20 September 2018
EMA/698539/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

POTELIGEO

International non-proprietary name: mogamulizumab

Procedure No. EMEA/H/C/004232/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AEs	adverse events
ALT	alanine aminotransferase
AMP	doxorubicin hydrochloride (DXR), ranimustine (MCNU), and prednisolone (PSL)
ANCOVA	ANCOVA (Analysis of covariance)
AS	Active substance
AST	asparagine aminotransferase
ATL	adult T-cell leukaemia-lymphoma
AUC	Area under the plasma or serum drug concentration-time curve
$AUC_{(0-\tau),ss}$	AUC to the end of the dosing period (τ) at steady state
$AUC_{0-7\ days}$	AUC up to day7 post-dose
BLA	Biologics Application
BLQ	Below Limit of Quantification
BSA	body surface area
CCR4	CC chemokine receptor 4
CDC	Complement dependent cytotoxic
CDR	omplementarity Determining Regions
CE-SDS-LIF	Capillary Electrophoresis Sodium Dodecyl sulfate Laser-induced fluorescence
CEX-HPLC	Cation Exchange High Performance Liquid Chromatography
CI	Confidence interval
CL	Clearance
C_{max}	Maximum drug concentration in plasma or serum
$C_{max,1st}$	C_{max} after first dose
$C_{max,ss}$	C_{max} at steady state
C_{min}	Minimum drug concentration in plasma or serum
$C_{min,1st}$	C_{min} after first dose
$C_{min,ss}$	C_{min} at steady state
CPA	Critical performance attributes
CPP	Critical process parameters
CPV	Continued Process Verification
CQA	Critical quality attributes
CrCL	creatinine clearance
CTCL	cutaneous T-cell lymphoma
DHAP	Dexamethasone, cisplatin and cytarabine
DoE	Design of experiments
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
EOI	End of infusion
ER	Exposure-response
ESI-TOF/MS	Electrospray ionization time of flight mass spectrometry
FBS	Foetal bovine serum
FCM f	low cytometry
FP	Finished product
GemOx	gemcitabine/oxaliplatin
HC	Heavy chain
HCDNA	Host Cell DNA
HCP	Host Cell Proteins
HMWS	High Molecular Weight Species
IIV	inter-subject variability
Inv	Investigator
IPC	In-process-control
IPM	In-process-monitoring
IR	independent review

IRR	Infusion related reactions
iv	intravenous
JP	Japanese Pharmacopoeia
KW-0761	mogamulizumab
LC	Light chain
LC/MS	Liquid chromatography-mass spectrometry
LCL	Lower limit of Confidence Interval
LCU	Upper limit of Confidence Interval
LIVCA	Limit of In Vitro Cell Age
LMWS	Low Molecular Weight Species
LPD	Lymphoproliferative disorders
Lyp	Lymphomatoid papulosis
MCB	Master cell bank
MF	Mycosis Fungoides
mLSG15	VCAP + AMP + VECP + Cytarabine (Ara-C) + Methotrexate (MTX) +Prednisolone (PSL)
MoA	Mode of action
MTX	Methotrexate
NA	not applicable
NCA	Non-compartmental analysis
NK	Natural killer
ORR	overall response rate
OS	overall survival
PCL	primary cutaneous lymphomas
PFS	progression-free survival
PK	Pharmacokinetic(s)
Pop-PK	Population pharmacokinetic(s)
PPQ	Process performance qualification
PRS	Primary reference standard
PS	performance status
PT	preferred term
PTCL	peripheral T-cell lymphoma
Q	Inter-compartmental clearance
QT	the time from the beginning of the QRS complex to the end of the T wave
QTcB	QT interval corrected for heart rate using Bazett's correction
QTcF	QT interval corrected for heart rate using Fridericia's correction
QTPP	Quality target product profile
RC_{max}	Accumulation ratios of C_{max}
RC_{min}	Accumulation ratios of Cmin
RPSFT	Rank-preserving structural failure time
RS	Reference Standards
SD	Standard Deviation
SE-HPLC	Size exclusion - High Performance Liquid Chromatography
SOC	system organ class
SPR	Surface plasmon resonance
SS	Sezary Syndrome
$t_{1/2}$	Plasma or serum elimination half-life
TEAE	Treatment emergent adverse events
TB	total bilirubin
TSE	Transmissible spongiform encephalopathy
TTF	time to treatment failure
TTR	time to response
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
V1	Volume of central compartment
V2	Volume of peripheral compartment
VCAP	vincristine sulfate (VCR), cyclophosphamide hydrate (CPA), doxorubicin hydrochloride (DXR), and prednisolone (PSL)
VECP	vindesine sulfate (VDS), etoposide (VP-16), carboplatin (CBDCA), and prednisolone (PSL)

VPC	Visual Predictive Check
WCB	Working cell bank
WFI	Water for Injection
ΔQTcF	changes in QTcF values from baseline

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Kyowa Kirin Limited submitted on 6 October 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for POTELIGEO, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 May 2015.

POTELIGEO, was designated as an orphan medicinal product EU/3/16/1756 on 14/10/2016 in the following condition: Treatment of cutaneous T-cell lymphoma.

The applicant applied for the following indication: POTELIGEO is indicated for the treatment of cutaneous T-cell lymphoma (CTCL) in adults who have received at least one prior systemic therapy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Poteligeo as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
(https://www.ema.europa.eu/en/medicines/human/summaries-opinion/poteligeo)

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0261/2015 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance mogamulizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant did not seek Protocol assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Daniela Melchiorri

The application was received by the EMA on	6 October 2017
The procedure started on	26 October 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 January 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 January 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 January 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 February 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 May 2018
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
A GMP inspection at 2 manufacturing sites on 23-27 July 2018 and on 16-17 April 2018 (Kyowa Hakko Kirin Co. Ltd). The outcome of the inspections carried out was issued on	4 June 2018 for Kyowa Hakko Kirin Co. Ltd. 12 September 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	05 July 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 July 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	26 July 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 August 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	06 September 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to POTELIGEO on	20 September 2018

The CHMP adopted a report on similarity of POTELIGEO with Ledaga and Adcetris on (Appendix 1)	20 September 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common forms of Cutaneous T-cell lymphoma (CTCL) a rare, heterogeneous group of mature T-cell lymphomas with primary cutaneous involvement. The current definition of CTCLs follows the 2016 revision of the World Health Organisation (WHO) classification of tumours of haematopoietic and lymphoid tissues.

In lymphoma classifications, CTCL is considered a subtype of the primary cutaneous lymphomas (PCLs), defined as non-Hodgkin lymphoma that presents in the skin with no evidence of extra-cutaneous disease at diagnosis. The term CTCL does not refer to a single disease entity, but to a group of diseases with different clinical behaviour, therapeutic requirements, and prognosis. For many years mycosis fungoides and Sézary's syndrome (SS) were the only known types of CTCL. In the last decade, based on a combination of clinical, histological, and immunophenotypical criteria, new types of CTCL have been defined and new classifications for this group of primary cutaneous lymphomas have been formulated.

2.1.2. Epidemiology

PCLs are the second most common group of extranodal non-Hodgkin's lymphomas with an estimated annual incidence of 1/100,000 in Western countries. CTCL constitutes ~75-80% of all PCLs in the western world, with mycosis fungoides (MF) as the most common type of CTCL (50-60%). The peak age of classic MF is between 55 and 60 years with an increased frequency in males compared to females (M/F ratio 2.2:1) and the incidence is between 1/350.000 and 1/110.000 (Orphanet). SS is the second most common CTCL type, accounting for 3-5% of all CTCL cases (Swerdlow et al, 2016.)
A group of primary cutaneous CD30+ lymphoproliferative disorders (LPD) account for around 15% of CTCLs. This group mainly constitutes of primary cutaneous anaplastic large cell lymphoma (pcALCL) and lymphomatoid papulosis (LyP). Other more rare CTCL subtypes (exact incidence unknown) are a.o. primary cutaneaous gamma-delta T cell lymphoma (<1% of PCLs), subcutaneous pannuculitis-like-T-cell lymphoma (SPTCL), and extranodal NK/T-cell lymphoma (Swerdlow et al, 2016, NCCN Guidelines Insights: T-Cell Lymphomas, Version 2.2018)

2.1.3. Biologic features

MF and SS arise from mature T-cells (Campbell et al, 2010), and the clonal nature of neoplastic lymphocytes can be demonstrated by the PCR characterisation of the T-cell receptor. Phenotype abnormalities (such e.g. lack of CD7 and CD26 expression) that can vary across different CTCL subtypes and disease stages are frequently observed on neoplastic T-cells.

Cytogenetic analyses have demonstrated that chromosomal abnormalities are frequent in advanced stage MF/SS, and molecular patterns related to P53, LYRT-10 (a member of the NF-kB family), BCL2 and STST3 are

frequently involved in disease pathogenesis. In this regard, the BCL2 and MYB oncogenes expression is up-regulated by exposure to IL-7 and IL-15, that act as growth factors in MF/SS.

Certain chemokine receptors are upregulated in CTCL that might play a critical role in the migration dynamics of malignant lymphocytes to the skin. The chemokine receptor CCR4 has been associated with skin-homing of T cells. CCR4 is overexpressed on the surface of and/or expressed by a high percentage of the cancerous cells in T-cell malignancies such as CTCL. In particular, MF and SS are known to frequently display a Th2-like phenotype, with an increased expression of CCR4 (Scarisbrick et al, 2018). However, the prevalence of patients with CCR4 positive malignant lymphocytes and the percentage of CCR4 positive cells and/or the level of CCR4 expression seems to vary between the different CTCL subtypes. The extent of CCR4 expression in rarer forms of CTCL is poorly characterised. The aetiology of CTCLs remains unknown. No genetic predisposition has been demonstrated.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

The clinical manifestation of CTCLs is manifold and is characterised by three classic cutaneous phases: patch, plaque and tumour. Blood, lymph nodes and viscera are usually involved in later stages. The clinical course and prognosis of CTCLs depend on disease type and stage. In the majority of patients with MF, the disease has an initial indolent course. Disease progression is usually sequential, from limited skin involvement in the form of one or more patches, to plaques, tumours and nodal/visceral involvement (Olsen et al, 2007).

The hallmark of SS is the diagnostic triad of intensely pruritic erythroderma, lymphadenopathy and abnormal T-cells in peripheral blood. In most advanced forms, patients suffer from alopecia, ectropion, leonine facies, hyperkeratosis, nail dystrophy, fissuring of the palms and soles, severe pruritus and pain (Kim et al, 2003).

Early stages MF patients have, in the absence of rapid progression, an almost normal life expectancy. On the other hand, advanced stage MF (i.e. subjects with significant nodal/visceral involvement and/or extensive skin involvement) and SS are characterized by a relatively short median life expectancy (e.g. 30 to 55 months).

Prognostic data on rarer CTCL subtypes are sparse, yet some forms, such as the primary cutaneous gamma-delta T cell lymphoma, are known to be aggressive malignancies with survival rates between 11% and 20% at 5 years. Other forms (e.g. the CD30+ primary cutaneous anaplastic large cell lymphoma) have a more benign prognosis. The type of skin involvement, as well as the presence of extracutaneous disease, are significant prognostic factors in this patient population. Accordingly, CTCL is staged using the four anatomical compartments potentially affected by disease (i.e., skin, lymph nodes, viscera, and blood), as each of the compartments has prognostic significance. Survival is related to stage of disease as well as disease type. The presence of disease in blood (leukaemia) and/or lymph nodes/viscera (lymphoma) is also correlated with a worse overall survival in patientsin MF, SS (NCCN Guidelines Insights: T-Cell Lymphomas, Version 2.2018).

MF is a disease with a persistent and relapsing course and prognosis is stage dependent. Classic MF is an epidermotropic CTCL clinically characterized by the progression from patch stage to plaques stage and in the end to tumour stage. MF stage IA or IB has excellent prognosis, however progression to advanced stages occurs in around 25% of the patients. MF Stage IIB and III has a median survival of 4-6 years and stage IV has a poor prognosis with a median survival of less than 4 years.

SS is a rare, aggressive, leukaemic form of CTCL that is distinguished from MF primarily by the presence of high levels of circulating atypical T cells (Sézary cells), extensive skin erythema and severe pruritus. While SS is generally considered separate from MF, progression from MF to SS is occasionally observed. Both MF and SS are

defined histologically and staged by the same criteria. In contrast to patch/plaque MF, SS is much more symptomatic, has a lower potential for remission, and lower expected survival.

The prognosis for LPD is good with a ten year survival of 90% for pcALCL and 100% for Lyp. Up to 40% of the pcALCL localized lesions show some spontaneous regression. Most patients with pcALCL will attain a CR following initial therapy, however, recurrences occur often (>40%) and patients can experience serial relapses. Extra-cutaneous spread occurs in up to 13% at time of relapse.

2.1.5. Management

The early stages of MF can be managed with skin direct therapies (e.g. topical steroids, PUVA, UVB, topical cytostatic agents, local EBT). In advanced stages (IIB-IV) recommended options include, in combination or alone: total skin EBT (CR44-74%), PUVA (CR 30-70%), interferon (RR30-60%) and retinoids (RR45-55%) including second line option bexarotene (RR30-50%). Many clinicians administer oral methotrexate in refractory (RR ±35%) or in advanced stage disease (RR30-50%), however methotrexate is currently not recommended for MF by the ESMO. In advanced refractory disease gemcitabine or liposomal doxorubicin (RR 40-80%) could be considered. Multi-agent chemotherapy is only indicated in patients with extensive disease (stage IV).

With SS, being a systemic disease by definition (i.e. leukaemia), systemic treatment is required. Skin-directed therapies like PUVA or potent topical steroids may be used as adjuvant therapy. Extracorporeal photopheresis (ECP), either alone or in combination with other treatment modalities such as interferon alpha retinoids, total skin electron beam and PUVA, has been suggested as treatment of choice in SS and erythrodermic MF. Low dose methotrexate, bexarotene, denileukin difitox, alemtuzumab (low-dose) and multiagent chemotherapy have been recommended as second-line treatment of SS. Comparison of treatment results between the different studies is extremely difficult due to differences in diagnostic criteria used for SS (Olsen et al, 2007).

Due to the heterogeneity and rarity of PCL, controlled trials are rare, there is no standard initial therapy, and treatment options are diverse. Systemic agents approved in the EU are interferon, which is approved in only some EU countries, and bexarotene; in the US methotrexate, bexarotene, vorinostat, and romidepsin are approved as systemic treatment of CTCL:

Although a broad spectrum of therapy regimens has been reported, these have been limited to small cohort series or case reports. PcALCL patients with isolated lesions should receive surgical excision or radiation, which can be again used in case of recurrence. With multiple recurrences and/or multiple lesions, systemic therapy is recommended due to the morbidity of repeated surgery/radiation. First choice is oral methotrexate (RR 87%). Patients often have recurrence after discontinuation. In case of progression bexarotene (RR ±50% in CTCL patients) and interferon (RR 60% in CTCL patients) are options. In case of wide spread nodal or visceral involvement or refractory disease gemcitabine and etoposide are options. Multi-agent chemotherapy is only indicated in patients presenting with extra-cutaneous disease or rapidly progressive skin disease (rare).

Unmet medical need

Few systemic agents are approved for MF, SS and CTCL in general, the condition often becomes treatment resistant. At present, there are no standard therapies for patients with higher stage treatment resistant disease. Therefore, a substantial medical need exists to develop new therapies for CTCL that can target all disease compartments (skin, blood, lymph nodes, and viscera) and provide a durable response in the treatment of this orphan disease.

About the product

POTELIGEO (mogamulizumab), is a defucosylated humanised IgG1 kappa antibody, that selectively binds to C-C chemokine receptor type 4 (CCR4), a molecular receptor on lymphocytes that binds CC chemokines involved in lymphocyte trafficking to various organs including the skin. Non-clinical *in vitro* and *in vivo* studies demonstrate mogamulizumab binding targets a cell and initiates antibody-dependent cellular cytotoxicity (ADCC) resulting in depletion of the target cells. 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 (Tregs). CCR4 is overexpressed on the surface or expressed by a high percentage of the cancerous cells in T-cell malignancies such as cutaneous T-cell lymphoma (CTCL) and adult T-cell leukaemia-lymphoma (ATL). As a defucosylated antibody, mogamulizumab intends to induce enhanced ADCC activity against CCR4-expressing target cells compared with conventionally fucosylated antibodies.

POTELIGEO has been granted Orphan designation for CTCL in Oct 2016 (EMA/OD/091/16).

The proposed indication for POTELIGEO was: "*POTELIGEO is indicated for the treatment of cutaneous T-cell lymphoma (CTCL) in adults who have received at least one prior systemic therapy.*"

The finally agreed indication is the treatment of mycosis fungoides (MF) or Sézary syndrome (SS) in adults who have received at least one prior systemic therapy.

The proposed posology is 1 mg/kg administered as an intravenous infusion over at least 60 minutes; weekly in the first 28 day cycle, followed by infusions every two weeks of each subsequent cycle until disease progression or unacceptable toxicity.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for intravenous administration containing 20 mg/vial of mogamulizumab as active substance.

Other ingredients are: citric acid monohydrate, glycine, polysorbate 80, sodium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment), and water for injection.

The product is available in 10-ml glass vial (type I glass) with a rubber stopper, an aluminium seal and a polypropylene flip-off cap.

2.2.2. Active Substance

General information

Mogamulizumab is a defucosylated humanised IgG1 kappa antibody that selectively binds to C-C chemokine receptor type 4 (CCR4).

Mogamulizumab is a glycoprotein (molecular weight: approximately 149,000) composed of two heavy chain (γ1-chain) molecules and two low chain (κ-chain) molecules. Mogamulizumab has secondary and tertiary structures that contain considerable β-sheet structure and aromatic amino acids that are located in asymmetrical, well-defined environments.

Mogamulizumab was produced using technology developed by Kyowa Hakko Kirin Co., Ltd. (KHK), which established a cell clone producing a defucosylated mAb. Due to the absence of fucose from the complex type oligosaccharide at the constant (Fc) region, mogamulizumab has enhanced antibody-dependent cellular cytotoxicity (ADCC) activity, but does not exhibit any complement dependent cytotoxic (CDC) activity or neutralizing activity of the ligand of CCR4.

Mogamulizumab has Complementarity Determining Regions (CDRs) derived from mouse anti-human CC-chemokine Receptor 4 (CCR4), which binds to CCR4 antigens on the surface of T-cells and induces Antibody-dependent Cellular Cytotoxicity (ADCC). The mechanism of action (MoA) of mogamulizumab is ADCC that is established via interactions between the CCR4 antigen on the target cells, the antibody, and the Fc gamma Receptor IIIa (FcγRIIIa) on the natural killer (NK) effector cells. The mode of action (MoA) is illustrated below.

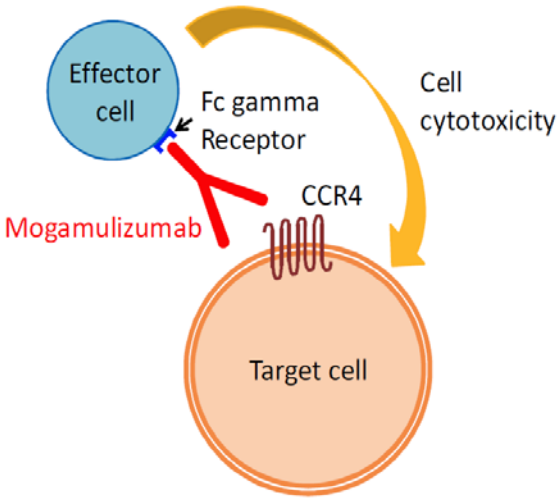


Figure 1: Mogamulizumab MoA

Manufacture, characterisation and process controls

The mogamulizumab active substance is manufactured at Kyowa Hakko Kirin Co., Ltd. (Takasaki Plant) in Japan.

The scale of the active substance manufacturing process is defined by the size of the production bioreactor.

Description of manufacturing process and process controls

The mogamulizmuab active substance manufacturing process has been adequately described. Main steps are cell culture expansion starting from a working cell bank (WCB) vial, fed-batch mode production of mogamulizumab, harvesting, purification and filtration. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The active substance manufacturing process is considered acceptable.

Mogamulizumab active substance can be stored for 36 months at -70 °C. No reprocessed material will be released for use without appropriate regulatory notification and approval, as required.

Validated pool hold times at defined temperatures have been established for in-process pools in the harvest and purification processes through validation of the commercial manufacturing process.

Control of materials

Specifications of compendial and non-compendial materials used during active substance manufacture are provided. No raw materials derived from animal origin are used during active substance manufacture.

A murine hybridoma monoclonal antibody KM2160 produced by the fusion of the immunized mice spleen cells and mouse myeloma cells was selected based on its specific binding activity to the CCR4-expressing human cancer cells. The humanized anti-CCR4 antibody, constructed by combining the Complementarity-Determining Regions of KM2160 with human framework regions and human IgG1κ constant regions, showed ADCC activity against the CCR4-expressing human cutaneous T-cell lymphoma HH cells. The expression plasmid for the mogamulizumab production was constructed using a humanized IgG1 expression plasmid by joining the humanized anti-CCR4 mogamulizumab VH and VL chain cDNAs with human γ1 and κ constant region cDNAs.

Mogamulizumab production cell line was constructed by introducing the mogamulizumab expression plasmid to the host cell line (CHO), selecting transformants, and amplifying the gene copy number by stepwise increase of methotrexate (MTX) concentration. To ensure the clonality and specific productivity of the cells, a single-cell cloning was performed twice, and the clone was selected to prepare a master cell bank (MCB).

The MCB was generated in GMP-like conditions. The vials are maintained in controlled liquid nitrogen freezers in limited access facilities in multiple geographic locations. The WCB lot was generated in accordance with GMP. The growth medium contained no animal derived materials.The vials are maintained in controlled liquid nitrogen freezers limited access facilities in multiple geographic locations.

Testing and characterization of MCB lot and WCB lot were performed according to the ICH Q5D guideline Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products. Sterility, mycoplasma testing, isoenzyme analysis, and viral testing were performed. The MCB and WCB are sterile and free of detectable mycoplasma and viruses, with the exception in the MCB of A-type retrovirus-like particles, which are routinely found in Chinese hamster ovary CHO cell lines.

Any new WCB will be created from a MCB vial following established manufacturing procedures as described and will be qualified to ensure comparability to the existing WCB with respect to safety, genetic stability, cell viability after thaw, cell growth, protein production and product quality.

The MCB, WCB, and LIVCA samples have been shown to be genetically stable.

Control of critical steps and intermediates

Process performance is continuously verified by in-process-control (IPC) testing with rejection and/or action limit and in-process-monitoring (IPM) for process monitoring and trending purpose with internal alert limits. IPCs/IPMs were set taking into consideration the process consistency and controllability of the step as demonstrated by the process development and the process performance qualification (PPQ). A number of identified steps in the manufacturing process are considered as the critical quality attributes (CQA) of mogamulizumab and are controlled through IPC and action limits; the CQAs include non glycosylated species and non concensus glysosilated species, fucosylated species, mycoplasma and viruses, aggregates, host cell protein (HCP), host cell DNA (HCDNA), protein A, bioburden and endotoxins.

There are no critical intermediates in the mogamulizumab active substance manufacturing process.

Process validation

Process performance qualification has been performed at the commercial facility. Several active substance lots were manufactured and complied with the proposed specification. Minor deviations occurred during the PPQ but satisfactory root cause analysis has been provided. The PPQ data provided show that the active substance manufacturing process has been successfully validated. Holding times of the pools have been established. The applicant has described chromatography column cleaning and re-use in an adequate manner. Media hold study results, buffer hold study results and uniformity of the filled bulk study results have all been provided. The active substance is shipped from the active substance site to the finished product site. Shiping validation has been performed.

Mogamulizumab active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces mogamulizumab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

Critical quality attributes, critical performance attributes (CPA) and critical process parameters (CPP) have been defined based on risk analysis. An integrated control strategy is discussed. Process characterisation studies were performed to evaluate the robustness of the active substance manufacturing process, these included single parameter examinations and/or designs of experiments (DoE). Suitable scaled-down models were used for these experiments. Justification for parameters which were not studied (due to the applicant's decision of non-criticality) has been provided.

The applicant has used two processes for the active substance batches, process 1 for several clinical and toxicological studies and process 2 for most clinical, toxicological, PPQ and stability studies. Process 2 will be used for the commercial process. Comparability data has been provided for active substance batches of process 1 and 2, showing comparable release analysis data.

Characterisation

Primary Structure

The primary structure of mogamulizumab was determined. The entire amino acid sequence (including N-terminal sequence and C-terminal amino acid), the disulfide linkage arrangement, and the location of the N-glycosylation site were defined.

Mogamulizumab contains eleven cysteine residues in each heavy chain and five cysteine residues in each light chain, which form twelve intramolecular disulphide bonds and four intermolecular disulphide bonds. There were no detectable disulfide mismatches (cross-bonds) or incomplete disulfide formation observed.

The amino acid at position 299, was identified as Asp residue on deglycosylated peptide (LD1), demonstrating that the N-glycosylation site is Asn^{299} on each heavy chain.

The main peaks in N-linked oligosaccharide profiling studies are identified as G2F0, G1F0, and G0F0 that correspond to the isoforms of asialo-, biantennary, and non-fucosylated complex type structures containing 2, 1, and 0 galactose residues, respectively.

Physicochemical characteristics

The molecular weight of mogamulizumab was determined using electrospray ionization time of flight mass spectrometry (ESI-TOF/MS).

Mogamulizumab showed β-sheet structure and regularly secondary and tertiary structures of antibodies. The aromatic amino acids were located in asymmetrical, well-defined environments.

There were two thermal transitions observed for mogamulizumab, derived from unfolding of the Fab domain and unfolding of the Fc CH3 domain.

Biological Characterisation

The biological properties of mogamulizumab were evaluated using binding and cell-based assays for various aspects, including:

- the specificity for antigen binding of mogamulizumab against CCR4 was evaluated using flow cytometry;
- the binding affinity between mogamulizumab and CCR4 was also evaluated using an antigen-binding ELISA and surface plasmon resonance (SPR). Mogamulizumab had high binding affinity to CCR4;
- the interaction between mogamulizumab and FcγRIIIa was evaluated using FcγRIIIa-binding ELISA and SPR.
- the interaction between the Fc domain and each FcγR (FcγRI, FcγRIIa, and FcγRIIb) were evaluated using a SPR
- ADCC activity was evaluated using cell-based assays. Mogamulizumab has ADCC activity against HH cells expressing CCR4, in a dose-dependent manner;
- binding of the Fc domain to FcRn was evaluated using an ELISA and SPR.
- Mogamulizumab binding affinity to CCR4-derived peptide
- size variants High and Low Molecular Weight Species (HMWS and LMWS) .

The drug substance was subjected to various stress conditions in order to characterize impurities.

Impurities

The applicant distinguishes between product-related impurities (molecular variants of the product arising during manufacture and/or storage, which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety), product-related substances (variants that have properties comparable to the desired product, are fully active, and have no deleterious effect on the efficacy and/or safety of the finished product) as well as process-related impurities (are derived from or introduced during the manufacturing process, such as cell substrates and raw materials used during upstream or downstream processing or contaminants).

Product-related impurities were identified based on criticality assessment of each variant's potential impact to the efficacy, pharmacokinetics, and safety.

The process-related impurities identified in mogamulizumab are HCP, HCDNA, residual protein A from purification process, contaminants (bacterial endotoxins, bioburden, mycoplasma and viruses), and cell culture media-derived components. The process-related impurities have been shown to be effectively reduced and/or controlled by the downstream process as assessed during development for commercial manufacturing process and process validation.

Specification

The specification for the active substance include; appearance, pH (Ph. Eur.), protein concentration (UV), identity, HMWS and LMWS, charge variants, host cell protein, oligosaccharide profile, potency, bacterial endotoxins and microbial enumeration.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. The validation of in-house methods is performed in line with recommendations as per ICH Q2 and is therefore deemed acceptable.

Batch analysis

Batch analysis data from several lots were provided for all the batches manufactured with both process 1 and process 2. All the batches were compliant to specification in place at the moment of the release and confirm consistency of the manufacturing process.

Reference materials

A two-tiered system, comprised of a primary reference standard (PRS) and a working reference standard (WRS), is used for the commercial mogamulizumab reference standard.The history of the mogamulizumab reference standards (RS) lots has been provided by the applicant.

The PRS is to be used for qualification of all the future WRS lots. The WRS is used for lot release and stability evaluation of the active substance and finished product (FP), and for requalification of the PRS in potency assay.

Stability

The Applicant claims an active substance shelf life of 36 months when stored at the designated storage condition.

Long-term stability studies were performed as per the ICH Q1A and Q5C. In addition, stability studies were conducted under elevated and stress conditions to evaluate the effect on the active substance quality. The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

Comparability exercise for Active Substance

A comprehensive comparability assessment was performed to ensure the quality, safety, and potency of process 1 (early clinical) and process 2 (Phase 3 and commercial). Release testing results of process 1 lots and process 2 lots were provided and considered comparable. In addition, further characterisation has been performed.

Stability data was also taken into account and no differences were observed for stability trends at accelerated and stressed conditions between batches of process 1 and process 2.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Mogamulizumab finished product is presented as a sterile, single-use, ready-to-use preservative-free, practically free of particles and clear to slightly opalescent, colourless solution for intravenous (iv) administration.

Each 10-mL vial contains 5 mL deliverable volume of mogamulizumab (20 mg) at a concentration of 4 mg/mL. The FP is provided in a 10-mL, Type I glass vial, sealed with a rubber stopper, and clamped with an aluminium seal with a polypropylene flip-off cap. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The excipients include polysorbate 80, glycine, citric acid monohydrate, sodium hydroxide, hydrochloric acid, and Water for Injection (WFI).

Excipients comply with European Pharmacopoeia (Ph.Eur.) and Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP).

There are no excipients of human or animal origin and no novel excipients used in the finished product formulation.

The choice of the formulation (glycine, citric acid, polysorbate) is mainly based on prior experience with other monoclonal antibodies. The formulation development studies support the chosen pH and concentrations of citric acid monohydrate, glycine and polysorbate 80. The amount of each excipient in the finished product is within the amounts commonly used for parenteral administration. From early clinical trials to commercial manufacturing, there have been no changes in the formulation and fill volume.

Development

During the course of development, mogamulizumab finished product has been manufactured at a number of filling facilities.

Two finished product manufacturing processes were used during the development. Process 1 was the initial small scale process; batches from process 1 were used for early nonclinical and clinical studies. Process 2 is a commercial-scale process. Process 2 was used to manufacture Phase 2/3 clinical batches and will be used for the commercial finished product manufacture.

A detailed comparison of process 1 and process 2 has been provided. Several process changes were implemented at the time of the switch from process 1 to process 2 and are related to the upscaling of the process.

The quality target product profile (QTPP) was defined by the route of administration, delivery system, dosage level, dosage form, dosage design, strength, container closure system, shelf life, storage temperature and finished product quality attributes.

The overall product development was focused on the following design features:

- Product quality attributes are retained during manufacture, transport, and shelf life.
- Product is manufactured by a robust and reproducible process that provides a high assurance of quality.

- Product is provided as a sterile, low-endotoxin solution packaged in a container/closure system that is non-interactive and ensures product integrity for the intended shelf life.

The critical quality attributes identified were:

- product related impurities,
- formulation-related attributes (excipient concentration, protein concentration, pH, osmolality),
- process/material - related impurities (impurities from active substance manufacturing process, impurities from excipients, impurities from container closure system, bacterial endotoxins and foreign particulates),
- general requirements (sterility, sub-visible particles, identity, appearance, potency, volume of the container),
- active substance-related quality attributes.

Compatibility

To support the use of mogamulizumab during administration to the patient, compatibility of the diluted finished product solution with the IV infusion bag and line was confirmed by performing an in-use compatibility study.It is demonstrated that the mogamulizumab solution diluted with normal saline can be stored at 25°C for up to 24 hours in commonly used infusion bags and is compatible with commonly used infusion lines with filter.

Manufacture of the product and process controls

The mogamulizumab finished product manufacturing process consists of seven steps: active substance (AS) thawing, formulation, sterile filtration, filling, stoppering and capping, inspection, and labelling and packaging.

The commercial mogamulizumab finished product manufacturing process is described in detail and includes materials, process parameters, and IPCs for each process step. The IPCs allow to monitor the process performance consistency, and to ensure continuous production of the finished product of appropriate quality. There are no reprocessing or reworking steps in the finished product manufacturing process.

The control strategy of manufacturing process for mogamulizumab finished product was proposed based on the results of a Process Characterization studies and confirmed through the PPQ. To continuously verify the process performance, critical steps of the manufacturing process were identified. IPCs for each critical step were set and will be continuously monitored during commercial production. The IPCs trends will be reviewed according to continued process verification protocol to identify potential improvements in the control strategy.

When a result of an IPC testing does not meet the acceptance criteria for action, it triggers an investigation which is conducted in accordance with the internal quality management system, and associated procedures.

Additional validation and/or evaluation activities, including filter validation, aseptic process simulation, manufacturing equipment qualification, and shipping validation, were successfully performed. Continued Process Verification (CPV) will ensure that the manufacturing process remains in a constant state of control during commercial manufacture.

Process Performance qualification.

The PPQ consisted of the primary PPQ and the supplemental PPQ. In the primary PPQ, several full-scale runs were conducted using the finished product manufacturing facility for the commercial production. After the

completion of the primary PPQ, the supplemental PPQ was conducted to complement the primary PPQ. In the supplemental PPQ, full scale runs were performed using the same manufacturing process as in the primary PPQ except for some minor process refinements.

Overall, the PPQ data demonstrated that the commercial manufacturing process has capability to produce consistent quality of the finished product. The primary and the supplemental PPQ results met the pre-defined acceptance criteria.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

Product specification

The finished product specifications to be used for the mogamulizumab commercial batch release and shelf-life testing include; appearance, pH (Ph. Eur.), osmolality (Ph. Eur.), particulate matter in injections (Ph. Eur.), volume in container (Ph. Eur.), protein concentration, identity, HMWS and LMWS, charge variants, host cell protein, potency, bacterial endotoxins (Ph.Eur.), sterility (Ph.Eur.) and container closuer integrity (Ph. Eur.).

Analytical methods

The analytical procedures used have been adequately described. Analytical methods were verified (compendial methods) or validated (non-compendial methods) according to the ICH Guideline Q2 (R2) and the current industry standards. Compendial assays such as particulate matter in injections, bacterial endotoxins, sterility, microbial enumeration and container closure integrity were evaluated for their suitability for use to control the finished product. Due to the differences in the active substance and finished product buffer composition specificity evaluation for identity, and potency was performed separately for AS and FP. All analytical procedure are deemed suitable for the control of the finished product.

