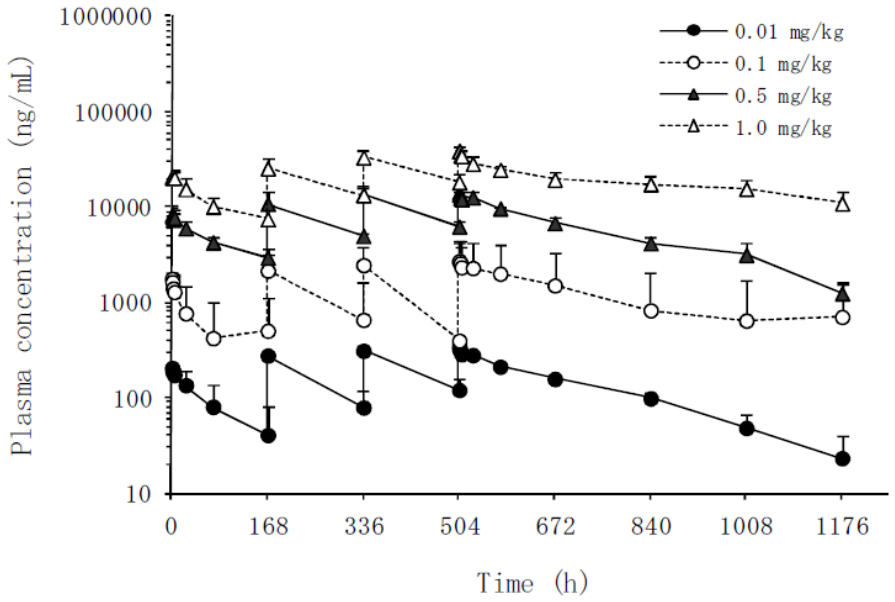


Figure 20: PK Profiles of Mogamulizumab After IV Administration of Mogamulizumab Once Weekly for 4 Weeks to Patients with CCR4-Positive ATL or PTCL in Trial 0761-0501 (Mean + SD, n=1-6)
Source: Summary of Clinical Pharmacology Studies, Figure 2.7.2.2.3.2.1-1

Table 41: PK Parameters of Mogamulizumab after IV Administration of Mogamulizumab Once Weekly for 4 Weeks to Patients with CCR4-Positive ATL or PTCL in Trial 0761-0501 (Mean ± SD)

Dose (mg/kg)	Dose Number	C_{max} (ng/mL)	C_{min} (ng/mL)	$AUC_{0\text{-}7\ days}$ (ng·h/mL)	$t_{1/2}$ (h)
0.01 (n=3)	1	206.0±23.1	41.0±39.0	14858±7665	80±52
	4	350.0±47.8 [a)]	158.2±7.4 [a)]	36586±2987 [a)]	179±40 [a)]
	R_{obs}	1.63 (1.38-1.87) [a)]	2.11 [b)]	3.42 (1.76-5.08) [a)]	NA
0.1 (n=4)	1	1831.7±334.1	254.9±447.4	87565±93652	74±85 [c)]
	4	2806.7±1664.5 [c)]	1515.2±1873.4 [c)]	327609±322298 [c)]	201±196 [c)]
	R_{obs}	1.39 (0.96-2.13) [c)]	13.65 (3.97-29.40) [c)]	3.48 (2.03-5.24) [c)]	NA
0.5 (n=3)	1	8353.2±1993.4	2985.0±605.8	761919±130770	141±23 [a)]
	4	15181.2±872.0	6824.7±872.9	1625609±142277	332±122
	R_{obs}	1.89 (1.52-2.42)	2.32 (2.09-2.75)	2.15 (1.97-2.34)	NA
1.0 (n=6)	1	21758.0±3495.4	7544.2±3008.8	1901206±466590	NC
	4	40428.4±5350.8 [d)]	19516.8±4264.7 [d)]	4190238±544757 [d)]	462±51 [d)]
	R_{obs}	1.95 (1.61-2.09) [d)]	3.53 (2.19-7.58) [d)]	2.43 (2.24-2.78) [d)]	NA

Source: Summary of Clinical Pharmacology Studies, Table 2.7.2.2.3.2.1-1

In Trial 0761-002, patients (n = 27) were administered with mogamulizumab at a dose of 1.0 mg/kg by iv infusion weekly for 8 weeks. The mean PK profiles and a summary of PK parameters of mogamulizumab are shown in **Figure 21** and **Table 42**, respectively. C_{max} and C_{min} increased with repeated doses, however, steady state was not achieved after eight repeated doses. The mean accumulation ratio after the 8th dose was 2.87 for $AUC_{0\text{-}7\ days}$.

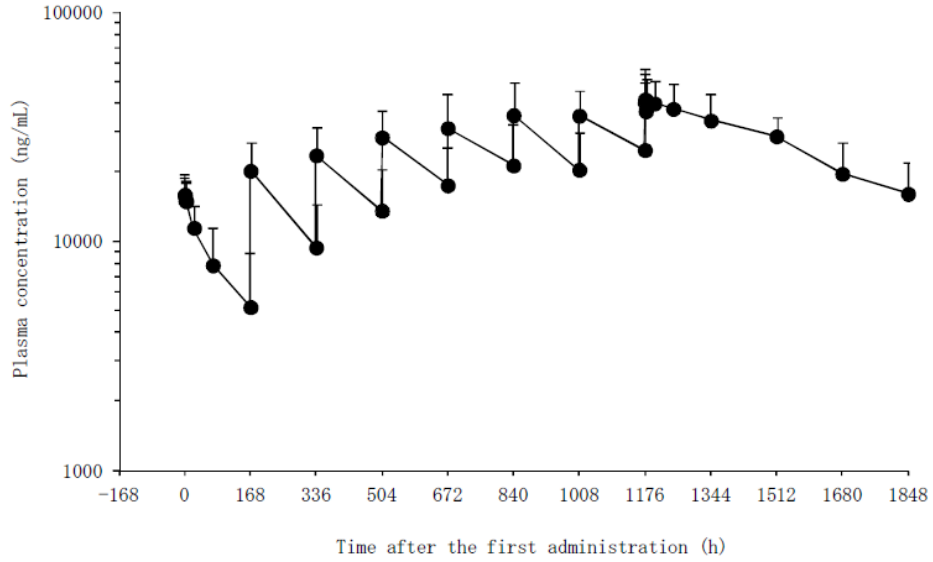


Figure 21: PK Profiles of Mogamulizumab after IV Administration of Mogamulizumab 1.0 mg/kg Once Weekly for Eight Weeks to Patients with CCR4-Positive ATL in Trial 0761-002 (Mean + SD, n = 3-27)
Source: Summary of Clinical Pharmacology Studies, Figure 2.7.2.2.3.2.2-1

Table 42: Plasma PK Parameters of Mogamulizumab after IV Administration of Mogamulizumab 1.0 mg/kg Once Weekly for Eight Weeks to Patients with CCR4-Positive ATL in Trial 0761-002 (Mean ± SD)

Dose Number	C_{max} (ng/mL)	C_{min} (ng/mL)	$AUC_{0\text{-}7days}$ (ng·h/mL)	$t_{1/2}$ (h)
1	16622.0±3324.0 (27)	5151.9±3713.6 (19)	1427204±571447 (19)	124±92 (23)
8	42943.2±14239.5 (5)	33638.3±10572.2 (4)	6297408±1812467 (4)	422±147 (5)
R_{obs}	2.25 (1.74-3.09, 5)	3.56 (3.24-3.86, 3)	2.87 (2.50-3.12, 3)	NC

Each value in parenthesis represents the number of subjects
NC: not calculated
Source: Summary of Clinical Pharmacology Studies, Table 2.7.2.2.3.2.2-1

Dose proportionality was evaluated based on C_{max} and $AUC_{0\text{-}7\ days}$ values from Trial 0761-0501. Plots of the mean concentration-time data show that PK profiles were presented in **Figure 22**. Linear regression analyses of C_{max} and $AUC_{0\text{-}7\ days}$ versus dose indicated no significant departures from dose linearity over the dose range of 0.01 to 1.0 mg/kg.

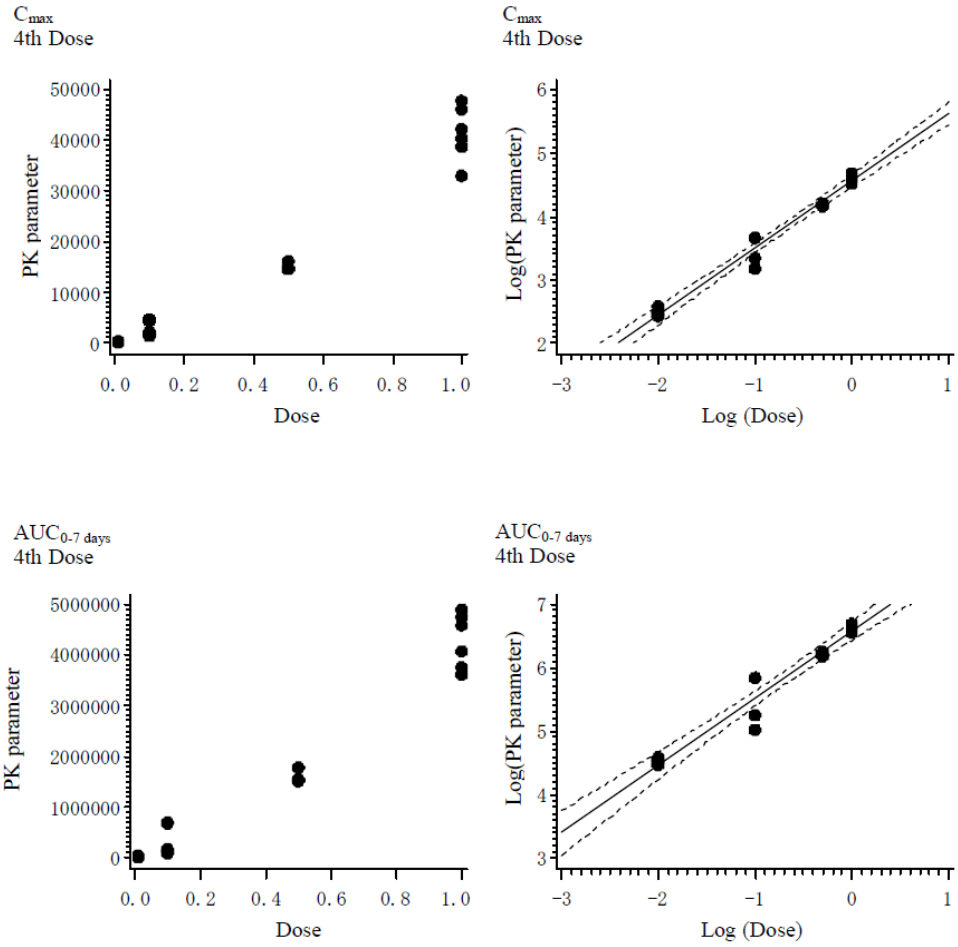


Figure 22: Dose Proportionality of the Pharmacokinetic Parameters after Four Repeated Doses of IV Mogamulizumab Once Weekly (Power Model)
Source: Summary of Clinical Pharmacology Studies, Figure 2.7.2.3.1-1

Immunogenicity Assessment

A comprehensive analysis of the immunogenicity data from 9 Trials (0761-0501, 0761-002, 0761-003, 0761-004, KW-0761-001, KW-0761-002, 0761-007, 0761-009, and 0761-010), with an emphasis on 3 Trials (0761-007, 0761-009, and 0761-010) was performed using ELISA and ECL methods.

The incidence of positive for treatment-emergent (treatment-induced or treatment-boosted) ADAs was 3.4% (11 of 328 patients) in the pooled data from the three studies, and the incidence of positive ADAs in patients with CTCL in the pivotal Phase 3 Trial 0761-010 was 3.9% (10 of 258 patients). There were no positive neutralizing antibody responses.

The effect of immunogenicity in patients with CTCL in Trial 0761-010 was examined with respect to PK, efficacy and safety; no discernible effect of ADAs on PK (**Figure 23**), efficacy (**Figure 24**) or safety (**Table 43**) was detected.

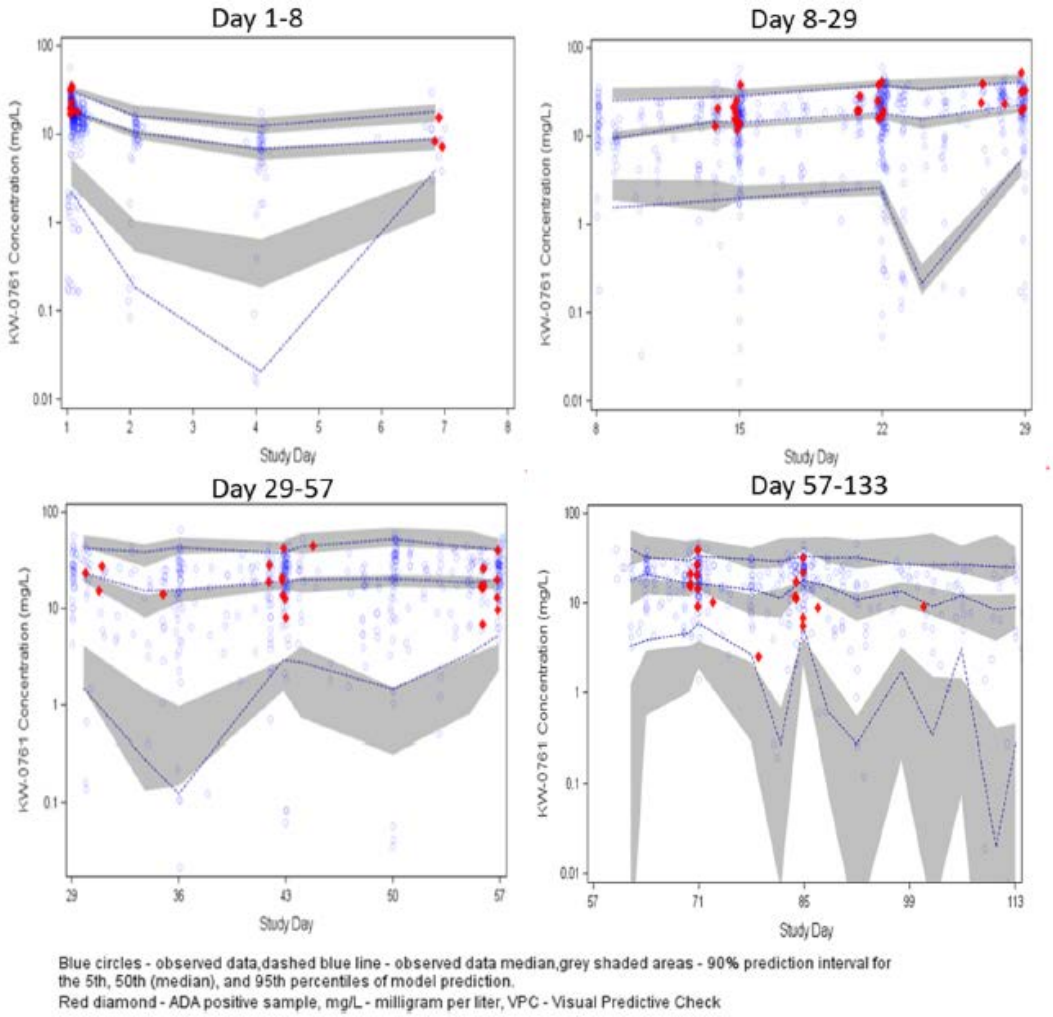


Figure 23: Mogamulizumab Concentrations in Individual Patients with ADA-positive versus 95% Range of Mogamulizumab Concentration Predicted by Population PK Model