The justification of each specification is based on several batches which have been manufactured with the commercial process 2 (up till 2016). According to the provided information all these batches have been used in clinical studies (although not necessarily for the current requested indication: treatment of CTCL).

Batch analysis

Tabulated batch information and release testing results for mogamulizumab process 1 and process 2 batches are provided. The batch genealogy includes batch information with manufacturing process, manufacturing site, manufacturing date, batch size, and lot use. All process 2 batches were manufactured at commercial scale at the planned commercial manufacturing facility. The mogamulizumab batches were tested according to the specification in place at the time of product release.

Batch analysis data of several active substance batches were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The reference standard used in the analysis of mogamulizumab finished product is the same as that used for mogamulizumab acvtive substance.

Stability of the product

The long-term stability studies at 5°C were performed per the ICH Guideline Q5C. Stability studies at accelerated (25°C) and stress conditions were also performed.

For the long-term stability study all vials were stored inverted. The commercial container closure system has been used.

Based on the stability data obtained from the 3 primary and 3 supportive lots, the shelf-life of 36 months is well justified when the finished product is stored at the recommended condition of 5°C in 10-mL, Type I glass vial stoppered with a rubber stopper and clamped by a polypropylene flip-off cap with an aluminium overseal. The product should be protected from light.

Comparability exercise for finished medicinal drug product

A comprehensive comparability assessment was performed on finished product lots in order to bridge the manufacturing process from process 1 to process 2.Comparability of the finished products lots manufactured by the two processes was demonstrated using the release and stability accelerated (25°C) storage results.

A second comparability assessment was performed in order to bridge the finished product manufacturing facility change Comparability of the lots manufactured using the two facilities was demonstrated using release testing and comparative stability evaluation at accelerated and stress storage conditions.

As demonstrated by the comparative analysis of the release and stability data, both processes produce batches of comparable product quality. The results of these comparability assessments met the acceptance criteria in all cases, indicating that the product quality was equivalent, regardless of the process and/or facility used.

Adventitious agents

Information regarding the raw materials of biological origin used in the manufacturing process of mogamulizumab is deemed acceptable. Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) is considered sufficiently demonstrated.

The testing programme of cell banks and unprocessed bulk harvest batches for adventitious agents is adequate and in compliance with ICH Q5A. No adventitious agents, mycoplasma, microbial or viral, were detected. The presence in the MCB of non-infectious endogenous A-type retrovirus particles can be considered a typical feature of murine cell lines. Unprocessed bulk harvest tested negative for bacteria, fungi, mycoplasma, and viral contaminants.

The mogamulizumab manufacturing process was investigated for its ability to remove/inactivate viruses:

The manufacturing steps considered for virus validation studies are acceptable. Viral removal/inactivation capacity by the mogamulizumab manufacturing process was evaluated. The selected model viruses are appropriate, as enveloped and non-enveloped viruses are included. Moreover, XMuLV represents a specific model virus for the RVLP produced by the production cell line. Preliminary studies were properly carried out to evaluate interference and cytotoxicity.

Overall, the safety of mogamulizumab towards adventitious agents is considered adequate.

GMO

Not applicable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the assessment a major objection was raised as two of the manufacturing sites did not have a EU GMP certificate. This major objection was subsequently resolved. Confirmation of EU GMP compliance of Kyowa Hakko Kirin site in Japan (responsible for active substance manufacturing, master cell bank storage, working cell bank storage and QC testing) was provided as part of the response to the D150 list of questions. Confirmation of EU GMP compliance for the finished product manufacturing site was received as part of the response to the D195 list of questions.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical development for mogamulizumab followed existing regulatory guidance for anticancer, biotechnology-derived pharmaceuticals, specifically, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines S9, S6 (R1), and M3 (R2).

The nonclinical program included studies examining the anti-tumor activity of mogamulizumab, pharmacokinetic parameters after single-dose and repeat-dose intravenous administration, absorption, distribution, immunogenicity, immunotoxicity, cross-reactivity, single- and repeat-dose toxicology, and effects on embryo-fetal development. Based on comparable binding affinity for cynomolgus monkey and human lymphocytes and pharmacological activity (reduction in CCR4 expressing cells in peripheral blood) in cynomolgus monkeys and mogamulizumab did not bind to lymphocytes from dog, rat, or mouse, the cynomolgus monkey was selected as relevant species for evaluation of mogamulizumab in nonclinical pharmacology, pharmacokinetics, and toxicology studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In Vitro

Affinity Measurement of mogamulizumab against CCR4 Peptide Using Biosensor (Study d-04-405)

The binding affinity of 4 different lots of mogamulizumab against CCR4 peptide (N terminal 12th to 29th amino acids) was determined by biosensor analysis using a Biacore 2000 instrument. The association rate constant (ka) ranged from 1.33 to 1.39 $\times 10^5$ $(mol/L)^{-1}s^{-1}$.

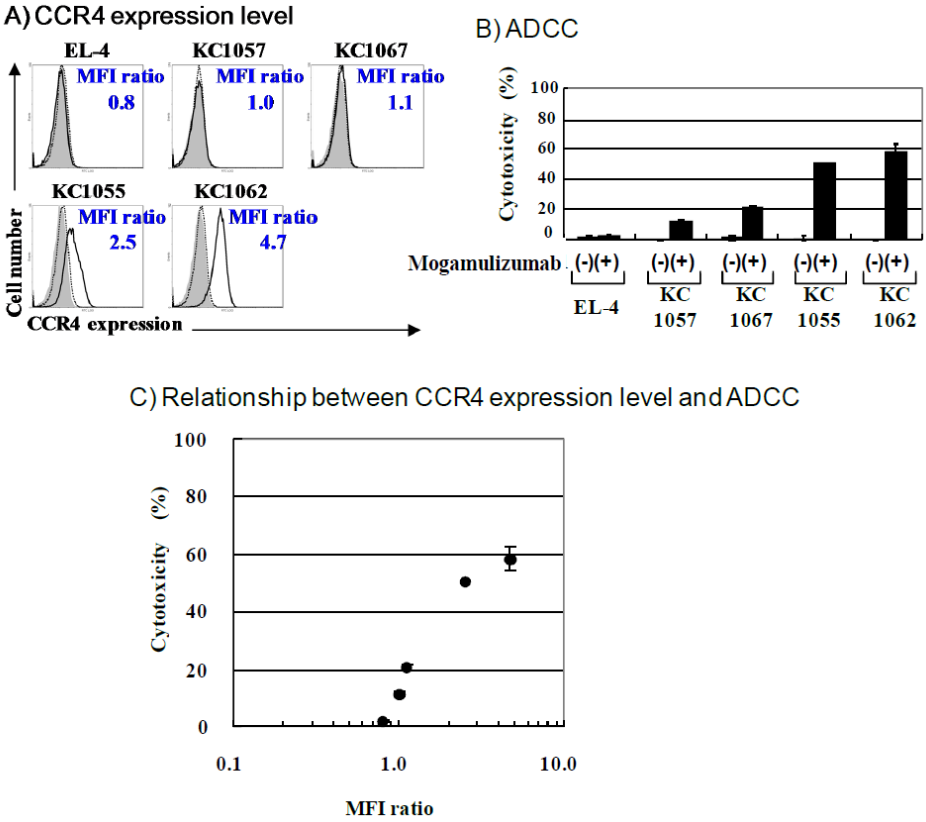
Affinity Measurement of mogamulizumab against FcγRIIIa Polymorphic Variants Using Biosensor (Study Number: d-15-0506)

The binding affinity of mogamulizumab against FcγRIIIa polymorphic variants, 158 phenylalanine (FcγRIIIa (F)) or 158 valine (FcγRIIIa(V)), was determined by biosensor analysis using a Biacore T100 instrument. The dissociation equilibrium constant (KD) values to FcγRIIIa(F) and FcγRIIIa(V) were 9.95×10^{-7} and 9.49×10^{-8} mol/L, respectively.

ADCC Activity of mogamulizumab against Murine Thymoma EL-4 cells with Various Expression Levels of Human CCR4 (Study Number: d-04-319)

Expression of human CCR4 on murine thymoma EL-4 (EL-4) cells and four human CCR4 gene transfected clones (CCR4/EL-4; KC1055, KC1057, KC1062, and KC1067) were determined by flow cytometry. Expression of human CCR4 on EL-4 cells was negative, whereas the CCR4/EL-4 clones expressed CCR4 at various levels as reflected by the mean fluorescence intensity (MFI) ratios (KC1055, 2.5; KC1057, 1.0; KC1062, 4.7 and KC1067, 1.1). ADCC activity of mogamulizumab against EL-4 cells and CCR4/EL-4 clones was determined using a ^{51}Cr-release assay with human PBMC as effector cells. Cytotoxicity against EL-4 cells was minimal (2.2%), whereas those against CCR4/EL-4 clones were detected at various levels (Cytotoxicities: KC1055, 50.7%; KC1057, 11.7%; KC1062, 58.4% and KC1067, 20.6%). The percent cytotoxicity increased in proportion to the level of expression of human CCR4 on the target cell surface.

Figure 2: Relationship between CCR4 Expression Levels and ADCC Activity of mogamulizumab in EL-4 and EL-4/CCR4 Cells



A) Flow cytometry. Gray; buffer. Dashed line; isotype control antibody (human IgG1). Black line; mogamulizumab. B) ADCC. Concentration of mogamulizumab was 0 µg/mL (-) or 10 µg/mL (+). Human PBMCs were used as effector cells. Effector/target ratio was 25/1. Mean + SD was shown (n=3). C) X and Y-axes show mean fluorescence intensity (MFI) ratio and cytotoxicity, respectively. MFI ratio=MFI obtained with mogamulizumab/MFI obtained with human IgG1.

CCR4 Expression on Human T cell Lymphoma and T cell Leukemia Cells (Study Number: d-04-318, NCU-04-001)

Expression of CCR4 on human T cell lymphoma and T cell leukemia cells (TL-Om1, CCRFCEM, HuT78, HH, ATN-1, ATL102) and human T-cell lymphotropic virus type I (HTLV-1) infected T cells (MT-2) were determined by flow cytometry. Mogamulizumab or an isotype control antibody (human IgG1) was used as the 1st antibody, and fluorescence labeled anti-human IgG antibody was used as the 2nd antibody. MFI ratios of TL-Om1, CCRF-CEM, HuT78, HH, ATN-1, ATL102 and MT-2 cells were 1.5, 1.3, 1.3, 3.1, 3.1, 2.5 and 9.8, respectively, suggesting that all the cells tested expressed CCR4 (Table 2.1.4-1).

Table 1: CCR4 Expression on T cell Lymphoma and T cell Leukemia Cells

Cell line		MFI			MFI Ratio	Study Number[a]
Name	Origin	Buffer	human IgG1	Mogamulizumab		
TL-Om1	ATL	1.4	1.4	2.1	1.5	d-04-318
CCRF-CEM	T-ALL	1.2	1.2	1.6	1.3	d-04-318
HuT78	CTCL	1.2	1.2	1.5	1.3	d-04-318
HH	CTCL	1.4	1.5	4.6	3.1	d-04-318
ATN-1	ATL	10.2	10.4	32.1	3.1	NCU-04-001
ATL102	ATL	9.9	10.2	25.6	2.5	NCU-04-001
MT-2	HTLV-1 infected T cell	5.2	5.6	54.6	9.8	NCU-04-001

a: Study number d-04-318 and NCU-04-001 were performed separately at different sites using different flow cytometers.ATL=adult T-cell leukemia-lymphoma; T-ALL=T-cell acute lymphoblastic leukemia; CTCL=cutaneous T-cell lymphoma;MFI=mean fluorescence intensity; MFI ratio=MFI obtained with mogamulizumab/MFI obtained with human IgG1

ADCC Activity of mogamulizumab against Human T cell Lymphoma and T cell Leukemia Cells (Study Number: d-04-189, d-04-182, d-04-185, d-04-186, NCU-04-001)

ADCC activity of mogamulizumab (0.0001 to 100 µg/mL) against CCR4 detectable (HH, CCRF-CEM, HuT78, TL-Om1, ATN-1, ATL102 and MT-2) and CCR4 undetectable (HUT102) cells was examined by a ^{51}Cr release assay using human PBMCs from 3 adult healthy donors as effector cells. Robust ADCC activity was detected against CCR4 detectable cells. Maximum cytotoxicities were induced by 0.1 to 100 µg/mL of mogamulizumab and ranged from 46% to 79%. In contrast, ADCC activity against cells with undetectable levels of CCR4 expression ranged from 14% to 23%.

ADCC Activity of mogamulizumab against Tumor Cells from Patients with ATL (Study Number: NCU-04-002)

ADCC activity of mogamulizumab was measured by a standard ^{51}Cr release assay using a CD3-positive subset as target cells and a CD3-negative subset as effector cells in an autologous setting. The CD3-negative subset isolated from PBMCs from a healthy donor was used to provide control allogeneic effector cells. Target cells were stained with fluorescence conjugated anti-CD4, CD25 and CCR4 antibodies, and the proportion of CCR4 expressing ATL cells, which were CD4, CD25 and CCR4 triple expressors, among target cells was analyzed by flow cytometry. The proportion of CD16 (FcγRIII) positive cells among effector cells was also analyzed by flow cytometry.
In the allogeneic setting, ADCC activity of mogamulizumab (0.1 to 10 µg/mL) was detected in all cases. In the autologous setting, ADCC activity in the presence of 10 µg/mL mogamulizumab was demonstrated with cytotoxicities ranging from 14% to 64%. ADCC activity was detected in all but one (IM-11) of the samples.

Table 2 ADCC Activity of mogamulizumab against ATL Cells, CCR4/CD4/CD25 Expression in Target Cells and CD16 Positivity in Effector Cells

Sample Name	Effector Cells	CCR4/CD4/CD25 Expression in Target Cells (%)	CCR4 Expression in ATL cells (%)	CD16 Positivity in Effector Cells (%)	Cytotoxicity (%)	
					Mogamu-lizumab (-)	Mogamu-lizumab (10 µg/mL)
IM-1	IM-1 (Auto.)	83	94	16	−4	30
	Adult healthy volunteer (Allo.)	-	-	28	−5	45
IM-2	IM-2 (Auto.)	95	99	16	0	49
	Adult healthy volunteer (Allo.)	-	-	28	−1	65
IM-3	IM-3 (Auto.)	26	83	19	−18	22
	Adult healthy volunteer (Allo.)	-	-	31	−22	83
IM-5	IM-5 (Auto.)	53	92	22	1	14
	Adult healthy volunteer (Allo.)	-	-	27	0	48
IM-6	IM-6 (Auto.)	51	94	37	5	60
	Adult healthy volunteer (Allo.)	-	-	33	4	79
IM-7	IM-7 (Auto.)	72	93	51	−3	52
	Adult healthy volunteer (Allo.)	-	-	23	0	93
IM-8	IM-8 (Auto.)	43	91	25	−6	48
	Adult healthy volunteer (Allo.)	-	-	23	8	85
IM-9	IM-9 (Auto.)	88	98	12	−1	17
	Adult healthy volunteer (Allo.)	-	-	28	−4	59
IM-10	IM-10 (Auto.)	49	97	15	1	31
	Adult healthy volunteer (Allo.)	-	-	23	0	93
IM-11	IM-11 (Auto.)	92	97	8	−5	−6
	Adult healthy volunteer (Allo.)	-	-	26	2	63
IM-12	IM-12 (Auto.)	94	99	35	4	64
	Adult healthy volunteer (Allo.)	-	-	26	2	82
IM-13	IM-13 (Auto.)	56	99	21	−1	45
	Adult healthy volunteer (Allo.)	-	-	26	3	105

Auto.; Autologous setting, target and effector cells were obtained from a same patient.
Allo.; Allogeneic setting, effector cells were obtained from an adult healthy donor.

Effect of mogamulizumab on Binding of CCR4 Ligands, MDC and TARC, to HuT78 Cells (Study Number: d-04-348, Report Number:r-08-152)

To evaluate the potential effect of mogamulizumab on the binding of CCR4 ligands, the effect of mogamulizumab on binding of MDC and TARC to HuT78 cells was examined. Under conditions in which the binding of [^{125}I]-MDC or [^{125}I]-TARC was competed by unlabeled MDC or TARC, respectively, mogamulizumab (0.01 to 2375 µg/mL) did not affect the binding of [^{125}I]-MDC or [^{125}I]-TARC to HuT78 cells.

Effect of mogamulizumab on CCR4 Expression (Study Number: d-04-316)

HH cells were incubated with mogamulizumab (50 µg/mL) on ice for 60 minutes, and then further incubated at 37°C for 0, 5, 15, 30 or 60 minutes. At each time point, residual cell surface expression of CCR4 was determined by fluorescence labeled anti-human IgG antibody to detect mogamulizumab using flow cytometry. The cell

surface expression of CCR4 at each time point (0, 5, 15, 30 or 60 minutes) was 100.0%, 96.9%, 87.4%, 85.3% or 81.3%, respectively.

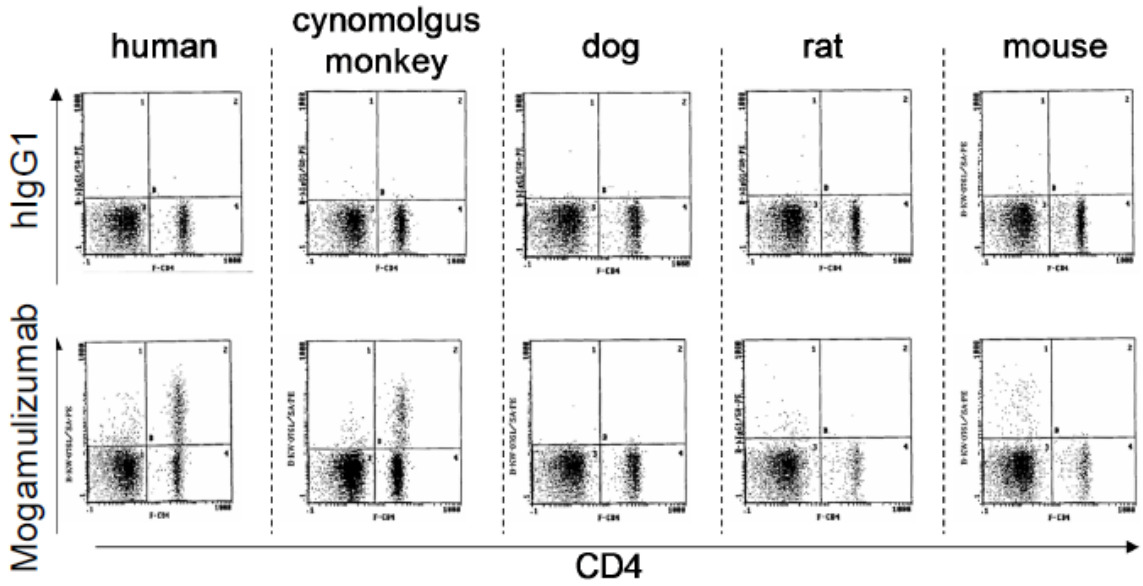
CDC Activity of mogamulizumab against Human T cell Lymphoma Cells (Study Number: d-04-317)

CDC activity of mogamulizumab (0.0001 to 100 µg/mL) was measured using human serum and T cell lymphoma cells (TL-Om1 and HH cells) by a ^{51}Cr release assay. No CDC activity was detected at any concentrations tested. Since it has been reported that CDC activity is suppressed by complement regulatory factors, such as CD55 and CD59, CDC activity of mogamulizumab was measured in the presence of neutralizing anti-human CD55 and CD59 antibodies. However, no CDC activity of mogamulizumab was detected.

Reactivity of mogamulizumab to Human, Cynomolgus Monkey, Dog, Rat and Mouse Leukocytes (Study Number: 03-055, Report number: 4566)

Reactivity of mogamulizumab to human, cynomolgus monkey, dog, rat and mouse peripheral blood leukocytes was examined by flow cytometry using biotinylated mogamulizumab. Biotinylated human IgG1 was used as an isotype control antibody. Detection of mogamulizumab was done using PE labeled streptavidin. Mogamulizumab bound specifically to human and cynomolgus monkey lymphocytes, but not to lymphocytes from dog, rat or mouse. In human and cynomolgus monkey lymphocytes, the majority of the specific binding was seen in the CD4-positive subset. There was no specific binding of mogamulizumab to monocytes or granulocytes of any of the species tested. The reactivity of mogamulizumab to peripheral leukocytes was similar in human and cynomolgus monkey.

Figure 3 Reactivity of mogamulizumab to Human, Cynomolgus Monkey, Dog, Rat, and Mouse Lymphocyte



Peripheral blood was stained with FITC labeled anti-CD4 antibody, biotinylated mogamulizumab or human IgG1 and PE labeled streptavidin, and then analyzed by flow cytometry. Three samples in each animal were analyzed and typical ones are shown here. Lymphocytes were gated in FS/SS dot plot and further plotted in FITC/PE dot plot.

In addition, confirmation that the amino acid sequence of the mogamulizumab binding region was identical in humans and cynomolgus monkeys was established by CCR4 cDNA cloning.

ADCC Activity of mogamulizumab with Cynomolgus Monkey PBMCs (Study Number: d-04-360)

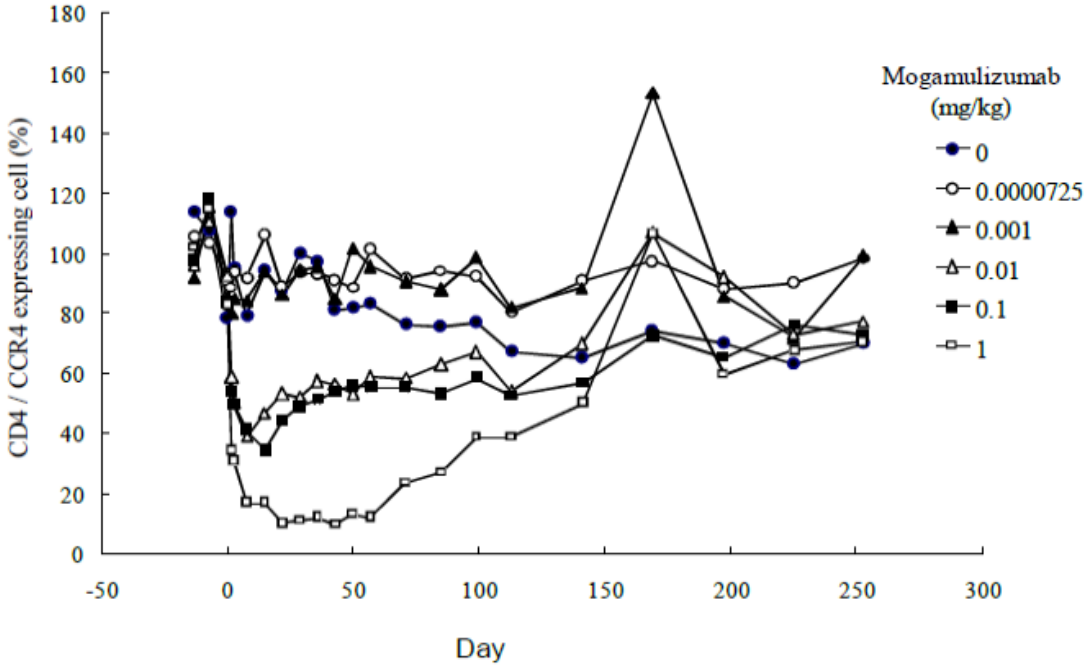
ADCC activity of mogamulizumab (0.0001 to 100 µg/mL) against HH cells was examined by a ^{51}Cr release assay using cynomolgus monkey PBMCs from 3 animals as the effector cells. ADCC activity was detected with all the PBMCs tested, and the cytotoxicity reached a maximum at a concentration of 1 or 10 µg/mL mogamulizumab.

In Vivo

Effect of mogamulizumab on CCR4 expressing Cells in Cynomolgus Monkey Peripheral Blood (Study Number: SBL27-01)

Mogamulizumab was intravenously administered once to male cynomolgus monkeys at dose levels of 0.0000725, 0.001, 0.01, 0.1 and 1 mg/kg (n=3/group). After the administration, CD4/CCR4 expressing cell count in peripheral blood was monitored by flow cytometry for 253 days. No mogamulizumab related changes were detected in clinical observations, body weight, haematology, blood coagulation parameters or blood chemistry. CD4/CCR4 expressing lymphocytes in peripheral blood were decreased by mogamulizumab administration at 0.01, 0.1 and 1 mg/kg.

Figure 4 Effect of mogamulizumab on CD4/CCR4 Expressing Cells in Cynomolgus Monkey Peripheral Blood

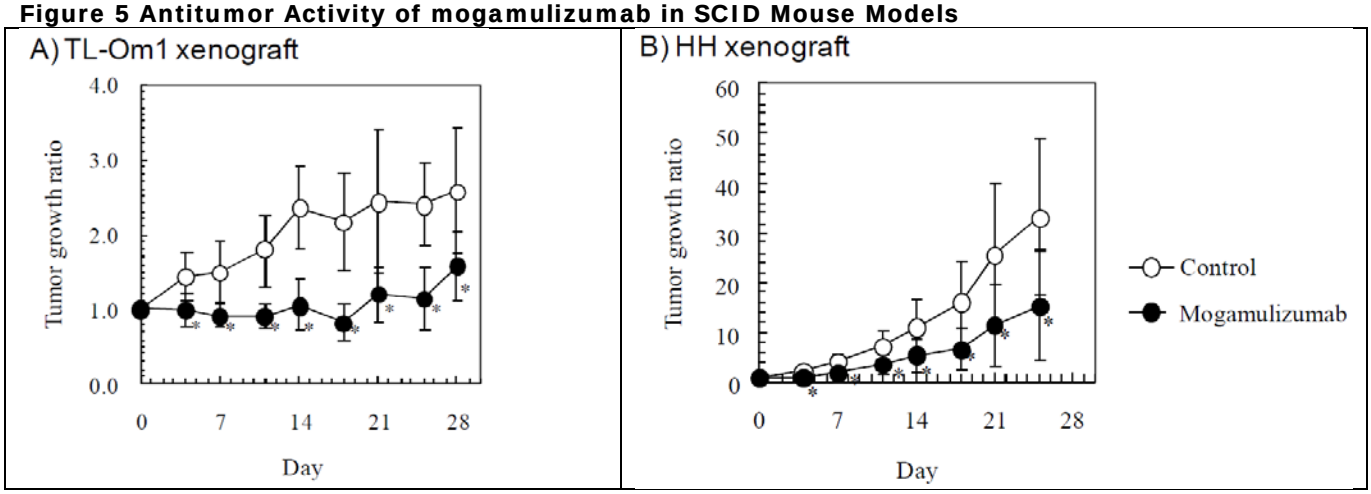


On Day 1, mogamulizumab was administered once at the indicated dose levels. Change form pre-dose value (mean of values at Day -13, -7 and 0) was shown. n=3.

Antitumor Activity of mogamulizumab against TL-Om1 and HH Xenograft in SCID Mouse Models (Study Number: d-04-333, d-04-334)

Antitumor activity of mogamulizumab in TL-Om1 and HH xenografts was investigated in SCID mouse models. In the TL-Om1 xenograft model, mice bearing 101 to 171 mm^3 tumors were selected. In the HH xenograft model, mice bearing 24 to 55 mm^3 tumors were selected. In both models, 10 mice each were assigned to control and mogamulizumab treated groups. Saline (as vehicle) or mogamulizumab (20 mg/kg/day) was intravenously administered once a week for 4 weeks.

Figure 5 Antitumor Activity of mogamulizumab in SCID Mouse Models



Administrations of mogamulizumab were started on Day 0.
Tumor growth ratio = tumor volume on each day/tumor volume on Day 0.
Mean ±SD was shown (n=10). *P<0.05 (Wilcoxon rank sum test)

Secondary pharmacodynamic studies

Effect of mogamulizumab on Human and Cynomolgus Monkey Platelets

It has been reported that CCR4 is expressed on human platelets and CCR4 ligands (MDC and TARC) induce platelet aggregation, raising the potential concern that mogamulizumab may influence platelet function. Therefore, the effects of mogamulizumab on human and cynomolgus monkey platelet functions were investigated. In all studies in this section, no effects of mogamulizumab altering platelet function were observed.

Binding of mogamulizumab to Human and Cynomolgus Monkey Platelets (Study Number: d-06-107, d-04-309)

Binding of mogamulizumab and a commercially available anti-CCR4 antibody, clone 1G1, to human platelets was evaluated by flow cytometry. Double staining of human platelets with an anti-platelet marker antibody (anti-CD41a or CD41b antibody) and CCR4 antibody (mogamulizumab or 1G1) demonstrated that 1G1 bound specifically to human platelets but mogamulizumab did not. Binding of mogamulizumab to platelets was further investigated by incubating 0.2, 10 and 500 µg/mL of mogamulizumab with human or cynomolgus monkey whole blood. In whole blood, mogamulizumab showed no significant binding to human or cynomolgus monkey platelets.

Effect of mogamulizumab on Human or Cynomolgus Monkey Platelet Aggregation (Study Number: d-04-310)

The effect of mogamulizumab on platelet aggregation was evaluated using platelet rich plasma (PRP) prepared from human or cynomolgus monkey blood. In PRP from both species, mogamulizumab (0.2 to 2000 µg/mL) had no effect on platelet aggregation induced by adenosine diphosphate (ADP) or collagen.

Effect of mogamulizumab on Human Platelet Aggregation (Report Number: r-06-300)

The effect of mogamulizumab and 1G1 on platelet aggregation was also evaluated using TARC and low concentration ADP to induce platelet aggregation in human PRP. Both antibodies (100 µg/mL) showed no effect on platelet aggregation in this setting.

Effect of mogamulizumab on Platelet Count in Human Whole Blood (Study Number: d-11-054)

After human whole blood was incubated with mogamulizumab (10 and 100 µg/mL) for a day, platelet count and the proportion of CCR4 expressing CD4-positive lymphocytes were measured. While mogamulizumab reduced the proportion of CCR4 expressing CD4- positive lymphocytes, there was no effect on platelet count.

Effect of mogamulizumab on Cytokine Release- Human Whole Blood (Study Number: 06/019-023)

The effect of mogamulizumab on release of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) from whole blood obtained from 6 donors (3 atopic and 3 non-atopic) was investigated *in vitro*. Samples of human whole blood were incubated for 4 hours with phosphate-buffered saline (PBS), a negative-control antibody (SM3, a non-binding variant of anti-CD52 antibody, 100 ng/ml), positive control antibodies (anti-CD52 antibody, 100 ng/ml, and anti-CD3 antibody, 100 ng/ml) or mogamulizumab (1, 10, 100, 1000 and 10000 ng/ml). Then concentrations of TNF-α and IFN-γ in the supernatants were measured by ELISA. In all donors, mogamulizumab did not induce TNF-α release. In 5 of 6 donors, mogamulizumab did not induce IFN-γ release. In blood from one donor, a very high concentration (10000 ng/ml) of mogamulizumab induced IFN-γ release, which was a comparable to the level of response induced by anti-CD52 antibody.

Effect of mogamulizumab on Cytokine Release - Human Whole Blood or PBMCs (Study Number: 14GR552)

The effect of mogamulizumab on TNF-α, IFN-γ and IL-6 release was further investigated *in vitro* with a soluble phase assay using whole blood and a solid phase assay using PBMCs. In the soluble phase cytokine release assay, human whole blood (from 8 healthy donors) was incubated for 24 hours with either PBS (negative control), a negative-control antibody (anti-dinitrophenyl [DNP] isotype matched POTELLIGENT® antibody, at concentrations of 10, 100 and 500 µg/ml), a positive control (lipopolysaccharide, 1 ng/mL), a positive-control antibody (anti-CD3 antibody, 5 and 50 µg/ml) or mogamulizumab (1, 10, 100 and 500 µg/ml). TNF-α, IFN-γ and IL-6 concentrations in the supernatants were measured by an electrochemiluminescent (ECL) method. In this assay, mogamulizumab increased TNF-α, IFN-γ and IL-6 release in samples from all donors compared to the negative-control antibody or PBS, but the cytokine concentrations induced by mogamulizumab were lower than those induced by the positive-control antibody.

In the solid phase cytokine release assay, human PBMCs (from 8 healthy donors) were incubated for 48 hours with either PBS (negative control), a negative-control antibody (anti-DNP isotype matched POTELLIGENT® antibody, dry-coated at 1, 10, 100 and 250 µg/ml), positive-control antibodies (anti-CD3 antibody, dry-coated at 5 µg/mL and anti-CD28 superagonist antibody, dry-coated at 10 µg/mL) or mogamulizumab (dry-coated at 1, 10, 100 and 250 µg/ml). TNF-α, IFN-γ and IL-6 concentrations in the supernatants were measured by an ECL method. In this assay, all donor PBMC samples that were incubated with mogamulizumab had elevated cytokines (TNF-α and IL-6) and most samples had elevated IFN-γ. In general, TNF-α and IL-6 concentrations were similar or equal to those produced by the positive-control antibodies.

Effect of mogamulizumab on Cytokine Release from Human Whole Blood or PBMCs (Study Number: OX-14/128-014)

The effect of mogamulizumab on TNF-α, IFN-γ, IL-2 and IL-6 release was further investigated *in vitro* with a soluble phase assay using whole blood and a wet-coated phase assay using PBMCs.

In the soluble phase cytokine release assay, human whole blood (from 6 healthy donors) was incubated for 24 hours with either PBS (negative control), a negative-control antibody (human IgG1, at concentrations of 1 µg/ml), positive-control antibodies (anti-CD3 antibody, anti-CD52 antibody and anti-CD28 superagonist antibody at concentration of 1 µg/ml) or mogamulizumab (6 and 50 µg/ml). Then concentrations of TNF-α, IFN-γ, IL-2 and IL-6 in the supernatants were measured by Luminex. In this assay, compared to the

negative-control antibody mogamulizumab produced statistically significant increases in TNF-α and IFN-γ release at 6 µg/ml, and IL-6 and IFN-γ release at 50 µg/ml.

In the wet-coated phase cytokine release assay, human PBMCs (from 6 healthy donors) were incubated for 24 hours with either PBS (negative control), a negative-control antibody (human IgG1, at concentration of 10 µg/ml), positive-control antibodies (anti-CD3 antibody, anti-CD52 antibody and anti-CD28 superagonist antibody at concentration of 10 µg/mL) or mogamulizumab (10 µg/ml). Then concentrations of TNF-α, IFN-γ, IL-2 and IL-6 in the supernatants were measured by Luminex. In this assay, statistically significant elevated cytokines (IL-6, TNF-α and IFN-γ) were observed in PBMC samples that were incubated with mogamulizumab compared to the negative-control antibody.

Safety pharmacology programme

The elements of the safety pharmacology assessment for mogamulizumab are summarized below:

Table 3 Parameters for Safety Pharmacology Assessment

Study type	Single-dose toxicity	Repeat-dose toxicity			Other toxicity (single-dose iv/sc)	
		4-week	13-week	26-week		
Study No.	QUK00001	QUK00003	SBL033-033	SBL303-139	FIA00527	FIA00561
Dose (mg/kg)	0.01, 0.5, 4, 20, 100	0.05, 1.2, 40	2.5, 10, 40	2.5, 10, 40	1.2, 10	1.2, 10
Route	iv	iv	iv	iv	iv, sc	iv, sc
Cardiovascular and Respiratory System	clinical observations and serum chemistry[a]	clinical observations, systolic and diastolic blood pressures and mean arterial blood pressure, heart rate, electrocardiogram[b], body temperature and serum chemistry[a]	clinical observations, systolic and diastolic blood pressures, heart rate, electrocardiogram[b] and body temperature	clinical observations, heart rate, respiration rate, blood gases and electrocardiogram[b]	clinical observations, physical examinations[c] and serum chemistry[a]	clinical observations, physical examinations[c] and serum chemistry[a]
Renal System	serum chemistry[d]	serum chemistry[d] and urinalysis	serum chemistry[d] and urinalysis	serum chemistry[d] and urinalysis	serum chemistry[d]	serum chemistry[d]
Central Nervous System	clinical observations	clinical observations, neurobehavioral assessment[e] and electrophysiologic assessment[f]	clinical observations	clinical observations	clinical observations	clinical observations

Effects on the Cardiovascular and Respiratory System

In the single-dose toxicity study (Study QUK00001), no effects of mogamulizumab on the cardiovascular and respiratory systems were observed in terms of clinical observations and serum chemistry.

In the 4-, 13-, and 26-week toxicity studies (Study QUK00003, Study SBL033-033, and Study SBL303-139, respectively), no effects of mogamulizumab on the cardiovascular and respiratory systems were observed with respect to clinical observations, blood pressure (in the 4- and 13-week toxicity studies), heart rate, electrocardiogram, body temperature (in the 4- and 13-week toxicity studies), respiratory rate (only in the 26-week toxicity study), serum chemistry (carbon dioxide concentration measured only in the 4-week toxicity study), and blood gases (only in the 26-week toxicity study).

In the single-dose iv/subcutaneous (SC) bridging study (Study FIA00527 and Study FIA00561), no effects of mogamulizumab on the cardiovascular and respiratory systems were observed with respect to clinical observations, physical examinations under ketamine sedation (respiration rate, body temperature and heart rate) and serum chemistry (carbon dioxide concentration).

Effects on the Renal System

In the single-dose toxicity study (Study QUK00001), there were no effects of mogamulizumab on the renal system in terms of serum chemistry (BUN, creatinine and electrolytes).

Similarly, in the 4-, 13-, and 26-week toxicity studies (Study QUK00003, Study SBL033-033, and Study SBL303-139, respectively), no effects of mogamulizumab on the renal system in terms of serum chemistry (BUN, creatinine and electrolytes) and urinalysis were evident. In the single-dose iv/sc bridging study (Study FIA00527 and Study FIA00561), no effects of mogamulizumab on the renal system were observed with respect to serum chemistry (BUN, creatinine and electrolytes).

Effects on the Central Nervous System

In the single-dose toxicity study (Study QUK00001), there were no effects of mogamulizumab on the central nervous system in terms of clinical observations. In the 4-, 13-, and 26-week toxicity studies (Study QUK00003, Study SBL033-033, and Study SBL303-139, respectively), no effects of mogamulizumab on the central nervous system were observed with respect to clinical observations. Moreover, no mogamulizumab related changes were observed in the neurobehavioral and electrophysiologic assessment performed in the 4-week toxicity study (Study QUK00003, only for recovery period). In the single-dose iv/sc bridging study (Study FIA00527 and Study FIA00561), no effects of mogamulizumab on the central nervous system were observed with respect to clinical observations.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted as no drug-drug interactions were expected based on the putative mechanism of mogamulizumab.

2.3.3. Pharmacokinetics

Methods of Analysis

Distribution and absorption is studied by administration and subsequent detection of radioactive labeled mogamulizumab. Toxicokinetics of mogamulizumab and development of anti-mogamulizumab antibodies in the cynomolgous monkey were analysed using Enzyme-Linked Immuno Sorbent Assay (ELISA) or ElectroChemiLuminescence Assay (ECLA). All assays were validated and are in accordance with Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) except for the assay 8203-375, measuring amount of neutralizing anti–mogamulizumab antibodies, for which the deviations in the inter- and intra-assay accuracy and precision are too high. Results may thus be variable. In addition, for this assay it was noted that it was insensitive to an excess of drug, while data also show that only in absence of the drug itself, the presence of anti-mogamulizumab antibodies gives a positive signal. This means that in the presence of the drug itself, the amount of antimogamulizumab antibodies is no longer reliably measured and that the measurement of anti – mogamulizumab – antibodies in such circumstances will result in an underestimation of the amount of ADA.

Absorption

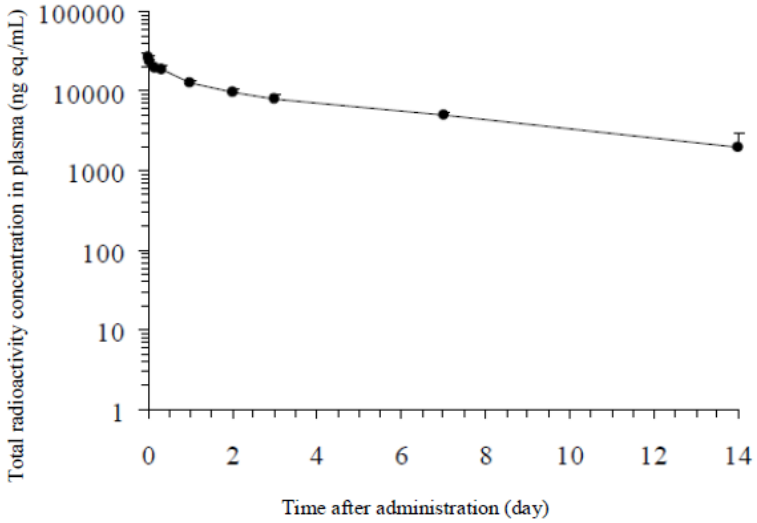
PK parameters after a single dose of 1 mg/kg $^{[125I]}$ mogamulizumab to cynomolgous monkey shows mean half-life (t1/2) of 5.42 days, a total clearance (CL) of 9.86 mL/day/kg and volume of distribution at steady state (Vss) of 67.6 ml/kg. Elimination from plasma is biphasic as it is a result of combination of target mediated disposition and FcRN mediated clearance. Administration of a single dose mogamulizumab ranging from 0.01 to 100 mg/kg to male and female cynomolgous monkey reveals elimination half-life (t1/2β, representing the target

mediated disposition) of 3.81 to 20.8 days, a CL of 2.60 to 10.3 ml/day/kg, and a Vss of 48.6 to 90.8 ml/kg. Toxicokinetic analyses in the repeated dose toxicology studies indicate absence of sex-related differences and a dose proportional increase of Cmax and AUC and suggest a steady state after the tenth administration. In the 26-week multiple-dose study maximum concentration (Cmax), AUC0-7d, and AUC0-∞ of mogamulizumab were higher as the dose level increased, yielding accumulation ratios of 2.6 to 8.2 across all dose groups.

Mogamulizumab mean plasma concentrations in the pregnant females were similar to those measured in non-pregnant females, indicating that pregnancy had little influence on plasma levels of mogamulizumab.

Detected anti-drug antibodies (ADA) against mogamulizumab appeared to increase clearance of mogamulizumab (See section on antigenicity).

Figure 6: Mean Total Radioactivity Concentration-time Profiles in Plasma after Single Intravenous Administration of [125I]mogamulizumab at a Dose of 1 mg/kg to Male Cynomolgus Monkeys



Each point with a bar represents the mean + standard deviation (SD) (n=3).

Table 4: Pharmacokinetic Parameters of Total Radioactivity after Single Intravenous Administration of [125I]mogamulizumab at a Dose of 1 mg/kg to Male Cynomolgus Monkeys

$t_{1/2}$ (day)	5.42 ± 1.67
$AUC_{0-\infty}$ (μg eq.·day/mL)	105 ± 22
CL (mL/day/kg)	9.86 ± 2.21
V_{ss} (mL/kg)	67.6 ± 3.2

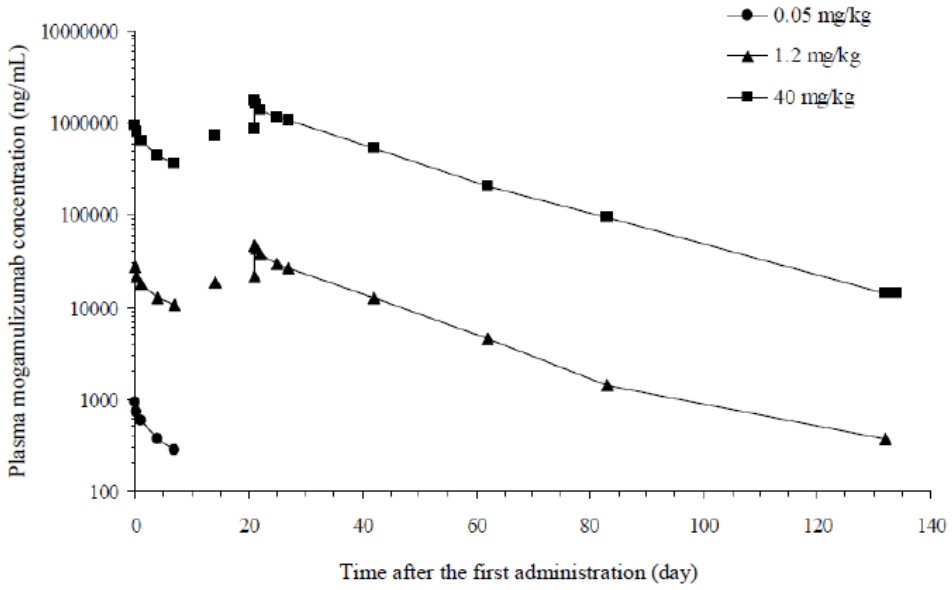
Values are expressed as the mean ± SD (n=3).

Table 5 Pharmacokinetic Parameters of mogamulizumab after Single Intravenous Administration to Male and Female Cynomolgous Monkeys

Dose (mg/kg)	0.01	0.5	4	20	100
$t_{1/2\alpha}$ (day)	0.334	0.513	0.282	0.367	0.352
$t_{1/2\beta}$ (day)	4.14	16.4	18.2	20.8	17.4
$AUC_{0-\infty}$ (μg·day/mL)	0.973	126	1310	8020	27000
CL (mL/day/kg)	10.3	3.99	3.09	2.60	3.98
V_{ss} (mL/kg)	58.1	90.8	78.6	73.4	90.2

Values are expressed as the mean (n=2).

Figure 7 Mean Plasma Concentration-time Profiles of mogamulizumab after Repeat-dose Intravenous Administration Once Weekly for 4 Weeks to Male and Female Cynomolgous Monkeys



Each point represents the mean (n=1 to 10).

Table 6: Pharmacokinetic Parameters of mogamulizumab after Repeat-dose Intravenous Administration Once Weekly for 4 Weeks to Male and Female Cynomolgous Monkeys

Dose (mg/kg)	0.05		1.2		40	
Sex	Male	Female	Male	Female	Male	Female
$t_{1/2\alpha}$ (day)	0.310 ± 0.212	0.359 ± 0.311	0.811 ± 0.626	0.368 ± 0.152	0.557 ± 0.0942	0.647 ± 0.0978
$t_{1/2\beta}$ (day)	7.18 ± 3.27	8.69 ± 7.10	12.7 ± 4.64	11.5 ± 4.59	16.5 ± 2.73	15.7 ± 3.20
$C_{min, Day 8}$ (ng/mL)[a]	271 ± 34.5	282 ± 54.6	10500 ± 776	10800 ± 999	356000 ± 36900	375000 ± 36000
$C_{min, Day 28}$ (ng/mL)[a]	ND	566[b]	24800 ± 9520	22500 ± 14100	1100000 ± 69600	1060000 ± 110000
$C_{min, Day 28}$/ $C_{min, Day 8}$[a]	NC	2.34[b]	2.34 ± 0.815	2.04 ± 1.19	3.12 ± 0.351	2.84 ± 0.315
$AUC_{0-\infty, Day 1}$ (µg·day/mL)[c]	5.10 ± 0.439	5.01 ± 0.619	203 ± 12.4	215 ± 50.8	7110 ± 568	6960 ± 528
$AUC_{0-6d, Day 22}$ (µg·day/mL)[c]	NC	5.44[b]	214 ± 54.9	210 ± 77.4	8630 ± 523	8620 ± 692
$AUC_{0-6d, Day 22}$/ $AUC_{0-\infty, Day 1}$[c]	NC	1.19[b]	1.06 ± 0.307	0.960 ± 0.236	1.22 ± 0.107	1.24 ± 0.0726
V_{ss} (mL/kg)	84.7 ± 9.89	80.1 ± 15.2	76.0 ± 17.3	67.8 ± 5.13	76.8 ± 7.18	73.0 ± 7.66
Production of anti-mogamulizumab antibodies (Number of animal)	10/10		4/10		0/10	

Values are expressed as the mean ± SD (n=5).
a: Cmin, Day 8 and Cmin, Day 28 represent the minimum concentration 7 days after the first dose and that 6 days after the fourth dose, respectively.
b: n=1, plasma mogamulizumab concentration was only detected in 1 of 5 monkeys.
c: AUCs were calculated from the concentrations of mogamulizumab for 7 days after the first administration or for 6 days after the fourth administration using a non-compartmental model.

NC=not calculated; ND=not detected in all monkeys.

Table 7: Pharmacokinetic Parameters of mogamulizumab after Repeat-dose Intravenous Administration Once Weekly for 13 Weeks to Male and Female Cynomolgous Monkeys

Dose (mg/kg)	2.5		10		40	
Sex	Male	Female	Male	Female	Male	Female
$C_{7d, Day 8}$ (ng/mL)	26870.6 ± 1953.0	23703.6 ± 3045.6	77857.0 ± 14530.7	73072.0 ± 8733.3	248740.0 ± 26375.4	237340.0 ± 42168.0
$C_{7d, Day 43}$ (ng/mL)	79945.0 ± 9765.9	75262.8 ± 11270.5	186080.0 ± 72114.6	135816.4 ± 68111.4	871900.0 ± 331032.6	944400.0 ± 255597.1
$C_{7d, Day 71}$ (ng/mL)	83757.8 ± 20789.4	78224.4 ± 21239.4	364100.0 ± 97854.1	254468.0 ± 143457.0	1339440.0 ± 542763.5	1333580.0 ± 314132.7
$C_{7d, Day 85}$ (ng/mL)	80538.4 ± 14925.4	79669.0 ± 22947.8	356160.0 ± 80438.0	273740.0 ± 119289.2	1476000.0 ± 526242.3	1263300.0 ± 295879.5
$C_{7d, Day 92}$ (ng/mL)	82140.6 ± 15976.4	78209.4 ± 14310.9	335480.0 ± 60144.7	264480.0 ± 97853.3	1497980.0 ± 444041.4	1263520.0 ± 282284.0
$AUC_{0-7d, Day 1}$ (µg·day/mL)	258.7069 ± 24.5790	227.8129 ± 26.8394	986.6328 ± 88.4475	906.6430 ± 52.7635	2825.4945 ± 296.0605	2664.0391 ± 340.8712
$AUC_{0-7d, Day 85}$ (µg·day/mL)	733.7836 ± 109.4619	715.7282 ± 106.3072	2859.9883 ± 420.9488	2268.7901 ± 630.9307	13528.8699 ± 3270.8586	10983.7644 ± 1762.7489
Production of anti-mogamu-lizumab antibodies (Number of animals)	0/10		0/10		0/10	

Values are expressed as the mean ± SD (n=5).

Table 8: Pharmacokinetic Parameters of mogamulizumab after Repeat-dose Intravenous Administration Once Weekly for 26 Weeks to Male and Female Cynomolgous Monkeys

Dose (mg/kg)	2.5		10		40	
Sex	Male	Female	Male	Female	Male	Female
$C_{max, Day 1}$ (ng/mL)	52180 ± 2360	50570 ± 10650	175800 ± 11000	139600 ± 18000	713700 ± 158000	459500 ± 22400
$C_{max, Day 85}$ (ng/mL)	142700 ± 44900	163900[a]	490500 ± 41500	342700 ± 50700	1508000 ± 96000	1117000 ± 258000
$C_{max, Day 176}$ (ng/mL)	170900 ± 58800	166700[a]	714300 ± 97300	468700 ± 26600	2359000 ± 189000	2236000 ± 694000
$AUC_{0-7d, Day 1}$ (µg·day/mL)	172 ± 12	213 ± 32	678± 39	582 ± 39	2360 ± 60	1490 ± 250
$AUC_{0-7d, Day 85}$ (µg·day/mL)	767 ± 300	933[a]	2730 ± 120	1790 ± 400	8360 ± 840	5130 ± 1670
$AUC_{0-7d, Day 176}$ (µg·day/mL)	936 ± 369	874[a]	3950 ± 520	2510 ± 230	12500 ± 600	9780 ± 3460
$AUC_{0-\infty, Day 1}$ (µg·day/mL)	371 ± 113	418 ± 62	1420 ± 450	1730 ± 460	4550 ± 800	3020 ± 1180
Production of anti-mogamulizumab antibodies (Number of animals)	1/6		0/6		0/6	

Values are expressed as the mean ± SD (n=3).

a: n=2, mogamulizumab in plasma was detected in two out of three monkeys.

Distribution

Distribution of mogamulizumab was investigated in cynomolgous monkey after a single dose of 1 mg/kg radioactive labelled $^{[125I]}$ mogamulizumab. Excluding plasma and blood, the maximum percentage of radioactivity distribution among all tissues was in the spleen with 4.86%. Compared to the concentration in plasma (100%) this accounts for 26%. Compared to presence of mogamulizumab in plasma and blood, tissue distribution of $^{[125I]}$mogamulizumab was relatively low. As the radioactive label can be removed from the antibody upon elimination, it cannot be excluded that a percentage of the label reflects radioactive label instead of radioactive labeled mogamulizumab.

In the fetuses, plasma concentrations on Day 140 of gestation (caesarian sections) were approximately 60% of that measured in the dams, indicating that mogamulizumab readily crosses the placenta and distributes to the fetus, similar to endogenous IgG1.

Metabolism

Studies on the metabolism of mogamulizumab were not conducted. As a monoclonal antibody, the expected metabolic pathway occurs via normal catabolic degradation to small peptides and individual amino acids.

Excretion

As a monoclonal antibody, no renal excretion is anticipated due to its molecular size. Therefore, studies to characterize the excretion routes of mogamulizumab were not conducted.

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were conducted as no drug-drug interactions were expected in the case of a mAb drug.

Other pharmacokinetic studies

No other pharmacokinetic studies were conducted with mogamulizumab.

2.3.4. Toxicology

Single dose toxicity

Single-dose Study in Cynomolgous Monkeys (Study Number: QUK00001, Non-GLP)

Mogamulizumab was administered by slow bolus iv injection at doses of 0.01, 0.5, 4, 20, and 100 mg/kg to cynomolgous monkeys (n=1/sex/group). The monkeys were evaluated for changes in clinical observations, food consumption, serum chemistry, haematology (including flow cytometry analysis and coagulation parameters) for 14 days after dosing. Toxicokinetics (TK) and anti-mogamulizumab antibody development were also assessed. The highest dose level in this study (100 mg/kg) was 100 times higher than the anticipated clinical dose (1 mg/kg).

Table 9 Findings in the single dose toxicity study conducted with mogamulizumab

Study ID	Species/ Sex/Number/ Group	Dose/Route	observed max non-lethal dose	Major findings
QUK00001 – non GLP	Cynomolgous monkey (1/dose/sex)	0, 0.01, 0.5, 4, 20, and 100 mg/kg IV	100 mg/kg	≥0.01 ↓ lymphocytes CD3+CD4+CCR4+, CD3+CD8+CCR4+, **CD3+CD25+ (activated lymphocytes) ,** ≥0.5 ≥4 ≥20 =100

Mean mogamulizumab exposures (AUC0-∞) for the 0.01. 0.5, 4, 20 and 100 mg/kg dose groups were 0.973, 126, 1310, 8020 and 27000 µg·day/mL, respectively. There were no deaths and no test article-related changes were noted in clinical observations, food consumption, serum chemistry, hematology and coagulation parameters. Peripheral blood immunophenotyping indicated there were reductions in specific populations beginning with the lowest dose tested in this study (0.01 mg/kg). There were decreases in CD3+CD4+CCR4+ lymphocytes, CD3+CD8+CCR4+ lymphocytes, and CD3+CD25+ lymphocytes. The reductions in CD3+CD4+CCR4+ and CD3+CD8+CCR4+ lymphocytes were anticipated pharmacologic activities of mogamulizumab. The reduction in CD3+CD25+ lymphocytes was most likely secondary to the decrease in CD3+CD4+CCR4+ lymphocytes. Therefore, mogamulizumab did not induce a toxicological response or unanticipated immunological effect at single doses up to 100 mg/kg.

Repeat dose toxicity

Table 10 Findings in the repeated dose toxicity studies conducted with mogamulizumab

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/week)	Major findings
QUK00003 - GLP	Cynomolgous monkey/ 5/sex/dose and 2/sex/dose for recovery	0.05, 1.2, and 40 mg/kg once weekly	28 days and 3 month recovery	40	≥0.05 ↓ lymphocytes CD3+CD4+CCR4+, CD3+CD8+CCR4+, **CD3-CD16+ (NK)** ≥1.2 axonal degeneration in thoracic spinal cord and posterior brainstem (determined as not treatment related) =40 Recovery Control animal: also axonal degeneration in thoracic spinal cord and posterior brainstem
SBL033-033 - GLP	Cynomolgous monkey/ 5/sex/dose and 2/sex/dose for recovery	2.5, 10, and 40 mg/kg once weekly	13 weeks and	40	≥2.5 ↓ lymphocytes CD3+CD4+CCR4+, CD3+CD4+CD25+ (m) ≥10 ↓ A/G, ↑ globulin (in 1/5 male) ↓ CD3+CD4+CD25+ lymphocytes, CD3+CD8+CCR4+ (m) =40↓ lymphocytes CD3+CD8+CCR4+, (after 13w) ↓ neut., albumin, A/G, ↑ LUC, fibrinogen, total protein, γ-globulin, total cholesterol (in 1/5 male)
SBL303-139 - GLP	Cynomolgous monkey/ 3/sex/dose	2.5, 10, and 40 mg/kg once weekly	26 weeks	40	≥2.5 ↓ CCR4+ lymphocytes ↓ CD3+CD4+CD25+ (m) ≥10 =40 ↓ CD3+CD4+CD25+, CD3-CD16+ (m)

A 4-week Repeat-dose Study in Cynomolgous Monkeys (Study Number: QUK00003, GLP)

Mogamulizumab at doses of 0 (vehicle), 0.05, 1.2, and 40 mg/kg was administered to male and female cynomolgous monkeys per dose by slow bolus iv injection once weekly for 4 weeks to evaluate its potential toxicity (5/dose/sex), and assess the reversibility of any possible toxicity during a 3-month recovery period after dosing (2/sex/dose).

No deaths and no test article-related toxicities were observed in this 4 week, repeat dosing study.

In peripheral blood immunophenotyping, the anticipated alterations were observed (decreases in CD3+CD4+CCR4+ lymphocyte count and CD3+CD8+CCR4+ lymphocyte count) which were related to the pharmacological activity of mogamulizumab. These reductions were identified on Day 2 and the lymphocyte subset counts continued to decrease up to Day 28. At study termination (Day 130), CD3+CD4+CCR4+ lymphocyte count had returned to baseline in the 0.05 mg/kg group but remained lower than baseline in the 1.2 and 40 mg/kg groups, while CD3+CD8+CCR4+ lymphocytes recovered to baseline in all mogamulizumab treated monkeys. Decreases in CD3−CD16+ lymphocytes (NK cell) counts were noted in all dose groups, as well, which is probably attributable to an immediate but transient effect of mogamulizumab. IgG responses to KLH challenge were similar across all treatment groups. Therefore, humoral responses upon challenge with KLH or TT are regarded unaffected by mogamulizumab. Mild to moderate axonal degeneration in the thoracic spinal cord and posterior brainstem was identified in five mogamulizumab-treated monkeys (two animals in the 1.2 mg/kg group and three animals in 40 mg/kg group). A similar finding in a vehicle control group monkey, however, was observed at the end of the recovery period in this study suggesting that this lesion may not have been attributable to treatment with mogamulizumab. This conclusion was strongly supported by reports that monkeys derived from the same shipment at the same test facility were found to have the same spinal cord lesion. Moreover, this lesion in nervous tissue was not observed in other repeat-dose toxicity studies we conducted in cynomolgous monkeys with mogamulizumab (13-week [Study SBL033-033], 26-week [Study SBL303-139], and an additional 4-week study [Study d-04-487]).

Given that there were no deaths or toxicological findings related to mogamulizumab, the NOAEL under the conditions of this study was identified as the maximum dose used in the study, 40 mg/kg/week.

A 13-Week Repeat-dose Toxicity Study in Cynomolgous Monkeys (Study Number: SBL033-033, GLP)

Mogamulizumab at doses of 0 (vehicle), 2.5, 10, and 40 mg/kg was administered to male and female cynomolgous monkeys by slow bolus iv injection once weekly for 13 weeks to (5/sex/dose) including a 13-week recovery period (2/sex/dose).

There were no deaths and no test article-related toxicities encountered in this study. One male (40 mg/kg) showed decreases in neutrophil count, albumin, albumin-to-globulin (A/G) ratio; increases in large unstained cell (LUC) count, fibrinogen, total protein, γ-globulin, and total cholesterol. Another male (10 mg/kg) showed increased globulin (mainly γ-globulin) and decreased A/G in one male from Week 6 of dosing. As no test article-related changes were observed in general condition, body temperature, morphology of leukocytes or in histopathology, these effects were not regarded adverse.

In peripheral blood immunophenotyping, there were no test article-related changes in CD3−CD16+ lymphocyte (NK cell) at any dose level throughout the study period. The CCR4-expressing cells in lymphocytes were not evaluable appropriately in some animals possibly due to multi-staining.

The NOAEL of mogamulizumab was considered to be 40 mg/kg under the conditions of this study.

A 26-Week Repeat-dose Toxicity Study in Cynomolgous Monkeys(Study Number: SBL303-139, GLP)

Mogamulizumab at doses of 0 (vehicle), 2.5, 10, and 40 mg/kg was administered to male and female cynomolgous monkeys by slow bolus iv injection once weekly for 26 weeks to evaluate its potential toxicity (3/sex/dose).

There were no deaths and no test article-related toxicities were observed. In peripheral blood immunophenotyping, the anticipated alterations (decreases in CCR4 expressing lymphocyte ratio and count)

were observed and related to the pharmacological activity of mogamulizumab. These reductions were identified in all males and females at 2.5, 10, and 40 mg/kg groups from Day 28 and throughout the study period.

Anti-KLH antibody production in animals treated with mogamulizumab were similar to those in control animals after KLH sensitization. In the conditions of this 26-week repeat-dose study, the NOAEL of mogamulizumab was 40 mg/kg.

Genotoxicity

No genotoxic assessment studies were submitted (see discussion on non-clinical aspects).

Carcinogenicity

No nonclinical studies were conducted for carcinogenic risk assessment.

Mogamulizumab has potent cytolytic activity against CCR4-expressing target cells, and has been shown in non-clinical studies *in vivo* to eliminate the CCR4-expressing cells. CCR4 is expressed on the Th2 cells, as well as Treg, Th17, and Th22 subsets of T cells, NK cells, macrophages, monocytes and platelets. The relationship between tumorigenesis and CCR4 expressing T cells is complex. There are reports suggesting that Th2 cell and Treg cells contribute to tumor growth in ovarian cancer, renal cell carcinoma, oral squamous cell carcinoma and melanoma. On the other hand, there are also reports in the literature suggesting that Th2 cells and Treg cells may exert anti-tumor effects in classical Hodgkin lymphoma and follicular lymphoma.

It has been reported that CCR4 knockout mice are viable, appear to develop normally, and show no overt morphological or behavioral defects. Moreover, tumor incidence in these mice has not been described. Although CCR4 expression was associated with increased tumor recurrence and impaired overall survival in patients with breast or gastric cancer, it was also reported that the expression of CCR4 does not affect the proliferation of breast cancer cells *in vitro* with or without thymus and activation-regulated chemokine (TARC), one of the endogenous ligands of CCR4.

Reproduction Toxicity

Table 11: Studies addressing effects of Mogamulizumab on fertility and embryo foetal development

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg &AUC)
Male fertility	No test article-related toxicity was observed in male and female reproductive organs (organ weights and histopathological evaluation) following administration of mogamulizumab at doses up to 40 mg/kg weekly to mature cynomolgous monkey (3-6 years old) for 13 and 26 weeks				
Female fertility					
Embryo-fœtal development - SBL303-049	Pregnant Cynomolgous monkey/12/dose	IV, 0, 40 mg/kg, once weekly	GD 20-139 (GD 140, caesarean section)	None	F0: 40 F1: 40

Following administration of mogamulizumab at doses up to 40 mg/kg weekly for 13 and 26 weeks to sexually mature cynomolgus monkeys (3 to 6 years old), no test article-related toxicity was observed in male and female reproductive organs (organ weights and histopathological evaluation) following administration of mogamulizumab at doses up to 40 mg/kg weekly for 13 and 26 weeks

Embryo-fœtal development (Study Number: SBL303-049,GLP)

Mogamulizumab at doses of 0 (vehicle) or 40 mg/kg was administered iv once weekly (total of 18 doses) to 12 pregnant cynomolgous monkeys in each group from the start of organogenesis (Day 20 of gestation [GD 20]) to GD 139 (late 3rd trimester), then animals underwent cesarean sectioning on GD 140, to investigate the effects of mogamulizumab on embryo-foetal development. In the 40 mg/kg group, foetal death was found in 1 dam on GD 100, and abortion occurred in 1 dam on GD 106. Abortion also occurred on GD 25 in 1 dam in the vehicle group. The loss incidence during the foetal development period in the 40 mg/kg group (2 of the 12 dams, 16.7%) was within the range of the control background data (0.0% to 16.7%). Macroscopic torsion and stenosis of the umbilical cord were detected in the dam where fetal death occurred, and microscopic suppurative and haemorrhagic placentitis were observed in the dam with the aborted fetus. Both findings observed in the mogamulizumab treated group were considered to be incidental and unrelated to mogamulizumab.

In peripheral blood immunophenotyping, no test article-related changes were noted in dams or fetuses, except for a decrease in CCR4 expressing lymphocyte count due to a pharmacodynamics activity of mogamulizumab, in both dams and fetuses.

Following repeated dosing, plasma mogamulizumab concentrations after the 10th and last dosing increased compared with the concentration at the first dosing. The mean plasma mogamulizumab concentration in foetuses removed by cesarean sectioning on G 140 was 983340.0 ng/mL and the mean ratio of mogamulizumab concentration in fetuses to that in dams at 24 hours after the last dosing was 0.6. Anti-mogamulizumab antibodies were not detected in any maternal or fetal samples. Under the conditions of this study, a dose level of 40 mg/kg is considered the NOAEL of mogamulizumab for general toxicity in dams, reproductive function of dams, and embryo-foetal development.

Table 12: Plasma Concentration of mogamulizumab in EFD Toxicity Study

Plasma concentration (ng/mL) in 40 mg/kg group						
Dams						Fetuses
GD 20 (first dosing)	GD 83 (10th dosing)		GD 139 (18th dosing)			
5 Minutes after Infusion	Pre	5 Minutes after Infusion	Pre	5 Minutes after Infusion	24 Hours after Infusion	GD 140
N=12	N=12	N=12	N=10	N=10	N=10	N=10
948933.3	1022536.4	1789208.3	1216980.0	2091900.0	1700200.0	983340.0

Table 13: The Ratio of the Mean AUC0-7d at Dose Level of NOAEL in a Reproductive and Developmental Toxicity with Cynomolgous Monkey (the first dosing) to the Recommended Clinical Dose, and Plasma Concentration of Dam and Fetus on the Following Day of the Last Dosing

		$AUC_{0\text{-}7d}$ (ng·day/mL)	The Ratio of NOAEL to the Recommended Clinical Dose[a]	Plasma Concentration (ng/mL)	The Ratio of Plasma Concentration in Dam to Fetus
Dam	GD 20	3849728.9	26.9	–	–
	GD 140	–	–	1700200.0[b]	–
Fetus	GD 140	–	–	983340.0[c]	0.6

Toxicokinetic data

4 weeks repeated dose study

There were no apparent gender differences in TK parameters of mogamulizumab at either dose level. The area under the plasma concentration time curve (AUC) values increased roughly in proportion to the dose increments. Production of anti-mogamulizumab antibodies was detected in 14 of 30 monkeys treated with mogamulizumab after Day 15. The information is summarized in Table 20.

Table 14: The Mean AUC Value and Anti-mogamulizumab Antibody Formation in a 4-week Repeat-dose Toxicity

Dose (mg/kg)	0.05		1.2		40	
Sex	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
AUC (ng·day/mL), N=5/sex/group						
Day 1[a]	2990	3220	102000	100000	3420000	3770000
Day 22[b]	NC	5440[c]	214000	210000	8630000	8620000
Anti-mogamulizumab antibody formation (positive animal/tested animal)						
Administration period	5/5	4/5	0/5	1/5	0/5	0/5
Recovery period	2/2	2/2	1/2	2/2	0/2	0/2

13-week repeated dose toxicology study

There were no gender differences apparent in the TK parameters of mogamulizumab at any dose level (Table 21). AUC values increased roughly proportionally with dose. Antimogamulizumab antibodies were not detected in any animal.