Source: Integrated Summary of Immunogenicity, Figure 9.7-1

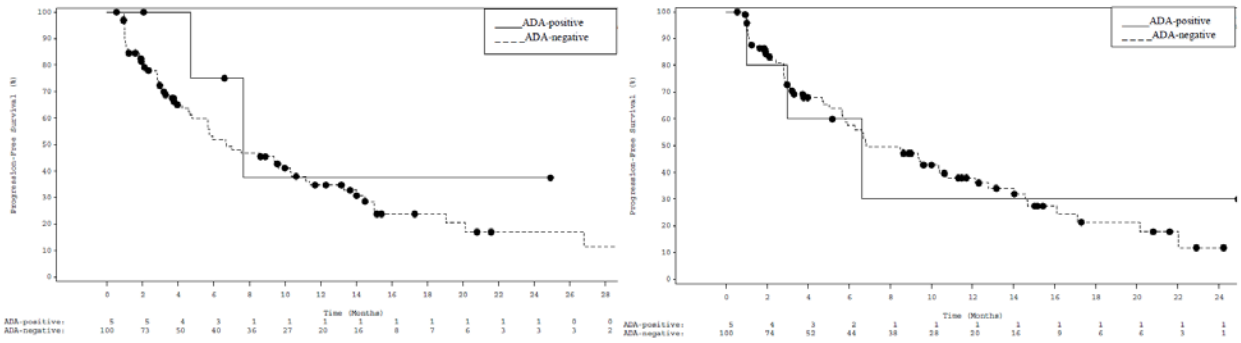


Figure 24: Kaplan-Meier Curve of Progression-Free Survival by Investigator's Assessment (Left) and by Independent Review (Right) in Patients with ADA-positive vs ADA-negative Randomized to Mogamulizumab

Source: Integrated Summary of Immunogenicity, Figures 9.8-1 and 9.8-2

Table 43: Effect of ADA Status on Adverse Events (Trials 0761-007, 0761-009, 0761-010)

Adverse Event Category	ADA Status	
	ADA-Positive (N=6) n (%)	ADA-Negative (N=148) n (%)
Adverse Events (AEs)		
Any TEAEs	6 (100.0)	144 (97.3)
Drug-related TEAEs	5 (83.3)	128 (86.5)
NCI/CTCAE Grade 3, 4, 5 TEAEs		
Any Grade 3, 4, 5 TEAEs	3 (50.0)	74 (50.0)
Drug-related Grade 3, 4, 5 TEAEs	2 (33.3)	46 (31.1)
AEs with Outcome of Death		
Any TEAE with outcome of death	0 (0.0)	6 (4.1)
Drug-related TEAE with outcome of death	0 (0.0)	3 (2.0)
Serious Adverse Events (SAEs)		
Any Treatment-emergent SAEs	3 (50.0)	67 (45.3)
Drug-related Treatment-emergent SAEs	2 (33.3)	34 (23.0)
Discontinuation due to AEs		
Any TEAEs	2 (33.3)	31 (20.9)
Drug-related TEAEs	2 (33.3)	22 (14.9)

Source: Integrated Summary of Immunogenicity, Table 9.9-1

19.4.3 Population PK and/or PD Analysis

Applicant's Analysis

A. Objectives

The objectives of Applicant's population PK analysis were:

- To develop a population PK model for mogamulizumab using data from 6 clinical trials in patients with T-cell malignancies.
- To identify and characterize patient factors which influence the variability in the PK of mogamulizumab.
- To estimate the magnitude of unexplained variability in the PK of mogamulizumab.
- To evaluate the model performance of the PK model developed for mogamulizumab.

B. Data

For the model development, the following 6 trials were included:

- KW-0761-0501 (n = 13): Phase I trial in patients with CCR4-positive ATL or those with CCR4-positive PTCL or CTCL.
- KW-0761-002 (n = 27): Phase II trial in patients with CCR4-positive ATL.
- KW-0761-003 (n = 29): Phase IIb trial in patients with CCR4-positive ATL.
- KW-0761-004 (n = 7): Phase IIb trial in patients with CCR4-positive peripheral T/NK-cell lymphoma.

- KW-0761-009 (n = 60): Multi-center, open-label, randomized trial in patients with previously treated ATL.
- KW-0761-010 (n = 308): Open-label, multi-center, randomized trial in patients with previously treated CTCL.

The summary of demographics is presented in **Table 44** and **Table 45**.

Table 44: Summary of Continuous Demographic Characteristics.

	Study						
	0761-501 (N=13)	0761-002 (N=27)	0761-003 (N=29)	0761-004 (N=7)	0761-009 (N=60)	0761-010 (N=308)	Pooled (N=444)
Age (yrs)							
Mean (SD)	62.2 (4.6)	65.2 (7.4)	61.2 (7.8)	51.3 (12.6)	52.5 (13.1)	63.0 (13.2)	61.4 (13.0)
Min, Max	55, 69	49, 83	49, 81	36, 70	22, 82	25, 101	22, 101
Weight (kg)							
Mean (SD)	57.96 (7.76)	55.45 (11.09)	55.83 (12.15)	57.90 (7.19)	67.71 (15.53)	79.03 (17.59)	73.60 (18.50)
Min, Max	48.5, 68.2	36.0, 79.6	39.0, 92.4	50.5, 72.8	37.3, 109.8	43.5, 149.7	36.0, 149.7
BMI (kg/m^2)							
Mean (SD)	23.55 (2.85)	22.83 (3.31)	22.36 (3.76)	22.54 (2.15)	24.49 (5.27)	27.55 (4.91)	26.31 (5.10)
Min, Max	20.43, 29.82	16.17, 29.36	16.14, 34.69	19.24, 25.34	16.80, 40.51	18.18, 47.35	16.14, 47.35
BSA (m^2)							
Mean (SD)	1.57 (0.14)	1.53 (0.18)	1.55 (0.18)	1.60 (0.13)	1.76 (0.23)	1.91 (0.25)	1.83 (0.27)
Min, Max	1.39, 1.80	1.19, 1.92	1.29, 1.98	1.44, 1.84	1.24, 2.35	1.35, 2.72	1.19, 2.72
Albumin (g/dL)							
Mean (SD)	4.0 (0.27)	3.9 (0.41)	3.5 (0.56)	3.9 (0.65)	3.8 (0.71)	4.0 (0.44)	3.9 (0.5)
Min, Max	3.4, 4.5	3.1, 4.8	2.1, 4.3	2.8, 4.7	1.7, 5.2	2.5, 5.1	1.7, 5.2
Bilirubin (mg/dL)							
Mean (SD)	0.60 (0.35)	0.68 (0.31)	0.72 (0.39)	0.63 (0.31)	0.55 (0.41)	0.49 (0.26)	0.53 (0.30)
Min, Max	0.3, 1.5	0.3, 1.6	0.3, 2.2	0.3, 1.1	0.1, 2.4	0.1, 1.8	0.1, 2.4
ALT (U/L)							
Mean (SD)	30.8 (16.7)	30.9 (23.3)	33.4 (27.6)	16.1 (8.5)	33.5 (27.2)	24.8 (14.5)	27.0 (18.6)
Min, Max	13.0, 61.0	4.0, 109.0	7.0, 105.0	9.0, 29.0	8.0, 134.0	4.0, 105.0	4.0, 134.0
AST (U/L)							
Mean (SD)	30.0 (10.5)	38.1 (24.6)	30.8 (19.4)	18.0 (4.7)	44.5 (35.7)	25.1 (9.6)	28.9 (18.6)
Min, Max	18.0, 51.0	13.0, 123.0	11.0, 82.0	13.0, 25.0	14.0, 199.0	8.0, 67.0	8.0, 199.0
CRCL (mL/min)							
Mean (SD)	83.5 (14.9)	79.0 (17.0)	86.5 (32.5)	115 (28.7)	95.5 (32.5)	89.9 (34.3)	90.0 (32.9)
Min, Max	54.0, 104.0	49.0, 106.0	31.0, 195.0	72.0, 153.0	27.0, 201.0	26.0, 216.0	26.0, 216.0
CCR4 Expression (%)							
Mean (SD)	NA	NA	NA	NA	39.63 (25.72)	72.25 (27.88)	NA
Min, Max	NA	NA	NA	NA	1.3, 96.3	1.0, 100.0	NA

Source: Population PK Analysis Report, Table 7

Table 45: Summary of Categorical Demographic Characteristics

	Study						
	0761-501 (N=13)	0761-002 (N=27)	0761-003 (N=29)	0761-004 (N=7)	0761-009 (N=60)	0761-010 (N=308)	Pooled (N=444)
Sex, n(%)							
Male	7 (53.8)	12 (44.4)	12 (41.4)	3 (42.9)	29 (48.3)	177 (57.5)	240 (54.1)
Female	6 (46.2)	15 (55.6)	17 (58.6)	4 (57.1)	31 (51.7)	131 (42.5)	204 (45.9)
Race, n(%)							
Unknown	0	0	0	0	2 (3.3)	48 (15.6)	50 (11.3)
Japanese	13 (100.0)	27 (100.0)	29 (100.0)	7 (100.0)	0	11 (3.6)	87 (19.6)
non-Japanese	0	0	0	0	58 (96.7)	249 (80.8)	307 (69.1)
Hepatic Impairment, n(%)							
Normal	12 (92.3)	14 (51.9)	20 (69.0)	7 (100.0)	33 (55.0)	275 (89.3)	361 (81.3)
Mild	1 (7.7)	13 (48.1)	8 (27.6)	0	26 (43.3)	32 (10.4)	80 (18.0)
Moderate	0	0	1 (3.4)	0	1 (1.7)	1 (0.3)	3 (0.7)
Severe	0	0	0	0	0	0	0
Renal Impairment, n(%)							
Normal	4 (30.8)	7 (25.9)	13 (44.8)	5 (71.4)	32 (53.3)	144 (46.8)	205 (46.2)
Mild	9 (69.2)	15 (55.6)	10 (34.5)	2 (28.6)	18 (30.0)	103 (33.4)	157 (35.4)
Moderate	0	5 (18.5)	6 (20.7)	0	10 (16.7)	59 (19.2)	80 (18.0)
Severe	0	0	0	0	0	2 (0.6)	2 (0.5)
Clinical Subtype, n(%)							
ATL							
Acute	11 (84.6)	14 (51.9)	20 (69.0)	0	28 (46.7)	0	73 (56.6)
Lymphmatous	2 (15.4)	6 (22.2)	6 (20.7)	0	23 (38.3)	0	37 (28.7)
Chronic	0	7 (25.9)	3 (10.3)	0	9 (15.0)	0	19 (14.7)
CTCL							
Mycosis Fungoides	0	0	0	7 (100.0)	0	166 (53.9)	173 (54.9)
Sezary Syndrome	0	0	0	0	0	142 (46.1)	142 (45.1)
Concomitant mLSG15, n(%)							
Yes	0	0	29 (100.0)	0	0	0	29 (6.5)
No	13 (100.0)	27 (100.0)	0	7 (100.0)	60 (100.0)	308 (100.0)	415 (93.5)
ECOG PS, n(%)							
ECOG Grade 0	7 (53.8)	15 (55.6)	16 (55.2)	7 (100.0)	21 (35.0)	175 (56.8)	241 (54.3)
ECOG Grade 1	6 (46.2)	7 (25.9)	10 (34.5)	0	18 (30.0)	131 (42.5)	172 (38.7)
ECOG Grade 2	0	5 (18.5)	3 (10.3)	0	21 (35.0)	2 (0.6)	31 (7.0)
CCR4 Expression Status							
Unknown	NA	NA	NA	NA	2 (3.3)	68 (22.1)	NA
Positive	NA	NA	NA	NA	56 (93.3)	231 (75.2)	NA
Negative	NA	NA	NA	NA	2 (3.3)	9 (2.9)	NA
Anti-Drug Antibody, n(%)							
Unknown	NA	NA	NA	NA	20 (33.3)	142 (46.1)	NA
Positive	NA	NA	NA	NA	1 (1.7)	10 (3.2)	NA
Negative	NA	NA	NA	NA	39 (65.0)	156 (50.6)	NA
Dose (mg/kg), n(%)							
0.01 mg/kg	2 (15.4)	0	0	0	0	0	2 (0.5)
0.1 mg/kg	4 (30.8)	0	0	0	0	0	4 (0.9)
0.5 mg/kg	3 (23.1)	0	0	0	0	0	3 (0.7)
1 mg/kg	4 (30.8)	27 (100.0)	29 (100.0)	7 (100.0)	60 (100.0)	308 (100.0)	435 (98.0)

Source: Population PK Analysis Report, Table 8

C. Results

19.4.3.1.C.1 PK parameter estimates

The PK of mogamulizumab across the 6 trials (doses ranged from 0.01 to 1 mg/kg) was described by a linear two-compartment model. The final population PK parameter estimates are presented in **Table 46**. The estimated typical population clearance (CL) was 0.014 L/h and typical central volume of distribution (V_1) was 3.65 L for a male patient with 3.9 g/dL of albumin, 33 U/L of AST, and normal hepatic function. The terminal half-life estimate was 18.8 days. Inter-individual variability (IIV) was estimated to be 51%, 21% and 73%, for CL, V_1 and V_2, respectively.

Table 46: PK parameter estimates in the final model

Parameter (units)	NONMEM Estimates		Bootstrap Derived Estimates		
	Estimate	SE%	Lower 95% CI for BS Mean	Median	Upper 95% CL for BS Mean
CL (L/hr)	0. 0138	4.2	0.0128	0.0138	0.0149
V1 (L)	3.65	1.8	3.5600	3.6500	3.7500
V2 (L)	2. 48	5.0	2.2700	2.4800	2.6900
Q (L/hr)	0.0532	22.4	0.0299	0.0520	0.0741
Albumin on CL	-1.81	8.7	-2.0500	-1.7800	-1.5400
AST on CL	0.282	29.7	0.1450	0.2730	0.4270
HI on CL	1.14	6.7	1.0200	1.1400	1.3200
Sex on CL	0.768	4.9	0.6980	0.7700	0.8370
BSA on V1	0.884	13.1	0.6910	0.8680	1.0700
Albumin on V2	-1.47	29.8	-2.1800	-1.3900	-0.6790
CL IIV (SD)	50.5	9.0	42.5	50.1	57.9
V1 IIV (SD)	20.5	15.2	14.5	20.1	25.8
V2 IIV (SD)	72.7	7.2	65.3	72.8	84.5
Residual Error	0.261	6.0	23.7	26.1	29.0

Source: Population PK Analysis Report, Table 18

19.4.3.1.C.2 Model Evaluation

The results of the visual predictive check revealed that the observed medians and upper and lower percentiles agree well with the simulated data (**Figure 25**).