Table 15: The Mean AUC0-7d Value in a 13-week Repeat-dose Toxicity

Dose (mg/kg)	2.5		10		40	
Sex	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
$AUC_{0\text{-}7d}$ (ng·day/mL), N=5/sex/group						
Day 1	258706.9	227812.9	986632.8	906643.0	2825494.5	2664039.1
Day 85	733783.6	715728.2	2859988.3	2268790.1	13528869.9	10983764.4

26-week repeated dose toxicology study

There were no gender differences apparent in the TK parameters of mogamulizumab at any dose level. AUC values increased in a manner roughly proportional to dose increments. Anti-mogamulizumab antibodies were detected in 1 female from Day 29 to the end of the study (Day 185) in the 2.5 mg/kg group.

Table 16: The Mean AUC0-7d Value in a 26-week Repeat-dose Toxicity

Dose (mg/kg)	2.5		10		40	
Sex	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
$AUC_{0\text{-}7d}$ (ng·day/mL), N=3/sex/group						
Day 1	172000	213000	678000	582000	2360000	1490000
Day 85	767000	933000[a]	2730000	1790000	8360000	5130000
Day 176	936000	874000[a]	3950000	2510000	12500000	9780000

Comparison of AUC 0-7d in cynomolgous monkey dosed 40 mg/kg for 4, 13 or 26 weeks

Table 17: The Ratio of the Mean AUC0-7d at Dose Level of NOAEL in a Repeat-dose Toxicity with Cynomolgous Monkey to the Recommended Clinical Dose

	NOAEL (mg/kg)	Mean AUC (ng·day/mL)		The Ratio of Exposure	
		Male	Female	Male	Female
Steady-state $AUC_{0-\tau}$ in humans (1 mg/kg)		286091.7 [a]		–	
Repeat-dose Toxicity Study					
4-week (QUK00003, GLP)	40	8630000 [b]	8620000 [b]	60.3	60.3
13-week (SBL033-033, GLP)	40	13528869.9 [c]	10983764.4 [c]	94.6	76.8
26-week (SBL303-139, GLP)	40	12500000 [c]	9780000 [c]	87.4	68.4
Fertility					
26-week (SBL303-139, GLP)	40	12500000 [c]	9780000 [c]	87.4	68.4
Embryo-Fetal Development					
(SBL303-049, GLP)	40	3849728.9 [d]		26.9	

a: The mean AUC(0-τ)ss is 6866.2 (mg·h/L) for once in 2-week dosing regimen.
b: The mean value of AUC0-6d
c: The mean AUC0-7d of the last dosing was described.
d: The mean AUC0-7d of the first dosing was described.

Local Tolerance

The local tolerance of mogamulizumab was assessed from clinical observation and pathological examination of injection sites in the single-dose toxicity study (Study QUK00001), 4-week repeat-dose toxicity study (Study QUK00003), 13-week repeat-dose toxicity study (Study SBL033-033), 26-week repeat-dose toxicity study (Study SBL303-139), reproductive and development toxicity study (Study SBL303-049), single-dose iv/sc bridging studies (Study FIA00527 and Study FIA00561), and 4-week repeat-dose study to evaluate the effects of mogamulizumab on the nervous tissue (Study d-04-487). No significant irritation or local tolerance issues were observed at the mogamulizumab injection sites in any studies.

Other toxicity studies

Antigenicity

Immunogenicity of mogamulizumab after Single- or Repeat-Dose Administration to Cynomolgous Monkeys (Study Number: QUK00001, Non-GLP; SBL27-01, Non-GLP; FIA00561, GLP; QUK00003, GLP; SBL033-033, GLP; SBL303-139, GLP; SBL303-049, GLP)

The presence of mogamulizumab-specific antibodies was assessed in the repeat-dose toxicity studies (Study QUK00003, SBL033-033, SBL303-139, and SBL303-049) and in the single dose studies (Study QUK00001, SBL27-01, and FIA00561).

Table 18 The Number of Animals Indicating Anti-mogamulizumab Antibody Positive in Single- and Repeat-dose Toxicities with Cynomolgous Monkeys

Study	Study No.	Dosing Period/ Recovery Period	Dose (mg/kg)	No. of Animals with Anti-mogamulizumab Antibodies
Single-dose toxicity	QUK00001	1 day/15 days	0.01	0/2
			0.5	0/2
			4	0/2
			20	0/2
			100	0/2
Repeat-dose toxicity	QUK00003	4 weeks	0.05	9/10
			1.2	1/10
			40	0/10
		4 weeks/3 months	0.05	4/4
			1.2	3/4
			40	0/4
	SBL033-033	13 weeks	2.5	0/10
			10	0/10
			40	0/10
		13 weeks/13 weeks	2.5	0/4
			10	0/4
			40	0/4
	SBL303-139	26 weeks	2.5	1/6
			10	0/6
			40	0/6

iv=intravenous; sc=subcutaneous

Anti-mogamulizumab antibody production in studies where detected, did not impact the results of toxicity assessment. Anti-mogamulizumab antibodies were detected in 10 mg/kg single-dosed animals, 0.05 or 1.2 mg/kg repeat-dosed (once weekly for 4 weeks) animals, a 2.5 mg/kg repeat-dosed (once weekly for 26 weeks) animal, and 0.0000725, 0.001, 0.01, 0.1 or 1 mg/kg single-dose animals. There were, however, no immune-mediated reactions (immune complex-related, vasculitis, anaphylaxis, etc).

Immunotoxicity

Immunotoxicity Study Number: QUK00001, Non-GLP; QUK00003, GLP; SBL303-033, GLP; SBL303-139, GLP; SBL303-049, GLP; FIA00561, GLP)

Peripheral blood immunophenotyping, haematology, organ weight and histopathology for lymphoid tissue (thymus, spleen and lymph node) were evaluated in the single-dose toxicity study (Study QUK00001), 4-week repeat-dose toxicity study (Study QUK00003), 13-week repeat-dose toxicity study (Study SBL033-033), 26-week repeat-dose toxicity study (Study SBL303-139), embryo-fetal development study (Study SBL303-049), and single-dose iv/sc toxicity study (Study FIA00561). An anticipated decrease in CCR4 expressing lymphocyte count was observed in all studies, consistent with the pharmacological actions of mogamulizumab. In the 4-week repeat-dose toxicity study (Study QUK00003), decreases in NK cell count were noted but no changes were evident in lymphoid organ weights and pathological examination of lymphoid tissues indicated they were normal.

Evaluation of humoral immune response was carried out in the 4-week and 26-week repeat-dose toxicity studies by using KLH for all cynomolgous monkeys and TT for recovery monkeys in the 4-week toxicity study as the T-lymphocyte dependent antigen. Measurements of anti-KLH or anti-TT IgM and IgG titers were performed using an ELISA assay. Humoral responses to challenge with KLH or TT were unaffected by treatment with mogamulizumab.

Dependence

In compliance with ICH M3 (R2) guidance, dependence studies were not conducted since there is no evidence to suggest that there is the potential for drug abuse or misuse of mogamulizumab. In repeat-dose toxicity studies there were no test article-related neurobehavioral abnormalities. Moreover, there is no theoretical concern for drug dependence.

Metabolites

No studies on metabolites were conducted with mogamulizumab, as it is a monoclonal antibody (see also PK Section).

Studies on impurities

The potential impacts of impurities were assessed through toxicological evaluation of the mogamulizumab drug product. Comparability of mogamulizumab was verified between the drug substance lots and the drug product lots used in all in vivo toxicity studies and clinical trials. However, concern is raised on the comparability of mogamulizumab lot used in non clinical studies and the clinical ones (See Quality AR).

2.3.5. Ecotoxicity/environmental risk assessment

Mogamulizumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use” (EMEA/CHMP/SWP/4447/00), mogamulizumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

CCR4 is overexpressed on the surface of and/or expressed by a high percentage of the cancerous cells in T-cell malignancies such as CTCL, adult T-cell leukemia-lymphoma (ATL), and peripheral T-cell lymphoma (PTCL). In healthy individuals, CCR4 is according to the applicant selectively expressed on a subset of T cells, including Type 2 T helper (Th2) T cells and regulatory T cells (Tregs). However, expression on other cell types has been reported as well, including human memory Th17 cells, platelets, NK cells, monocytes, macrophages, and DCs (Scheu et al 2017*).

Immunophenotyping by flow cytometry in the animal studies shows a consistent and statistical significant dose dependent decrease in CCR4 positive CD4 cells following mogamulizumab treatment. A statistical significant decrease in CD3+CD4+CD25+ cells is also observed. This population of cells is typed as activated T-lymphocytes by the applicant, but may also include regulatory T-cells. With regard to the influence of mogamulizumab on NK cells, CD8+ T cells and monocytes, the picture is less clear. The effect of mogamulizumab on Tregs alone (CD4+,CD25+, FOXP3+ and CD45RA+) and macrophages was not investigated. Reductions in CCR4+ T-cytotoxic/suppressor lymphocytes (CD3+/CD8+/CCR4+) seem to be dose independent. Reductions in NK cells are limited and dose independent and seem to be most apparent short after

start the first dose. The effect of mogamulizumab treatment on the levels and function of Treg cells and on the different lymphocyte populations is investigated in humans (see clinical pharmacodynamics).

Mogamulizumab can induce ADCC on cell lines KC1057 (Transfected EL-4 cell lines expressing very low levels of hCCR4) and HUT102 cells. It is assumed that these cell lines expressing very low levels of CCR4, undetectable by flow cytometry (FCM). This suggests that the detection threshold of CCR4 by FCM is just below the level at which minimal ADCC could be induced. Although from the non-clinical in vitro data a relation between CCR4 expression and ADCC induction might be suggestive, clinically a relationship between CCR4 expression level and ADCC activity has not been established, however it can be assumed that CCR4 expression on skin infiltrating lymphocytes, albeit at very low levels, already result in a treatment effect.

Two NK-cell related issues are identified that may interfere with mogamulizumab mediated ADCC; decrease (of functional) NK-cells due to underlying the disease and elimination of CCR4 expressing NK-cells. The level and functionality CCR4-expressing of NK-cells have not been monitored during clinical studies. If indeed a minority of NK cells expresses CCR4, a potential depletion would likely not have a measurable effect on the clinical response. Thus, the durable response does not exclude the potential of mogamulizumab mediated CCR4+ NK-cell depletion. It remains uncertain whether decrease of number and functionality of NK-cells related to the underlying disease influences the success of the treatment.

A single intravenous treatment of mogamulizumab with dosages up to 100 mg/kg was well tolerated by cynomolgus monkeys, with no treatment-related alterations from cage side observations, or from evaluations of serum chemistry, hematology or coagulation parameters. No evidence of anti-mogamulizumab antibody formation was detected through Day 15. Toxicokinetic parameters were similar between groups dosed from 0.5 to 100 mg/kg with an average elimination half-life of 18.2 days.

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity.

No mogamulizumab-related toxic effects in the male and female reproductive organs were observed in repeat-dose toxicology studies in sexually mature monkeys up to 26 weeks. The NOAEL of mogamulizumab was judged to be 40 mg/kg or greater since no toxicologically significant changes were observed in any examination.

Carcinogenicity or genotoxicity studies have not been conducted with mogamulizumab. It is highly unlikely that mogamulizumab would react directly with DNA or other chromosomal material because mogamulizumab is a monoclonal antibody. As per ICH S6 (R1) guidance, no genotoxicity studies were conducted. No specific studies have been conducted to evaluate potential effects on fertility.

In an animal reproductive and developmental toxicity study, administration of mogamulizumab to pregnant cynomolgus monkeys from the start of organogenesis through delivery did not show a potential for embryo-foetal lethality, teratogenicity, or foetal growth retardation. In general, IgG molecules are known to cross the placental barrier and mogamulizumab concentrations in foetus plasma were detected. Pharmacological activity of mogamulizumab was noted in fetuses as was evident from a decrease in CCR4 expressing lymphocytes (see SmPC section 5.3).

Prenatal and postnatal development studies were not conducted, according to ICH S9. No juvenile Toxicity studies were conducted with mogamulizumab, as it is not developed for pediatric indication.

Local tolerance was evaluated in the context of single- and repeat-dose toxicity studies, where no findings which could suggest local injection site irritation were detected.

Immunogenicity of mogamulizumab was evaluated in the single- and repeat-dose toxicity studies, the reproductive and developmental toxicity study and a single-dose iv/sc bridging study. Anti-mogamulizumab

antibodies were detected in some animals receiving a single i.v. dose of 0.0000725, 0.001, 0.01, 0.1, 1.0 and10 mg/kg, and also in some animals receiving repeat doses of 0.05 or 1.2 mg/kg (once weekly for 4 weeks).

In the 26-week repeat-dose study, development of anti-mogamulizumab antibodies was observed in only one animal (1 female in the 2.5 mg/kg group). The plasma mogamulizumab concentrations of the animals in which anti-mogamulizumab antibodies were observed decreased more rapidly than the plasma concentration in animals that did not produce anti-mogamulizumab antibodies. There were no anti-mogamulizumab antibodies-related toxicological findings in the animals in which production of anti-mogamulizumab antibodies was observed.

Mogamulizumab is a human IgG 1 monoclonal antibody and can reasonably be expected to be subject to the same degradative pathways as naturally occurring proteins so it is not expected to pose a risk to the environment, therefore it is exempted from ERA studies as per the guideline EMEA/CHMP/SWP/4447/00.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical studies on mogamulizumab are sufficient. Non-clinical information has been included in the SmPC section 5.3 and appropriate warnings under section 4.6.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 19: Tabular overview of clinical studies

Phase; Type of Study; Study Status (Region of Study Conduct); Type of Report	Study Title	Primary and Secondary Objective(s) of the Study	Indication; Number of Subjects Enrolled (n)	Test Product(s); Dosage Regimen; Route of Administration; Duration of Treatment
Phase 3; Pivotal safety and efficacy study supporting marketing approval Ongoing: Data Cut-off date: 31 Dec 2016 (Conducted in US, Europe, Australia, Japan) Interim	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	**Primary Objective:** • To compare the progression free survival of KW-0761 versus vorinostat for subjects with relapsed or refractory CTCL **Secondary Objectives:** • To compare the overall response rate of KW-0761 versus vorinostat in subjects with relapsed or refractory CTCL; • To evaluate and compare improvements in QoL measurements, Skindex-29, FACT-G, and EQ-5D-3L for subjects receiving KW-0761 versus vorinostat; • To evaluate and compare improvements in the Pruritus Evaluation (Likert scale & Itchy QoL) for subjects receiving KW-0761 versus vorinostat; • To estimate the duration of response for both the KW-0761 and vorinostat arms for those subjects with relapsed or refractory CTCL responding to treatment; • To determine if subjects who relapse on vorinostat can achieve response upon cross over to treatment with KW-0761; • To further assess the safety of KW-0761; • To describe the immunogenicity of KW-0761. **Exploratory Objectives:** • To compare the overall survival of KW-0761 versus vorinostat for subjects with relapsed or refractory CTCL; • To conduct exploratory evaluation of KW-0761 exposure-response relationships.	CTCL; (Enrolled n=372) Safety Set n=370 KW-0761: 184; Vorinostat: 186 Efficacy Evaluable Set n=361 KW-0761: 180 Vorinostat: 181	**KW-0761**: Administered 1.0 mg/kg iv weekly for 4 weeks, then every other week. **Vorinostat**: 400 mg orally once daily Treated until: • Progressive disease; • Drug intolerance; • Unacceptable toxicity; • Other criteria for removal from study

Table 20: Supportive studies in subjects with T-cell lymphomas

Supportive Studies in Subjects with T-cell Lymphomas				
Phase 1/2; Completed; (Conducted in US); Full	Open-label, Multi-center, Dose Escalation Phase 1/2 Study of Anti-CCR4 Monoclonal Antibody KW-0761 as Monotherapy in Subjects with Previously Treated Peripheral T-cell Lymphoma or Cutaneous T-cell Lymphoma	**Primary Objective:** • Phase 1: To establish the safety profile, PK profile, MTD, if achieved and DLT of KW-0761; and • Phase 2: To determine the safety and preliminary efficacy of KW-0761 administered intravenously in subjects with previously treated PTCL or CTCL. **Secondary Objectives:** • Phase 1: to describe the, immunogenicity and preliminary efficacy of KW-0761 at different dose levels; and • Phase 2: to determine the response rate, response duration, and time-to-progression of subjects treated with KW-0761.	PTCL and CTCL Enrolled n=42; CTCL n=41; PTCL n=1 Safety Set n=42 Efficacy Evaluable Set n=39	KW-0761: 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg Administered iv weekly for 4 weeks, followed by 2-week observation period in the first treatment course. Subjects demonstrating PR, CR or stable disease were permitted to receive additional courses of treatment every other week Treated until: • Progressive disease; • Drug intolerance; • Unacceptable toxicity; • Other criteria for removal from study.
Phase 2; Completed; (Conducted in Japan); Full	A Late Phase 2 Study of KW-0761 in Subjects with CCR4-positive Peripheral T/NK-cell Lymphoma	**Primary Objective:** • Antitumor effect (best overall response). **Secondary Objectives:** • Assess antitumor effect (best response by disease lesion), PFS and OS; • Adverse events and anti-KW-0761 antibody levels; • Plasma KW-0761 concentrations and pharmacokinetic parameters.	Peripheral T/NK Cell Lymphoma Enrolled n=38 Safety Set n=37 CTCL = 8, PTCL = 29 Efficacy Evaluable Set n=37	KW-0761: 1.0 mg/kg Administered iv weekly for 8 weeks. Treated until: • Progressive disease; • Drug intolerance; • Unacceptable toxicity; • Other criteria for removal from study.

Table 21. List of clinical studies yielding mogamulizumab pharmacokinetic data

Study No. (Region)	Design	Dose/Route schedule	Study Population	Number of Subjects for PK Analysis	PK Sampling Point	Assesment
0761-0501 (Japan)	Phase 1, open label	0.01, 0.1, 0.5 and 1.0 mg/kg iv weekly for 4 weeks	Subjects with CCR4-positive relapsed ATL and PTCL[a)]	16 subjects (0.01 mg/kg, 3 subjects; 0.1 mg/kg, 4 subjects; 0.5 mg/kg, 3 subjects; 1.0 mg/kg, 6 subjects)	Dose 1: Pre-dose, 0.5, 2, 4, 24 and 72 hrs Dose 2 -3: Pre-dose and EOI; Dose 4: Pre-dose, 0.5, 2, 4, 24 and 72 hrs and 7, 14, 21 and 28 days after dosing	Single-dose PK. (NCA), Multiple-dose PK (NCA), PPK
0761-002 (Japan)	Phase 2, open label	1.0 mg/kg iv weekly for 8 weeks	Subjects with CCR4-positive relapsed ATL	27 subjects	Dose 1: Pre-dose, 0.5, 2, 4, 24 and 72 hrs; Dose 2 -7: Pre-dose and EOI; Dose 8: Pre-dose, 0.5, 2, 4, 24 and 72 hrs and 7, 14, 221 and 28 days after dosing	Multiple-dose PK (NCA), PPK
0761-003 (Japan)	Phase 2, multicenter, randomized, open-label, parallel group study in combination with chemotherapy	mLSG15[c)] or 1.0 mg/kg mogamulizumab+ mLSG15; mogamulizumab given iv every two weeks for 16 weeks Randomized 1:1	Subjects with CCR4-positive ATL (untreated primary disease)	29 subjects[b)]	Dose 1-7: Pre-dose and EOI; Dose 8: Pre-dose, EOI and 14 days after dosing	PPK
0761-004 (Japan)	Phase 2, open-label	1.0 mg/kg iv weekly for 8 weeks	Subjects with CCR4-positieve relapsed PTCL[b)] and CTCL	37 subjects	Dose 1: Pre-dose; Dose 4: EOI; Dose 5: Pre-dose; Dose 8: EOI and 7 and 28days after dosing	PPK
0761-009 (US, EU, South America)	Phase 2, open-label, multi-center, randomized	mogamulizumab: 1.0 mg/kg iv weekly (Day1, 8. 15 and 22) in Cycle1, then biweekly (Day1 and 15) in subsequent cycles. Investigator's choice (pralatrexate, GemOx or DHAP) until progression; Randomized 2:1	Subjects with relapsed/refractory ATL	59 subjects (including subjects who were initially assigned to the investigator's choice and then crossed over into mogamulizumab)	Cycle 1 Day1; Pre-dose and EOI; Day 8,15,22,; Pre-dose Cycles 2-3 Day 1 and 15; Pre-dose EOT	PPK, ER (Concentration effect on QTc)
0761-010 (US, EU, Japan, and Australia)	Phase 3, open-label, multi-center, randomized	mogamulizumab: 1.0 mg/kg iv weekly for 4 weeks, then every other week or vorinostat until progression; Randomized 1:1	Subjects with relapsed/refractory CTCL	298 subjects (including subjects who were initially assigned to vorinostat and then then crossed over into mogamulizumab)	Cycle 1 Day1; Pre-dose and EOI; Day 8,15,22; Pre-dose Cycles 2-3 Day 1 and 15; Pre-dose EOT	PPK, ER

a) 2 subjects with PTCL were not included in the pop-PK analysis

b) 29 subjects with PTCL were not included in the pop-PK analysis

2.4.2. Pharmacokinetics

Methods

Bioanalytical methods for the quantitative determination of mogamulizumab in human plasma and serum using an enzyme-linked immunosorbent assay (ELISA) were developed and validated during the course of the clinical development program for mogamulizumab.

The methods applied were adequately validated. Concerning the robustness of the analytical assay, the validation of the assay yielded acceptable results. With one exception, Incurred Sample Reanalysis (ISR) showed acceptable reproducibility (≥67% samples demonstrated the reanalysed values to be within ±30% of

their initial values). After a slightly modified analysis method, subsequent ISR was adequate for all other analyses.

Population modelling was conducted using NONMEM Version 7.3. In this pop-PK analysis, plasma or serum mogamulizumab concentration data from 444 subjects with ATL or CTCL who received mogamulizumab over a dose range of 0.01 to 1.0 mg/kg in 6 clinical studies were used (Studies 0761-0501, 0761-002, 0761-003, 0761-004, 0761-009 and 0761-010).

The selected pop-PK model was a two-compartment model with linear clearance for description of the mogamulizumab PK. PK of mogamulizumab administered at doses of 0.01, 0.1, 0.5 and 1 mg/kg were described. The results of the non-parametric bootstrap showed that the median of the bootstrap parameters are in line with the population estimates. The bootstrap 95% confidence intervals did not contain the null value for any covariate effects. Graphical evaluations of the final model suggested adequate performance. Shrinkage for CL was low (5%). Other metrics suggested adequate performance.

Absorption

Bioavailability

The bioavailability of mogamulizumab is 100% per definition, since it is administered as a IV infusion.

In Study 0761-002, a Phase 2, multiple-dose study conducted in Japan in subjects with CCR4-positive relapsed ATL (n=27), mogamulizumab was administered at a dose of 1.0 mg/kg by iv infusion weekly for 8 weeks. Serial plasma samples for PK analysis were collected after the first and eighth doses; additional samples were collected pre-dose and at the end of infusion of the second through seventh doses. The mean plasma concentration-time profiles are shown in Figure 8, with PK parameters on day 1 and 8 summarised in Table 22. Maximum plasma levels were generally obtained at end of infusion.

Figure 8. Plasma concentration-time profiles of mogamulizumab after IV administration of mogamulizumab once weekly for eight weeks to subjects with CCR4-positive ATL (1.0 mg/kg) (Mean + SD, n=3-27) (Study 0761-002)

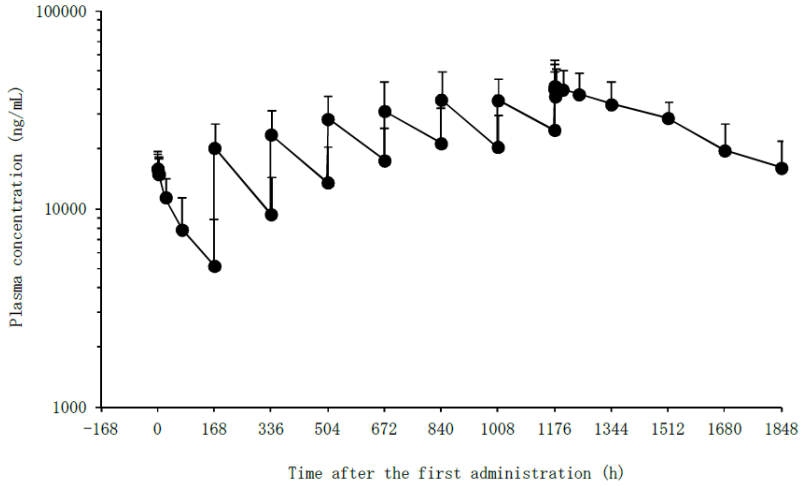


Table 22. Summary of pharmacokinetic parameters for mogamulizumab (non-compartmental model) (Study 0761-002)

Blood sampling point	Summary statistics	C_{max} (ng/mL)	C_{trough} (ng/mL)	$AUC_{0\text{-}7\ days}$ (ng·h/mL)	$t_{1/2}$ (h)
First dosing	n	27	19	19	23
	Mean	16622.0	5151.9	1427204	124
	SD	3324.0	3713.6	571447	92
	Minimum to maximum	10602.7 - 23702.1	69.8 - 13546.4	628049 - 2876824	20 - 404
Eighth dosing	n	5	4	4	5
	Mean	42943.2	33638.3	6297408	422
	SD	14239.5	10572.2	1812467	147
	Minimum to maximum	24601.3 - 59555.2	21371.0 - 45242.4	4156278 - 8324929	285 - 583
Accumulation rate	n	5	3	3	-
	Mean	2.25	3.56	2.87	-[a)]
	SD	0.52	0.31	0.33	-
	Minimum to maximum	1.74 - 3.09	3.24 - 3.86	2.50 - 3.12	-

- **Bioequivalence**

No bioequivalence studies are needed for this product, since it is an aqueous solution administered via i.v. infusion.

Influence of food

Pharmacokinetics of mogamulizumab is not expected to be affected by food, since it is administered via i.v. infusion.

Distribution

Based on pop-PK analysis, the geometric mean [% coefficient of variation (CV%)] central volume of distribution (Vc) was 3.57 L (20.1%).

Elimination

Based on pop-PK analysis, the geometric mean (% coefficient of variation [CV%]) clearance (CL) is 12.0 ml/h (83.7%). The geometric mean elimination half-life (t1/2) is 17 days (65.5%), which is similar to the $t_{1/2}$ of circulating endogenous human IgG (approximately 21 days). Similar to other IgG1-class antibody proteins, mogamulizumab is believed to be degraded by enzymatic proteolysis into small peptides and amino acids in the same manner as endogenous IgG. Under steady-state conditions at a 1.0 mg/kg dose, CCR4 binding sites are expected to be saturated.

Inter- and intra-individual variability in exposure was estimated based on observed Cmax values, simulated AUC(0-τ),ss levels and subsequent mixed effect modelling. Inter-individual variability was mild to moderate, i.e., 21.6% and 36.9% for Cmax and AUC, respectively, Intra-individual variability was mild, i.e., 16.7% and 11.23%, respectively.

Dose proportionality and time dependencies

Dose proportionality

In Study 0761-0501, C_{max} and $AUC_{0\text{-}7\ days}$ values after four repeated administrations of iv mogamulizumab once weekly at doses of 0.01, 0.1, 0.5, or 1.0 mg/kg in subjects with CCR4-positive ATL or subjects with CCR4-positive PTCL were evaluated for linearity by applying a linear model (power model) using the log-transformed value of each parameter and the log-transformed dose. The estimates of μ and β and 95% confidence intervals for C_{max} and $AUC_{0\text{-}7\ days}$ are presented below.

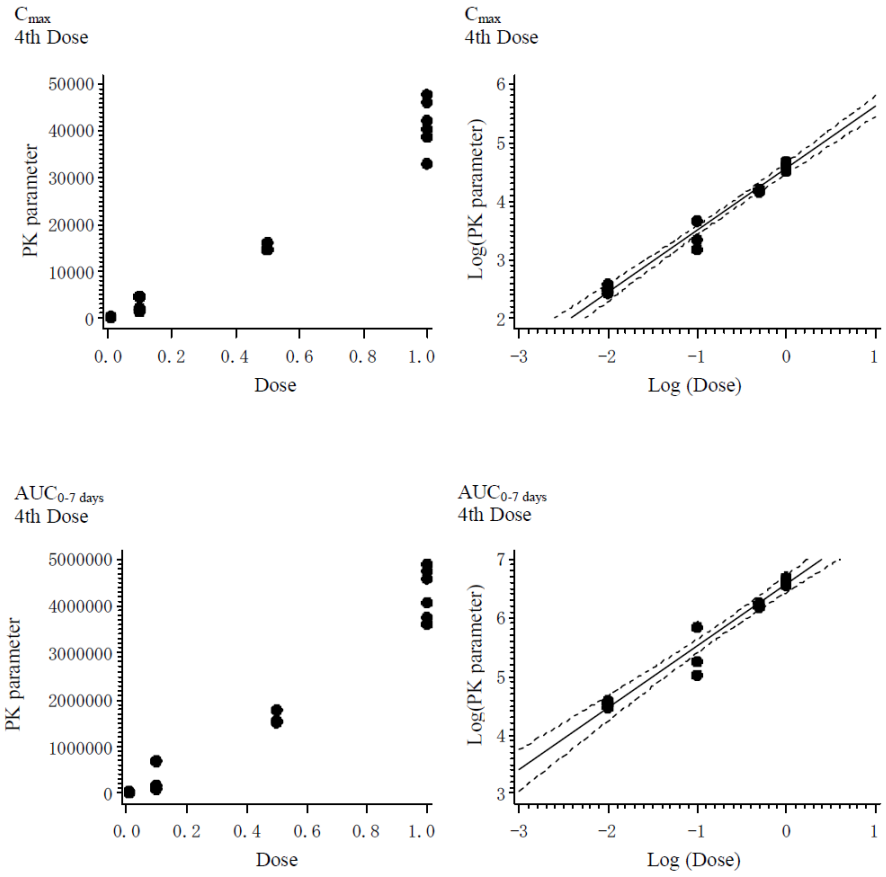
The graphs for C_{max} and $AUC_{0\text{-}7\ days}$ as a function of dose, expressed as untransformed and logarithmic numbers, are presented in Figure 9. The 95% confidence interval of estimate of β for both C_{max} and $AUC_{0\text{-}7\ days}$ included 1.0, indicating linearity over the dose range of 0.01 to 1.0 mg/kg.

Table 23. Dose proportionality of the pharmacokinetic parameters after four repeated doses of IV mogamulizumab once weekly (Study 0761-0501)

Pharmaco-kinetic parameter	Dose range (mg/kg)	n	Test statistic[a)]	p-value	Power model[b)] parameter	Estimate	Str Error	95% LCL[c)]	95% UCL[d)]
C_{max}	0.01~1.0	15	5.746	0.057	μ	4.5614	0.0417	4.4712	4.6515
					β	1.0584	0.0414	0.9690	1.1477
$AUC_{0\text{-}7\ days}$	0.01~1.0	15	3.542	0.170	μ	6.5744	0.0613	6.4419	6.7068
					β	1.0593	0.0608	0.9281	1.1906

a) Likelihood Ratio Test: Test of the Power Model against the Model without dose proportionality: log10 (Pharmacokinetic parameter) = μ + βi × log10 (Dose) (βi: Parameter of the i th Dose)
b) Power Model: log10 (Pharmacokinetic parameter) = μ + β × log10 (Dose)
c) LCL: Lower limit of Confidence Interval
d) UCL: Upper limit of Confidence Interval

Figure 9. Dose proportionality of the pharmacokinetic parameters after four repeated doses of IV mogamulizumab once weekly (Power Model, Study 0761-0501))

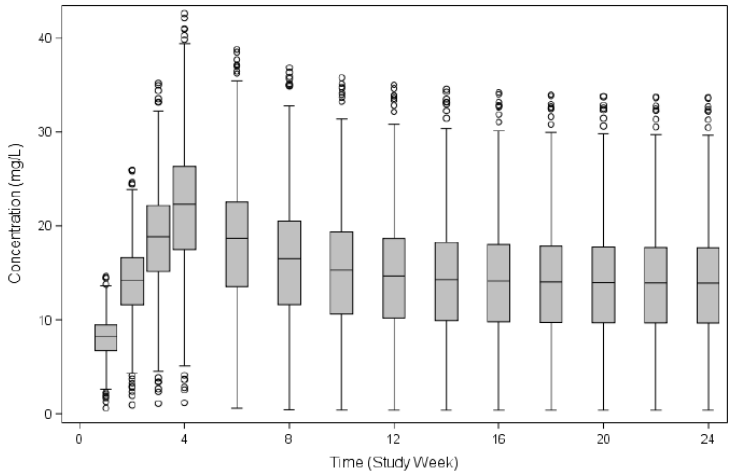


Time dependency

In Study 0761-0501, the mean accumulation ratio for $AUC_{0\text{-}7\ days}$ after the 4th dose ranged from 2.15 to 3.48. In Study 0761-002, plasma C_{max} and C_{min} increased with repeated doses of mogamulizumab; however, steady state was not attained after eight repeated doses given once weekly (see Figure 8). The mean accumulation ratio after the 8th weekly dose was 2.87 for $AUC_{0\text{-}7\ days}$. The $t_{1/2}$ after the 8th dose was 422±147 hours (17.6±6.1days, mean ± SD), similar to the $t_{1/2}$ of approximately 21 days for normal immunoglobulin G1 (IgG1).

The time course to steady-state for mogamulizumab C_{min} was predicted using the pop-PK model with the dose regimen employed in Studies 0761-009 (Subjects with relapsed/refractory ATL) and 0761-010 (subjects with relapsed/refractory CTCL) (i.e., 1.0 mg/kg, once weekly for 4 weeks and then once every 2 weeks) (Figure 10). Steady state was achieved approximately after the 8th dose (12 weeks) with an accumulation ratio of approximately 1.7-fold for C_{min} and C_{max}. The median simulated C_{min} achieved at the 1.0 mg/kg dose at steady-state was approximately 14 µg/ml.