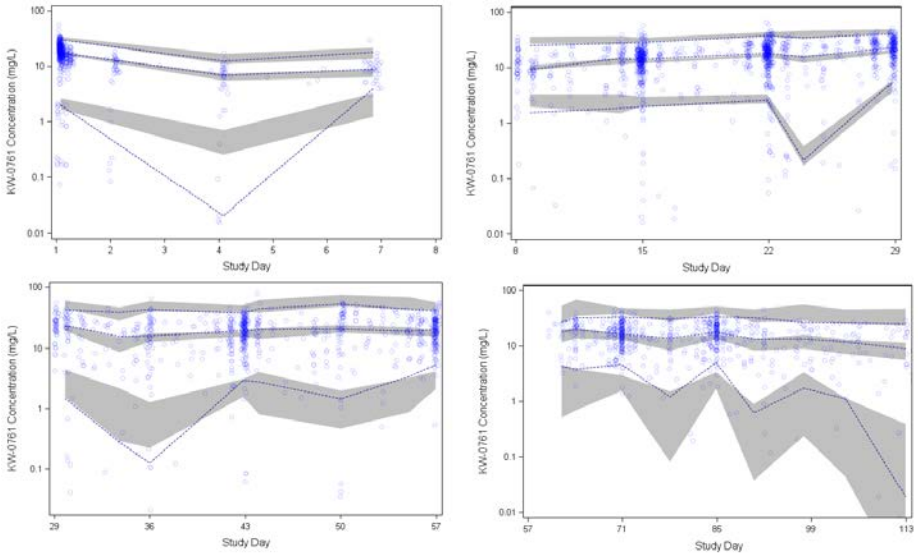


Figure 25: VPC Results for Final Model - Study Days 1 through 8 (upper left), Study Days 8 through 29 (upper right), Study Days 29 through 57 (bottom left), and Study Days 57 through 113 (bottom right).
Source: Population PK Analysis Report, Figure 25-28

Reviewer's comments: *Applicant's population PK model seems acceptable.*

19.4.3.1.C.3 Covariate Analyses

The following statistically significant parameter-covariate relationships were identified:

$$CL = \theta_1 \bullet \left(\frac{\text{Albumin}}{3.9}\right)^{\theta_8} \bullet \left(\frac{\text{AST}}{33}\right)^{\theta_9} \bullet (\theta_6)^{HI} \bullet (\theta_7)^{SEX} \bullet \exp(\eta_1)$$

$$V1 = \theta_2 \bullet \left(\frac{\text{BSA}}{1.82}\right)^{\theta_{10}} \bullet \exp(\eta_2)$$

$$Q = \theta_3 \bullet \exp(\eta_3 = 0)$$

$$V2 = \theta_4 \bullet \left(\frac{\text{Albumin}}{3.9}\right)^{\theta_{11}} \bullet \exp(\eta_4)$$

19.4.3.1.C.3.1 Hepatic Impairment

The effect of hepatic function on CL of mogamulizumab was evaluated in patients with normal hepatic function (total bilirubin ≤ ULN and AST ≤ ULN, n = 371), mild impairment (total bilirubin > 1 to 1.5 times ULN or AST > ULN, n = 80) and moderate impairment (total bilirubin >1.5 to 3 times ULN and any AST, n = 3). **Figure 26** shows that no clinically relevant differences in the CL of mogamulizumab were found between patients with hepatic impairment and patients with normal hepatic function. The final model identified approximately a 14% increase in CL in the mild to moderate hepatic impairment group compared to normal hepatic function group.

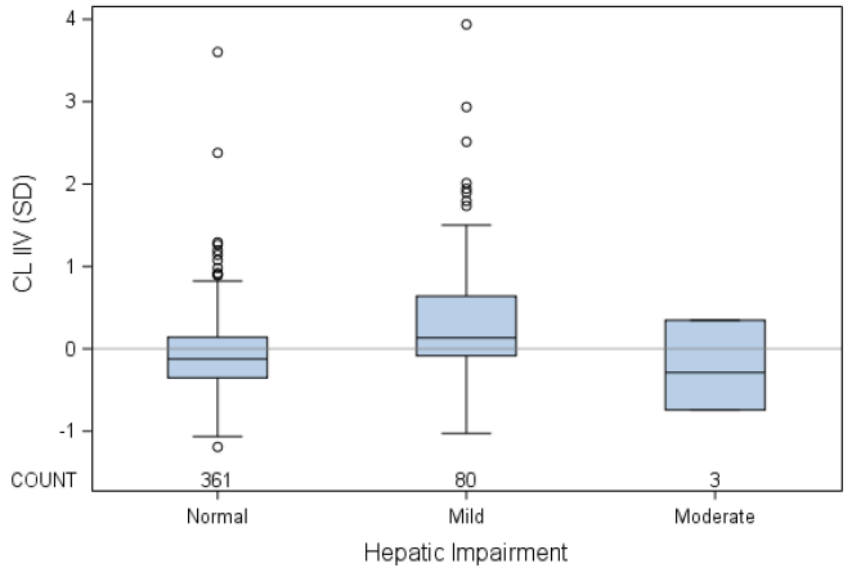


Figure 26: Mogamulizumab Clearance by Hepatic Impairment
Source: Population PK Analysis Report, Figure 34

19.4.3.1.C.3.2 Renal Impairment

The effect of renal function on mogamulizumab CL was evaluated in patients with normal renal function (CRCL ≥ 90 mL/min calculated by Cockcroft-Gault formula, n = 205), mild impairment (CRCL ≥ 60 and < 90 mL/min, n = 157), moderate impairment (CRCL ≥ 30 and <60 mL/min, n = 80) and severe impairment (CRCL < 30 mL/min, n = 2). No clinically important differences or trends in mogamulizumab CL were found between patients with renal impairment and patients with normal renal function (**Figure 27**).

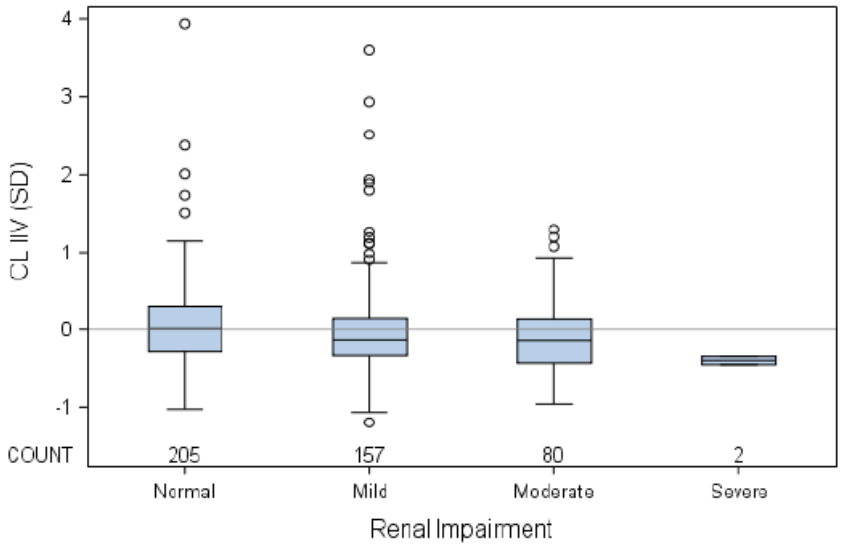


Figure 27: Mogamulizumab Clearance by Renal Impairment
Source: Population PK Analysis Report, Figure 35

19.4.3.1.C.3.3 CCR4 expression

CCR4 expression measured by flow cytometry (CD45+CD4+CD25+CCR4+CD7-) ranged from 1.3% to 93.5% in Trial 0761-009. CCR4 expression measured by IHC method ranged from 1% to 100% in Trial 0761-010. CCR4 expression status was defined as positive if ≥ 10% of cells were stained in specimens by CCR4 IHC method or if ≥ 5% of cells were stained in the CD45+CD4+CD25+CCR4+CD7- cell population by flow cytometry. Linear regression of CL IIV on baseline CCR4 expression (%) was not significant for Trial 0761-009 or for Trial 0761-010. (**Figure 28**).

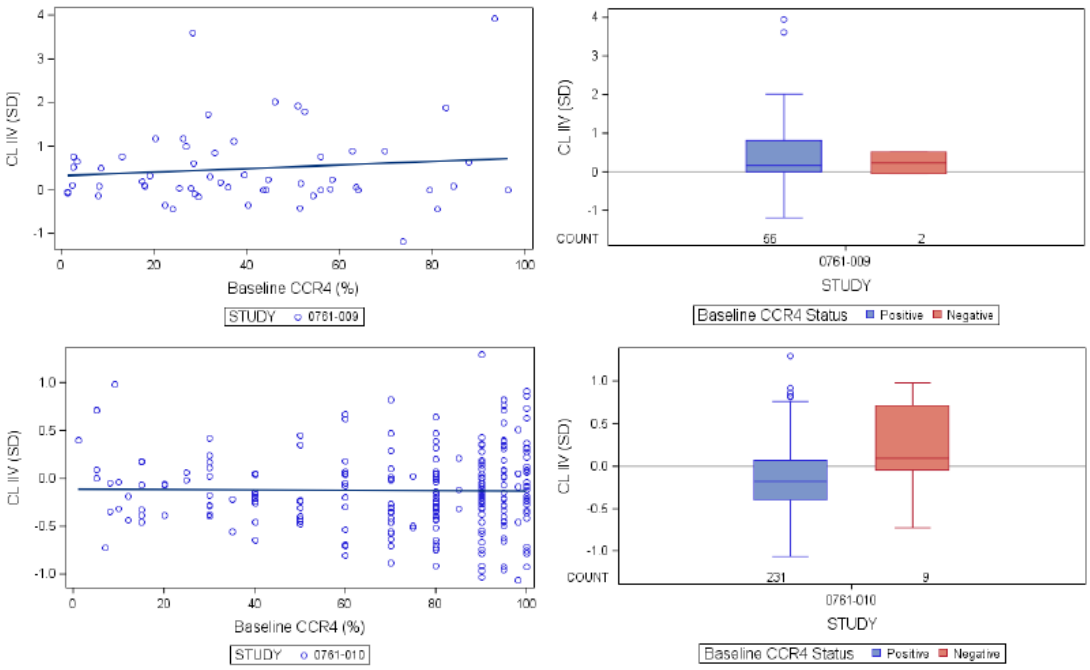


Figure 28: Mogamulizumab Clearance by CCR4 Expression in Trial 0761-009 (upper) and Trial 0761-010 (bottom)
Source: Applicant's Pop PK Report, Figure 54-55

19.4.3.1.C.3.4 Body Weight

The $C_{min,ss}$ at Week 24 was simulated based on final population PK model and used to evaluate the effect of body weight adjusted dosing regimen on steady-state exposure. **Figure 29** illustrates this relationship. $C_{min,ss}$ increased with increasing body weight. The median $C_{min,ss}$ value for the highest body weight quintile was approximately 2-fold higher than for the lowest body weight quintile.

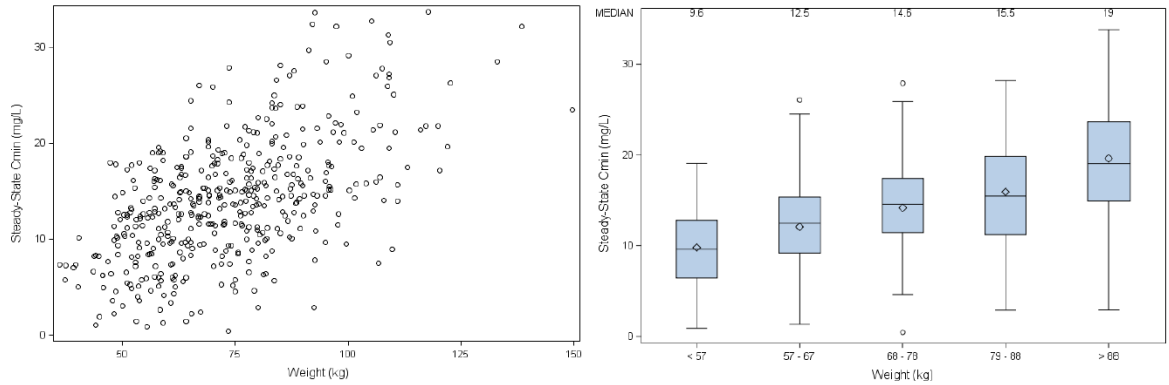


Figure 29: Week 24 Simulated $C_{min,ss}$ by Patient Weight (Left) and Patient Weight Quantile (Right)
Source: Applicant's Pop PK Report, Figure 31-32

Reviewer's comments: *Since body weight is not strongly correlated with clearance, as shown in* ***Figure 29****, body weight based dose may result in extra variability of the mogamulizumab exposure (e.g., AUC_{SS}) as compared with flat dose. Patients with greater body weight may have higher exposure. Considering ER for efficacy and safety was flat under the studied dose, the proposed body weight based dose was acceptable but may not be optimal.*

19.4.3.1.C.3.5 Other covariates

CL was estimated to be 22% lower in females than that in males. CL was estimated to be 78% and 164% in patients with the 5^{th} and 95^{th} percentiles of albumin, 84% and 130% in patients with the 5^{th} and 95^{th} percentiles of AST, as compared to the reference CL in male patients with BSA of 1.82 m^2, albumin of 4.0 g/dL, AST of 24 U/L, and normal hepatic function. V_1 in patients with the 5^{th} and 95^{th} percentiles of BSA was estimated to be 80% and 122% of the reference V_1 in typical patients, respectively.

D. Conclusion

- The PK of mogamulizumab is linear.
- Albumin, AST, sex and hepatic impairment (mild to moderate) were identified as statistically significant covariates on CL. However, none of them results in more than a 44% change in $AUC_{(0-\tau),ss}$ or $C_{min,ss}$ compared to a typical male patient with BSA of 1.82 m^2, albumin of 4.0 g/dL, AST of 24 U/L, and normal hepatic function.
- BSA was identified as a statistically significant covariate on V_1. No more than 6% change in $C_{min,ss}$ for 5^{th} and 95^{th} percentiles of BSA range compared to a typical patient.
- No statistically significant impact of age, race, renal impairment, disease type, ECOG performance score, ADA, and CCR4 expression on mogamulizumab CL was identified.

Reviewer's comments: *The reviewer agrees with Applicant's assessment that no dose adjustment based on race, gender, hepatic/renal function, disease type (ATL or CTCL), ECOG, ADA, CCR4 expression is needed.*

19.4.4 Exposure-Response Analyses for Efficacy

Applicant's Analysis

ER relationship was assessed for two efficacy endpoints, PFS and ORR, based on data from 184 patients with CTCL in Trial 0761-010. $AUC_{(0-\tau),ss}$ and $C_{min,1st}$ were employed in the analyses. Observed $C_{min,1st}$ were available for 144 of the 184 patients for this analysis. The population PK model was used to simulate a $C_{min,1st}$ values for the remaining 40 patients. $AUC_{(0-\tau),ss}$ was predicted by population PK model.

PFS was evaluated using Kaplan-Meier analysis. There was no apparent relationship between PFS and $C_{min,1st}$ or $AUC_{(0-\tau),ss}$ (**Figure 30**). PFS was also evaluated by quartiles of albumin, AST, body weight, or BSA, hepatic impairment, sex, CTCL clinical subtype, baseline ECOG performance score, and clinical stage at diagnosis. Except for CTCL clinical subtype (**Figure 31**), none of these covariates demonstrated a significant relationship with PFS.

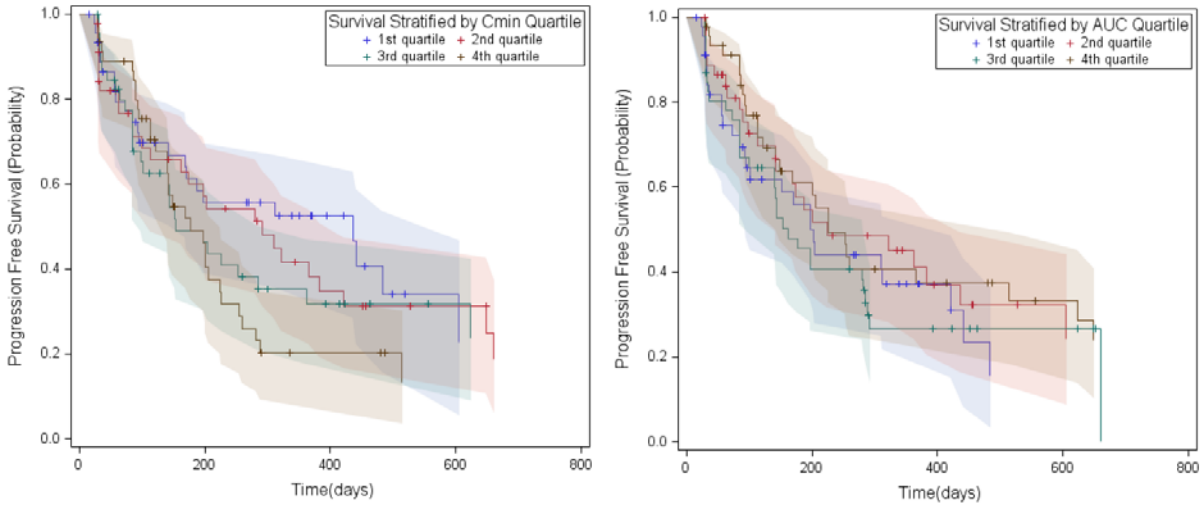


Figure 30: PFS based on Independent Review Assessment by $C_{min,1st}$ Quartile (left) and $AUC_{(0-\tau),ss}$ Quartile (right)

Source: Applicant's Exposure-Response Analysis Report, Figure 14-15

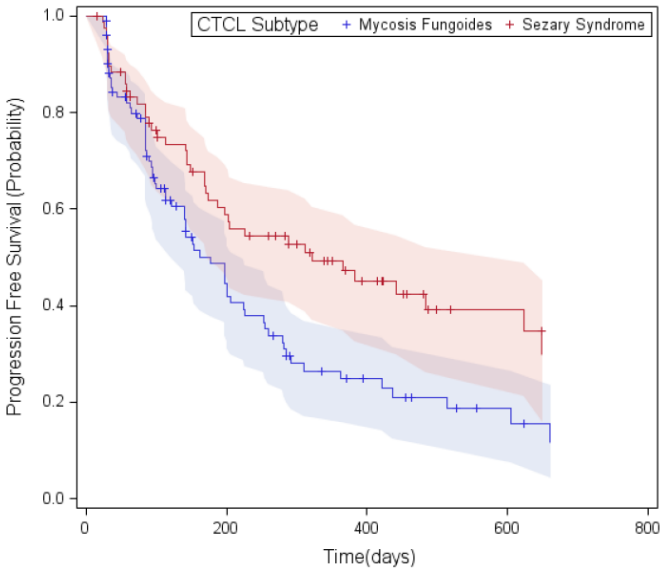


Figure 31: PFS based on Independent Review Assessment by CTCL Clinical Subtype

Source: Applicant's Exposure-Response Report, Figure 22

ORR was assessed by independent review assessment by $C_{min,1st}$ and $AUC_{(0-\tau),ss}$ quartile. There is no apparent relationship between $C_{min,1st}$ or $AUC_{(0-\tau),ss}$ and ORR (**Figure 32**). ORR was also evaluated by albumin (range: 2.7-5.1 g/dL), AST (8-57 U/L), BSA (1.46-2.72 m^2) and weight (47.3-149.7 kg) quartiles, hepatic impairment (normal: n = 161, mild: n = 22, moderate: n = 1),

sex (male: n = 107, female: n = 77), clinical subtype (MF: n = 105, SS: n = 79), ECOG performance score (0: n = 105, 1: n = 77, 2: n = 2) and clinical stage at diagnosis (1: n = 46, 2: n = 23, 3: n = 35, 4: n = 55, unknown: n = 25). There is no apparent relationship between ORR and albumin, AST, hepatic impairment, sex, BSA, weight or ECOG performance score. ORR differs by CTCL clinical subtype and clinical stage at diagnosis (**Figure 33**).

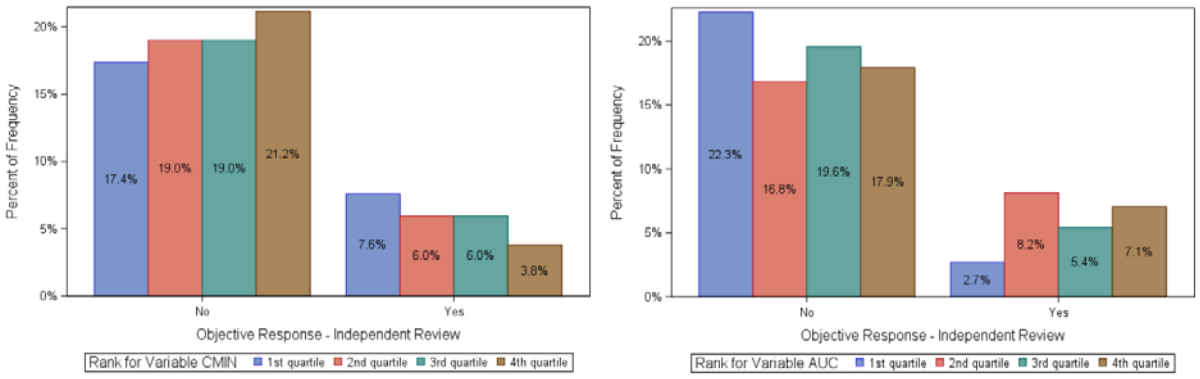


Figure 32: Clustered Histogram of ORR by Independent Review by $C_{min,1st}$ Quartile (left) and $AUC_{(0-\tau),ss}$ Quartile (right)
Source: Applicant's Exposure-Response Analysis Report, Figure 48 and 50

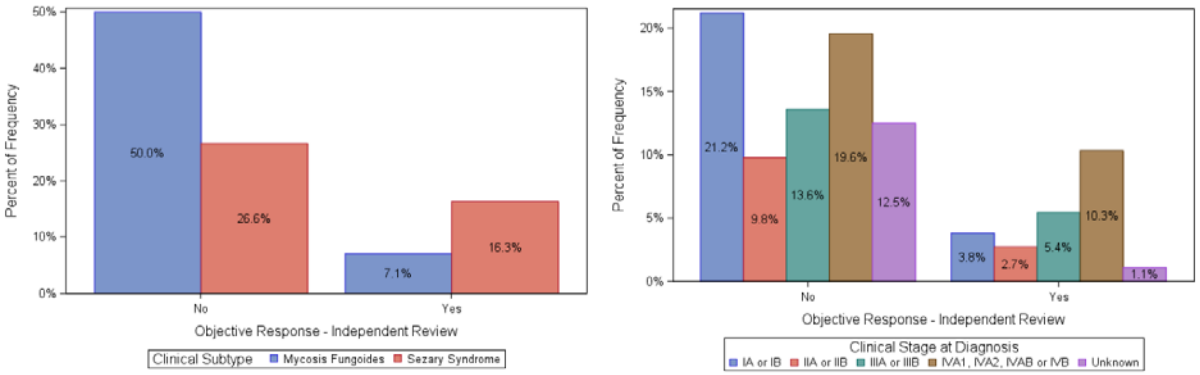


Figure 33: Clustered Histogram of ORR by Independent Review by CTCL Clinical Subtype (left) and Clinical Stage (right)
Source: Applicant's Exposure-Response Analysis Report, Figure 64 and 68

Reviewer's comment: *Applicant's ER analysis seems reasonable. As 1 mg/kg mogamulizumab was the only dose in Trial 0761-010 for the ER analysis, the impact of other dosing regimens cannot be evaluated. This analysis is based on the univariate analysis, which may be confounded by factors associating with both mogamulizumab exposure and efficacy endpoints. Multi-variant analysis would address this issue (at least partially). Therefore, the following multi-variant analysis was conducted by the FDA reviewer independently to assess potential confounders which may affect the ER relationship between PFS/ORR and $C_{min,1st}$. In addition, the FDA reviewer also explored the correlation between CCR4 expression and PFS to evaluate the appropriateness of the proposed indication regardless of CCR4 expression.*

Reviewer's Analysis

A. Objectives

The analysis objectives are

- To explore ER relationship for PFS and ORR for patients with CTCL in Trial 0761-010.
- To explore ER relationship for PFS and ORR in subpopulations group by clinical subtype.
- To explore CCR4-response relationship for PFS and ORR for patients with CTCL in Trial 0761-010.

B. Methods

19.4.4.1.B.1Data Sets

Data sets used are summarized in **Table 47**.

Table 47: Analysis Datasets for Reviewer's Analysis

Trial Number	Name	Link to EDR
0761-010	kw07.xpt	\\cdsesub1\evsprod\BLA761051\0005\m5\datasets\0761-pop-pk\analysis\adam\datasets\ kw07.xpt
0761-010	adpfs.xpt adrsirc.xpt	\\cdsesub1\evsprod\BLA761051\0001\m5\datasets\0761-bla-maa-ise-ctcl\analysis\adam\datasets
0761-010	adsl.xpt	\\cdsesub1\evsprod\BLA761051\0023\m5\datasets\0761-010\analysis\legacy\datasets

19.4.4.1.B.2Software

R (Version 3.0.2) was used for the reviewer's analysis.

C. Results

19.4.4.1.C.1ER Relationship for PFS using multivariate analysis

ER relationship was explored for PFS using univariate and multivariate analysis (**Figure 34**). The univariate analysis showed no clear separation in PFS among the mogamulizumab exposure quartiles. The multivariate analysis showed clinical subtype was significantly associated with PFS while exposure was not.

Table 48 Multivariate Cox Model Estimates for PFS vs. $C_{min,1st}$

Parameter	Estimate	SE	P-value
$\theta_{Cmin,1st}$	1.048	0.0397	0.242
$\theta_{SUBTYPE}$	0.604	0.2108	0.017

Source: FDA reviewer's analysis based on dataset kw07.xpt for Study 0761-010.

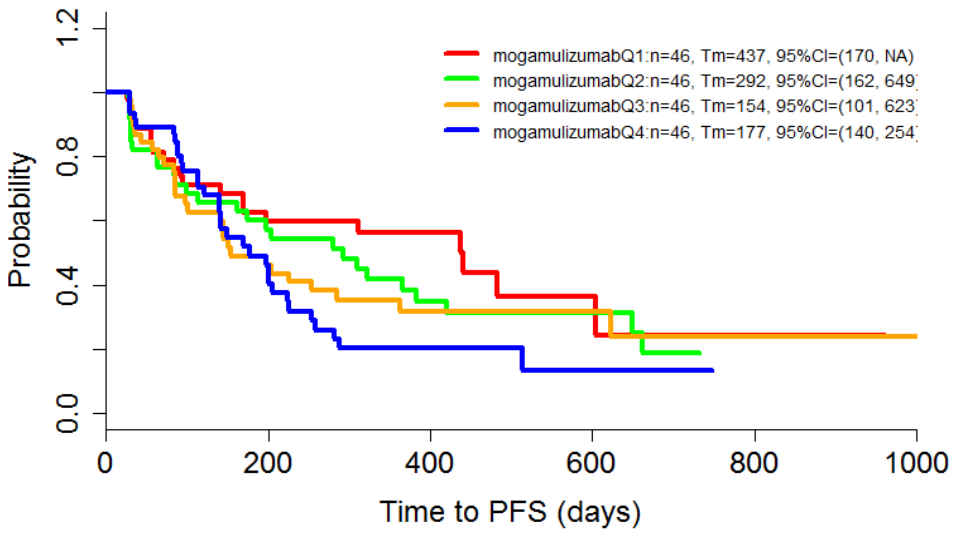


Figure 34: Exposure-Response Analysis for Kaplan-Meier Plots of PFS versus $C_{min,1st}$ for Trial 0761-010
Source: FDA reviewer's analysis based on dataset kw07.xpt for Study 0761-010.

19.4.4.1.C.2 ER Relationship for ORR using multivariate analysis

The patients with relapsed or refractory MF or SS (n = 184) from Trial 0761-010 were included in the ER analysis for ORR. Univariate analysis was performed using logistic models and the results showed that there is no relationship between ORR and $C_{min,1st}$ (**Figure 35**). Multivariate analysis was performed to adjust for other covariates. Based on multivariate analysis (**Table 49**), clinical subtype was identified as a statistically significant covariate for ORR. Patients with SS showed higher response rate than patients with MF. However, such difference was exposure independent; no correlation was identified between ORR and mogamulizumab $C_{min,1st}$ for both two clinical subtype groups (SS and MF) (**Figure 36**).

Table 49: Multivariate Logistic Regression Model Parameter Estimates for ORR vs. $C_{min,1st}$

Parameter	Estimate	SE	P-value
(Intercept)	-2.184	0.7528	0.0037
$\theta_{Cmin,1st}$	0.023	0.0696	0.7412
$\theta_{SUBTYPE}$	1.505	0.3948	0.0001

Source: FDA reviewer's analysis

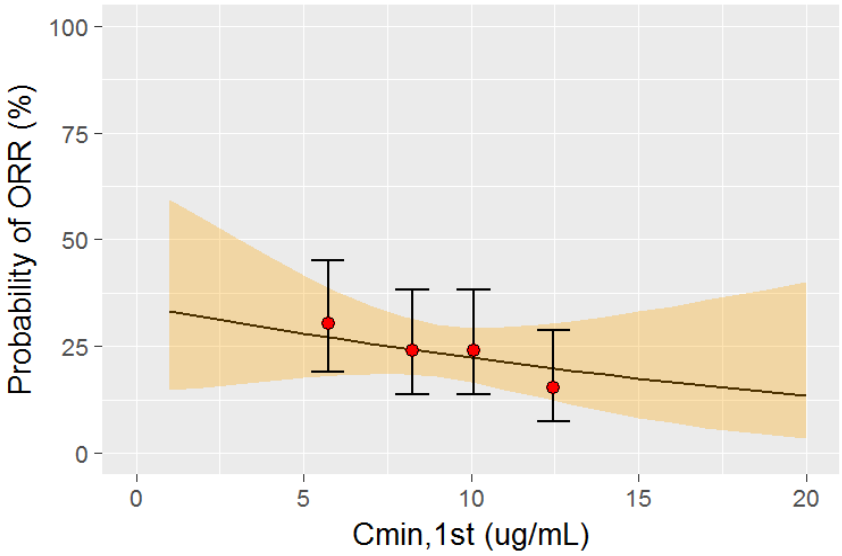


Figure 35: Exposure-Response for $C_{min,1st}$ versus ORR for Trial 0761-010
Solid line is the univariate logistic regression of the predicted probability of response and the orange area is the 95% CI. Red circles are observed ORR. For each C_{min1} quartile, the observed ORR is plotted at the mean value of the quartile with the vertical bar as the 95% CI.
Source: FDA reviewer's analysis based on dataset kw07.xpt for Trial 0761-010.