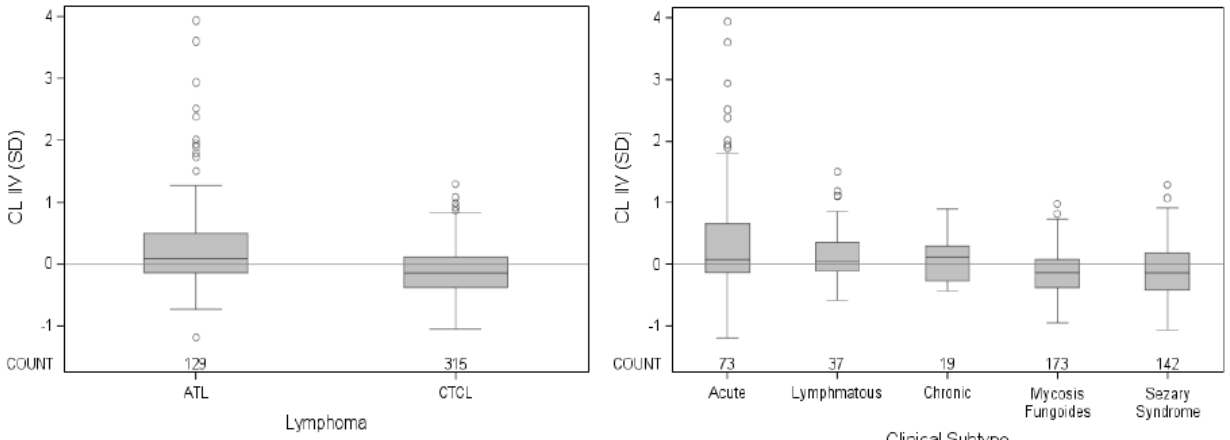
Figure 10. Pop-PK predicted mogamulizumab Cmin after IV administration of mogamulizumab (1.0 mg/kg) once weekly for 4 weeks (Cycle 1) and then once every 2 weeks (Pop-PK Study 0761-bla-ctcl-pop-pk-r-en)



Pharmacokinetics in target population

The PK of mogamulizumab was only evaluated in patients with ATL and CTCL. The effect of disease type (i.e., ATL (n=129, 29.1%) or CTCL (n=315, 70.9%)) and clinical subtypes on mogamulizumab CL was evaluated by pop-PK analysis. Of the 129 ATL subjects included in the analysis, 73 subjects (56.6%) were classified as acute type; 37 subjects (28.7%), lymphomatous type; and 19 subjects (14.7%), chronic type. Of the 315 subjects diagnosed with CTCL; 173 subjects (54.9%) were classified with Mycosis Fungoides (MF) type and 142 subjects (45.1%) with Sezary Syndrome (SS) type. Neither disease type nor clinical subtype were identified as statistically significant covariates on mogamulizumab CL (Figure 11).

Figure 11. Effect of disease type (ATL or CTCL) and clinical subtype (acute, Lymphomatous and chronic type ATL. MF and SS type CTCL) on CL (Pop-PK Study 0761-bla-ctcl-pop-pk-r-en)



Special populations

Renal impairment. Mogamulizumab is an antibody with a molecular mass of 149 kDa and is therefore not expected to be excreted in urine. Therefore, formal studies in patients with renal impairment to study the effect of renal function are considered not necessary. The expected lack of effect of mild and moderate renal impairment is confirmed by the pop-PK analysis, in which 157, 80 and 2 patients (out of 444 patients in total) with mild, moderate or severe renal impairment were included.

Hepatic impairment. No direct effect of hepatic function on the pharmacokinetics of mogamulizumab is expected because antibodies are principally cleared by catabolism. Still, in the provided pop-PK study, mogamulizumab PK was shown to be dependent on hepatic function, albumin and AST. In this model, including 80 patients with mild, and 3 patients with moderate hepatic impairment (out of 444 patients in total), mogamulizumab exposure (i.e., $AUC_{(0-\tau),ss}$) was estimated to be approximately 61% and 129% of the reference for low and high albumin concentration, 119% and 77% of the reference for low and high AST, and there was a 12% reduction in subjects with mild to moderate hepatic impairment compared to subjects with normal hepatic function. Based on the exposure-response analysis, none of these factors affected either efficacy or safety and therefore it is agreed that no dose modification is needed under these conditions.

Gender. In the provided pop-PK study, PK data from 240 male (54.1%) and 204 (45.9%) female patients were included. Mogamulizumab PK was shown to be dependent on gender. In this model, mogamulizumab exposure (i.e., $AUC_{(0-\tau),ss}$ and C_{max}) at a 1 mg/kg dose was estimated to be approximately 30% higher in female compared to male subjects, i.e, estimated $AUC_{(0-\tau),ss}$ and Cmax were approximately 5217 mg.h/l and 10.1 mg/l in male, vs 6793 mg.h/l and 14.6 mg/l in female. Based on the exposure-response analysis, gender does not affect either efficacy or safety and therefore no dose modification is needed for male or female patients.

Race. Overall, patients with a White (224), Asian (93, of which 87 Japanese), Black or African American (74), Native American or Alaska Native (1), Pacific Islander (1) background were included in the pop-PK analysis. No marked differences in mogalizumab exposure were observed between these different ethnic populations.

Weight. Due to the body weight based dosing, $C_{min,ss}$ increases with increase in weight. The $C_{min,ss}$ after 1 mg/kg weight-based dosing was 2 fold higher in the highest weight quintile compared to the lowest weight quintile. Exposure-analyses indicated that, despite the somewhat lower exposure in low weight patients, this does not affect efficacy in a negative manner. With respect to safety, a trend is observed for increased safety at higher exposure at higher weight (i.e. for infections and infestations, as well as gastrointestinal disorders). Considering the nature of these safety issues, this is considered not sufficient to limit the dose ate a certain weight.

Age was not a statistically significant covariate for mogamulizumab PK. Clinical studies included subjects aged from 22 to 101 years old. A relatively large proportion of patients, i.e., 43,5%, was >65 years of age, which is in line with the relatively late age of occurrence of cutaneous T-cell lymphoma (CTCL).

Table 24: Older patients in PK trials

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	133/444	51/444	9/444

The PK of mogamulizumab in children and adolescents aged below 18 years has not been established.

Based on pop-PK data, the presence of ADAs did not significantly affect mogamulizumab CL. Further, disease type (ATL or CTCL) and clinical subtype (acute, lymphomatous and chronic type ATL, MF and SS type CTCL), ECOG performance status as well as CCR4 expression did not significantly affect mogamulizumab CL.

Pharmacokinetic interaction studies

Pharmacokinetic interaction studies have not been conducted (see discussion on clinical pharmacokinetics).

Pharmacokinetics using human biomaterials

Not applicable.

2.4.3. Pharmacodynamics

Mechanism of action

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 fucosylated antibodies.

Primary and Secondary pharmacology

Biomarker analysis

CCR4 expression (Study 0761-010)

Patients were enrolled in the study irrespective of their CCR4 expression status. Since mogamulizumab targets cells expressing CCR4, the potential clinical utility of testing for CCR4 expression status prior to treatment was investigated by assessing the relationship between CCR4 status and effect of treatment for primary and key secondary endpoints.

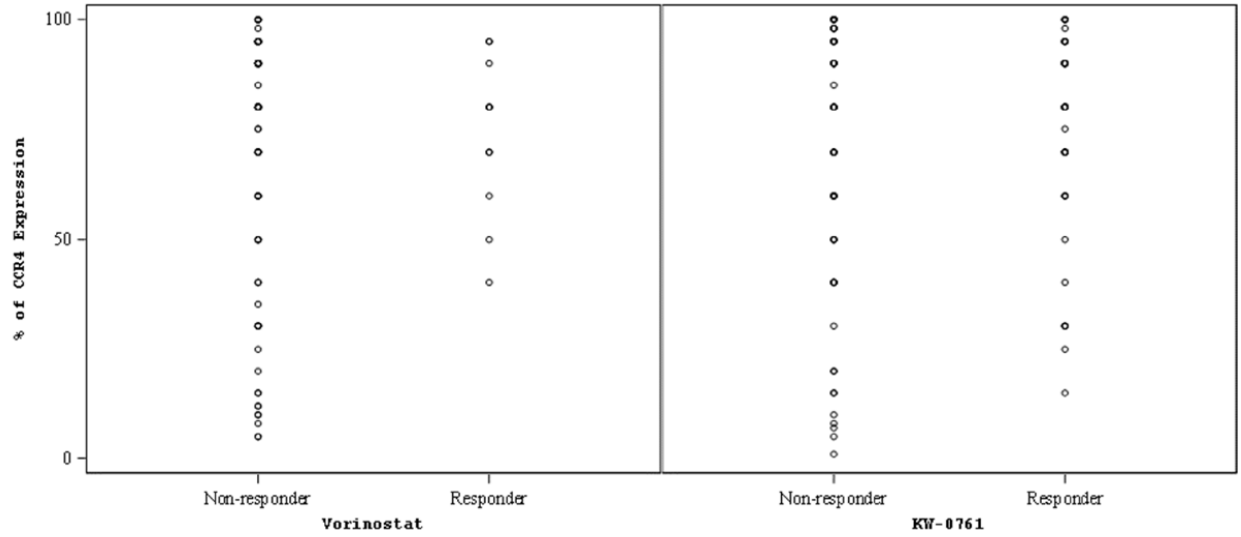
Analysis method: The CCR4 status of subject samples (formalin-fixed, paraffin embedded human tissue) from this trial were analyzed with a pre-planned analysis at the completion of the trial using the VENTANA CCR4 Assay with a 10% cutoff for CCR4 expression status (i.e., CCR4 percent positive malignant lymphocytes ≥ 10% versus CCR4 percent positive malignant lymphocytes < 10%). This cut off was based on literature using the same anti-CCR4 mAb (KM2160, which is a parent antibody of mogamulizumab) (Ishida, 2003; Ogura, 2014).

Patients analysed: Of the 372 patients in the ITT, 311 (84%) were analysed for CCR4 expression. Of these 311 subjects, 290 (78% of ITT) had biopsies that were evaluable for tumour CCR4 results (n=150 vorinostat and n=140 mogamulizumab).

Expression level: The median percent CCR4 expression level of the 290 patients with evaluable CCR4 on a continuous scale was 80% and the range was (1%, 100%). Approximately 97% (280 subjects) had ≥10% CCR4 expression. The remaining 10 subjects (3.4%) had <10% CCR4 expressing malignant lymphocytes.

Efficacy by CCR4 expression: The ORR as a function of percent CCR4 expression is depicted below.

Figure 12. Scatterplot of CCR4 Expression Percentage and Overall Response Rate Based on Investigator's Assessment CCR4 ITT Set.



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In patients expressing ≥10% CCR4, the Investigator based ORR was 45.3% (n=48) in the mogamulizumab arm vs. 10.8% (n=11) in the vorinostat arm. In the 10 patients expressing <10% CCR4, no patients obtained a CR or PR, resulting in an ORR of 0% in both arms. Two of the 6 patients with <10% CCR4 in the mogamulizumab arm had a response to treatment in individual compartments. Similar results for ORR in patients with <10% vs. ≥10% CCR4 expression were obtained with the independent review based analysis.

PFS of CCR4 expressing subjects receiving mogamulizumab was significantly longer than those of CCR4 expressing subjects receiving vorinostat (9.4 months [5.77, 14.03] vs 3.1 months [2.87, 4.63], respectively; HR=0.50 [0.37, 0.68], p < 0.0001;) (see section of Clinical Efficacy). Varying the CCR4 positivity cut points from 10% through 90% in order to select CCR4-expressing patients did not significantly increase median PFS of the mogamulizumab (CCR4-expressing) population as compared to the mogamulizumab (ITT) population.

CCR4 expression MF, SS and other CTCL subtypes in literature

A literature review was performed to investigate whether CCR4 is expressed in all subtypes of CTCL. Nineteen articles were identified between the years 2000-2016 containing relevant CCR4 expression data including MF, transformed MF, SS, pcALCL, PTCL unspecified, lymphomatoid papulosis, and other T-cell lymphomas. Prior published CCR4 prevalence has been reported from 79%-100% in MF patients, and the percentage of CCR4 positive lymphocytes ranged from 1-90%. Prior published CCR4 prevalence has been reported from 83%-100% in SS patients, and expression levels ranged from 0-100%. When CTCL subtypes other than MF and SS, were examined for CCR4 prevalence and expression using category A testing (similar to pivotal study 0761-010), prevalence ranged from 38-100% and expression from 10->50%, with the exception of other T cell tumours (15% prevalence, no data on CCR4 expression).

Natural ligands

Concentrations of CCL17/TARC and CCL22/MDC were analysed as a measure of clinical activity following treatment with mogamulizumab or vorinostat. There were no apparent differences in TARC/MDC concentration trajectories in responders versus non-responders based on the visual inspection of subject trajectories.

FGR3A polymorphisms

There did not appear to be apparent differences in response rate between FGR3A genotype categories (i.e. Phe/Phe, Phe/Val and Val/Val).

Secondary Pharmacodynamics

ECG / QT prolongation *Study 0761-010*

Electrocardiograms (12-lead) were performed at baseline, if clinically indicated during treatment, and at the End of Treatment visit. A total of 35 subjects in the vorinostat group and 104 subjects in the mogamulizumab group had valid assessments of QTcB and QTcF both at baseline and at the end of the randomized treatment period (difference from total treated due to subjects who crossed over from vorinostat to mogamulizumab and those continuing randomized treatment in both groups). Among these subjects, there were no marked mean or median changes from baseline or differences between treatment groups. Shifts to higher QTcB and QTcF values appeared to be somewhat more frequent among subjects receiving mogamulizumab compared to those receiving vorinostat; however, the differences in number of subjects assessed makes comparisons difficult.

Table 25 Shifts from Baseline in QTcF Interval (msec) During Randomized Treatment Period (Safety Analysis Set)

Treatment Arm	N[a]	Baseline	Highest Value Observed During Randomized Treatment Period			
			≤ 450	> 450 and ≤ 480	> 480 and ≤ 500	> 500
Vorinostat (N=186)	35	≤ 450	31 (88.6)	1 (2.9)	0	0
		> 450 and ≤ 480	2 (5.7)	0	0	0
		> 480 and ≤ 500	0	1 (2.9)	0	0
		> 500	0	0	0	0
Mogamulizumab (N=184)	104	≤ 450	76 (73.1)	6 (5.8)	1 (1.0)[b]	2 (1.9)[c]
		> 450 and ≤ 480	10 (9.6)	7 (6.7)	0	0
		> 480 and ≤ 500	1 (1.0)	0	1 (1.0)	0
		> 500	0	0	0	0

a: N=number of subjects with both baseline and post-baseline QTcF measurement.
b: Subject 503-004
c: Subjects 501-001 and 503-002
Source: Table 14.3.6.3, Listing 16.2.8.18

Among subjects in the mogamulizumab group with any post-baseline ECG assessments, including scheduled and unscheduled measurements, increases from baseline in QTcF of >30 msec were observed for 8 of 109 (7.3%) subjects and increases of >60 msec were observed for 3 (2.8%) subjects. No increases in QTcF of this magnitude were observed among subjects in the vorinostat group with post-baseline assessments (n=35). The three subjects in the mogamulizumab group with increases in QTcF of >60 msec.

During the crossover portion of study, Subject 125-004, who had a pre-treatment (prior to start of randomized treatment period) QTcF of 466 msec, had a value of 556 msec measured at an unscheduled visit at the start of crossover. This value was indicated as clinically significant and was reported as AE of electrocardiogram QT prolonged (Grade 3) on Day 183 of study (Day 1 of crossover treatment); the AE was considered possibly related to both vorinostat and mogamulizumab.

The relationship between mogamulizumab concentration and change in QT interval was evaluated using data from 43 subjects in Study 0761-009. There was no apparent relationship between mogamulizumab concentration and ΔQTcF.

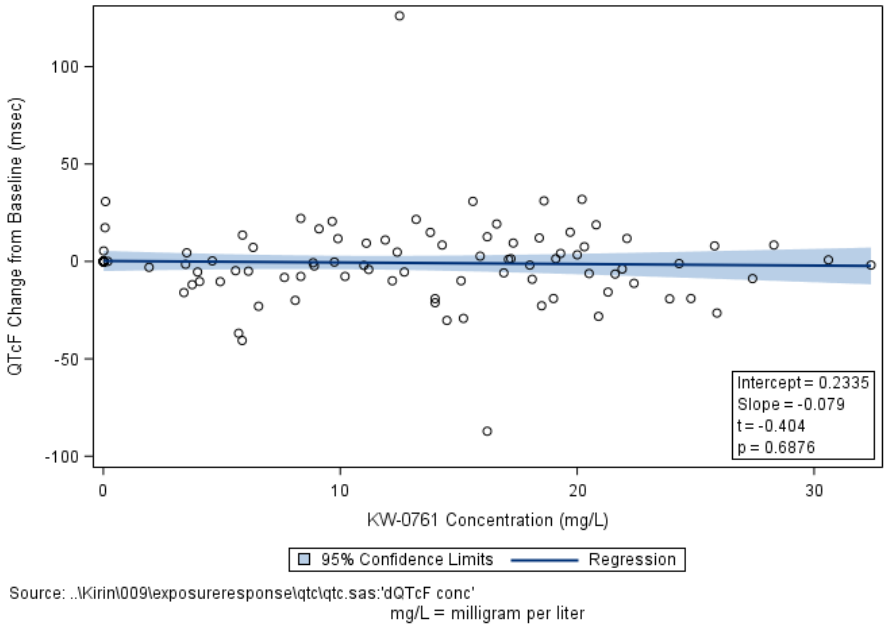


Figure 13 Relationship between Observed Mogamulizumab Concentrations and QTcF Change from Baseline (ΔQTcF) (Study 0761-009)

This result is expected as large molecule monoclonal antibodies such as mogamulizumab have low potential to cause QT prolongation.

Exposure-effect relationships

There was no apparent relationship between mogamulizumab exposure ($C_{min,1st}$ or $AUC_{(0-\tau)ss}$) and efficacy (PFS and ORR) with the exception of a modest relationship between $AUC_{(0-\tau)ss}$ and ORR. In the latter case, the number of overall responder increased with increasing exposure at steady state. With respect to safety, the Applicant concluded that there is no evidence that AEs were related to $C_{min,1st}$ or $AUC_{(0-\tau)ss}$. No apparent relationship was observed between mogamulizumab exposure and QT interval.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics (PK) of mogamulizumab was evaluated in adult patients with T-cell leukaemia-lymphoma (ATL) and CTCL over a dose range of 0.01 to 1 mg/kg administered as multiple doses of mogamulizumab every week or every 2 weeks, and included the recommended 1.0 mg/kg dose and regimen (days 1, 8, 15 and 22 for the first 28-day cycle and on Days 1 and 15 for subsequent 28-day cycles). The population PK analysis included 444 patients receiving mogamulizumab in six clinical trials. The exposure to mogamulizumab increased proportionally with dose over the dose range of 0.1 to 1.0 mg/kg.

Mogamulizumab is dosed via intravenous route and therefore is immediately and completely bioavailable. Based on a population PK analysis, the geometric mean [% coefficient of variation (CV%)] central volume of distribution (Vc) was 3.57 L (20.1%). This rather small distribution volume suggests that mogamulizumab is only minimally distributed to the extravascular tissues. These values are similar to those of other IgG1-class antibodies. Mogamulizumab PK was shown to be dose proportional up to a 1.0 mg/kg dose.

The metabolic pathway of mogamulizumab has not been characterised. Mogamulizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Based on a population PK analysis, the geometric mean (% coefficient of variation [CV%]) clearance (CL) is 12.0 mL/h (83.7%) and geometric mean elimination half-life (t1/2) is 17 days (65.5%).

Mogamulizumab exhibits linear PK from the dose in a dose range of 0.01 mg/kg to 1 mg/kg. Based on a population PK analysis, the steady-state concentrations of mogamulizumab were reached after 12 weeks of repeated dosing when administered using the recommended regimen, and systemic accumulation was 1.7-fold. On a power model analysis, no deviation from dose proportionality was evident.

The effect of renal impairment on the clearance of mogamulizumab was evaluated by a population PK analysis in patients with mild (creatinine clearance [CrCL] between 60 and 89; n= 157), moderate (CrCL between 59 and 30; n= 80), or severe renal impairment (CrCL less than 30 mL/min; n= 2). No clinically important differences in the clearance of mogamulizumab were found between patients with mild to severe renal impairment and patients with normal renal function.

The effect of hepatic impairment on the clearance of mogamulizumab was evaluated by a population PK analysis in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST; n= 80) or moderate (TB greater than 1.5 to 3 times ULN and any AST; n=3) hepatic impairment. No clinically important differences in the clearance of mogamulizumab were found between patients with mild to moderate hepatic impairment and patients with normal hepatic function. Mogamulizumab has not been studied in patients with severe hepatic impairment (TB greater than 3 times ULN and any AST).

The effects of various covariates on the PK s of mogamulizumab were assessed in population PK analyses. The following factors had no clinically important effect on the CL of mogamulizumab: age (range: 22 to 101 years), sex, ethnicity (other than Japanese, limited data are available in other ethnic populations), renal impairment, mild or moderate hepatic impairment, disease subtype (mycosis fungoides (MF) or Sézary Syndrome (SS)), degree of CCR4 expression or ECOG status, although it should be noted that patients with ECOG PS ≥2 were excluded from the clinical trials.

Exposure-Response analysis indicated that efficacy was not correlated with mogamulizumab exposure in the pivotal study. Efficacy, as measured by improvement in PFS based on investigator assessment, was not associated with increasing mogamulizumab exposure (see section 5.2 of the SmPC).

The majority of the samples was classified as non-conclusive for ADA, due to the fact that the mogalizumab concentrations exceeded the ADA assay tolerance levels. However, additional efficacy and PK data of the few patients classified as positive for ADAs do not indicate an effect on these parameters. The applicant is currently in the process of developing and validating a new ADA assay with a higher DTL. It is anticipated that with the enhanced ADA assay having an increased DTL, it may be possible to detect ADA in the subjects who were previously determined to be inconclusive using the current assay. If the data from subjects that were previously considered “inconclusive” will with the new test be classified as ADA positive, the Applicant should re-analyse the effect of ADA on safety, efficacy and mogamulizumab PK.

While, two of the 6 patients with <10% CCR4 in the mogamulizumab arm had a response to treatment in individual compartments, no confirmed responses were observed in the few MF/SS patients with CCR4 expression <10%. In addition, a larger PFS improvement was observed for mogamulizumab in ≥10% CCR4 expressing patients (6.3 months: 9.4 with mogamulizumab vs. 3.1 with vorinostat) compared to the ITT (4.6 month improvement), in which also patients with CCR4 expression <10% were included. Furthermore, in a PFS analysis by CCR4 expression cut off point, a trend for increasing PFS HR was observed with increasing CCR4 expression levels. In vitro, ADCC seems to be more effective with higher CCR4 intensity (number of receptors

per cell). The possible consequence of potential differences in CCR4 intensity in relation to efficacy in vivo, or to different CTCL subtypes is largely unknown.

The initially proposed target population included patients with all subtypes of CTCL. However, very limited data was provided for CTCL subtypes other than MF and SS. Further extrapolation of data in MF and SS to non-MF/SS subtypes was considered problematic (see discussion on clinical efficacy). As literature review indicated that the prevalence of CCR4 expression varied to a large extent in other subtypes of CTCL than observed in MF or SS in the pivotal trial. As the CCR4 is needed for mogamulizumab binding and thus activity, it was of concern that a lower prevalence of CCR4 positivity, to as low as 38% of the subjects, was published for other CTCL subtypes than MF and SS with similar category A testing as the pivotal trial. This low prevalence would imply that the majority of patients (within the subtype) do not express the target of mogamulizumab, and would not benefit from mogamulizumab treatment. Given the important role of CCR4 in the pathophysiology of MF/SS and the fact that all evaluable subjects tested positive for CCR4 at a minimum of 1% of skin infiltrating lymphocytes in the largest randomized-controlled trial ever conducted in MF/SS, it was concluded that MF and SS can be considered as inherent CCR4 positive diseases and that thus there is no need to restrict the indication to subjects with CCR4 positive disease nor to mention the target in the indication.

From the literature it is known that vorinostat could lower CCR4 expression *in vitro*. It was planned to analyse CCR4 expression levels in cross-over patients, but these results were not included in the dossier. During the second round of assessment, the applicant indicated that samples were only collected in 18% of patients and CCR4 expression levels were therefore not analysed. Nevertheless, the ORR data suggest that CCR4 expression levels in cross over patients were still sufficient to obtain a response on mogamulizumab.

Based on the data provided, for the AEs skin and subcutaneous tissue disorders, general disorders and administration site conditions as well as gastrointestinal disorders, a trend of increased reporting upon increased mogamulizumab exposure was noted. Considering the nature of these safety issues, this is considered not sufficient to limit the dose at a certain weight.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of POTELIGEO has been sufficiently characterised and all available information has been reflected in the SmPC.

The CHMP recommends that the applicant submits the report on the development and validation of the new enhanced ADA assay with a higher DTL which is anticipated to be available by 1Q-2Q 2019.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

In ex vivo tests using human cells that were CD4+ CD25+ CCR4+, mogamulizumab was shown to exhibit significant ADCC activity at concentrations of 0.1 to 10 µg/mL (Ishida, 2004). Based on a PK simulation using PK parameters calculated from relapsed CCR4-expressing ATL patients (n=27) in a Phase 2 study (0761-002), the proposed dosing regimen was predicted to result in minimum mogamulizumab serum concentrations ≥ 10 µg/mL.

Phase 1/2 study KW-0761-001

Open label, multi-center (US), dose escalation Phase 1/2 study KW-0761-001, investigated the safety, PK, maximum tolerated dose (MTD), dose limiting toxicities (DLTs), and preliminary efficacy of mogamulizumab

monotherapy in patients with CTCL (n=41; MF or SS) or PTCL (n=1) who had failed at least one prior systemic therapy.

No dose limiting toxicities were observed for doses up to and including 1.0 mg/kg, when administered once weekly for 4 weeks followed by administration every 2 weeks until progression at doses of 0.1, 0.3, and 1.0 mg/kg.

The number of patients per cohort (n=3) were too limited to select a dose based on efficacy results. One best overall response of CR was observed in the 0.1 mg/kg cohort (cohort 1) and one in the 1.0 mg/kg cohort of the dose escalation Phase. One additional CR was reported in extension Phase 2 of the study, in which 30 patients were treated in total. PR was observed in 3 patients in Phase 1 (1 patient in 0.1 mg/kg cohort, and 2 in 0.3 mg/kg cohort) and 8 patients in Phase 2 of the study.

2.5.2. Main study(ies)

Study 0761-010: a Phase 3, randomized, open-label, active controlled study to study evaluate efficacy and safety of mogamulizumab in patients with previously treated CTCL.

Methods

Pivotal study 0761-010 was an open-label, Phase 3, multinational, randomized, controlled study comparing mogamulizumab vs. vorinostat in subjects with CTCL who had failed at least one prior course of systemic therapy.

Study Participants

The key inclusion criteria of Study 0761-010 were:

- Male or female ≥18 years if age, except in Japan where patients must have been ≥20.
- Histologically confirmed diagnosis of MF or SS.
- Stage IB, II-A, II-B, III and IV (Olsen, 2011).
- Patients who had failed at least one prior course of systemic therapy.
- Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 1.
- Adequate haematological function:
    - Absolute neutrophil count (ANC) ≥ 1,500 cells/μL;
    - Platelets ≥ 100,000 cells/μL;
    - In patients with known bone marrow involvement, ANC ≥ 1,000 cells/μL and platelets ≥ 75,000 cells/μL.
- Adequate hepatic function:
    - Bilirubin ≤ 1.5 times the specific institutional upper limit of normal (ULN), except for patients with Gilbert's syndrome;
    - aspartate transaminase (AST) and alanine transaminase (ALT) each ≤ 2.5 x ULN or ≤ 5.0 x ULN in the presence of known hepatic involvement by CTCL.
- Adequate renal function:
    - serum creatinine ≤ 1.5 x ULN
    - or calculated creatinine clearance > 50 ml/min using the Cockcroft-Gault formula.

- Patients previously treated with anti-CD4 antibody or alemtuzumab were eligible provided their CD4+ cell counts were > 200/mm3.

The key exclusion criteria of Study 0761-010 were:

- Current evidence of large cell transformation (LCT).
- Diagnosed with a malignancy in the past two years. However, patients with nonmelanoma skin cancers, melanoma in situ, localized cancer of the prostate with current prostate-specific antigen of < 0.1 ng/mL, treated thyroid cancer or cervical carcinoma in situ or ductal/lobular carcinoma in situ of the breast within the past two years may have enrolled as long as there was no current evidence of disease.
- Clinical evidence of central nervous system (CNS) metastasis.
- Significant uncontrolled intercurrent illness.
- Known or tests positive for HIV, HTLV-1, hepatitis B or C disease; active herpes simplex or –zoster.
- Experienced allergic reactions to monoclonal antibodies or other therapeutic proteins.
- Known active autoimmune disease.
- Prior treatment with mogamulizumab or vorinostat. However, patients who were exposed to vorinostat for a short time, did not progress while on treatment, and did not have intolerable toxicity but were discontinued for another reason (e.g., comorbidity) were permitted to enter the study after discussion with the Medical Monitor.
- Had any therapy directed against the patient's underlying cancer or any investigational medications within four weeks of randomization (skin directed treatments, including topicals and radiation within two weeks of randomization). However, patients with rapidly progressive malignant disease may have been enrolled prior to this period after discussion with the Medical Monitor. Initiation of treatment with systemic/topical corticosteroids or increase in dose while on study was not permitted except to treat an infusion reaction/ acute rash.
- Patients on a stable dose of a low dose systemic corticosteroid (≤ 20 mg prednisone equivalent) or on a stable dose of medium or low potency topical corticosteroid for at least 4 weeks prior to the Pre-treatment Visit could continue use although the Investigator was to attempt to taper the use to the lowest dosage tolerable while on study.
- History of allogeneic transplant.
- Autologous hematopoietic stem cell transplant within 90 days of the Pre-treatment visit.
- Patients on any immunomodulatory drug for concomitant or intercurrent conditions other than T-cell lymphoma or who had received any of these agents within 4 weeks of treatment.

Treatments

Patients were randomized to receive one of the following study treatments:

- Mogamulizumab 1.0 mg/kg as an IV infusion over at least 1 hour on Days 1, 8, 15, and 22 of the first 28-day cycle and on Days 1 and 15 of subsequent 28-day cycles.

- Vorinostat (Zolinza) 400 mg orally once daily beginning on day 1 for 28-day cycles, administered on an outpatient basis.

For both study treatments, each treatment cycle was 28 days and treatment was to be continued until progressive disease, drug intolerance or unacceptable toxicity.

Cross-over eligibility: patients randomized to vorinostat who had received two full treatment cycles and demonstrated progression of disease; or were unable to tolerate treatment despite attempts of dose reduction, were allowed to cross-over to treatment with mogamulizumab.

Objectives

Primary objective

- To compare progression free survival of KW-0761 (mogamulizumab) vs. vorinostat for patients with relapsed or refractory CTCL

Secondary objectives

- To compare the overall response rate of KW-0761 versus vorinostat in patients with relapsed or refractory CTCL;
- To evaluate and compare improvements in QoL measurements, Skindex-29, FACT-G, and EQ-5D-3L.
- To evaluate and compare improvements in the Pruritus Evaluation (Likert scale & Itchy QoL).
- To estimate the duration of response for both treatment arms for those patients with relapsed or refractory CTCL responding to treatment;
- To determine if patients who relapse on vorinostat can achieve response upon cross-over to treatment with KW-0761.
- To further assess the safety of KW-0761;
- To describe the immunogenicity of KW-0761.

Exploratory objectives

- To compare the overall survival of KW-0761 versus vorinostat for patients with relapsed or refractory CTCL;
- To conduct exploratory evaluation of KW-0761 exposure-response relationships.

Outcomes/endpoints

Primary efficacy endpoint

- Progression-free survival (PFS) as assessed by the Investigator based on the global composite response score, i.e. response in each compartment (skin, blood, lymph nodes and viscera; *Olsen, 2011*).

Secondary efficacy endpoints

- Overall response rate (ORR: CR or PR) as assessed by the Investigator.
- Change in Skindex-29 score from baseline through the 6-month assessment
- Change in FACT-G total score from baseline through the 6-month assessment
- Change in EQ-5D-3L index score from baseline through the 6-month assessment
- PFS as assessed by independent review (IR)
- ORR by IR
- Best overall response

- Duration of response (DOR; INV and IR based)
- Time to response (TTR)
- ORR in the crossover portion of the trial
- Changes from baseline in Skindex-29, FACT-G, and EQ-5D-3L at other time points
- Changes from baseline in Pruritus Evaluation (Likert scale & Itchy QoL)

Exploratory efficacy endpoints

- Overall survival (OS)
- Time to treatment failure (TTF)

Response in skin and blood was evaluated every 4 weeks. Response in lymph nodes and viscera was evaluated at 4 weeks, then every 8 weeks in the first year, and then every 16 weeks thereafter.

Sample size

The reference median PFS for vorinostat was assumed to be 169 days. The median PFS for mogamulizumab therapy was predicted as 254 days, a 50% improvement over this reference median. A total of 255 PFS events was required given 90% power, and a total sample size of 288 patients was considered necessary for 255 PFS events to occur within the projected 36 months of the trial. Applying a 10% inflation factor to this total (about 29 patients) to take into account those patients that may be lost to follow-up prior to documented progression, a total of 317 patients were planned to be enrolled.

Randomisation

Eligible patients were randomized 1:1 to either mogamulizumab or vorinostat. The randomization to treatment groups was stratified by disease type (MF or SS) and disease stage (IB/II or III/IV).

Blinding (masking)

This was an open-label study. Blinding of treatment groups was not considered appropriate due to different routes of administration (IV vs. oral) and different side effect profiles.

Statistical methods

Efficacy analysis sets

Intent-to-treat (ITT): Includes all patients randomized to a therapy (mogamulizumab or vorinostat) and assigned a study number.

Efficacy evaluable set: Includes all patients who received the first cycle of treatment (at least one dose) and who had a baseline tumour assessment and at least one post-baseline assessment for response.

Primary endpoint analysis

The primary efficacy variable was PFS based upon the assessment by the Investigator, defined as the time from the day of randomization to a treatment arm until documented PD or death due to any cause.

The primary comparison of PFS between mogamulizumab and vorinostat was performed on the ITT set based upon the results of the on-site investigator's assessment using a stratified Log-rank test at the one-sided 2.5% significance level. A Cox proportional hazard model with treatment, disease type, disease stage, and region

(U.S., Japan, and Rest of World) as covariates was used to assess the magnitude of the treatment difference in PFS.