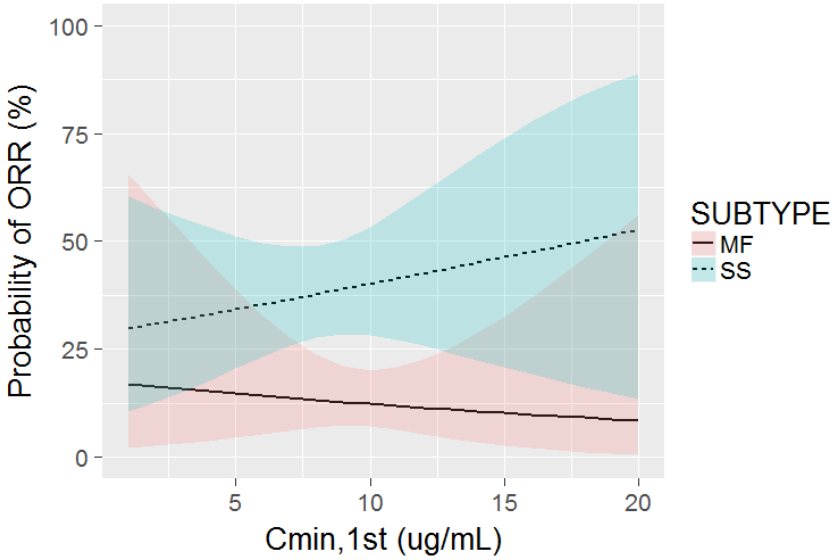


Figure 36: Exposure-Response for $C_{min,1st}$ versus ORR stratified by clinical subtype group
Line are predicted probability of response by univariate logistic regression and the shaded area is the 95% CI.
Source: FDA reviewer's analysis based on dataset kw07.xpt for Trial 0761-010.

Overall, the exposure-PFS/ORR relationships for mogamulizumab appeared to be flat at the proposed dose regimen.

19.4.4.1.C.3 Correlation between CCR4 expression and PFS/ORR

The correlation between CCR4 expression and PFS was explored for both treatment arm and control arm (vorinostat). A total of 288 patients with CCR4 expression information from Trial 0761-010 was included in the analysis. The patients were grouped by using a threshold of CCR4 expression of 25% within each arm. The results showed that the patients in treatment arm with CCR4 equal to or higher than 25% have a better treatment effect than those less than 25%. The patients with CTCL in treatment arm with CCR4 less than 25% have a similar treatment effect to the patients in control arm.

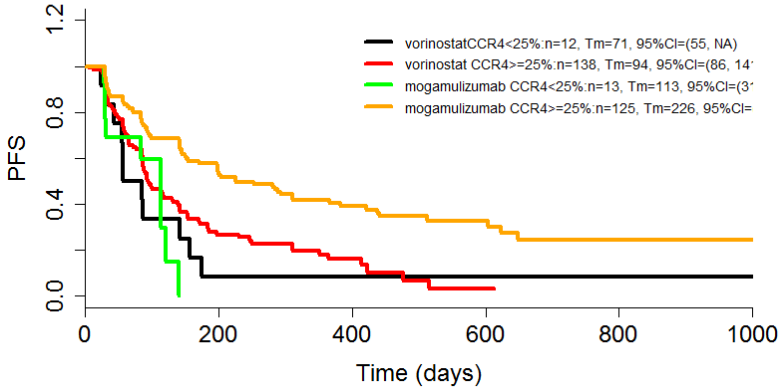


Figure 37 Correlation between CCR4 expression and PFS for Trial 0761-010
Source: FDA reviewer's analysis

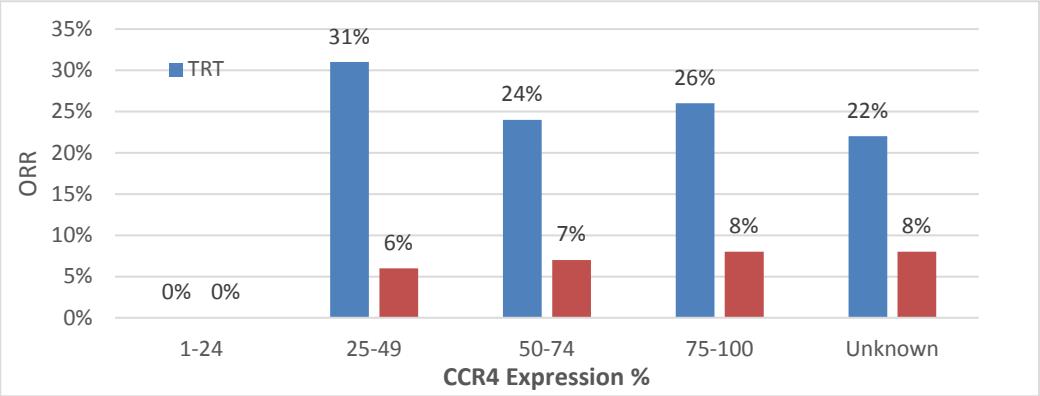
The correlation between CCR4 expression and ORR was also analyzed by using univariate logistic regression based on a total of 138 patients with log-transformed CCR4 expression information from Trial 0761-010. Although no statistically significant correlation was identified between CCR4 expression and ORR (**Error! Reference source not found.**), there was a trend that low CCR4 expression was associated with worse efficacy.

Table 50: Parameter Estimates of Univariate Logistic Regression Model (log-linear) for CCR4 Expression vs. ORR

Parameter	Estimate	SE	P-value
(Intercept)	-3.9049	1.7926	0.0294
$Log(\theta_{CCR4})$	0.6515	0.4154	0.1168

Source: FDA reviewer's analysis

No responders (IRC assessment) were identified in both treatment arm and control arm (vorinostat) when CCR4 expression was less than 25% (**Figure 38**). The ORR assessed by investigator or in specific compartment was not considered in this analysis. It is worth noting that due to the limited sample size, the data were not robust enough to provide a conclusive answer that whether patients with low CCR4 expression would have inferior efficacy for mogamulizumab or vorinostat.



% CCR4 expression	1-24	25-49	50-74	75-100	Unknown	Total
TRT-ORR	0/13	4/13 (31%)	6/25 (24%)	23/87 (26%)	10/46 (22%)	43/184 (23%)
Control-ORR	0/12	1/16 (6%)	2/27 (7%)	8/95 (8%)	3/36 (8%)	13/186 (7%)

Figure 38: Correlation between CCR4 expression and ORR for Trial 0761-010
Source: FDA reviewer's analysis based on dataset kw07.xpt for Trial 0761-010.

D. Conclusion

- No statistically significant ER relationships were identified with ORR or PFS following the administration of mogamulizumab at the proposed dose regimen for patients with refractory or relapsed MF or SS in Trial 0761-010.
- Although the clinical stage at diagnosis was identified as a covariate on ORR, disease stage at the first exposure to mogamulizumab could be more relevant, as clinical stage may have been changed from diagnosis to mogamulizumab treatment.
- CCR4 was not associated with PFS or ORR. However, based on the small number of patients and PFS or overall ORR by independent review committee, the patients with CCR4 less than 25% poorly responded.

19.4.5 Exposure-Response Analyses for Safety

A. Applicant's Analysis

The ER analyses for safety endpoints were performed for 184 patients with relapsed or refractory MF or SS in Trial 0761-010. Four safety endpoints: injury, poisoning and procedural complications (**Figure 39**), skin and subcutaneous tissue disorders (**Figure 40**), general disorders and administration site conditions (**Figure 41**), infections and infestations (**Figure 42**), and gastrointestinal disorders (**Figure 43**) were evaluated by $C_{min,1st}$ and $AUC_{(0-\tau),ss}$ quartiles. The impact of the following covariates on safety endpoints were also tested: albumin, AST, hepatic impairment, sex, BSA, and weight. No apparent relationship between mogamulizumab exposure or selected covariate and the number of percent of patients reporting an adverse event was identified.

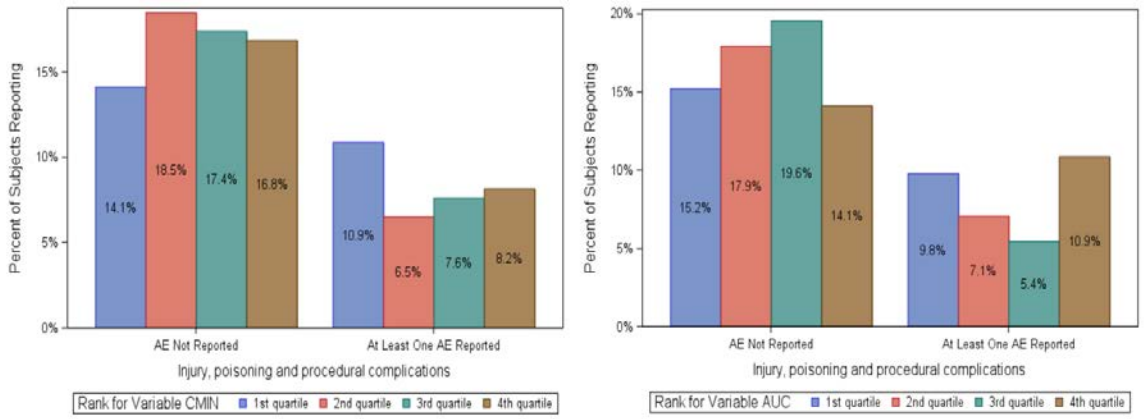


Figure 39: Clustered Histogram of Injury, Poisoning and Procedural Complications by $C_{min,1st}$ Quartile (left) and $AUC_{(0-\tau),ss}$ (right)
Source: Applicant's Exposure-Response Report, Figure 70 and 72

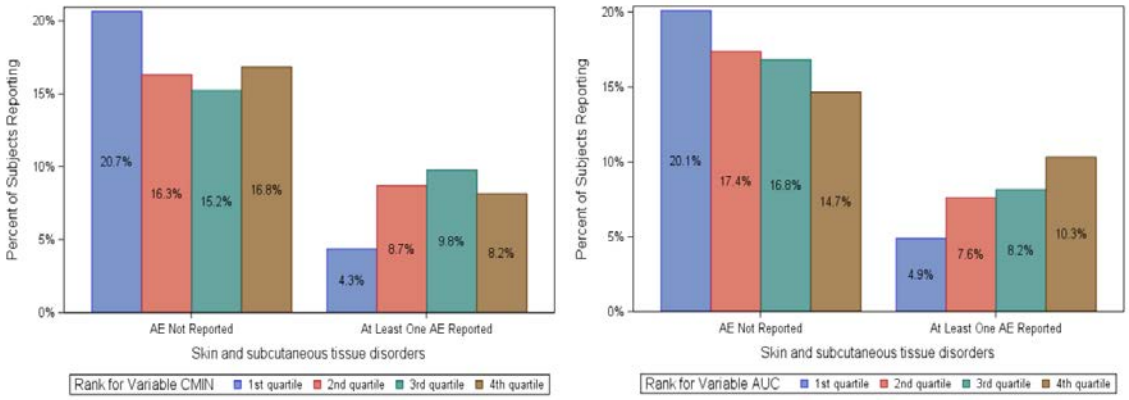


Figure 40: Clustered Histogram of Skin and Subcutaneous Tissue Disorders by Cmin,1st Quartile (left) and $AUC_{(0-\tau),ss}$ (right)
Source: Applicant's Exposure-Response Report, Figure 86 and 88

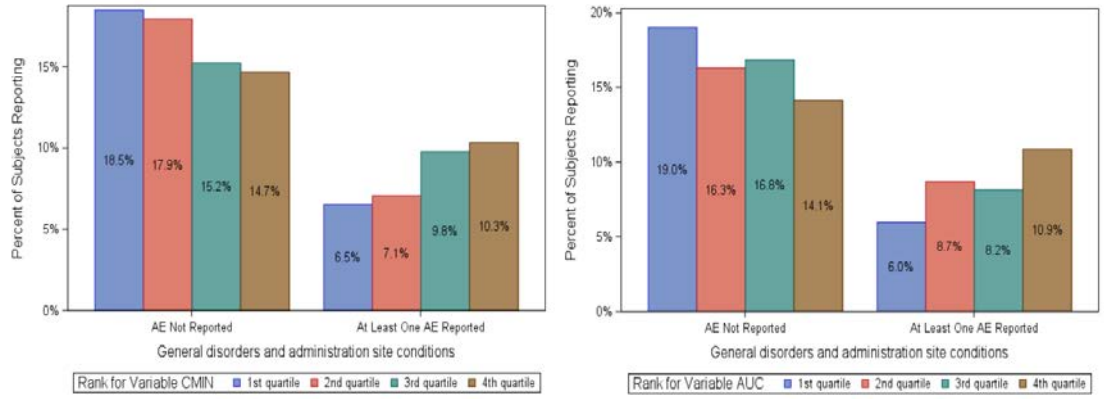


Figure 41: Clustered Histogram of General Disorders and Administration Site Conditions by $C_{min,1st}$ Quartile (left) and $AUC_{(0-\tau),ss}$ Quartile (right)
Source: Applicant's Exposure-Response Report, Figure 102 and 104

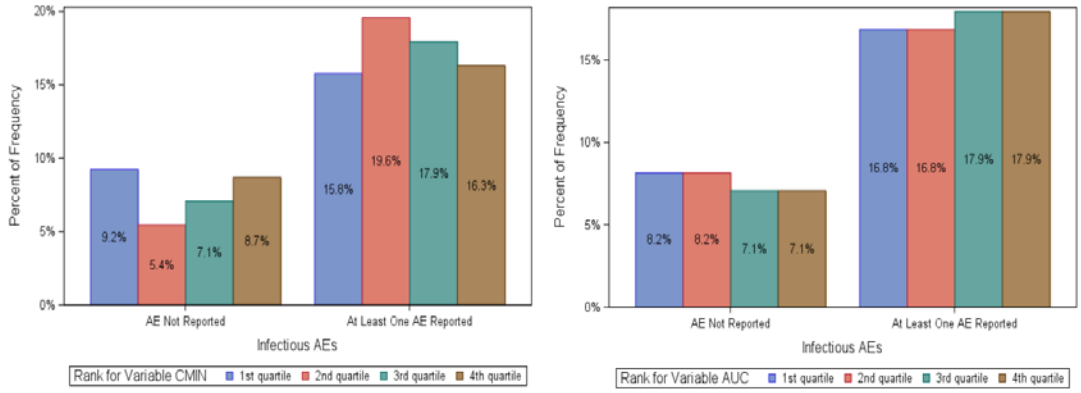


Figure 42: Clustered Histogram of Infections and Infestations by $C_{min,1st}$ Quartile (left) and $AUC_{(0-\tau),ss}$ Quartile (right)

Source: Applicant's Exposure-Response Report, Figure 118 and 120

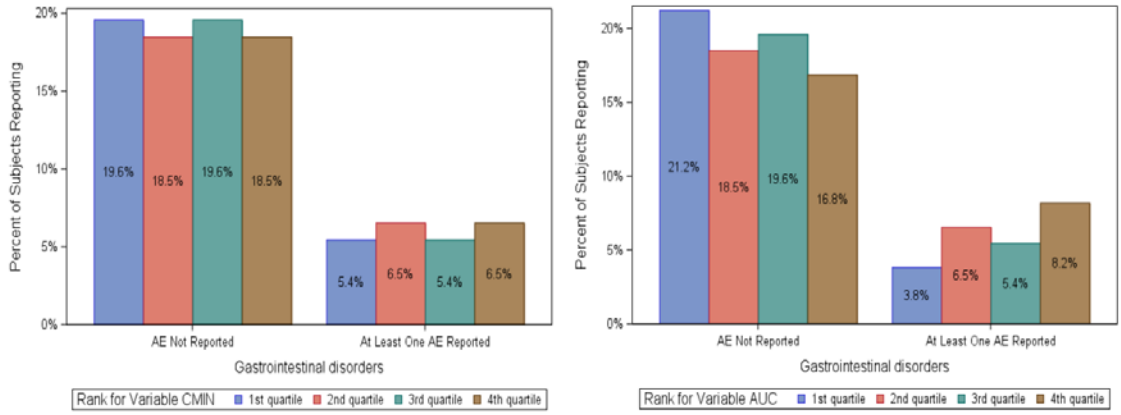


Figure 43: Clustered Histogram of Gastrointestinal Disorders by $C_{min,1st}$ Quartile (left) and $AUC_{(0-\tau),ss}$ Quartile (right)

Source: Applicant's Exposure-Response Report, Figure 134 and 136

Reviewer's comment: *Applicant's exposure-safety analysis seems reasonable. No evident exposure-safety relationship was identified for five selected safety endpoints. The FDA reviewer conducted the following univariate logistic regression for these safety endpoints to confirm the Applicant's conclusion.*

B. Reviewer's Analysis

Overall, there appeared to be no clear ER relationships for various safety endpoints following the administration of mogamulizumab at proposed dose regimen for the proposed indication, based on the data from Trial 0761-010. The relationship between $AUC_{(0-\tau),ss}$ and the safety endpoints were explored by univariate logistic regression. The result shows the relationships between the steady-state AUC and safety endpoints appear to be flat **(Figure 4)**.