PFS censoring rules

The following censoring rules were applied:

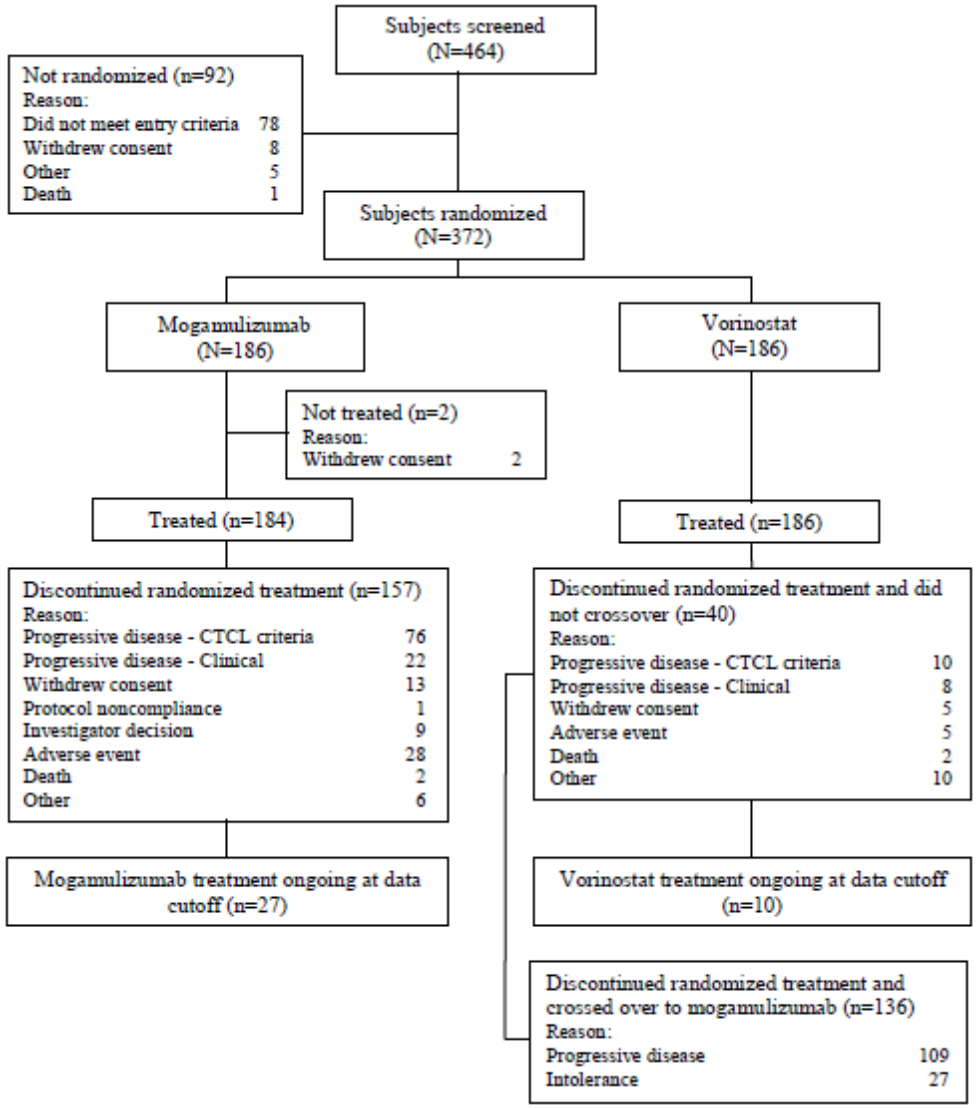
- In the event that a randomized patient withdrew from the study for any reason before documented progression, the time from the day of randomization to the last post-baseline tumour assessment from any compartment (skin, blood, bone marrow, lymph node, or viscera) was used as a censored time point.
- For patients who were randomized to a treatment arm but had an unknown baseline assessment for a compartment, the PFS time was censored at the randomization date if there was no post-baseline tumour assessment for that compartment or if there was any evidence of lymphoma in that compartment at post-baseline evaluation.
- For patients randomized to a treatment arm who withdrew from treatment prior to the first post-baseline tumour assessment for any reason other than disease progression, the PFS time was censored at the last documented visit.
- For patients who initiated a new anticancer therapy (including crossover to mogamulizumab) in the absence of a PFS event, the PFS time was censored at the last tumour 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 data cut-off date for primary analysis, the PFS time was censored at the date of the last tumour assessment (from any compartment) prior to data cut-off.

Results

Participant flow

A total of 372 patients were randomized (n=186 mogamulizumab; n=186 vorinostat) and included in the ITT analysis set.

Figure 14: Disposition of Patients – Study 0761-010.



Recruitment

The study was initiated in Dec 2012 (first dose). The clinical data cut-off date was 31 Dec 2016.

Conduct of the study

The original study protocol was dated 19 Jun 2012 and was subsequently amended 8 times. Protocol deviations were observed in a large proportion of patients in both arms (56.5%). No substantial imbalances in type of protocol deviations were observed between treatment arms. The protocol deviations and amendments are not considered to have impacted the analysis or interpretation of most important efficacy outcomes.

Baseline data

Table 26: Baseline Demographic Characteristics (ITT set)

Variable Statistic/Category	Vorinostat N=186 n (%)	Mogamulizumab N=186 n (%)	Total N=372 n (%)
Age (years) at Screening			
Mean (Std Dev)	63.3 (12.58)	62.8 (13.34)	63.0 (12.95)
Median	65.0	63.5	64.0
Min, Max	25, 89	25, 101	25, 101
Age Group (n, %)			
< 65 years	89 (47.8)	99 (53.2)	188 (50.5)
≥ 65 years	97 (52.2)	87 (46.8)	184 (49.5)
Gender (n, %)			
Male	107 (57.5)	109 (58.6)	216 (58.1)
Female	79 (42.5)	77 (41.4)	156 (41.9)
Race (n, %)			
White	135 (72.6)	125 (67.2)	260 (69.9)
Asian	7 (3.8)	12 (6.5)	19 (5.1)
Black or African American	13 (7.0)	24 (12.9)	37 (9.9)
Native American or Alaska Native	1 (0.5)	0	1 (0.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.5)	1 (0.3)
Other	5 (2.7)	0	5 (1.3)
Not Applicable[a]	25 (13.4)	24 (12.9)	49 (13.2)
Ethnicity (n, %)			
Hispanic or Latino	9 (4.8)	6 (3.2)	15 (4.0)
Not Hispanic or Latino	152 (81.7)	155 (83.3)	307 (82.5)
Not Applicable[a]	25 (13.4)	23 (12.4)	48 (12.9)
Missing	0	2 (1.1)	2 (0.5)
Region (n, %)			
US	103 (55.4)	98 (52.7)	201 (54.0)
Japan	6 (3.2)	9 (4.8)	15 (4.0)
Rest of World (Europe/Australia)	77 (41.4)	79 (42.5)	156 (41.9)
Europe	70 (37.6)	70 (37.6)	140 (37.6)
Australia	7 (3.8)	9 (4.8)	16 (4.3)
Body weight (kg)			
n	184	186	370
Mean (Std Dev)	79.21 (16.949)	78.72 (17.686)	78.96 (17.302)
Median	78.75	78.00	78.44
Min, Max	43.5, 120.2	47.3, 149.7	43.5, 149.7

a: Not applicable = not reported for those countries that do not allow race/ethnicity to be collected.

Max=maximum; Min=minimum; Std Dev=standard deviation;

In the ITT set, 54.8% of patients had MF, and 45.2% SS. Most patients had stage III or IV (62.4%), and the median time from initial diagnosis was 3.1 years. CCR4 expression was ≥ 10% in 75.3% of patients (and the analysis was missing in 22%).

Table 27. Baseline Disease Characteristics (ITT Set).

Variable Statistic/Category	Vorinostat N=186 n (%)	Mogamulizumab N=186 n (%)	Total N=372 n (%)
ECOG Performance Status[a] (n, %)			
0	104 (55.9)	106 (57.0)	210 (56.5)
1	82 (44.1)	78 (41.9)	160 (43.0)
2	0	2 (1.1)[b]	2 (0.5)
Time from Initial Diagnosis (months)[c]			
n	186	183	369
Mean (Std Dev)	53.92 (55.929)	62.12 (65.830)	57.99 (61.095)
Median	35.43	41.03	37.63
Min, Max	1.0, 306.4	1.2, 362.3	1.0, 362.3
Disease Type (n, %)			
Mycosis Fungoides (MF)	99 (53.2)	105 (56.5)	204 (54.8)
Sézary Syndrome (SS)	87 (46.8)	81 (43.5)	168 (45.2)
Current Clinical Stage (n, %)			
IB	27 (14.5)	15 (8.1)	42 (11.3)
IIA	22 (11.8)	21 (11.3)	43 (11.6)
IIB	23 (12.4)	32 (17.2)	55 (14.8)
IIIA	9 (4.8)	9 (4.8)	18 (4.8)
IIIB	7 (3.8)	13 (7.0)	20 (5.4)
IVA1	82 (44.1)	73 (39.2)	155 (41.7)
IVA2	12 (6.5)	19 (10.2)	31 (8.3)
IVB	4 (2.2)	4 (2.2)	8 (2.2)
Stratification:			
IB or II	72 (38.7)	68 (36.6)	140 (37.6)
III or IV	114 (61.3)	118 (63.4)	232 (62.4)
Current Sites of Disease (n, %)			
Skin	186 (100.0)	186 (100.0)	372 (100.0)
Nodes	122 (65.6)	124 (66.7)	246 (66.1)
Viscera	3 (1.6)	3 (1.6)	6 (1.6)
Blood	122 (65.6)	122 (65.6)	244 (65.6)
Other (includes Bone Marrow)	7 (3.8)	13 (7.0)	20 (5.4)
CCR4 Expression Status (n, %)			
≥10% CCR4 expression	146 (78.5)	134 (72.0)	280 (75.3)
<10% CCR4 expression	4 (2.2)	6 (3.2)	10 (2.7)
Missing (no available sample or test failure)	36 (19.4)	46 (24.7)	82 (22.0)
LDH (U/L) at Baseline			
n	183	184	367
Mean (Std Dev)	302.2 (187.32)	341.2 (250.00)	321.7 (221.54)
Median	245.0	255.0	248.0
Min, Max	121, 1432	136, 1986	121, 1986

Except for one patient, all randomized patients had received at least one prior systemic CTCL therapy. The vast majority (>80%) had received more than one prior systemic therapy. When specified by disease stage it is noted that stage IB/II subjects were the most heavily pretreated population enrolled in the study.

Table 28. Prior CTCL Therapy (ITT Set).

Variable Statistic/Category	Vorinostat N=186 n (%)	Mogamulizumab N=186 n (%)	Total N=372 n (%)
Received Any Prior CTCL Therapy (skin-directed or systemic)	186 (100.0)	186 (100.0)	372 (100.0)
Type of Prior Therapy Received (n, %)			
Skin-directed therapies			
PUVA	63 (33.9)	80 (43.0)	143 (38.4)
Topical Steroid	65 (34.9)	67 (36.0)	132 (35.5)
Bexarotene-Topical	6 (3.2)	11 (5.9)	17 (4.6)
Systemic therapies			
Bexarotene	110 (59.1)	107 (57.5)	217 (58.3)
Interferon-a	94 (50.5)	81 (43.5)	175 (47.0)
Methotrexate	73 (39.2)	69 (37.1)	142 (38.2)
Extracorporeal Photopheresis (ECP)	65 (34.9)	71 (38.2)	136 (36.6)
Romidepsin	32 (17.2)	45 (24.2)	77 (20.7)
Nitrogen Mustard	40 (21.5)	28 (15.1)	68 (18.3)
Doxorubicin HCL Liposome	19 (10.2)	23 (12.4)	42 (11.3)
Pralatrexate	13 (7.0)	14 (7.5)	27 (7.3)
Carmustine	13 (7.0)	13 (7.0)	26 (7.0)
Brentuximab Vedotin	4 (2.2)	16 (8.6)	20 (5.4)
Denileukin Diftitox	3 (1.6)	5 (2.7)	8 (2.2)
Chlorambucil	4 (2.2)	3 (1.6)	7 (1.9)
Etoposide	4 (2.2)	3 (1.6)	7 (1.9)
IL-12	1 (0.5)	0	1 (0.3)
Other (skin-directed and systemic)	121 (65.1)	131 (70.4)	252 (67.7)
Number of Prior Systemic Regimens Received			
0	1 (0.5)	0	1 (0.3)
1	40 (21.5)	28 (15.1)	68 (18.3)
2	38 (20.4)	40 (21.5)	78 (21.0)
3	37 (19.9)	40 (21.5)	77 (20.7)
4	18 (9.7)	22 (11.8)	40 (10.8)
5	21 (11.3)	12 (6.5)	33 (8.9)
≥ 6	31 (16.7)	44 (23.7)	75 (20.2)
Mean (Std Dev)	3.4 (2.34)	4.1 (3.17)	3.7 (2.80)
Median	3.0	3.0	3.0
Min, Max	0, 14	1, 18	0, 18
Best Response to Last Systemic CTCL Therapy Prior to Study Entry (n, %)			
Complete response or partial response	69 (37.1)	62 (33.3)	131 (35.2)
Stable disease	32 (17.2)	46 (24.7)	78 (21.0)
Progressive disease	67 (36.0)	59 (31.7)	126 (33.9)
Not applicable	3 (1.6)	2 (1.1)	5 (1.3)
Unknown	15 (8.1)	17 (9.1)	32 (8.6)
Prior Radiotherapy (n, %)			
No	134 (72.0)	131 (70.4)	265 (71.2)
Yes	52 (28.0)	55 (29.6)	107 (28.8)

Note: Percentage was calculated by using the number of subjects in the column heading as the denominator.
CTCL=cutaneous T-cell lymphoma; HCL=hydrochloride; IL-12=interleukin 12; max=maximum; min=minimum; PUVA=psoralen plus ultraviolet light of A wavelength; Std Dev=standard deviation

Table 29 Number of prior systemic therapies by disease stage

	Early Stage (IB/II)		Late Stage (III/IV)		Total	
	Vorinostat N=72	Moga N=68	Vorinostat N=114	Moga N=118	Vorinostat N=186	Moga N=186
Variable						
Number of Prior CTCL Therapies (n, %)						
0	1 (1.4)	0	0	0	1 (0.5)	0
1	15 (20.8)	12 (17.6)	25 (21.9)	16 (13.6)	40 (21.5)	28 (15.1)
2	12 (16.7)	13 (19.1)	26 (22.8)	27 (22.9)	38 (20.4)	40 (21.5)
3	16 (22.2)	17 (25.0)	21 (18.4)	23 (19.5)	37 (19.9)	40 (21.5)
4	9 (12.5)	3 (4.4)	9 (7.9)	19 (16.1)	18 (9.7)	22 (11.8)
5	5 (6.9)	4 (5.9)	16 (14.0)	8 (6.8)	21 (11.3)	12 (6.5)
>=6	14 (19.4)	19 (27.9)	17 (14.9)	25 (21.2)	31 (16.7)	44 (23.7)
Statistics/Category						
Number of Prior CTCL Therapies						
n	72	68	114	118	186	186
Median	3.0	3.0	3.0	3.0	3.0	3.0
Minimum	0	1	1	1	0	1
Maximum	8	18	14	15	14	18

Concomitant medication

Use of premedications recommended prior to infusion of mogamulizumab (acetaminophen or paracetamol orally and diphenhydramine 50 mg iv or equivalent antihistamine) was more frequent in the mogamulizumab arm. Other medications used by a higher percentage of patients in the mogamulizumab arm were primarily anti-infective agents. A higher rate of anti-propulsive use was observed for patients receiving vorinostat (23.7%) compared to those receiving mogamulizumab (3.3%) during randomized treatment. The use of steroids was comparable between subjects randomized to mogamulizumab and those randomized to vorinostat, but higher in the stage III/IV subjects (48%) than in the stage IB/II subjects (19%). Among the Safety Analysis Set, pruritus medication use was similar for the two treatment groups: 136 (73.1%) patients in the vorinostat group and 140 (76.1%) patients in the mogamulizumab group.

Numbers analysed

The ITT population included 372 patients: 186 in the mogamulizumab arm, and 186 in the vorinostat arm. The Efficacy Evaluable Set included 361 patients.

Outcomes and estimation

Primary endpoint - PFS by investigator

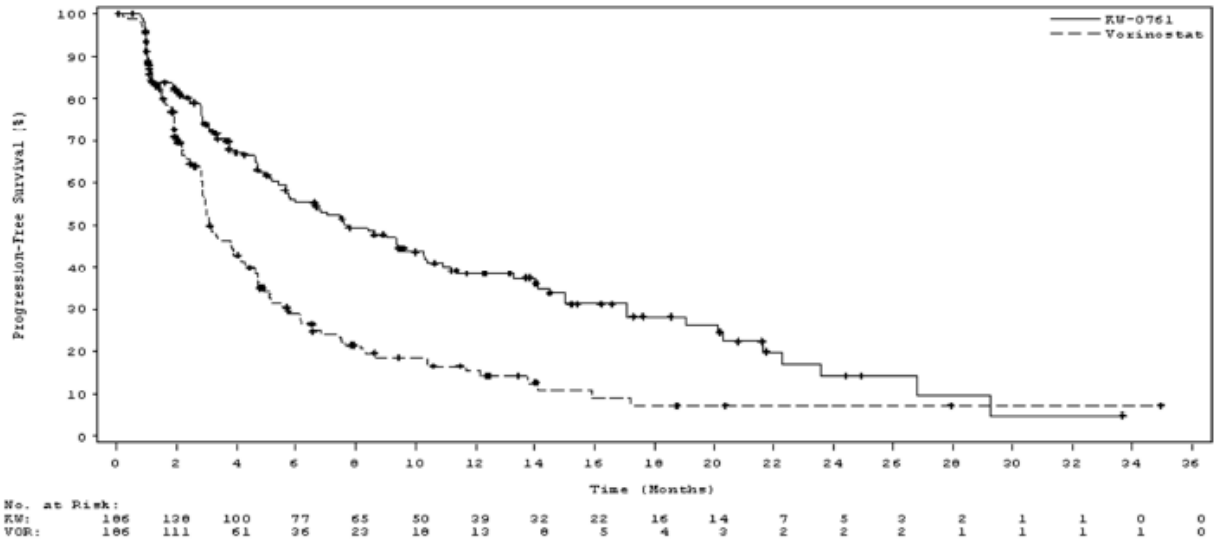
At the time of data cut-off (31 Dec 2016), a total of 241 PFS events had been observed based on investigator's assessment, 110 (59.1% of patients) in the mogamulizumab group and 131 (70.4%) in the vorinostat group.

Table 30. Summary of PFS by Investigator and IR (ITT Set)

	Investigator's Assessment		Independent Review	
	Vorinostat N=186	Mogamulizumab N=186	Vorinostat N=186	Mogamulizumab N=186
Number of Subjects with PFS Event (n, %)	131 (70.4)	110 (59.1)	122 (65.6)	110 (59.1)
Earliest Contributing Event:				
Progressive disease	128 (68.8)	104 (55.9)	118 (63.4)	108 (58.1)
Death	3 (1.6)	6 (3.2)	4 (2.2)	2 (1.1)
Number of Subjects Censored (n, %)	55 (29.6)	76 (40.9)	64 (34.4)	76 (40.9)
Progression-free Survival (Months)				
Kaplan-Meier Estimate of PFS				
Q1	1.9	2.9	1.9	2.9
Median (95% CI)[a]	3.10 (2.87, 4.07)	7.70 (5.67, 10.33)	3.83 (3.00, 4.70)	6.70 (5.63, 9.37)
Q3	6.6	20.1	8.2	20.8
Treatment Comparison (Mogamulizumab vs. Vorinostat)[b]				
Hazard ratio (95% CI)	0.53 (0.41, 0.69)		0.64 (0.49, 0.84)	
Log rank p-value	<.0001		0.0007	
Rate (%) of Being Alive without Progression for at least[c]				
6 months (95% CI)	28.8 (21.6, 36.3)	55.3 (47.1, 62.6)	35.1 (27.4, 42.9)	54.7 (46.6, 62.1)
12 months (95% CI)	15.3 (9.5, 22.3)	38.3 (30.2, 46.4)	22.1 (15.4, 29.7)	37.1 (29.3, 44.9)
18 months (95% CI)	7.2 (2.7, 14.5)	28.0 (19.8, 36.8)	13.8 (7.0, 22.8)	27.9 (20.1, 36.3)
24 months (95% CI)	7.2 (2.7, 14.5)	14.1 (6.4, 24.8)	13.8 (7.0, 22.8)	19.6 (11.5, 29.3)
30 months (95% CI)	7.2 (2.7, 14.5)	4.7 (0.5, 17.7)	10.3 (3.9, 20.4)	19.6 (11.5, 29.3)

a: 95% CIs are obtained from SAS proc lifetest using loglog 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.
c: Kaplan-Meier estimate.
CI=confidence interval; max=maximum; min=minimum; PFS=Progression-free Survival

Figure 15. Kaplan-Meier Curve of PFS by Investigator (ITT set)



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

Censoring: The majority of censored observations were due to patients who discontinued 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.

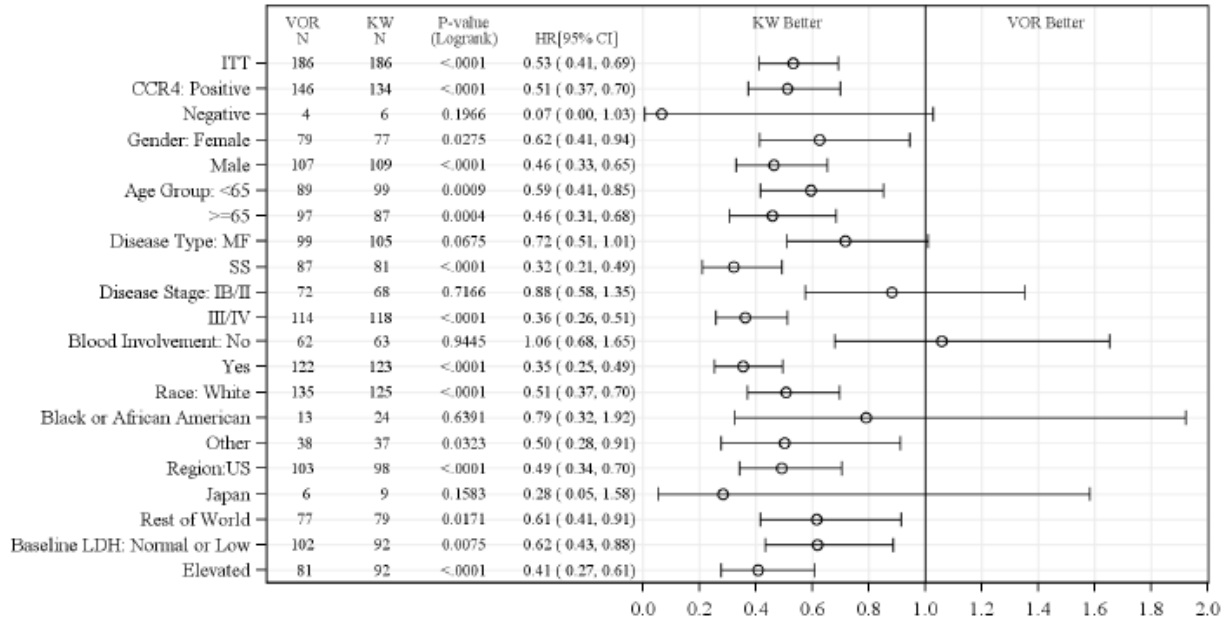
When specified for disease stage it was noted that an AE was a far less common reason for censoring in subjects with less advanced disease (stage IB/II) treated with mogamulizumab (11.1%) compared to subjects with advanced disease (stage III/IV, 22.4%). In contrast, compared to stage III/IV subjects, a higher percentage of stage IB/II subjects treated with mogamulizumab were censored due to withdrawal of consent (18.5% vs. 8.2%

for stage IB/II vs. stage III/IV, respectively), withdrawal prior to first post-baseline assessment (7.4% vs. 2%) and “other reasons” (14.8% vs. 2%).

Sensitivity analyses: Four sensitivity analyses were performed for PFS during the randomized treatment period based on Investigator’s assessment and the ITT Set. Across all analyses, the results favoured mogamulizumab with a HR between 0.52-0.72. However, a difference in HR between stage IB/II disease and stage III/IV disease, and between subpopulations with or without blood involvement is notable (see also Table 31) .

Subgroup analyses: A forest plot of hazard ratios for PFS by subgroup is shown in Figure 16.

Figure 16. Forest Plot of HR’s of PFS by Investigator for Pre-defined Subgroups (ITT Set).



Note: CCR4 positive indicates ≥10% CCR4 expressing malignant lymphocytes and CCR4 negative indicates <10% CCR4 expressing malignant lymphocytes
KW=KW-0761 (mogamulizumab); VOR=vorinostat; ITT=intent-to-treat set; CCR4=CC chemokine receptor 4; MF=mycosis fungoides; SS=Sézary syndrome; LDH=lactate dehydrogenase; US=United States

Table 31 Summary of PFS during randomized treatment period based on investigator's assessment by disease Stage and blood involvement

Disease Stage, Blood Involvement = IB/II, Yes	Vorinostat N=22	Mogamulizumab N=17
Number of Subjects with PFS Event (n, %)	18 (81.8)	10 (58.8)
Number of Subjects Censored (n, %)	4 (18.2)	7 (41.2)
Kaplan-Meier Estimate of PFS (months)		
Median (95% CI)*	2.17 (1.40, 4.13)	8.43 (2.07, 9.63)
Hazard Ratio (95% CI)	0.48 (0.20, 1.23)	
P value	0.1009	
Disease Stage, Blood Involvement = IB/II, No	**Vorinostat N=49**	**Mogamulizumab N=51**
Number of Subjects with PFS Event (n, %)	28 (57.1)	31 (60.8)
Number of Subjects Censored (n, %)	21 (42.9)	20 (39.2)
Kaplan-Meier Estimate of PFS (months)		
Median (95% CI)*	4.63 (2.97, 8.67)	4.67 (2.83, 6.67)
Hazard Ratio (95% CI)	1.12 (0.67, 1.89)	
P value	0.5414	
Disease Stage, Blood Involvement = III/IV, Yes	**Vorinostat N=100**	**Mogamulizumab N=106**
Number of Subjects with PFS Event (n, %)	74 (74.0)	60 (56.6)
Number of Subjects Censored (n, %)	26 (26.0)	46 (43.4)
Kaplan-Meier Estimate of PFS (months)		
Median (95% CI)*	3.17 (2.83, 4.07)	11.40 (7.63,17.07)
Hazard Ratio (95% CI)	0.34 ((0.23, 0.49)	
P value	<0.0001	
Disease Stage, Blood Involvement = III/IV, No	**Vorinostat N=13**	**Mogamulizumab N=12**
Number of Subjects with PFS Event (n, %)	10 (76.9)	9 (75.0)
Number of Subjects Censored (n, %)	3 (23.1)	3 (25.0)
Kaplan-Meier Estimate of PFS (months)		
Median (95% CI)*	2.87 (1.90, 6.80)	5.07 (0.97, 9.00)
Hazard Ratio (95% CI)	0.53 (0.19, 1.45)	
P value	0.0985	

Cross-over population: For the 133 patients who crossed over from vorinostat and received mogamulizumab, median PFS calculated from the first dose of mogamulizumab was 8.87 months (95% CI: 5.37, 14.77).

Secondary endpoints

The below table summarises ORR and DOR, and response by compartment. The study demonstrated statistically significant improvements in ORR and response by compartment in the blood, skin, and lymph nodes as compared to vorinostat. Response in the viscera could not be evaluated due to limited efficacy data in subjects with visceral involvement; the benefit-risk of mogamulizumab in subjects with visceral involvement is currently undetermined due to lack of data.

Table 32: Response during randomised treatment period in study 0761-010 (intent-to-treat)

	Mogamulizumab N=186	**Vorinostat N=186**
Overall response rate (confirmed CR + PR, %)	28.0	4.8
95% CI	(21.6, 35.0)	(2.2, 9.0)
P-value[a]	<.0001	
Duration of response (months)		
Median (95% CI)	14.1 (9.4, 19.2)	9.13 (4.7,-)
Response by compartment		
Blood	n=124	n=125
Response rate (confirmed CR + PR, %)	66.9	18.4
95% CI	(57.9, 75.1)	(12.0, 26.3)
P-value[a]	<0.0001	
Skin	n=186	n=186
Overall response rate (confirmed CR + PR, %)	41.9	15.6
95% CI	(34.8, 49.4)	(10.7, 21.6)

P-value[a]	<.0001	
Lymph nodes	n=136	n=133
Overall response rate (confirmed CR + PR, %)	15.4	3.8
95% CI	(9.8, 22.6)	(1.2, 8.6)
P-value[a]	0.0008	
Viscera	n=6	n=4
Overall response rate (confirmed CR + PR, %)	0	0
95% CI	(0.0, 45.9)	(0.0, 60.2)

Note: Overall response rate is based on Global Composite Response score.
[a]: P-value was obtained from Cochran-Mantel-Haenszel test adjusting for disease type, disease stage, and region.
CI=confidence interval; CR=complete response; PR=partial response

ORR was than 28.0% in the mogamulizumab arm vs 4.8 in the vorinostat arm %; risk difference=23.1; 95% CI: 12.8, 33.1; p<0.0001), MF (21·0% vs 7·1%, respectively; P=0·0042) and SS (37·0% vs 2·3%; P<0·0001). duration of response was at 14.07 months (95% CI: 9.43, 19.17) for the mogamulizumab arm vs 9.13 months (95% CI; 4.67,-) for the vorinostat arm.

Table 33: Confirmed response rate, best overall response, and duration of response - by disease compartment

	Vorinostat		Mogamulizumab	
	N	n (%)	N	n (%)
All subjects	186	9 (4.8)	186	52 (28.0)
Disease Type				
MF	99	7 (7.1)	105	22 (21.0)
SS	87	2 (2.3)	81	30 (37.0)
Disease Stage				
IB/IIA	49	5 (10.2)	36	7 (19.4)
IIB	23	1 (4.3)	32	5 (15.6)
III	16	0 (0)	22	5 (22.7)
IV	98	3 (3.1)	96	35 (36.4)
Compartment				
Skin	186	29 (15.6)	186	78 (41.9)
Blood	123	23 (18.7)	122	83 (68.0)
Lymph nodes	122	5 (4.1)	124	21 (16.9)
Viscera	3	0 (0)	3	0 (0)

Sources: 0761-010-r-en, Table 11.4.2-1, and 043-0761-010-ADHOC_ORR_by_Each_Stage

Quality of Life

A statistically significant difference in MID based categorical QoL change from baseline in favour of mogamulizumab measured at Cycle 1,3,5,7,9,11 was observed at:

- *Skindex summary score:* Cycle 5
- *FACT-G total score*: Cycle 1,3 and 5
- *EQ-5D-3L*: Cycle 5 and 11
- *Itchy QoL & Pruritus Likert*: No statistically significant difference at any pre-specified time point, except Cycle 3 in the Emotions domain.
- *Responder analysis*: Significant difference in Skindex emotions domain (63.2% mogamulizumab, 43.6% vorinostat, p=0.0451), Skindex symtoms domain (67.1% vs. 47.5%, p=0.0402) and EQ-5D-3L VAS (43.5% vs. 23.7%, p=0.0356).

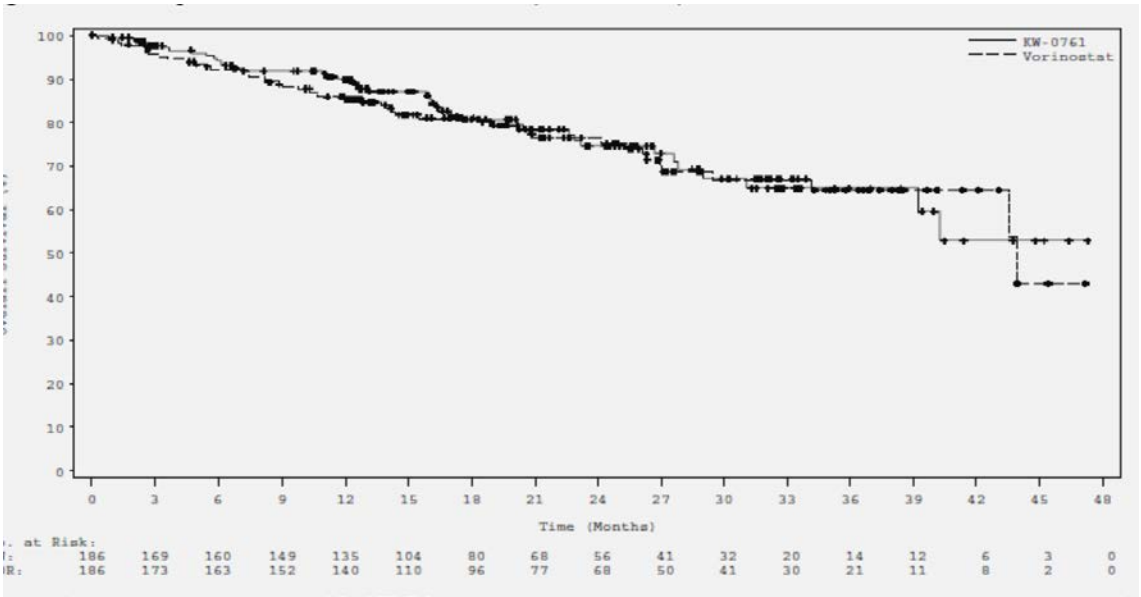
The results from the Skindex Symptoms Scale for disease-specific symptoms showed statistically significant longitudinal, between-group differences at cycles 3, 5, 7 and 9 favoring mogamulizumab ($p<0.05$);statistically significant differences favouring mogamulizumab in the proportions of patients who improved, remained stable or declined based on the minimum important difference (MID) threshold at cycles 3, 5 and 7 ($p<0.05$); and median time to clinically meaningful deterioration of 27 months vs 7 months, favoring mogamulizumab (non-significant). Based upon the MID thresholds established at each cycle,disease-specific symptoms improved in 47.8% (cycle 1) 61.1% (cycle 3), 64.5% (cycle 5),67.1% (cycle 7), 67.7% (cycle 9), and 84.1% (cycle 11) of mogamulizumab-treated subjects.