C. Conclusion

- No statistically significant exposure-safety relationships were identified with the selected safety endpoints following the administration of mogamulizumab at recommended dose regimen for patients with relapsed or refractory MF or SS in Trial 0761-010.

19.5 Study 0761-010 Evaluation Schedule

Study Procedures: First Treatment Cycle

Procedures	Pre-treatment Visit	First Treatment Cycle				
		D 1	D 8	D 15	D 22	D 26-28[a]
Visit Window	Up to Day -30		±2 days	±2 days	±2 days	+ 2 days
Informed consent	X					
Review of subject eligibility	X					
Medical history	X					
Physical examination[b]	X	X		X		X
ECOG performance status (PS)	X	X		X		X
Vital signs, Weight	X	X[c]	X[c]	X[c]	X[c]	X
ECG	X					
Pregnancy test (within 7 days)	X					
Urinalysis	X					X
Hematology profile	X	X[d]	X[d]	X[d]	X[d]	X
Chemistry profile	X	X[d]	X[d]	X[d]	X[d]	X
Coagulation profile	X	X[d]				
Thyroid function tests (Free T4, TSH)	X					X
Hepatitis B & C, HIV, HTLV-1	X					
Flow Cytometric Analysis	X					X
Blood sample for determination of natural ligands	X					X
Serum sample for KW-0761 concentration assessment[e]		X	X	X	X	X
Saliva sample for genetic analysis		X[f]				
KW-0761 Administration[g]		X	X[h]	X[h]	X[h]	
Vorinostat Administration		X[i]				
Adverse event assessment[j]	X	X	X	X	X	X
Concomitant medication assessment[k]	X	X	X	X	X	X
CT (diagnostic quality)	X					X
Bone marrow aspiration & biopsy[l]	X					X
Skin biopsy for assessment of disease	X[m]					X[n]
Skin biopsy or archival tissue for CCR4 expression[o]	X					
Skin photographs		X				X
Modified Severity Weighted Assessment Tool (mSWAT)		X				X
Pruritus Evaluation (Likert Scale & Itchy QoL)		X				X
Skindex-29 , FACT-G & EQ-5D-3L		X				X
Immunogenicity[p]		X				X

Table 2 Study Procedures: Subsequent Cycles in Year 1

Procedures	Subsequent Cycles 2 through 13[a]			
	D 1	D 15	D 26-28 (Cycles 2, 4, 6, 8, 10, 12)[b]	D 26-28 (Cycles 3, 5, 7, 9, 11, 13)[b]
Visit Window		± 2 days	+ 2 days	+ 2 days
Physical examination[c]	X	X	X	X
ECOG PS	X	X	X	X
Vital signs, Weight	X[d]	X[d]	X	X
ECG				
Urinalysis	X			
Hematology profile	X[e]	X[e]	X	X
Chemistry profile	X[e]	X[e]	X	X
Coagulation profile	X[e]			
Thyroid function tests (Free T4, TSH)				X
Flow Cytometric Analysis[f]			X	X
Blood sample for determination of natural ligands				X
Serum sample for KW-0761 concentration assessment	X[g]	X[g]		
KW-0761 Administration	X[h]	X[h]		
Vorinostat Administration	X[i]			
Adverse event assessment[j]	X	X	X	X
Concomitant medication assessment[k]	X	X	X	X
CT (diagnostic quality)[f]				X
Bone marrow aspiration & biopsy[l]				X
Skin biopsy				X[m]
Skin photographs[f]			X	X
Modified Severity Weighted Assessment Tool (mSWAT)[f]			X	X
Pruritus Evaluation (Likert scale & Itchy QoL)			X	X
Skindex-29, FACT-G & EQ-5D-3L				X
Immunogenicity[n]				X

Source: Protocol 0761-010 version 8, Tables 1-3

In year 2 onward: Physical exams and labs (hematology, chemistry, coagulation) occurred on days 1, 15, and 26-28 of each cycle; flow cytometry and skin photographs at the end of each cycle; QoL assessments every other cycle; and CT every 16 weeks.

19.6 Response Rates by Independent Review in Study 0761-010

Table 51: Confirmed Response Rate Overall and by Compartment According to IRC

	Vorinostat N=186	Mogamulizumab N=186
Overall Response Rate - All Subjects		
Overall response rate (confirmed CR + PR) (n, %)	7 (3.8)	43 (23.1)
95% CI[a]	(1.5, 7.6)	(17.3, 29.8)
Treatment Comparison (Mogamulizumab vs. Vorinostat)		
Risk Diff (95% CI)[a]	19.4 (9.0, 29.4)	
P-value[b]	<.0001	
Response by Compartment:		
Blood	n=133	n=130
Response rate (confirmed CR + PR) (n, %)	23 (17.3)	77 (59.2)
95% CI[a]	(11.3, 24.8)	(50.3, 67.8)
Treatment Comparison (Mogamulizumab vs. Vorinostat)		
Risk Diff (95% CI)[a]	41.9 (30.4, 52.3)	
P-value[b]	<0.0001	
Skin	n=186	n=186
Overall response rate (confirmed CR + PR) (n, %)	27 (14.5)	73 (39.2)
95% CI[a]	(9.8, 20.4)	(32.2, 46.7)
Treatment Comparison (Mogamulizumab vs. Vorinostat)		
Risk Diff (95% CI)[a]	24.7 (14.5, 34.6)	
P-value[b]	<.0001	
Lymph nodes	n=153	n=158
Overall response rate (confirmed CR + PR) (n, %)	6 (3.9)	15 (9.5)
95% CI[a]	(1.5, 8.3)	(5.4, 15.2)
Treatment Comparison (Mogamulizumab vs. Vorinostat)		
Risk Diff (95% CI)[a]	5.6 (-5.6, 16.7)	
P-value[b]	0.0440	
Viscera	n=13	n=12
Overall response rate (confirmed CR + PR) (n, %)	0	1 (8.3)
95% CI[a]	(0.0, 24.7)	(0.2, 38.5)
Treatment Comparison (Mogamulizumab vs. Vorinostat)		
Risk Diff (95% CI)[a]	8.3 (-30.3, 44.6)	
P-value[b]	0.4795	

Note: Overall response rate is based on Global Composite Response score.

a: 95% CIs for response rate is the exact 95% confidence interval. 95% CI for difference is the exact 95% unconditional confidence interval for the risk difference (mogamulizumab - vorinostat).

b: P-value was obtained from Cochran-Mantel-Haenszel test adjusting for disease type, disease stage, and region. Adjusted P-value (for overall response rate) was calculated using Sidak method.

Source: CSR Table 11.4.2-9

19.7 FDA Grouped Preferred Terms for Study 0761-010 Safety Analysis

Note: Bracketed terms were not reported in 0761-010 ADAE.xpt

FDA Grouped PT	Included	Excluded
Abdominal pain	Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain, Abdominal discomfort, Epigastric discomfort	Abdominal discomfort, Abdominal distension, Abdominal rigidity
Abscess	Abscess, specific types of abscess (e.g., limb/tooth/subcutaneous/Staphylococcal/perirectal/joint)	
Anemia	Anemia, Anemia macrocytic, Hemolytic anemia, Hemorrhagic anemia, Hemoglobin decreased, Hematocrit decreased, RBC count decreased	Pancytopenia
Arrhythmia	Arrhythmia, Atrial fibrillation, Atrial flutter, Bradycardia, Sinus bradycardia, Atrial tachycardia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular fibrillation, Ventricular tachycardia, [Cardiac flutter], Extrasystoles, [Heart rate irregular]	Palpitations
Bronchospasm	Bronchospasm, Wheezing, Asthma	
Cardiac failure	Cardiac failure, Congestive cardiomyopathy, [Left ventricular failure, Cor pulmonale, Cardiac failure congestive, Cardiac failure chronic]	[Cardiac arrest, Cardiac hypertrophy, Ejection fraction decreased, Left ventricular dysfunction, Diastolic dysfunction, Ventricular dysfunction, Ventricular hypokinesia]
Candidiasis	Candidiasis, Oropharyngeal candidiasis, Oral candidiasis, Intertrigo candida, Genital candidiasis	Candiduria, Vulvovaginal mycotic infection
Chest pain	Chest discomfort, Chest pain, Noncardiac chest pain, Angina pectoris	Angina pectoris, Musculoskeletal chest pain
Conjunctivitis	Conjunctivitis, Conjunctivitis allergic/bacterial/infective/viral	
Cough	Cough, Productive cough, Upper airway cough syndrome	
Depression	Depression, Depressed mood, [Depressive symptom], [major depression]	
Diarrhea	Diarrhea, Defecation urgency, Gastroenteritis, Colitis	Ileitis, Clostridium difficile colitis

FDA Grouped PT	Included	Excluded
Dizziness	Dizziness, [Dizziness exertional, Dizziness postural], Vertigo, Vertigo positional	
Dyspnea	Dyspnea, Dyspnea exertional	[Acute respiratory failure, Respiratory failure, Tachypnea, Respiratory rate increased, Wheezing, Bronchospasm]
Edema	Generalized edema, Face edema, Edema peripheral, Fluid overload, Pulmonary edema	Localized edema, Joint swelling, Eyelid edema, Lip edema, Periorbital edema, Mouth edema, Edema genital, Lymphedema, Lymphatic edema
Fatigue	Asthenia, Fatigue, Lethargy, ECOG performance status worsened	Malaise
Febrile neutropenia	Febrile neutropenia, [Neutropenic infection, Neutropenic sepsis]	
Gastroenteritis	Gastroenteritis, Gastroenteritis viral	
Gastrointestinal hemorrhage	Gastric hemorrhage, Large intestinal ulcer hemorrhage, Hematochezia, [Hematemesis], Intestinal hemorrhage, Upper gastrointestinal hemorrhage, Gastrointestinal hemorrhage, Intestinal hemorrhage, Melena, Rectal hemorrhage	Hemorrhoidal hemorrhage
Headache	Headache, tension headache, sinus headache	
Hemorrhage intracranial	Hemorrhage intracranial, subdural hematoma, subdural hemorrhage, [Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage]	
Hepatitis	Hepatitis, Hepatitis acute	
Hepatitis	AST increase, ALT increase, Hepatic enzyme increased, Hepatic enzyme abnormal, Transaminases increased, [Hypertransaminemia], Hepatocellular injury, Hepatotoxicity	Hepatic failure, Liver function test abnormal, Hepatic encephalopathy
Herpesvirus infection	Herpes simplex, Herpes simplex pneumonia, Herpes virus infection, Herpes zoster, Herpes dermatitis, Herpes ophthalmic, Oral herpes, [Genital herpes], Herpes zoster ophthalmic, [Varicella, Varicella zoster virus infection]	
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia, Jaundice	
Hyperglycemia	Hyperglycemia, Blood glucose increased, Diabetes mellitus, Diabetes mellitus inadequate control, Type 2 diabetes mellitus, Glycosylated hemoglobin increased	
Hypersensitivity	Drug hypersensitivity, Hypersensitivity, Urticaria, Angioedema, [Anaphylactic reaction, Anaphylactic shock]	Infusion related reaction, Skin reaction, Swollen tongue, Erythema multiforme

FDA Grouped PT	Included	Excluded
Hypertension	Hypertension, Essential Hypertension, Blood pressure increased, Blood pressure systolic increased	
Hypokalemia [a]	Hypokalemia, blood potassium decreased	
Hypoesthesia	Hypoesthesia, Hypoesthesia oral	
Hypotension	hypotension, Diastolic hypotension, Orthostatic hypotension	
Influenza	Influenza, H1N1 influenza	
[Injection site reaction]	Injection site erythema, Injection site extravasation, injection site reaction	
Leukopenia	Leukopenia, White blood cell count decrease	
Lower respiratory tract infection	Bronchitis, specific types of bronchitis (Bronchitis bacterial/viral/chronic), Lower respiratory tract infection, Lung infection, [Tracheitis, Bacterial tracheitis, Tracheobronchitis]	
Lymphopenia	Lymphopenia, lymphocyte count decreased	
Mucositis	Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Tongue ulceration, Oral pain, Oral discomfort, Oropharyngeal pain	Proctalgia, Proctitis, Radiation mucositis, Vaginal inflammation, Gingival pain, Gingival swelling, Gingivitis, Gingival erythema, Glossitis, Mucosal hemorrhage, Esophagitis, Erosive esophagitis, Gastrointestinal tract irritation
Muscle spasms	Muscle spasms, Muscle contracture, Muscle contractions involuntary, [Muscle spasticity]	
Musculoskeletal pain	Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Musculoskeletal discomfort, Neck pain, Pain in extremity, Myalgia, [Spinal pain]	Arthralgia, Flank pain, Noncardiac chest pain
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina Pectoris, Angina unstable, [Troponin increased, Acute coronary syndrome, Myocardial infarction]	Cardiac arrest

FDA Grouped PT	Included	Excluded
Nausea	Nausea, Retching	
Neuropathy peripheral	Neuropathy peripheral, Peripheral sensory neuropathy, [Peripheral sensorimotor / motor neuropathy], Neuralgia	Hypoesthesia, Paresthesia, Sensory loss, Peripheral nerve palsy, [Polyneuropathy]
Neutropenia	Neutropenia, Neutrophil count decreased	Pancytopenia
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, Basal cell carcinoma, Bowen's disease	Squamous cell carcinoma
Otitis	Otitis media, otitis media acute, otitis externa	
Paresthesia	Paresthesia, Paresthesia oral	
Pneumonia	Pneumonia, specific types of pneumonia (e.g. pneumonia influenzal/legionella/pneumococcal/mycoplasmal/pneumocystis jirovecii/atypical), Bronchopneumonia, Lung infiltration	Bronchopulmonary aspergillosis, Herpes simplex pneumonia
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease	
Pruritus	Excoriation, Pruritus, Pruritus allergic, Prurigo	Eye pruritus
Pulmonary edema	Pulmonary edema, [Pulmonary congestion]	
Pulmonary hemorrhage	[Pulmonary hemorrhage, Pulmonary alveolar hemorrhage]	
Rash	Dermatitis, Dermatitis allergic/atopic/bullous/contact/exfoliative/infected/psoriasiform, Exfoliative rash, Rash, Rash generalized, Rash erythematous/macular/maculopapular/papular/pruritic/pustular, Toxic skin eruption, Palmoplantar keratoderma, Palmar-plantar erythrodysesthesia syndrome, Skin reaction	Drug hypersensitivity, Dermatitis infected, Herpes dermatitis, Skin exfoliation, Eczema, Rosacea, Seborrheic Dermatitis, Seborrheic keratosis, Actinic keratosis, Acarodermatitis, Acne, Rosacea, Pityriasis rosea, Poikiloderma, Chronic actinic dermatitis, Macule, Psoriasis
Renal insufficiency	[Acute kidney injury], Blood creatinine increase, Glomerular filtration rate decreased, Renal failure, Renal failure acute/chronic, Renal impairment, Nephropathy, Hypercreatinemia	Renal disorder
Respiratory tract infection	Respiratory tract infection + specific types (e.g. respiratory tract infection viral, respiratory syncytial virus infection)	Upper / lower respiratory tract infection

FDA Grouped PT	Included	Excluded
Sepsis	Bacteremia, Sepsis, Septic shock, Sepsis syndrome, specific types of sepsis or bacteremia (e.g. Staphylococcal), Septic embolus, [Neutropenic sepsis, Urosepsis]	Candida sepsis, Device related infection
Skin infection	Skin infection, Skin bacterial infection, Staphylococcal skin infection, Erysipelas, Impetigo, specific types of impetigo (e.g. Staphylococcal impetigo), Periorbital cellulitis, Cellulitis, Dermatitis infected, Infected skin ulcer	Intertrigo candida, Skin candida, other references to candida infection
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Pancytopenia
Thrombosis or thromboembolism	Deep vein thrombosis, Pulmonary embolism, Thrombosis, Thrombosis in device, specific sites of thrombosis (e.g., jugular vein, aortic, intracranial venous sinus thrombosis)	Air embolism, Embolism, Septic embolism, Thrombophlebitis superficial
Upper respiratory tract infection	[Acute sinusitis], Chronic sinusitis, Laryngitis, Laryngitis viral, Nasopharyngitis, Pharyngitis, specific types of pharyngitis (e.g. Viral pharyngitis, Pharnygitis streptococcal), Rhinitis, Viral rhinitis, Sinusitis, [Tonsillitis], Upper respiratory tract infection, [Upper respiratory tract infection bacterial], Viral upper respiratory tract infection, Rhinovirus infection	Respiratory tract infection, Rhinitis allergic, Rhinorrhea
Urinary tract infection	Cystitis, Urinary tract infection + specific types (e.g. Escherichia UTI), [Pyelonephritis, Kidney infection]	Bacteriuria, Candiduria, Dysuria, Urine leukocyte esterase positive
Visual impairment	Vision blurred, Visual acuity reduced, Visual impairment, [Vision decreased, Visual field defect, Blindness, Diplopia]	
Wound infection	Wound infection, specific types of wound infection (e.g. Wound infection staphylococcal)	
Xerosis	Dry skin, Dry eye, Dry mouth, Xerosis	

[a] Grouping for other lab-related AEs was similar.

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/

WONME K CHON
08/07/2018
electronically signed by Katie Chon, PharmD, RPh

HAIYAN N CHEN
08/07/2018

YUAN L SHEN
08/07/2018
Tom signs on behalf of Raji Yuan-Li signs on behalf of Jingjing

THOMAS E GWISE
08/07/2018
Acting on behalf of RAJESHWARI SRIDHARA

YVETTE L KASAMON
08/07/2018

CHRISTOPHER M SHETH on behalf of MICHAEL L MANNING
08/07/2018

CHRISTOPHER M SHETH
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JOHN K LEIGHTON
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LUNING ZHUANG
08/08/2018

CHAO LIU
08/08/2018

OLANREWAJU OKUSANYA
08/08/2018

NAM ATIQUR RAHMAN
08/08/2018
I concur with the recommendation.

ROMEO A DE CLARO
08/08/2018

ANN T FARRELL
08/08/2018
I am signing on behalf of myself and Dr. Pazdur.

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

Full Review Template version: December 26, 2017

COA ID	**C2017336**
BLA #	**761051**
Referenced IND for NDA/BLA	
Established Name/Trade Name	**Mogamuluzimab/POTELIGEO**
Sponsor/Applicant	**Kyowa Kirin Pharmaceutical**
Indication	**Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy**
Meeting Type/Deliverable	**Not applicable**
Sponsor Letter Date/SDN #	**10/4/2017**
Date of Consult Request	**10/31/2017**
Review Completion Date	**3/20/2018**
Review Division	**DHP**
Clinical Reviewer/Clinical Team Leader(CTL)	**Yvette Kasamon/Angelo DeClaro**
Review Division PM	**Katie Chon**
COA Reviewer	**Jing (Julia) Ju, PharmD., PhD**
COA TL/Secondary Reviewer	**Selena Daniels, PharmD., MS**
COA Associate Director	**Elektra Papadopoulos, MD., MPH**
Instrument 1	**Skindex-29**
Instrument 2	**ItchyQoL**
Instrument 3	**Functional Assessment of Cancer Therapy-General (FACT-G)**
COA Type 1 and Endpoint Concepts	**PRO, skin disease symptoms and impacts**
COA Type 2 and Endpoint Concepts	**PRO, pruritus and impacts**
COA Type 3 and Endpoint Concepts	**PRO, health-related quality of life**
Intended Population	**Adult patients with cutaneous T-cell lymphoma (CTCL)**
Internal Meeting	**1/4 Mid-Cycle meeting**
Sponsor Meeting/WRO	**Not applicable**

Please check all that apply: ☒Rare Disease/Orphan Designation
☐Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Hematology (DHP) regarding BLA 761051. The applicant is seeking approval for mogamulizumab for the treatment of cutaneous T-cell lymphoma (CTCL). The proposed indication is treatment of CTCL in patients who have received at least one prior systemic therapy.

The applicant used the following patient-reported outcome (PRO) assessments in their open-label, multi-center, randomized phase 3 clinical trial (Study 0761-010) as secondary efficacy measures in adult CTCL patients:

Table 1. PRO assessments in Study 0761-010

Instrument name (COA Type)	Concept(s)	Endpoint[1]	Copy of Instrument
Skindex-29 (PRO)	Skin disease symptoms and impacts	Secondary	Appendix A
Functional Assessment of Cancer Therapy-General (FACT-G; PRO)	Health-related quality of life	Secondary	Appendix B
ItchyQoL (PRO)	Pruritus and impacts	Secondary	Appendix C
Pruritus Likert Scale	Pruritus intensity	Secondary	Appendix D

(b) (4)

DHP has requested COA Staff to evaluate the adequacy of the PRO assessments in the pivotal study (Study 0761-010) (b) (4)

(b) (4) For additional details on study design and missing data issues, refer to the Clinical and Statistical reviews. In addition, the conflicting results across the PRO measures raises questions on the reliability of the measures and treatment effect on skin symptoms. For example, the Skindex-29 Symptom domain shows improvement in items 1 (skin hurts) and 7 (skin burns or stings); however, those same concepts measured in ItchyQoL (items 2 and 3) did not show improvement. Additionally, both results from Skindex-29 item 10 (skin itchy) and the Pruritus Likert Scale (itch intensity) did not show improvement in itch. Based on issues with data interpretability, (b) (4)

[1] Please see Section D 1.3 for a complete endpoint hierarchy.

There are also some potential limitations with the instrument, which are described in Section C.3 of this review.

For future medical product development, we recommend sponsors prospectively put in place procedures for minimizing missing data, including obtaining PRO data from patients at time of early withdrawal, and include these procedures in the protocol. Reasons for missing PRO data at the overall score- and item-level should be documented and included in the analysis dataset. We recommend sponsors to engage FDA early (e.g., Pre-IND) and throughout drug development to discuss the COA endpoint strategy to ensure the selected instruments are fit-for-purpose and are well-defined and reliable for the contexts of use prior to initiation of pivotal studies.

B. BACKGROUND

Cutaneous T-cell lymphoma (CTCL) is rare form of non-Hodgkin's lymphoma (NHL) accounting for about 4% of all NHL cases, with an estimated incidence of 7.7 cases per million persons. Cutaneous T-cell lymphoma mainly affects the skin, presenting as patches, plaques, tumors or erythroderma, and may be associated with severe pruritus. The 2 most common subtypes, accounting for approximately 65% of all CTCL, are mycosis fungoides (MF) and Sézary syndrome (SS).

Patients with early stage CTCL are treated topically. As the disease progresses, systemic therapy may become necessary. There are very few systemic agents that are approved exclusively for CTCL and no standard therapy for patients with later stage relapsed/refractory disease. Cutaneous T-cell lymphoma often becomes treatment resistant, and there is a substantial medical need to develop new therapies that can target all disease compartments (skin, blood, lymph nodes, and viscera) and provide a durable response in the treatment of this orphan disease.

Mogamulizumab, also known as KW-0761, is a defucosylated humanized IgG1 kappa monoclonal antibody that selectively binds to CCR4, a G protein-coupled receptor for C-C chemokines. In healthy individuals, CCR4 is known to be selectively expressed on a subset of T cells, including Type 2 T helper (Th2) T cells and regulatory T cells (Treg). CCR4 is over expressed or expressed at high frequency on the surface of cancer cells in T-cell malignancies such as CTCL, adult T-cell leukemia-lymphoma (ATL), and peripheral T-cell lymphoma (PTCL). Non-clinical in vitro and in vivo studies using CCR4-expressing lymphoma cell lines demonstrate that mogamulizumab binding to CCR4 directly targets a cell for antibody-dependent cellular cytotoxicity (ADCC) activity. As a defucosylated antibody, mogamulizumab induces greater ADCC activity against CCR4-expressing target cells compared with conventionally glycosylated antibodies.

Mogamulizumab has been granted an orphan designation in the EU, Japan and the US for CTCL.

Materials reviewed:

- Pertinent regulatory history
- The current submission for COA Staff review (b) (4)
- Sponsor's response to IR letters
- Discussion with Clinical and Biostatistics colleagues

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

1.1 Clinical Trial Population

The clinical trial population consisted of patients with CTCL who had failed at least 1 prior course of systemic therapy. The key inclusion criteria included adult patients (≥ 18 years of age at the Pre-treatment Visit, i.e., at the time that written informed consent was obtained) with histologically confirmed diagnosis of MF or SS (regardless of tumor CCR4 expression status). The trial excluded patients with histologic transformation, prior allogeneic HSCT, autologous HSCT within 90 days, active autoimmune disease or active infection. The trial required patients to have ANC ≥ 1500/μL (≥ 1000/μL if bone marrow was involved), platelet count ≥ 100,000/μL (≥ 75,000/μL if bone marrow was involved), creatinine clearance > 50 mL/min or serum creatinine ≤ 1.5 mg/dL and hepatic transaminases ≤ 2.5 times ULN.

Refer to the Clinical review for additional background.

1.2 Clinical Trial Design

Study 0761-010 was an open-label, multi-center randomized, Phase 3 study with 1:1 randomization of study drug mogamulizumab versus the comparator, vorinostat, in subjects with previously treated CTCL including MF and SS.

Treatment was administered on an outpatient basis. Patients received 1.0 mg/kg of mogamulizumab as an intravenous infusion over at least 1 hour on Days 1, 8, 15, and 22 of the first cycle and on Days 1 and 15 of subsequent cycles. Vorinostat was dosed at 400 mg orally once daily, continuously for 28-day cycles. Treatment continued until disease progression or unacceptable toxicity. Vorinostat-treated patients with disease progression or unacceptable toxicities were permitted to cross over to mogamulizumab.

Refer to the Clinical Review for additional details on the clinical trial design.

Patient-reported outcome (PRO) assessments were administered throughout the trial, including the Skindex-29, ItchyQoL, Pruritus Likert scale, Functional Assessment of Cancer Therapy-General (FACT-G), and the EuroQoL Five Dimensions scale (EQ-5D-3L).

The Skindex-29, FACT-G, and EQ-5D-3L were evaluated at Baseline (Cycle 1, Day 1), end of Cycle 1, then every 8 weeks (i.e., end of Cycle 3, 5, …, 25) through Cycle 25, and at the End of

Treatment visit. The ItchyQoL and the Pruritus Likert scale were evaluated every 4 weeks at each cycle. Measurements at the end of Cycle 1 were defined as the latest value obtained from Cycle 1 (Days 26 through 28) or Cycle 2 (Day 1). Measurements at the end of Cycle X, where x = 1, 2, 3, …, 25 were defined as the latest value obtained from Cycle X (Days 26 through 28), Cycle X every 8 weeks, or Cycle (X+1) Day 1.

Reviewer's comments: *To provide adequate data on acute effects, assessment frequency should be higher within the first few cycles and can be less frequent in later cycles. Monthly (or every cycle) assessment for the first 6 months is reasonable for most PRO assessments.*

If a patient crossed over before Cycle 3, their PRO data continued to be collected for potential analysis of the crossover period, however it was not included in the analyses of the control arm because of the potential influence of mogamulizumab therapy.

As subjects experienced progression events, the Investigators discontinued administration of their randomized therapy and did not complete further PRO assessments beyond that point.

This reviewer recommends that sponsors prospectively put in place procedures for minimizing missing data, including obtaining PRO data from patients at time of early withdrawal, and include these procedures in the protocol. Reasons for missing PRO data at the overall score- and item-level should be documented and included in the analysis dataset.

1.3 Endpoint Hierarchy and Definition

Table 2 below describes the intended placement of the PRO assessments in the endpoint hierarchy. Other secondary endpoints were measured and are described in the Clinical Review.

Table 2. Endpoints for Study 0761-010

Concept	Endpoint	Assessment
Primary Endpoint		
Progression-Free Survival (PFS)	Time from the day of randomization until documented progression in any compartment per CTCL response criteria or documented disease progression reported during the follow-up period or death due to any cause	Investigator assessment
PRO Secondary Endpoint		
Skin disease symptoms and impacts	Change in Skindex-29 score from baseline through the 6-month assessment	Skindex-29
Health-related quality of life (HRQL)	Change in FACT-G total score from baseline through the 6-month assessment	FACT-G
Health status	Change in EQ-5D-3L index score from baseline through the 6-month assessment	EQ-5D-3L
Itch symptoms and impacts	Difference in the median change of the ItchyQoL score from baseline at different time points up to cycle 11	ItchyQoL
Itch severity	Difference in the median change of the Likert Scale score from baseline at different time points up to cycle 11	Pruritus Likert Scale

Reviewer's comments:

The Skindex-29 Symptoms Scale demonstrated statistically significant differences in mogamulizumab-treated patients versus vorinostat-treated patients at Cycles 3, 5, and 7 ($p<0.05$). The median time to meaningful deterioration on the Skindex-29 Symptoms Scale was 27.4 months for mogamulizumab-treated patients versus 6.6 months for vorinostat-treated patients.

164 patients (73 in mogamulizumab arm and 91 in vorinostat arm), which counts for 44% of the ITT population of 372, missed values for the Skindex-29 total score at cycle 3. Because of the large amount of missing values and uncertain mechanism of the missingness (non-informative vs. informative), the comparison of changes of the Skindex-29 total score between treatment arms may not be reliable. Please see Statistical Review for additional details on missingness.

The applicant noted that when data was missing for reasons other than study design, the reason was lack of completion of PRO questionnaires, in general, because forms were reportedly inadvertently not completed or completed incorrectly.

1.4 1.4 Labeling or promotional claims based on the COA

(b) (4)

Reviewer's comments *The proposed labeling above is the applicant's revised labeling proposal.*

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2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The conceptual frameworks of the PRO assessments are provided in table 3 below.