The FACT-G Functional Well-Being instrument for cancer-specific functioning results showed differences favoring mogamulizumab at cycles 3, 7 and 9 ($p<0.05$); statistically significant differences favoring mogamulizumab in the proportions of patients who improved, remained stable or declined based on the MID threshold at cycle 3 ($p<0.05$); and median time to clinically meaningful deterioration of 8 months vs 4 months, favoring mogamulizumab ($p<0.05$). Based upon the MID thresholds established at each cycle, cancer-specific functioning was improved in 31.5% (cycle 1), 39.2% (cycle 3), 39.4% (cycle5), 45.8% (cycle 7), 46.3% (cycle 9), and 41.7% (cycle 11) of mogamulizumab-treated subjects.

Exploratory endpoints

Overall survival (OS)
At the time of data cut-off for analysis, 23.4% (87/372) of randomized subjects had died (47, vorinostat; 40, mogamulizumab).

Figure 17: Kaplan-Meier of OS (ITT)



Time to Treatment Failure (TTF)

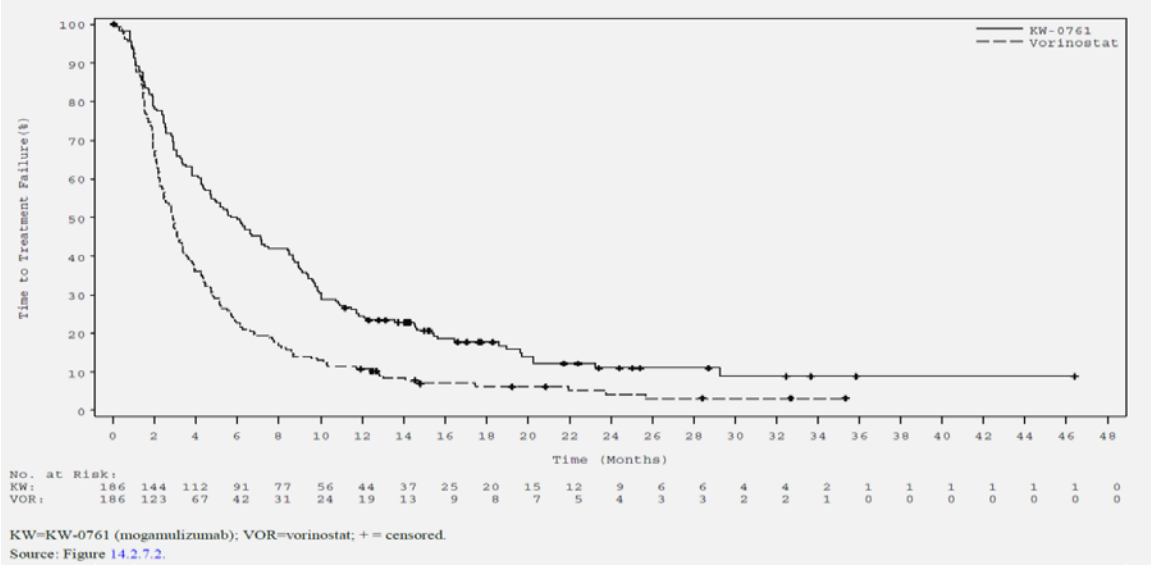
The median time to treatment failure was significantly longer for mogamulizumab (5.80 months) than for vorinostat (2.87 months) ($p<0.0001$).

Table 34: Summary of TTF (ITT)

	Vorinostat N=186	Mogamulizumab N=186
Number of Subjects with Treatment Failure (n, %)	176 (94.6)	157 (84.4)
Earliest contributing event:		
Discontinuation of randomized treatment due to		
Progressive disease per CTCL response criteria	12 (6.5)	76 (40.9)
Progressive disease - clinical	8 (4.3)	22 (11.8)
Withdrawal of consent	5 (2.7)	13 (7.0)
Protocol noncompliance	0	1 (0.5)
Investigator decision	0	9 (4.8)
Adverse event	5 (2.7)	28 (15.1)
Death	2 (1.1)	2 (1.1)
Other	11 (5.9)	6 (3.2)
Initiation of another new anti-cancer therapy	133 (71.5)	0
Number of Subjects Censored (n, %)	10 (5.4)	29 (15.6)
Time to Treatment Failure (months)		
Kaplan-Meier Estimate of TTF		
Q1	1.7	2.4
Median (95% CI)[a]	2.87 (2.37, 3.30)	5.80 (4.43, 7.13)
Q3	5.7	11.7
Treatment Comparison (KW-0761 vs. Vorinostat)[b]		
Hazard ratio (95% CI)	0.58 (0.47, 0.72)	
Log rank p-value	<0.0001	

a: 95% CIs are obtained from SAS proc lifetest using loglog 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.

Figure 18: Kaplan- Meier of TTF (ITT)



KW=KW-0761 (mogamulizumab); VOR=vorinostat; + = censored.
Source: Figure 14.2.7.2.

Ancillary analyses

Patients with stage IB/II disease treated with mogamulizumab had confirmed ORR of 17.6% compared to 8.3% for vorinostat, and compartment level (blood, skin, lymph node) response rates that were higher than those for vorinostat treated patients (Table **34**). Overall, the median period of progression free survival for stage IB/II subjects treated with mogamulizumab was 4.7 months compared to 3.9 months for vorinostat-treated patients (Table **35**). In patients with stage IB/II disease, given the limited number of subjects with a response and immaturity of the data, no conclusion on duration of response can be made.

Time to compartment level response in Stage IB/II patients was approximately 3 months, which is consistent with time to response for the ITT population overall (approximately 3 months). If a compartment level response or overall response is not observed after 3 months of treatment, discontinuation of treatment should be considered.

Table 35: Overall and Compartmental Response Rate in Early Disease Stages

	Mogamulizumab	Vorinostat	Risk Diff (M vs. V)
Disease stage IB/II	**N=68**	**N=72**	
Overall response rate (ORR), n (%)	12 (17.6)	6 (8.3)	9.3
Compartment:			
Blood (n) Response Rate (n, %) 95% CI[a]	17 8 (47.1) (23.0, 72.2)	23 4 (17.4) (5.0, 38.8)	 29.7 (-2.2, 57.1)
Skin (n) Response Rate (n, %) 95% CI[a]	68 19 (27.9) (17.7, 40.1)	72 14 (19.4) (11.1, 38.8)	 8.5 (-8.3, 24.9)
Nodal (n) Response Rate (n, %) 95% CI[a]	41 4 (9.8) (2.7, 23.1)	40 1 (2.5) (0.1, 13.2)	 7.3 (-14.3, 28.6)

M=mogamulizumab. V= vorinostat

Table 36: Progression Free Survival (PFS) by Treatment Group and Disease Stage (Randomised Treatment Period)

	Mogamulizumab	Vorinostat	P value
PFS, months			
ITT Population	7.70 (5.67, 10.33)	3.10 (2.87, 4.07)	<0.0001
IB/II	4.7 (2.9 -7.47)	3.9 (2.87-4.73)	0.6790
III/IV	10.9 (7.03-15.03)	3.0 (2.83-3.87)	<0.0001

ITT=intent to treat

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application.

These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37. Summary of efficacy for trial 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 (CTCL).			
Study identifier	Study 0761-010		
Design	Phase 3, open label, multi-center, randomized trial.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		~4 years at time of data cut-off 31 Dec 2016 (Study initiation date 12 Dec 2012; ongoing)
Hypothesis	Superiority		
Treatments groups	Mogamulizumab (n=186)		Mogamulizumab 1.0 mg/kg IV on Days 1, 8, 15, and 22 of the first 28 day cycle and on Days 1 and 15 of subsequent cycles until progressive disease or unacceptable toxicity.
	Vorinostat (n=186)		Vorinostat (Zolinza) 400 mg orally once daily, until progressive disease or unacceptable toxicity.
Endpoints and definitions	Primary endpoint	PFS	Time from the day of randomization until PD in any compartment per CTCL response criteria or PD reported during the follow-up period (prior to the start of alternative CTCL therapy) or death due to any cause.
	Secondary endpoints	ORR	The proportion of patients who had a confirmed CR or PR, defined as documented CR or PR per Global Composite Response Score by Investigator, that was confirmed by a subsequent observation at least 4 weeks later.
		DOR	Time from the date that criteria for CR/PR (whichever was first recorded) were first met until the first date that PD or death was objectively documented.
		TTR	Time from the date of randomization to the date that criteria for confirmed CR/PR (whichever was first recorded) were first met.
		QoL	HRQoL: Changes from baseline in Skindex-29, FACT-G, and EQ-5D-3L. Changes from baseline in pruritus using ItchyQoL and Pruritus Likert scale.
	Exploratory endpoints	OS	Time from the date of randomization until the date of death due to any cause.
		TTF	Time from the day of randomization until discontinuation of randomized treatment due to any reason.
Database lock	Data cut-off: 31 Dec 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT population Data cut-off: 31 Dec 2016, report date 28 Aug 2017.		
Descriptive statistics and estimate variability	Treatment group	Mogamulizumab	Vorinostat
	Number of subject	n=186	n=186
	Median PFS (Investigator)	7.7 months	3.1 months
	95% CI	(5.67, 10.33)	(2.87, 4.07)
	ORR (Investigator)	28%	4.8%
	95% CI	(21.6, 35.0)	(2.2, 9.0)
	Median DOR (Investigator)	14.07 months (9.43, 19.17; n=52)	9.13 months (4.67, -; n=9)
	Median TTR	3.32 months (n=52)	5.10 months (n=9)
	QoL *Skindex sum.* *FACT-G total* *EQ-5D-3L* *Itchy QoL & Pruritus Likert* *Responder analysis*	Statistically significant difference in MID based categorical QoL change from baseline in favour of mogamulizumab measured at Cycle 1,3,5,7,9,11 observed at: Cycle 5. Cycle 1,3, 5. Cycle 5 and 11. No statistically significant differences at any pre-specified time point, except Cycle 3 in Emotions domain. Only significant difference in Skindex emotions domain (63.2% mogamulizumab, 43.6% vorinostat, p=0.0451), Skindex symtoms domain (67.1% vs. 47.5%, p=0.0402) and EQ-5D-3L VAS (43.5% vs. 23.7%, p=0.0356).	
	Median OS	-	43.93 (43.57,-)
	Median TTF	5.8 months	2.87 months

Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Mogamulizumab vs. vorinostat
		Hazard ratio (HR)	0.53
		95% CI	(0.41, 0.69)
		P-value	<0.0001
	Secondary endpoint ORR	Comparison groups	Mogamulizumab vs. vorinostat
		Risk difference	23.1
		95% CI	(12.8, 33.1)

		P-value	<0.001
	Tertiary endpoint OS	Comparison groups	Mogamulizumab vs. vorinostat
		Hazard ratio (HR)	0.93
		95% CI	(0.61, 1.43)
		P-value	0.9439
Notes	The primary comparison of PFS was investigator based on the ITT set, with a stratified log rank test at the one-sided 2.5% significance level, adjusted for stratification factors disease type (MF or SS, disease stage (IB/II or III/IV) and region (U.S., Japan, and rest of the world)..		
Abbreviations	*CI: Confidence Interval, DOR: Duration of Response, HRQoL: Health-related quality of life, (Inv: investigator, ITT: intent to treat, MID: minimal important difference, ORR: Objective Response Rate, OS: Overall Survival, PD: Progressive Disease, PFS: Progression Free Survival, TTF: Time to Treatment Failure, TTR: Time to response.*		

Clinical studies in special populations

Elderly:

Table 38: Number of older patients in efficacy trials.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	112	45	9
Non Controlled Trials	21	6	0

Subgroup analysis for the primary endpoint, were provided in patients < 65 and ≥ 65 years of age.

Hepatic impairment: Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild or moderate hepatic impairment. There is no data for patients with severe hepatic impairment.

Renal impairment: Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild to severe renal impairment.

Paediatric patients: There is no data available in children and adolescents below 18 years of age.

Pregnancy and lactation: No formal clinical studies have been performed with mogamulizumab in pregnant or lactating women. Based on the enrolment criteria of the clinical studies, women who were pregnant or lactating were not eligible for participation in the studies.

Supportive studies

Two supportive efficacy study were submitted, that included patients with CTCL:

Study KW-0761-001: Open label, Phase 1/2 multicenter dose escalation study. The dose escalation phase of this study is discussed in the section - *Dose response study* of this report.

Study 0761-004: Single arm Phase 2 Study conducted in Japan, investigating mogamulizumab in a.o. 8 patients with CTCL (7 MF and 1 pcALCL). All patients received 1.0 mg/kg mogamulizumab IV, administered 8 times at one-week intervals. All 8 CTCL patients had a PFS event, with a median Investigator based PFS of 3.4 months (95% CI 1.0, 5.4). There were 3 responders among the 8 patients (37.5%), which included the patient with pc-ALCL. All 3 responders had PR. The duration of response was not reported. The KM estimate of OS was 17.1 months (95% CI 3.7,-).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Clinical efficacy of mogamulizumab in the treatment of patients with mycosis fungoides (MF) or Sézary syndrome (SS) has been investigated in pivotal Study 0761-010, a Phase 3, multinational, open label trial of anti-CCR4 monoclonal antibody mogamulizumab versus vorinostat in 372 adult patients randomised 1:1 to treatment with either mogamulizumab or vorinostat.

Each arm enrolled 186 patients. Mogamulizumab infusion was administered at a dose of 1 mg/kg once weekly for the first 28-day cycle (on Days 1, 8, 15 and 22), and on days 1 and 15 of subsequent 28-day cycles. Vorinostat was administered at a starting dose of 400 mg orally, once daily beginning on day 1 for 28-day cycles. Vorinostat patients with disease progression or unacceptable toxicities were permitted to cross over to mogamulizumab therapy. Crossover patients received up to 46 months of mogamulizumab therapy, as of December 2016 data cut. Treatment with mogamulizumab continued until disease progression or unacceptable toxicity. The trial excluded patients with active autoimmune diseases, central nervous system metastasis, and medical conditions that required systemic corticosteroids or other immunosuppressive medicinal products, or an active infection requiring therapy, including HIV, or hepatitis B or C. Patients with ECOG performance status ≥2 were also excluded. At study baseline, 38% had stage IB-II disease, 10% stage III, 52% stage IV. This study included patients regardless of their baseline level of CCR4 expression in skin biopsy.

Patients were a median age of 64 years at the time of screening (range 25 to 101 years), 49.5% were 65 years or older, and 58.1% were male.

All patients had a histologically confirmed diagnosis of either mycosis fungoides (MF), 56.5%, 53.2%, or Sézary Syndrome (SS), 43.5%, 46.8%, in the mogamulizumab and vorinostat groups, respectively, and had received at least one prior systemic therapy. As expected, a high proportion of patients (~70% of EU patients) previously received bexarotene, the only registered treatment for CTCL in the EU. Other prior systemic therapies were interferon (59%), methotrexate (49%), extracorporeal photopheresis (ECP) (31%) and gemcitabine/ gemcitabine regimens (28%).

The primary efficacy endpoint was progression-free survival (PFS) based on investigator assessment using a global composite response criteria that took into account all potentially affected disease compartments (skin, blood, lymph nodes and viscera). PFS is considered an acceptable primary endpoint, in particular as CTCL is characterized by frequent recurrences and an indolent course in early stages reflected by the relatively long OS. However, clinical relevance of the observed effect should be reinforced by supportive secondary endpoints. The primary endpoint is based on investigator assessment, which is acceptable as it is more representative of clinical practice in this disease where visual skin inspection is an important part of response assessment. Moreover, investigator based PFS provided a more consistent application of the Olsen et al guidelines compared to IR PFS, and can be considered, therefore, more reliable in terms of diagnosis of progression and response data.

Response in skin and blood was evaluated every 4 weeks. Response in lymph nodes and viscera was evaluated at 4 weeks, then every 8 weeks in the first year, and then every 16 weeks thereafter.

The median duration of exposure with mogamulizumab was 5.6 months (range: <1 to 45.3 months). 56% of patients received mogamulizumab for at least 6 cycles, and 25% of patients received mogamulizumab for at least 12 cycles.

CCR4 expression was assessed retrospectively on pretreatment skin biopsies (formalin fixed paraffin embedded) using immunohistochemistry. In the mogamulizumab arm, baseline CCR4 expression levels were available in 75% of patients (N=140). CCR4 was detected on ≥1% of lymphocytes in 100% of patients, and 96% (134/140) had CCR4 detected on ≥10% of skin lymphocytes.

Responses are measured by the global response score (GRS; Olsen 2011), investigating the impact of treatment in different body compartments. This is recommended by EORTC/ISCL, and therefore regarded acceptable.

The effect size of mogamulizumab is not compared to treatment regimens used in the EU. Moreover, vorinostat has been approved in the US for progressive, persistent or recurrent disease on or following two systemic therapies, this represents a later line of therapy as claimed in the proposed indication for mogamulizumab, and thus further questions placing the obtained results for the current pivotal trial in context. Additionally, the fact that patients were allowed to cross-over to mogamulizumab in case of progression on vorinostat, and even when unable to tolerate vorinostat treatment, complicates interpretation of available OS and PFS data for mogamulizumab.

Efficacy data and additional analyses

The recommended dose of POTELIGEO is 1.0 mg/kg administered as an intravenous infusion over at least 60 minutes. It should be administered weekly on days 1, 8, 15 and 22 of the first 28-day cycle, followed by infusions every two weeks on Days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.

Mogamulizumab treatment resulted in a statistically significant improvement in investigator-based PFS, with a HR of 0.53 and a median improvement of 4.6 months with mogamulizumab compared to vorinostat (7.7 vs. 3.1 months, respectively).

At 6, 12, 18 and 24 months after the start of randomised treatment, the percent of subjects alive without disease progression was higher for mogamulizumab (55.3%, 38.3%, 28.0%, and 14.1%, respectively) compared to vorinostat (28.8%, 15.3%, 7.2%, and 7.2%, respectively). Median PFS for the mogamulizumab group was 7.70 months (95% CI: 5.67, 10.33) and 3.10 months (95% CI: 2.87, 4.07) for the vorinostat group with resultant hazard ration of 0.53 (95% CI: 0.41, 0.69), p<0.0001 (2-sided, stratified log rank test).

The PFS effect size was not consistent across subgroups; subgroup analyses indicate that the effect size of PFS depends on the stage of disease. The available data demonstrate a clinically relevant PFS advantage with mogamulizumab compared to vorinostat in subjects with SS (median PFS 13.3 vs. 3.13 months, respectively, HR 0.32, p<0.0001) and with advanced disease (stage III/IV, median PFS 10.9 vs. 3 months, HR 0.36, p<0.0001). In the less advanced patients a limited 0.8 months advantage in PFS was observed with mogamulizumab vs. vorinostat (median PFS 4.7 vs. 3.9 months, HR 0.88, p=0.7166). In line with the PFS subgroup analysis, ORR was lower for patients with MF (risk difference 13.9, p=0.0042), than for patients with SS (34.7, p<0.0001). Also in subjects with less advanced disease (stage IB/II) ORR was lower (9.3, p=0.0896) than in the ITT. Still, the frequency of confirmed ORR in stage IB/II subjects receiving mogamulizumab treatment (17.6%, 12/68) was higher than in those receiving the comparator vorinostat (8.3%, 6/72).

Response rates by compartment showed that responses were in particular observed in the blood compartment, i.e. patients with blood involvement. Supportive dose escalation study 0761-001 also showed a lower rate of response (28.6%) in patients with MF, than patients with SS (47.1%). Overall, the available data confirm that subjects with less advanced disease and with no blood involvement seem to experience a reduced clinical benefit with mogamulizumab compared to patients in advanced stages and/or with blood involvement. On the other hand, most analyses still point to better outcomes with mogamulizumab compared to vorinostat, and encouraging (yet far from outstanding) rates of skin responses have been observed in this subpopulation of patients with less advanced disease without blood involvement.

Of the patients randomised to vorinostat, 136 patients (73.1%) crossed over to mogamulizumab during the study. Reasons for crossover to mogamulizumab were disease progression (109 patients) and treatment intolerance (27 patients). The number of infusions of mogamulizumab administered to crossover patients ranged from 1 to 94 (up to 46 months of treatment) as of the December 2016 datacut.

At the time of data cut-off for analysis, 23.4% (87/372) of randomized subjects had died [47, vorinostat (25.3%); 40, mogamulizumab (21.5%)]. OS data were largely immature; this is not unexpected, since subjects with MF often have a chronic disease course. Further, interpretation of OS data is hampered buy the crossover design. It is noted, however, that no sign of any possible detrimental effect of mogamulizumab on OS can be observed, which is reassuring.
The The results from the TTF analysis showed a 3-month advantage with mogamulizumab (HR 0.58); median time to treatment failure was significantly longer for mogamulizumab (5.80 months) than for vorinostat (2.87 months) ($p<0.0001$). which is overall consistent with the primary PFS analysis. As expected, due to the study design, causes for treatment failure differ between the two treatment arms, discontinuation of randomized treatment due to PD according to CTCL criteria (40.9%) or AEs (15.1%) being the main causes in the mogamulizumab arm and initiation of a new anti-cancer treatment (71.5%) in the vorinostat arm. In this regard, it is noted that discontinuation due to PD according to CTCL criteria was the earliest TTF event only in the 6.5% of all patients who received vorinostat.

Interpretation of the difference in time to next line therapy (TTNT) (11 months vs 3.5 months), is complicated by the cross over design as patients in the control group may be more prone to starting next line systemic therapy than the mogamulizumab treated patients. Still, it is considered unlikely that this bias will account for the full magnitude of the estimated difference. Notably, in chronic conditions with a remitting/relapsing behaviour such as MF, TTNT represents a useful endpoint to also assess the actual clinical benefit obtained with a single treatment beyond the strict criteria often used to define disease progression in clinical trials. Of note, TTNT was not defined in the statistical analysis plan and thus concerns a post-hoc analysis.

The open-label design is also hindering interpretation of the QoL PRO data for demonstration of benefit, although it may be reassuring that some of the parameters showed improvement in QoL. Further, as MF and SS patients can suffer tremendously from symptoms related to their disease (eg, pain, pruritus, fatigue, sleep disturbance) and the social stigma of having obvious unsightly skin lesions, having a durable response could also be interpreted as beneficial to the patient. In this context it can be agreed that the response rates of 28% with a median DoR of 14 months, obtained using a stringent global composite assessment, is clinically meaningful. Altogether, the difference in median PFS of 4.6 months (HR 0.53; 95% CI: 0.41, 0.69; $p<0.0001$) is considered clinically relevant when compared to the observed median PFS and supported by ORR+ DOR and TTNT.

The possibility to assess the efficacy of mogamulizumab in subjects with lower levels of CCR4 expression has been limited as data are available for only 10 subjects with <10% CCR4 positive lymphocytes in skin biopsies who were treated with mogamulizumab. No confirmed responses were noted, 3 subjects experienced a compartment level response to mogamulizumab; 2 of 6 initially randomised to mogamulizumab and 1 of 4

subjects randomized to vorinostat and crossing over to mogamulizumab. While, two of the 6 patients with <10% CCR4 in the mogamulizumab arm had a response to treatment in individual compartments, no confirmed responses were observed in the few MF/SS patients with CTCL expression <10%. In addition, a larger PFS improvement was observed for mogamulizumab in ≥10% CCR4 expressing patients (6.3 months: 9.4 with mogamulizumab vs. 3.1 with vorinostat) compared to the ITT (4.6 month improvement), in which also patients with CCR4 expression <10% were included. Furthermore, in a PFS analysis by CCR4 expression cut off point, a trend for increasing PFS HR was observed with increasing CCR4 expression levels.

Therefore, in the context of the indication in MF and SS there is no need to specify that the disease should be CCR4 positive. However, the uncertainties on the clinical benefit of mogamulizumab in subjects with low CCR4 expression need to be described in the SmPC (section 5.1).

The initial proposed indication included all subtypes of CTCL, but no data had been provided in other subtypes than MF or SS, except for 1 patient with pcALCL achieving a PR in the supportive Phase 2 study 0761-004; the indication was later revised to include MF and SS patients.

Despite the low frequency of patients (~15%) in the mogamulizumab arm that received only 1 prior treatment, additional analysis suggested almost similar PFS and response rates in mogamulizumab treated subjects with 1 or 2 prior treatment lines. Therefore the indication specifies “at least one prior systemic therapy’.

2.5.4. Conclusions on the clinical efficacy

The efficacy of mogamulizumab in terms of 4.6 months improvement in PFS supported by the ORR+DoR and TTNT is a beneficial and clinically relevant effect in the context of a relapse/remitting disease where patients continue through therapies, which makes this product with a new mode of action a valuable additional treatment option for MF/SS.

2.6. Clinical safety

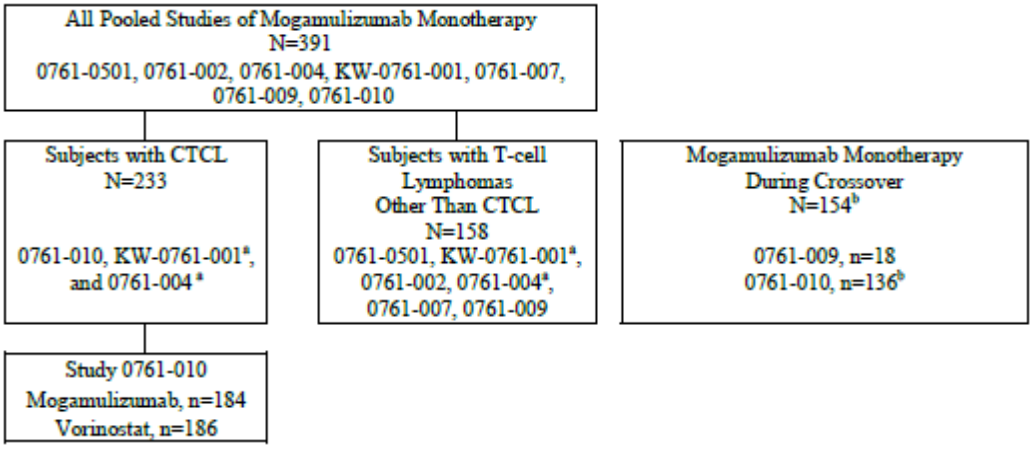
Safety data of mogamulizumab, administered as monotherapy is available from 7 clinical studies in patients with T-cell lymphoma (CTCL, PTCL, and ATL;

Figure 17). From these studies, several safety populations were defined (i.e. the pooled CTCL population, all patients with T cell lymphomas (i.e. CTCL and other T cell lymphomas), and for all patients with T cell lymphomas other than CTCL). The data from the pivotal Phase 3 Study 0761-010, including the cross-over population are discussed here, where relevant supplemented by data from the other safety populations.

Similarly, also the post-marketing experience in Japan (approved patient populations with CCR4- expressing T-cell lymphomas, including CTCL, PTCL and ATL, estimated exposure 3700 patients, data cut-off 31 May 2017), will be included in the discussion when relevant.

Of note: the pivotal Phase 3 Study 0761-010 contributed to 79.0% (184/233) of subjects to the pooled data of all subjects with CTCL, and CTCL represents 59.6% (233/391) of all subjects with T-cell lymphomas. Also, there are differences in the protocol-defined reporting of AEs between studies conducted in Japan and in the Rest of the World. In Japan (Studies 0761-002 and 0761-004), if signs or symptoms of illness were atypical or very severe, both the individual Patient exposure signs or symptoms and the underlying diagnosis were to be reported as AEs. In Study 0761-0501 (also in Japan), the symptom or diagnosis was reported as an AE. In the other 4 studies (Studies KW-0761-001, 0761-007, 0761-009, 0761-010), the underlying illness or diagnosis (when known), instead of signs or symptoms, was to be recorded as the AE.

Figure 19 Clinical Safety dataset



a: Studies KW-0761-001 and 0761-004 contributed data from subjects with CTCL and subjects with T-cell lymphomas other than CTCL.

b: 136 subjects crossed over; 133 subjects were treated with mogamulizumab

CTCL=cutaneous T-cell lymphoma; N=number of subjects treated with mogamulizumab; n=number of subjects who received a specific treatment.

Patient exposure

A total of 542 subjects received at least 1 dose of mogamulizumab monotherapy in the 7 clinical studies included in this dossier.

Table 39 Protocol-defined Dose and Treatment Duration by Study.

Study Number	Indication, n	Protocol-defined Mogamulizumab Dose and Treatment Duration
0761-0501	PTCL, n=3 ATL, n=13	4 weekly doses of 0.01, 0.1, 0.5, or 1.0 mg/kg
0761-002	ATL, n=27	8 weekly doses of 1.0 mg/kg
0761-004	CTCL, n=8 PTCL, n=29	
KW-0761-001	CTCL, n=41 PTCL, n=1	0.1 mg/kg, 0.3 mg/kg, or 1.0 mg/kg weekly for 4 weeks followed by a 2-week observation period, then every other week thereafter until disease progression[a]
0761-007	PTCL, n=38	1.0 mg/kg weekly for 4 weeks, then every other week until disease progression
0761-009	ATL, n=47	
0761-010	CTCL, n=184	

a: Intra-subject dose escalation was permitted in Study KW-0761-001.

ATL=adult T-cell leukemia-lymphoma; CTCL=cutaneous T-cell lymphoma; n=number of subjects; PTCL=peripheral T-cell lymphomas.

A total of 233 subjects with CTCL received at least 1 dose of mogamulizumab monotherapy as initial treatment in 3 clinical studies: 184 in study 0761-010, 41 in dose finding study KW-0761-001 and 8 in single arm Phase 2 study 0761-004. All subjects in Study 0761-010 and nearly all subjects with CTCL in the pooled safety data (99.6%, 230/236) received mogamulizumab 1.0 mg/kg. Six subjects with CTCL received mogamulizumab ≤ 0.5 mg/kg.

The design of the pivotal study contemplated a single cross-over from the comparator arm to mogamulizumab, based on disease progression and/or occurrence of intolerable adverse events. Of the 186 patient initially randomised to vorinostat, 138 crossed over to mogamulizumab.

Study 0761-010

At the time of cut-off date in Study 0761-010 at 31 Dec 2016, the median number of 28 day-cycles during the randomized treatment period was 6 in the mogamulizumab arm (170 days), and 3 in the vorinostat arm (84 days). The median relative dose intensity was 97.49% for mogamulizumab, and 95.12% for vorinostat.

Among subgroups in the mogamulizumab arm, a difference emerges between disease subtypes the length of treatment, which was longer in SS (295 days) than MF (208 days) patients. These data are consistent with the longer exposure observed in patients with a more advanced stage of disease (184 vs 281 days in stage IB/II and III/IV respectively, this latter including MF stage III/IV and SS). In the control arm, exposure was longer in MF (164 days) than SS (122 days) and exposure was rather similar between the disease stages (151 vs 140 days for stage IB/II and stage III/IV disease respectively).

For those subjects who crossed over to treatment with mogamulizumab, the median number of cycles initiated during the cross-over portion was 7 (169.0 days).

During randomisation, 103 (56.0%) subjects in the mogamulizumab received ≥ 6 cycles, and 50 (27.2%) subjects received ≥ 12 cycles. In the cross-over group, 76 (55.9%) subjects received ≥ 6 cycles mogamulizumab, and 35 received ≥ 12 cycles.

Long term safety data are available from 155 subjects (48.9%) exposed for ≥6 months and 74 subjects (23.3%) exposed for >12 months. More subjects were exposed long-term to mogamulizumab than vorinostat.

Dose modifications

Study 0761-010

During the randomized treatment period, 35.5% (n=65) of patients in the mogamulizumab arm had at least one dose withheld, and 70 (38%) subjects did not receive the total planned dose for a given infusion. The reasons for withholding of a dose (drug eruption, thrombocytopenia/platelet count decreased, neutrophil count decreased/neutropenia, infusion related reaction) are among the most commonly observed AEs.

Table 40. Summary of Drug Dosing Status During Randomized Treatment Period (Safety Analysis Set Study 0761-010).

	Vorinostat N=186 n (%)	Mogamulizumab N=184 n (%)
Subjects with a Dose Withheld for Mogamulizumab	-	65 (35.3)
Subjects with Total Planned Dose of Mogamulizumab Not Administered (for a given infusion)	-	70 (38.0)
Reason:	-	
Infusion reaction	-	4 (2.2)
Other adverse event	-	48 (26.1)
Mechanical equipment issue	-	1 (0.5)
Other	-	24 (13.0)
Subjects With a Mogamulizumab Infusion Temporarily Interrupted	-	17 (9.2)
Reason:	-	
Infusion reaction	-	9 (4.9)
Other adverse event	-	1 (0.5)
Mechanical equipment issue	-	4 (2.2)
Other	-	3 (1.6)
Subjects with Dose Modifications for Vorinostat	101 (54.3)	
Subjects with Non-compliance with Dosing for Vorinostat[a]	34 (18.3)	

Subjects with multiple reasons were counted in each applicable category.

a: Non-compliance is based on investigator assessment.

- = not applicable

There were no major demographic and disease characteristic differences in the group of patients at the time of crossover from vorinostat to mogamulizumab when compared to those initially assigned to mogamulizumab.

Adverse events

Safety was assessed by reported adverse events (AEs), changes in physical examinations, vital sign measurements, electrocardiograms (ECGs) and laboratory analyses until 90 days after the last dose or initiation of alternative therapy, whichever came first. Events that occurred beyond 90 days after the last dose that were considered to be related to the study treatment, were included as TEAEs.

The investigators evaluated all AEs as to seriousness, severity, causality, start and stop dates, action taken with study drug, and outcome.

During the randomized treatment period in Study 0761-010, almost all patients experienced at least one TEAE (97.3% in the mogamulizumab arm and 99.5% in the vorinostat arm; The incidence of *treatment-related* TEAEs was lower for mogamulizumab (84.8%) compared to vorinostat (95.7%). The incidence of Grade ≥3 TEAEs was similar between the 2 treatment groups (42.4% vs 45.7%), the incidence of *treatment-related* Grade ≥3 TEAEs was lower for mogamulizumab (25.5%) compared to vorinostat (34.9%).

For cross-over patients, the incidence of all TEAEs was similar (93.4%) to the incidence in the mogamulizumab arm during the randomized treatment period. However, incidences of treatment-related TEAEs, and all (or related) Grade ≥3 TEAEs were lower for patients who crossed over compared to patients in either treatment group during the randomized treatment period.

During the randomized treatment period in Study 0761-010, the incidence of TEAEs by severity was similar between treatment groups. Approximately one-third of subjects in each treatment group had TEAEs of maximum Grade 3 severity, and less than 10% of subjects had TEAEs of maximum Grade 4 or 5 severity.