Table 3. Conceptual framework of Skindex-29 (developed by this reviewer*)

Items	Domain/Subscale	General Concept
My skin hurts	Symptom	Skin symptoms and impacts (HRQL)
My skin condition burns or stings		
My skin itches		
Water bothers my skin condition		
My skin is irritated		
My skin condition bleeds		
My skin is sensitive		
My skin condition affects how well I sleep	Functioning	
My skin condition affects my social life		
I tend to stay at home because of my skin condition		
My skin condition affects how close I can be with those I love		
I tend to do things by myself because of my skin condition		

Items	Domain/Subscale	General Concept
My skin condition affects my interactions with others		
My skin condition makes showing affection difficult		
My skin condition is a problem for the people I love		
My skin condition affects my desire to be with people		
My skin condition interferes with my sex life		
My skin condition makes me tired		
I worry that my skin condition may be serious	Emotion	
My skin condition makes me feel depressed		
I am ashamed of my skin condition		
I worry that my skin condition may get worse		
I am angry about my skin condition		
I worry about side effects from skin medications/treatments		
I am embarrassed by my skin condition		
I am frustrated by my skin condition		
I am humiliated by my skin condition		
I am annoyed by my skin condition		

*The reviewer grouped the items under the domain that seemed appropriate; however, there may be a chance that some of the items are under different domains

Table 4. Conceptual framework of FACT-G (summarized by this reviewer)

Items	Domain/Subscale	General Concept
I have a lack of energy.	Physical Well-being	HRQL
I have nausea.		
Because of my physical condition, I have trouble meeting the needs of my family.		
I have pain.		
I am bothered by side effects of treatment.		
I feel ill.		
I am forced to spend time in bed.		
I feel close to my friends.	Social Well-being	
I get emotional support from my family.		
I get support from my friends.		
My family has accepted my illness.		
I am satisfied with family communication about my illness.		
I feel close to my partner (or the person who is my main support).		
I am satisfied with my sex life.		
I feel sad.	Emotional Well-being	
I am satisfied with how I am coping with my illness.		
I am losing hope in the fight against my illness.		
I feel nervous.		
I worry about dying.		
I worry that my condition will get worse.		
I am able to work (include work at home).	Functional Well-being	
My work (include work at home) is fulfilling.		
I am able to enjoy life.		
I have accepted my illness.		
I am sleeping well.		
I am enjoying the things I usually do for fun.		

Items	Domain/Subscale	General Concept
I am content with the quality of my life right now.		

Table 5. Conceptual framework of ItchyQoL (developed by this reviewer*)

Items	Domain/Subscale	General Concept
My skin condition bleeds.	Symptoms	Pruritus symptoms and impacts (HRQL)
My skin hurts . . .		
My itchy skin burns or stings.		
I get scars		
I need to scratch. .		
Temperature or seasonal changes aggravate my itchy skin . . .		
I spend a lot of money treating my itchy skin . . .		
My itchy skin makes it hard to work or do what I enjoy	Function	
My itchy skin affects my interactions with others		
My itchy skin affects how well I sleep		
My itchy skin limits the types of clothes I can wear		
My itchy skin forces me to buy special soaps . . .		
I am frustrated by my itchy skin	Emotion	
I am embarrassed by my itchy skin		
My itchy skin drives me crazy/nuts		
My itchy skin makes me angry or irritable		
My itchy skin makes me feel depressed or sad		
I worry about what other people think about me		
I worry that the itching will last forever		
I feel self-conscious because of my itchy skin		
My personality has changed because of my itchy skin		

*The reviewer grouped the items under the domain that seemed appropriate; however, there may be a chance that some of the items are under different domains

Table 6. Conceptual framework of Pruritus Likert Scale (summarized by this reviewer)

Item	Domain/Subscale	General Concept
Rate level of itching	N/A	Itch intensity

Reviewer's comments: *There appears to be measurement redundancy across some of the assessments specifically the Skindex-29 Symptom domain and ItchyQoL Symptom domain. As such, one would expect that that the results from these measures would be consistent with each other. However, this was not observed which questions the reliability of these measures.*

3 CLINICAL OUTCOME ASSESSMENT(S)

Skindex-29

The Skindex-29 is a generic instrument to measure the effect of skin disease on HRQL. It is composed of 29 items assessing 3 domains: emotions, symptoms, and functioning. The items are scored on a 5-point Likert-type scale ("never," "rarely," "sometimes," "often," or "all the time"). Responses to each item are transformed to a linear scale of 100 (where 0 equals "never", 25 equals "rarely," 50 equals "sometimes," 75 equals "often," and 100 equals "all the time") for the purpose of scale score calculation (See Section D.4). The recall period is 4 weeks.

FACT-G
The FACT-G is an instrument for assessing HRQL in subjects with cancer. The FACT-G consists of 27 items in the following 4 domains: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. The recall period is 'past7 days.'

ItchyQoL
The ItchyQoL is a pruritus-specific instrument. It includes 22 pruritus-specific questions covering 3 major domains: symptoms, functioning, and emotions. The recall period is 'past 7 days' and 'past 4 weeks.'

Pruritus Likert Scale
The Likert Scale for pruritus evaluation uses a numbered scale from 0 to 10 to measure the level of itching for pruritus with 0 indicating "no itch" and 10 indicating "worst itch imaginable." The recall period is undefined.

4 SCORING ALGORITHM

Skindex-29
A subscale score is the mean of a subject's responses to the items in a given scale and the composite Skindex- 29 score is calculated as the average of the 3 subscale scores to measure the overall impact on QoL. Scores range from 0 to 100 with higher scores indicate a higher impact of skin disease.

FACT-G
The total FACT-G score is obtained by summing individual subscale scores. Response scores on negatively-phrased questions are reversed before summing. The total score ranges from 0 to 108. Higher scores for the scales and subscales indicate better HRQL.

ItchyQoL
The subscale scores consist of the average of the responses to the items in a given subscale. The overall score is the average of the responses to all items. The total score ranges from 22-110 and higher ItchyQoL scores indicate worse HRQL.

Pruritus Likert Scale
Scores range from 0 to 10 where higher scores indicate greater itch severity and lower scores indicate lesser itch severity.

5 CONTENT VALIDITY

The submission did not provide evidence to support content validity of the instruments used in Study 0761-010.

Reviewer's Comments:

Comments regarding Skindex-29

On face, the Skindex-29 appears to include some concepts that might be relevant in the context of this drug development program (e.g., skin symptoms), however there may be some important concepts that are missing that should be measured since this is a generic dermatological instrument. Without patient input from this target population we cannot determine whether this instrument includes the most important concepts for this population.

The instructions in the Skindex-29 are not specific to CTCL, but very vague (i.e., patients are asked to report on their "skin problem"). It is unclear whether patients were trained to think about the condition that is being treated (i.e., CTCL) when answering the questions. However, this is not a critical concern for this program.

Comments regarding FACT-G

The FACT-G is a generic HRQL PRO instrument. The FACT-G is challenging to interpret because it combines disease-related symptoms, treatment-related symptoms, and disease impacts into its summary and domain scores, (b) (4) *This reviewer encourages the use of instruments with well-defined and interpretable domain content.*

Comments regarding ItchyQoL

The ItchyQoL is a pruritus-specific instrument. The different recall periods of 'past week' and 'past 4 weeks' in the same instrument may be susceptible to recall error. Additionally, the instruction (the following questions concern your feelings about your itchy skin condition) may be confusing when the items are for symptoms and function.

Comments regarding Pruritus Likert Scale

A single item, in principle, is acceptable to assess pruritus intensity at its worst; however, we recommend including a recall period with. The copy of the tool provided does not indicate a recall period. It is unclear what time frame the patient was recollecting when completing the assessment.

6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

This submission did not provide evidence to support other measurement properties of the instruments used in Study 0761-010.

7 INTERPRETATION OF SCORES

The applicant calculated minimal important difference (MID) estimates for all PRO endpoints using a distribution-based approach. Based on the MID estimates, subjects improved by an

amount greater than the MID threshold and were classified as responders and all other subjects were classified as non-responders.

Reviewer's Comments: *Distribution-based methods are viewed as a supportive method to anchor-based methods. This reviewer recommends using an anchor-based approach supplemented with both cumulative distribution function and probability density function curves to generate a within-patient meaningful change score, as well as qualitative data. The applicant did not use any patient global rating scales in Study 0761-010 to serve as an anchor for their PRO instruments. However, additional analyses were requested from the applicant to use other items from the concurrent measures as anchors. However, because of the presence of missing data it makes interpretation very difficult.*

Because of the missing data at Cycle 7, the applicant proposed to use earlier time points. As such, additional CDF curves at those earlier time points were requested. However, there continues to appear to be a missing data issue at those time periods.

While the CDF curves for Skindex-29 are more interpretable at Cycles 3 and 5and show separation between the treatment arms, they should be interpreted cautiously as the item-level and domain-level data shows that the treatment effects seen in the total score of Skindex-29 may be driven by the Emotion domain and two items in the symptom domain (items 1 and 7). The positive treatment effects observed in two items (my skin hurt; my skin condition burns or stings) in the Skindex-29 symptom scale were not observed in the similar ItchyQoL symptom items. Additionally, Skindex-29 item 10 (itchy skin) and the Pruritus Likert Scale did not produce significant results.

8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

This trial was conducted in the US, Japan, and other countries. However, this submission did not report on language translation or cultural adaptation of the COA instruments.

9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable.

10 REVIEW USER MANUAL

Not applicable.

E. APPENDICES

Appendix A: Skindex29
Appendix B: FACT-G

Appendix C: ItchyQoL
Appendix D: Pruritus Likert Scale

APPENDIX A: SKINDEX-29

These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My skin hurts	☐1	☐2	☐3	☐4	☐5
2. My skin condition affects how well I sleep	☐1	☐2	☐3	☐4	☐5
3. I worry that my skin condition may be serious	☐1	☐2	☐3	☐4	☐5
4. My skin condition makes it hard to work or do hobbies	☐1	☐2	☐3	☐4	☐5
5. My skin condition affects my social life	☐1	☐2	☐3	☐4	☐5
6. My skin condition makes me feel depressed	☐1	☐2	☐3	☐4	☐5
7. My skin condition burns or stings	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my skin condition	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my skin condition	☐1	☐2	☐3	☐4	☐5
10. My skin itches	☐1	☐2	☐3	☐4	☐5
11. My skin condition affects how close I can be with those I love	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my skin condition	☐1	☐2	☐3	☐4	☐5
13. I worry that my skin condition may get worse	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my skin condition	☐1	☐2	☐3	☐4	☐5
15. I am angry about my skin condition	☐1	☐2	☐3	☐4	☐5
16. Water bothers my skin condition (bathing, washing hands)	☐1	☐2	☐3	☐4	☐5
17. My skin condition makes showing affection difficult	☐1	☐2	☐3	☐4	☐5
18. I worry about side-effects from skin medications / treatments	☐1	☐2	☐3	☐4	☐5
19. My skin is irritated	☐1	☐2	☐3	☐4	☐5
20. My skin condition affects my interactions with others	☐1	☐2	☐3	☐4	☐5

Please turn to next page

HOW OFTEN DURING THE PAST 4 WEEK DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
21. I am embarrassed by my skin condition	☐1	☐2	☐3	☐4	☐5
22. My skin condition is a problem for the people I love	☐1	☐2	☐3	☐4	☐5
23. I am frustrated by my skin condition	☐1	☐2	☐3	☐4	☐5
24. My skin is sensitive	☐1	☐2	☐3	☐4	☐5
25. My skin condition affects my desire to be with people	☐1	☐2	☐3	☐4	☐5
26. I am humiliated by my skin condition	☐1	☐2	☐3	☐4	☐5
27. My skin condition bleeds	☐1	☐2	☐3	☐4	☐5
28. I am annoyed by my skin condition	☐1	☐2	☐3	☐4	☐5
29. My skin condition interferes with my sex life	☐1	☐2	☐3	☐4	☐5
30. My skin condition makes me tired	☐1	☐2	☐3	☐4	☐5

APPENDIX B: FACT-G

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-G (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

APPENDIX C: ITCHYQOL

Subject ID# ___ ___ ___ -- _____ Date of Interview: __/__/____
Interviewer:_____

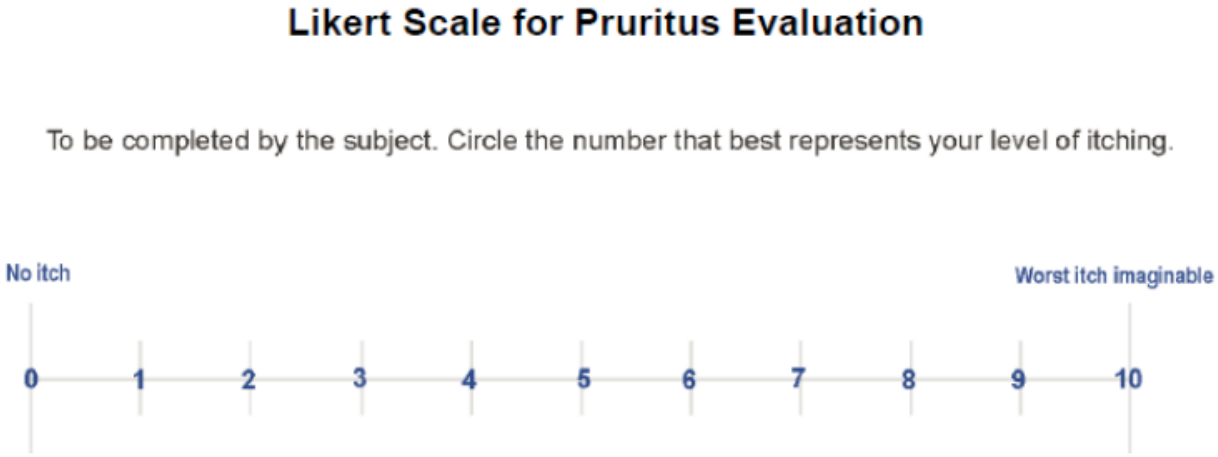
ItchyQoL
ITCHING QUALITY OF LIFE SURVEY

The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My itchy skin condition bleeds.	☐1	☐2	☐3	☐4	☐5
2. My skin hurts because of my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
3. My itchy skin condition burns or stings.	☐1	☐2	☐3	☐4	☐5
4. I get scars from my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
5. I need to scratch my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
6. Temperature or seasonal changes aggravate my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
7. I spend a lot of money treating my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
8. My itchy skin condition makes it hard to work or do what I enjoy.	☐1	☐2	☐3	☐4	☐5
9. My itchy skin condition affects my interaction with others. (For example: family, friends, close relationships, etc.)	☐1	☐2	☐3	☐4	☐5

The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
10. My itchy skin condition affects how well I sleep.	☐1	☐2	☐3	☐4	☐5
11. My itchy skin condition often makes it difficult to concentrate.	☐1	☐2	☐3	☐4	☐5
12. My itchy skin condition limits the types of clothes I can wear.	☐1	☐2	☐3	☐4	☐5
13. My itchy skin condition forces me to buy special soaps, detergents, and lotions.	☐1	☐2	☐3	☐4	☐5
14. I am frustrated by my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
15. I am embarrassed by my itchy skin condition.	☐1	☐2	☐3	☐4	☐5

	How often during the past 4 weeks do these statements apply to you?				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
16. My itchy skin condition drives me crazy/nuts.	☐1	☐2	☐3	☐4	☐5
17. My itchy skin condition makes me angry or irritable.	☐1	☐2	☐3	☐4	☐5
18. My itchy skin condition makes me feel depressed or sad.	☐1	☐2	☐3	☐4	☐5
19. I worry about what other people think about me because of my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
20. I worry that the itching will last forever.	☐1	☐2	☐3	☐4	☐5
21. I feel self-conscious because of my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
22. My personality has changed because of my itchy skin condition.	☐1	☐2	☐3	☐4	☐5

APPENDIX D: PRURITUS LIKERT SCALE



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

/s/

JING JU
03/28/2018

SELENA R DANIELS
03/28/2018

ELEKTRA J PAPADOPOULOS
04/09/2018