Table 41. Overall Summary of AEs – Study 0761-010 and All Subjects with CTCL (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)

TEAEs (all grades) reported by ≥5% of patients in study 0761-010 in either treatment group during the randomized treatment period were summarized by system of organ class (SOC) and preferred term in

Table 41.

Table 42. TEAEs Reported by ≥5% of Subjects in Either Treatment Group during randomisation (Safety Population).

	Vorinostat N=186		Mogamulizumab N=184	
System Organ Class Preferred Term[a]	All Grades n (%)	Grades ≥3 n (%)	All Grades n (%)	Grades ≥3 n (%)
Subjects with any TEAEs	185 (99.5)	85 (45.7)	179 (97.3)	78 (42.4)
Gastrointestinal Disorders	152 (81.7)	17 (9.1)	93 (50.5)	4 (2.2)
Diarrhoea	115 (61.8)	9 (4.8)	43 (23.4)	1 (0.5)
Nausea	79 (42.5)	3 (1.6)	28 (15.2)	1 (0.5)
Constipation	34 (18.3)	2 (1.1)	21 (11.4)	1 (0.5)
Vomiting	24 (12.9)	1 (0.5)	11 (6.0)	0
Abdominal pain	21 (11.3)	0	7 (3.8)	0
Dry mouth	17 (9.1)	0	4 (2.2)	0
Abdominal pain upper	11 (5.9)	1 (0.5)	1 (0.5)	0
Dyspepsia	11 (5.9)	0	1 (0.5)	0
General Disorders and Administration Site Conditions	126 (67.7)	17 (9.1)	106 (57.6)	8 (4.3)[b]
Fatigue	70 (37.6)	11 (5.9)	43 (23.4)	3 (1.6)
Oedema peripheral	27 (14.5)	1 (0.5)	27 (14.7)	0
Pyrexia	11 (5.9)	0	31 (16.8)	1 (0.5)
Asthenia	27 (14.5)	4 (2.2)	10 (5.4)	0
Chills	14 (7.5)	0	13 (7.1)	0
Infections and Infestations	93 (50.0)	19 (10.2)	118 (64.1)	32 (17.4)[c]
Skin infection	13 (7.0)	3 (1.6)	17 (9.2)	0
Upper respiratory tract infection	9 (4.8)	2 (1.1)	19 (10.3)	0
Nasopharyngitis	15 (8.1)	0	12 (6.5)	0
Urinary tract infection	15 (8.1)	0	12 (6.5)	0
Folliculitis	4 (2.2)	1 (0.5)	13 (7.1)	0
Cellulitis	10 (5.4)	4 (2.2)	6 (3.3)	4 (2.2)
Oral candidiasis	1 (0.5)	0	10 (5.4)	0
Skin and Subcutaneous Tissue Disorders	78 (41.9)	9 (4.8)	97 (52.7)	10 (5.4)
Alopecia	36 (19.4)	0	13 (7.1)	0
Drug eruption	1 (0.5)	0	44 (23.9)	8 (4.3)
Nervous System Disorders	101 (54.3)	7 (3.8)	65 (35.3)	2 (1.1)
Dysgeusia	54 (29.0)	1 (0.5)	6 (3.3)	0
Headache	29 (15.6)	1 (0.5)	23 (12.5)	0

	Vorinostat N=186		Mogamulizumab N=184	
System Organ Class Preferred Term[a]	All Grades n (%)	Grades ≥3 n (%)	All Grades n (%)	Grades ≥3 n (%)
Dizziness	19 (10.2)	0	12 (6.5)	0
Paraesthesia	14 (7.5)	0	5 (2.7)	0
Investigations	95 (51.1)	11 (5.9)	65 (35.3)	8 (4.3)
Blood creatinine increased	52 (28.0)	0	6 (3.3)	0
Weight decreased	33 (17.7)	2 (1.1)	11 (6.0)	1 (0.5)
Platelet count decreased	19 (10.2)	0	4 (2.2)	0
Aspartate aminotransferase increased	12 (6.5)	1 (0.5)	8 (4.3)	2 (1.1)
Alanine aminotransferase increased	9 (4.8)	1 (0.5)	10 (5.4)	0
Weight increased	2 (1.1)	0	14 (7.6)	1 (0.5)
Metabolism and Nutrition Disorders	77 (41.4)	15 (8.1)	59 (32.1)	13 (7.1)
Decreased appetite	46 (24.7)	2 (1.1)	14 (7.6)	2 (1.1)
Hyperglycaemia	14 (7.5)	2 (1.1)	15 (8.2)	2 (1.1)
Hypokalaemia	12 (6.5)	2 (1.1)	10 (5.4)	0
Musculoskeletal and Connective Tissue Disorders	59 (31.7)	6 (3.2)	67 (36.4)	5 (2.7)[d]
Muscle spasm	29 (15.6)	2 (1.1)	9 (4.9)	0
Back pain	9 (4.8)	1 (0.5)	18 (9.8)	1 (0.5)
Arthralgia	11 (5.9)	0	13 (7.1)	1 (0.5)
Pain in extremity	9 (4.8)	1 (0.5)	12 (6.5)	0
Myalgia	8 (4.3)	2 (1.1)	11 (6.0)	0
Blood and Lymphatic System Disorders	76 (40.9)	18 (9.7)	47 (25.5)	3 (1.6)
Thrombocytopenia	57 (30.6)	13 (7.0)	21 (11.4)	0
Anemia	19 (10.2)	2 (1.1)	19 (10.3)	2 (1.1)
Neutropenia	10 (5.4)	3 (1.6)	5 (2.7)	1 (0.5)
Injury, Poisoning and Procedural Complications	28 (15.1)	2 (1.1)	81 (44.0)	7 (3.8)
Infusion related reaction	1 (0.5)[e]	0	61 (33.2)	3 (1.6)
Fall	3 (1.6)	0	11 (6.0)	1 (0.5)
Respiratory, Thoracic and Mediastinal Disorders	42 (22.6)	7 (3.8)	56 (30.4)	7 (3.8)
Cough	15 (8.1)	0	18 (9.8)	0
Oropharyngeal pain	5 (2.7)	0	10 (5.4)	1 (0.5)

	Vorinostat N=186		Mogamulizumab N=184	
System Organ Class Preferred Term[a]	All Grades n (%)	Grades ≥3 n (%)	All Grades n (%)	Grades ≥3 n (%)
Vascular Disorders	38 (20.4)	13 (7.0)	29 (15.8)	12 (6.5)
Hypertension	25 (13.4)	12 (6.5)	17 (9.2)	8 (4.3)
Eye Disorders	32 (17.2)	0	34 (18.5)	3 (1.6)
Vision blurred	12 (6.5)	0	8 (4.3)	0
Dry eye	11 (5.9)	0	7 (3.8)	0
Psychiatric Disorders	28 (15.1)	2 (1.1)	32 (17.4)	2 (1.1)
Insomia	14 (7.5)	0	16 (8.7)	0
Depression	6 (3.2)	0	11 (6.0)	2 (1.1)

a: MedDRA Version 15.1 was used for coding.
b: Includes 1 Grade 5 TEAE (disease progression)
c: Grade ≥3 Infections and Infestations TEAEs reported for subjects in the mogamulizumab group but not shown in table (i.e., reported by <5.0% of subjects in either group) include pneumonia (n=4), sepsis (n=3; 1 Grade 5), bacteraemia (n=2), herpes simplex (n=2), osteomyolitis (n=2); all other events occurred in 1 subject each, including Grade 5 pneumonia pneumococcal.
d: Includes 1 Grade 5 TEAE (polymyositis)
e: Subject 402-003 had an infusion reaction on Day 1 of crossover to mogamulizumab treatment (17 days after the last dose of vorinostat) that was indicated as possibly related to vorinostat (and mogamulizumab).
MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event

TEAEs that occurred with higher frequency in the mogamulizumab group than in the vorinostat group included infusion-related reaction (33.2% vs 0.5%) and drug eruption (23.9% vs 0.5%) and pyrexia (16.8% vs 5.9%). The majority of these events were mild or moderate in severity; Grade ≥3 infusion-related reaction occurred in 3 (1.6%) subjects, and Grade ≥3 drug eruption occurred in 8 (4.3%) subjects in the mogamulizumab group.

When pooled by SOC, higher incidences (≥10% difference) of TEAEs in the mogamulizumab group compared with the vorinostat group was noted for SOC Infections and Infestations (64.1% of subjects in the mogamulizumab group vs. 50.0% in the vorinostat group) with higher rates of upper respiratory tract infection, folliculitis, and oral candidiasis (none of ≥ Grade 3 severity), SOC Skin and Subcutaneous Tissue Disorders (52.7% vs. 41.9%, respectively) with higher rates for drug eruption, and Injury, SOC Poisoning and Procedural Complications (44.0% vs. 15.1%, respectively) with higher rates for infusion reactions. For other SOCs and individual preferred terms, the frequency in the mogamulizumab group was either comparable to or lower than that observed for vorinostat.

Compared with Study 0761-010, the incidence of Grade 3, 4 or 5 TEAEs was higher in the pooled data for all subjects (overall [51.9% and treatment-related [37.1%] than in the mogamulizumab group in Study 0761-010 (overall [42.4%] and treatment-related [25.5%]).

Related Adverse Events

Most subjects in study 0761-010 experienced at least 1 treatment-related TEAEs with a lower incidence in the mogamulizumab group (84.8%) than in the vorinostat group (95.7%; Table **42**). During the crossover portion of study, 57.4% of subjects had treatment-related TEAEs.

During the randomized treatment period, the most frequently reported treatment-related TEAEs in the mogamulizumab group (with a ≥15% higher incidence compared to vorinostat) were infusion-related reaction (33.2% vs. 0.5%) and drug eruption (22.8% vs. 0.5%).

Treatment-related Grade 3 TEAEs reported in more than 1 subject were drug eruption (8 [4.3%] subjects), hypertension (5 [2.7%] subjects), infusion-related reaction and pneumonia (3 [1.6%] each), and fatigue, AST

increased, and cellulitis (2 [1.1%] subjects each). The only treatment-related Grade 4 TEAE reported in more than 1 subject was respiratory failure (2 [1.1%] subjects).

In the vorinostat group, the most frequently reported treatment-related TEAEs (with a ≥ 15% greater incidence compared to mogamulizumab) were diarrhoea (10.3% in the mogamulizumab group vs. 55.4% in the vorinostat group), nausea (9.2% vs. 38.2%), fatigue (8.5% vs. 33.3%), dysgeusia (3.3% vs. 28.0%), blood creatinine increased (0.5% vs. 24.2%), thrombocytopenia (7.6% vs. 30.1%), and decreased appetite (2.7% vs. 21.5%).

Table 43. Treatment-related TEAEs Reported by ≥5% of Subjects in Either Treatment Group During Randomized Treatment (Safety Analysis Set Study 0761-010).

	KW-0761 (N=184)				Vorinostat (N=186)			
Body System/ SOC Class	All Grades n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood And Lymphatic System Disorders								
Anaemia	11 (5.98)	10 (5.43)	1 (0.54)	0	13 (6.99)	12 (6.45)	1 (0.54)	0
Thrombocytopenia	14 (7.61)	14 (7.61)	0	0	56 (30.11)	44 (23.66)	11 (5.91)	1 (0.54)
Gastrointestinal Disorders								
Abdominal Pain	1 (0.54)	1 (0.54)	0	0	15 (8.06)	15 (8.06)	0	0
Constipation	7 (3.80)	6 (3.26)	1 (0.54)	0	17 (9.14)	16 (8.60)	1 (0.54)	0
Diarrhoea	19 (10.33)	19 (10.33)	0	0	103 (55.38)	94 (50.54)	9 (4.84)	0
Dry Mouth	2 (1.09)	2 (1.09)	0	0	15 (8.06)	15 (8.06)	0	0
Nausea	17 (9.24)	16 (8.70)	1 (0.54)	0	70 (37.63)	67 (36.02)	3 (1.61)	0
Vomiting	6 (3.26)	6 (3.26)	0	0	21 (11.29)	20 (10.75)	1 (0.54)	0
General Disorders And Administration Site Conditions								
Asthenia	5 (2.72)	5 (2.72)	0	0	25 (13.44)	21 (11.29)	4 (2.15)	0
Fatigue	34 (18.48)	32 (17.39)	2 (1.09)	0	62 (33.33)	51 (27.42)	11 (5.91)	0
Oedema Peripheral	5 (2.72)	5 (2.72)	0	0	11 (5.91)	11 (5.91)	0	0
Pyrexia	17 (9.24)	16 (8.70)	1 (0.54)	0	1 (0.54)	1 (0.54)	0	0
Injury, Poisoning And Procedural Complications								
Infusion Related Reaction	61 (33.15)	58 (31.52)	3 (1.63)	0	0	0	0	0
Investigations								
Blood Creatinine Increased	1 (0.54)	1 (0.54)	0	0	45 (24.19)	45 (24.19)	0	0
Platelet Count Decreased	4 (2.17)	4 (2.17)	0	0	19 (10.22)	19 (10.22)	0	0
Weight Decreased	1 (0.54)	1 (0.54)	0	0	24 (12.90)	23 (12.37)	1 (0.54)	0
Metabolism And Nutrition Disorders								
Decreased Appetite	5 (2.72)	5 (2.72)	0	0	39 (20.97)	37 (19.89)	2 (1.08)	0
Hyperglycaemia	4 (2.17)	4 (2.17)	0	0	10 (5.38)	9 (4.84)	0	1 (0.54)
Musculoskeletal And Connective Tissue Disorders								
Muscle Spasms	5 (2.72)	5 (2.72)	0	0	19 (10.22)	18 (9.68)	1 (0.54)	0
Nervous System Disorders								
Dizziness	2 (1.09)	2 (1.09)	0	0	10 (5.38)	10 (5.38)	0	0
Dysgeusia	6 (3.26)	6 (3.26)	0	0	52 (27.96)	51 (27.42)	1 (0.54)	0
Headache	10 (5.43)	10 (5.43)	0	0	16 (8.60)	15 (8.06)	1 (0.54)	0
Paraesthesia	3 (1.63)	3 (1.63)	0	0	10 (5.38)	10 (5.38)	0	0
Skin And Subcutaneous Tissue Disorders								
Alopecia	8 (4.35)	8 (4.35)	0	0	30 (16.13)	30 (16.13)	0	0
Drug Eruption	42 (22.83)	34 (18.48)	8 (4.35)	0	1 (0.54)	1 (0.54)	0	0

For those subjects who crossed over to treatment with mogamulizumab, the most frequently reported treatment-related TEAEs were infusion-related reaction (36.8%) and drug eruption (22.85).

During the crossover portion of study, 57.4% of subjects had treatment-related TEAEs of maximum Grade 1 or 2 severity; 15.4% had treatment-related TEAEs of maximum Grade 3 severity.

Adverse Events by Time of Onset

An analysis for the time to onset of TEAEs was provided for the pooled safety data for patients with CTCL, with time intervals of 4 weeks (i.e. TEAEs occurring ≤4 weeks, >4 weeks and ≤8 weeks, or >8 weeks of treatment)

and 24 weeks (i.e. TEAEs occurring ≤24, >24 to ≤48, and >48 weeks of treatment). The number subjects patients with long term treatment were 102 for >24 weeks and 51 for >48 weeks.

For the majority of subjects with CTCL, the onset of any TEAE and any treatment related TEAE occurred in the first ≤4 weeks of treatment with mogamulizumab (88.4% [overall] and 65.2% [treatment related]). This trend was primarily driven by the TEAE of infusion-related reaction, which was the most common TEAE occurring in the first ≤4 weeks. The type of TEAE occurring early or late was different, with the majority of infusion-related reactions and pyrexia occurring within the first weeks of treatment (<4 weeks), while infections and infestations and skin and subcutaneous tissue disorders also occurred later on (>8 weeks).

In the analysis of TEAE onset by time intervals of 24 weeks, the onset of any TEAE and any treatment-related TEAE occurred in the first ≤24 weeks of treatment with mogamulizumab for approximately half of the subjects with CTCL (52.8% [overall] and 52.8% [treatment-related]). Similar proportions of subjects with CTCL experienced the onset of any TEAE and any treatment-related TEAE between >24 to ≤48 weeks (24.5% [overall] and 19.3% [treatment-related]), and after >48 weeks (20.2% [overall] and 12.0% [treatment-related]).

Adverse Events of special interest

Eight TEAEs were identified as categories of special interest because they were either known to be associated with mogamulizumab's mechanism of action or were selected from review of the post-marketing experience in Japan. TEAEs of special interest include: infusion-related reactions; infections; rash, tumour lysis syndrome; stress cardiomyopathy, myocardial infarction and acute coronary syndrome; severe cutaneous reactions; immune-related AEs; and GVHD.

Infusion-related reaction (IRR; PT) was the most frequently reported TEAE and treatment-related TEAE in the mogamulizumab group (TEAE all grades: 33.2%, grade ≥3: 1.6%, SAE: 1.6%). The incidence of IRRs was highest after the first infusion (28.8% of subjects), reducing to ≤3.8% of subjects after 2 or more infusions. In the randomisation part of the study there were no cases of infusion-related reactions that led to discontinuation of treatment. After crossover the incidence of treatment-related IRR was 36.8% (grade ≥3:4.4%, SAE: 2.9%) with 4 (2.9%) subjects discontinuing treatment due to IRR (2 SAE, 2 non-serious AE). Infusion-related reaction is considered as an identified risk associated with the use of mogamulizumab.

Infections were reported at a higher frequency in the mogamulizumab group in Study 0761-010 (all grades: 64.1%, grade ≥3: 17.4%, SAE: 24.7%) compared to the vorinostat group (all grades: 50.0%, grade ≥3: 10.2%, SAE: 10.8%). A total of 9 (4.9%) subjects in the mogamulizumab group had treatment-emergent infections (regardless of relationship) that led to discontinuation. Exposure-adjusted analyses revealed a lower exposure-adjusted incidence rate in the mogamulizumab group (0.058 events per patient-months of exposure) compared to the vorinostat group (0.091 events per patient months of exposure).

The most frequently reported infections were upper respiratory tract infection and cough (10.3% and 9.8% of subjects in the mogamulizumab group). Grade ≥3 Infections and infestations in the mogamulizumab group include pneumonia (n=4), sepsis (n=3; 1 Grade 5), bacteraemia (n=2), herpes simplex (n=2), osteomyolitis (n=2). All other events occurred in 1 subject each. The incidence of infection was highest after >8 weeks (37.5%), compared to the first ≤4 weeks (17.9%) or >4 to ≤8 weeks (10.3%) of exposure in the mogamulizumab group. Infection is considered as an identified risk associated with the use of mogamulizumab.

Drug eruption was the most frequent AE leading to discontinuation of treatment (13 subjects, 7.1%). In the mogamulizumab arm the incidence of drug eruption was 23.9% (all grades, grade≥ 3: 4.3%, SAE: 1.1%). The

highest incidence was observed after >8 weeks (16.3%). Rash (drug eruption) is considered as an identified risk associated with the use of mogamulizumab.

Tumour lysis syndrome (TLS) was recorded for 2 subjects in the mogamulizumab group (one Grade 3 and one Grade 1 event) (incidence 1.1%). The incidence of TLS (PT) was 0.9% of all subjects with CTCL, 2.5% of subjects with T-cell lymphomas other than CTCL, and 1.5% of all subjects. The majority of these events were considered related to treatment with mogamulizumab. TLS is considered to be a potential risk associated with the use of mogamulizumab.

Cardiac disorders (Stress cardiomyopathy, myocardial infarction, acute coronary syndrome) were reported during treatment with mogamulizumab. Across all studies, 1 (0.3%) subject (with PTCL) experienced stress cardiomyopathy (PT) and 2 (0.5%) subjects (1 subject with CTCL and 1 subject with ATL) experienced acute myocardial infarction (PT). Stress cardiomyopathy, myocardial infarction and acute coronary syndrome are considered as potential risks associated with the use of mogamulizumab.

Severe cutaneous adverse reactions were recorded the post authorisation safety analyses (estimated 3700 patients, mostly non-CTCL), including Stevens-Johnson syndrome (15), toxic epidermal necrolysis (11), and dermatitis exfoliative (n=9). In all clinical studies with subjects with T-cell lymphomas (n=391), most events in the category of severe cutaneous adverse reactions were considered not related to treatment and were Grade 1 or 2 in severity. Three subjects had Grade 3 events (mouth ulceration, toxic skin eruption, and Stevens-Johnson syndrome reported for 1 subject each). There were no Grade 4 or 5 events. There were no reports of toxic epidermal necrolysis. Severe cutaneous reactions are considered as potential risks associated with the use of mogamulizumab.

Graft versus host disease (GVHD) after allogeneic HSCT: Recent publications have suggested that mogamulizumab treatment prior to HSCT in ATL patients is associated with poor transplant outcomes, specifically the risk of more severe or treatment-refractory acute GVHD seems to be increased in mogamulizumab treated patients, particular when the interval from the last mogamulizumab administration and performance of allo-HSCT is short (roughly less than 3 months). As subjects with a history of allo-HSCT were excluded from the clinical studies with mogamulizumab (except study KW-0761-001) and allo-HSCT was not included as a treatment option, only a few CTCL patients underwent allo-HSCT after mogamulizumab treatment. Follow up of all Western patients treated with mogamulizumab for hematologic malignancies who went on to receive HSCT identified 35 subjects who were reported to have gone onto transplant. As of 20 Jul 2017, 32 completed surveys were received, 24 CTCL subjects and 8 non-CTCL subjects (6 ATL and 2 PTCL). Of these 10 CTCL subjects and 2 non-CTCL subjects developed acute GVHD. The overall median time from last mogamulizumab dose to transplant was >200 days. Increased severity of GVHD, including post-HSCT NCTL subjects, is considered as a potential risk associated with the use of mogamulizumab.

Dermatologic reactions

Patients receiving POTELIGEO have experienced drug rash (drug eruption), some of which were severe and/or serious. The majority of treatment-related dermatologic reactions were Grade 1 or 2, with Grade ≥3 drug rash occurring in 4.3% of patients. No trend in latency to event onset was identified for drug eruptions and rashes; both early and late-onset events occurred.

Infusion-related reactions

Infusion-related reactions have been observed in 33% of patients treated with POTELIGEO. The majority of treatment-related infusion-related reactions were Grade 1 or 2 and occurred during or shortly after the first infusion. Severe reactions (Grade 3) were experienced by 4% of patients.

The incidence of infusion related reactions was highest after the first infusion (28.8% of subjects), reducing to ≤ 3.8% of subjects after two or more infusions. Infusion interruptions occurred in approximately 6% of patients, most of which (approximately 90%) occurred within the first cycle of treatment with mogamulizumab. Less than 1% of patients treated in Study 0761-010 discontinued treatment due to infusion-related reactions.

Serious infections

Patients with MF or SS are at increased risk of serious infection due to the disruption of dermal integrity caused by cutaneous disease, as well as the immunosuppressive effects of extracutaneous disease, and treatment with mogamulizumab may increase that risk. Serious infections, including sepsis, pneumonia and skin infections, were experienced by 14.3% of subjects receiving mogamulizumab. The latency to event onset following the first dose varied considerably. The majority of patients recovered from infection. In the clinical trial (0761-010), there were 2 reports of respiratory failure with fatal outcome in patients with severe pneumonia occurring more than 9 months after starting treatment with mogamulizumab.

Serious adverse events and deaths

During the randomized treatment period, 37.5% of subjects in the mogamulizumab group (16.3% in SOC) and 24.7% of subjects in the vorinostat group experienced SAEs including deaths. With the highest frequency noted in the SOC infections and infestations (16.3% mogamulizumab group vs 10.8% in vorinostat group). Of the 320 subjects exposed to mogamulizumab in Study 0761-010, 21 (6.6%), experienced at least one serious adverse drug reaction (SADR) that occurred within 90 days from the date of last study drug administration.

In the mogamulizumab group, the most frequently reported SAEs were pyrexia (4.3% vs. 0.5% in the vorinostat group), cellulitis (2.7% vs. 3.2%), pneumonia (2.2% vs. 1.1%), and disease progression (2.2% vs. 0.5%). In the vorinostat group, the most frequently reported SAEs were cellulitis, pulmonary embolism (0% mogamulizumab vs. 3.2% vorinostat), and sepsis (1.6% vs. 2.7%).

During the crossover portion of study 10.3% (n=14) of the subjects experienced SAEs. The SAEs reported in ≥2 subjects were cellulitis (n=2), pyrexia (n=2) and infusion related reaction (n=4).

It should be noted that there was inconsistent reporting of disease progression as a TEAE (instead of only as an efficacy variable).

Related SAEs

Treatment related SAEs were reported for 19.6% of patients in the mogamulizumab group and 16.1% in the vorinostat group. In the mogamulizumab group, treatment-related SAEs included pneumonia (2.2%), pyrexia (2.2%), cellulitis (1.6%), and infusion-related reaction (1.6%). All other treatment-related SAEs were reported by ≤2 subjects each. One subject in the mogamulizumab group experienced an SAE of acute myocardial infarction (Grade 3) from which the subject recovered.

During the cross-over portion of study, treatment-related SAEs were reported for 14 (10.3%) of 136 subjects, including 4 (2.9%) subjects with infusion-related reactions and 2 (1.5%) subjects with cellulitis. One subject experienced an SAE of acute myocardial infarction (Grade 3) during the crossover period from which the subject recovered.

Deaths

During the randomized treatment period of study 0761-010, the incidence of TEAEs that led to death was 1.6% (3 subjects) in the mogamulizumab group and 4.8% (9 subjects) in the vorinostat group. During cross-over, 4 (2.9%) subjects experienced TEAEs leading to death.

The incidence of subjects with TEAEs leading to death reported for mogamulizumab group in Study 0761-010 lower than for all subjects with CTCL (3.0%; 7 subjects), and the highest in subjects with T-cell lymphomas other than CTCL (8.9%; 14 subjects). In the overall safety population the incidence of TEAEs leading to death was 5.4% (21 subjects) for all subjects. Other than disease progression, TEAEs leading to death in more than 2 subjects in the Safety population were pneumonia (4 subjects) and respiratory failure (3 subjects).

Table 44. Treatment-emergent Adverse Events Leading to Death (Safety Population).

	Number (%) of Subjects				
	Study 0761-010				
	Randomized Treatment		Crossover		
Preferred Term	Vorinostat N=186	KW-0761 1.0 mg/kg N=184	KW-0761 1.0 mg/kg N=136	All Subjects with CTCL[a] N=233	T-cell Lymphomas Other than CTCL N=158
Subjects with TEAEs Leading to Death[b]	**8 (4.3)**	**3 (1.6)**	**4 (2.9)**	**7 (3.0)**	**14 (8.9)**
TEAEs leading to death					
Sepsis	1 (0.5)	1 (0.5)	1 (0.7)	1 (0.4)	1 (0.6)
Pneumonia pneumococcal	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)
Disease progression	1 (0.5)	1 (0.5)	0 (0.0)	3 (1.3)	1 (0.6)
Polymyositis	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)
Death	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.5)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Septic shock	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)
Pneumonia	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.9)
Empyema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Urosepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Endocarditis	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchopneumonia	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)
Pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Pneumothorax	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Intestinal obstruction	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haematemesis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Upper gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Mycosis fungoides	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Depressed level of consciousness	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin disorder	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Left ventricular hypertrophy	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The review of the updated safety data (01 Sep 2017) on SAEs and AEs leading to death across study 0761-010 and pooled CTCL and other lymphoma studies does not impact the benefit risk of the use of the mogamulizumab in the CTCL patient population.

Laboratory findings

Shift tables in CTCAE grade from baseline to the worst post-baseline toxicity grade (Grade≤2 vs Grades≥3) were presented by treatment group for selected haematology and chemistry parameters. During the randomized treatment period in Study 0761-010, 44.0% of subjects in the mogamulizumab group had shifts in lymphocytes (decreased) from Grade ≤2 at baseline to Grades ≥3 post-baseline compared to 10.3% of subjects in the vorinostat group.

For other haematology parameters, the percentages of subjects with shifts from Grade ≤2 at baseline to Grades ≥3 post-baseline were similar or lower in the mogamulizumab group (≤1.6% of subjects) compared to the vorinostat group (≤7.6% of subjects).

The frequency of shifts in CTCAE grade in serum chemistry parameters (albumin, alkaline phosphatase, ALT, AST, total bilirubin, creatinine, glucose, magnesium, and phosphorus), from Grade ≤2 at baseline to Grade ≥3 (based on highest grade observed) was low (< 10% of patients) in both treatment groups and generally similar or lower in the mogamulizumab group compared to the vorinostat group, except for a shifts to Grade ≥3 elevations in serum glucose (non-fasting), which was twice as frequent in the vorinostat group as in the mogamulizumab group.

The frequencies of abnormal haematology and serum chemistry values reported as TEAE are similar between the treatment arms, except for lymphocyte counts which were more often decreased in the mogamulizumab treated patients. Flow cytometry analysis showed that the target subset of lymphocytes specifically expected to be reduced by the treatment with mogamulizumab were CD26- and CD7- populations of CD4+ cells. The median time to first reduction of lymphocytes was approximately 4 weeks (29 days; minimum 26 days and maximum 283 days). In these patients, the mean duration of exposure was 1.1 months and 8.6 months before and after experiencing lymphocyte reduction, respectively, whereas in 25 patients who did not experience lymphocyte reduction the mean duration of exposure was 2.5 months.

Safety in special populations

Safety in MF and SS populations

The overall incidence of TEAEs was similar between subjects with MF (95.5%) and SS (100.0%). The proportion of subjects with the most frequently reported TEAEs (≥10% of subjects with CTCL) were similar between subjects by baseline CTCL diagnosis (see Table **44**).

The incidence of treatment-related TEAEs was higher in subjects with SS (91.8%) than in subjects with MF (78.4%). Similarly, the incidence of treatment-emergent SAEs was higher in subjects with SS (41.8%) than in subjects with MF (30.6%). This difference was in part due to higher incidences of treatment-emergent SAEs in subjects with SS for cellulitis and pneumonia (5.1% each [vs. 0% each in subjects with MF]), and pyrexia (5.1% [vs. 2.2%]).

No clinically meaningful differences were observed in the incidences of TEAEs leading to death or TEAEs leading to treatment discontinuation for subjects by baseline diagnosis status.

Table 45 TEAE reported for ≥10 % of all Subjects with CTCL by Baseline Diagnosis Status (MF or SS) – All Subjects with CTCL (Safety Population)

	Number of Subjects (%)		
	Subjects with Relapsed or Refractory CTCL		
Preferred Term[a]	MF (N=134)	SS (N=98)	All Subjects (N=233)
Any TEAE	128 (95.5)	98 (100.0)	227 (97.4)
Infusion related reaction	36 (26.9)	34 (34.7)	70 (30.0)
Drug eruption	24 (17.9)	26 (26.5)	50 (21.5)
Fatigue	30 (22.4)	20 (20.4)	50 (21.5)
Diarrhoea	24 (17.9)	24 (24.5)	48 (20.6)
Nausea	20 (14.9)	22 (22.4)	42 (18.0)
Pyrexia	22 (16.4)	19 (19.4)	41 (17.6)
Headache	20 (14.9)	13 (13.3)	33 (14.2)
Oedema peripheral	14 (10.4)	11 (11.2)	25 (10.7)
Upper respiratory tract infection	13 (9.7)	11 (11.2)	24 (10.3)

Some differences in safety profile between the MF stage I/II, MF stage III/IV, and SS patient subcategories were observed: in particular, an increased incidence of some infections (mainly cellulitis and pneumonia), drug-related thrombocytopenia, and increased incidence of ALT increased and AST increased in patients with SS compared to the MF subtypes. It is agreed with the applicant that the longer exposure to treatment in the SS/stage III-IV populations, as well as the higher proportion of elderly and more severe disease in the SS subpopulation might have confounded safety subgroup analyses. It is reassuring that exposure adjusted frequencies showed smaller differences for most AEs between the disease subcategories.

Age

In study 0761-010, among subjects randomized to receive mogamulizumab, the incidence of TEAEs associated with the Infections and Infestations SOC was higher among subjects <65 years of age (37.0%) than those ≥65 years (27.2%). The incidence of diarrhoea was somewhat higher among subjects <65 years old (14.7%) compared to those ≥65 years (8.7%). There were no other marked differences in incidence of TEAEs by SOC or preferred terms. The incidence of drug eruption (9.8% and 14.1%, respectively) and infusion-related (16.3% and 16.8%, respectively) were similar for the two age groups.

In the pooled safety population (all studies), the overall incidence of TEAEs was similar between subjects <65 years old (97.3%) and ≥65 years old (98.9%). Some AEs occurred more frequent in the older patients, for example, in patients randomized to and treated with mogamulizumab, serious AEs (38.3% vs 35.4%), AEs leading to drop-out (16% vs 12.1%), the SOC Cardiac disorders (13.6% vs 4%), vascular disorders (16% vs 14.1%), sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures (22.2% vs 14.1%) and some of the AEs of special interest such as infusion related reactions (72.8% vs 65.7%), rash (33.3% vs 22.2%), tumour lysis syndrome (21% vs 13.1%), cardiac AEs of special interest (i.e. cardiomyopathy, myocardial infarction, acute coronary syndrome) (18.5% vs 5.1%), and severe cutaneous reactions (13.6% vs 7.1%). However, for most of these AEs the same trend is observed, not only in the cross-over patients, but also in the vorinostat group.

Table 46 Frequency various MedDRA Terms according to age

	KW-0761				Vorinostat				Cross-over population			
	Age <65 (N=99) n (%)	Age 65-74 (N=52) n (%)	Age 75-84 (N=29) n (%)	Total (N=180) n (%)	Age <65 (N=89) n (%)	Age 65-74 (N=65) n (%)	Age 75-84 (N=27) n (%)	Total (N=181) n (%)	Age <65 (N=59) n (%)	Age 65-74 (N=54) n (%)	Age 75–84 (N=18) n (%)	Total (N=131) n (%)
Total AEs	95 (96.0)	52 (100.0)	28 (96.6)	**175 (97.2)**	89 (100)	64 (98.5)	27 (100)	**180 (99.4)**	52 (88.1)	52 (96.3)	18 (100.0)	**122 (93.1)**
Total Serious AEs	35 (35.4)	23 (44.2)	8 (27.6)	**66 (36.7)**	19 (21.3)	15 (23.1)	11 (40.7)	**45 (24.9)**	12 (20.3)	14 (25.9)	8 (44.4)	**34 (26.0)**
Fatal	0	2 (3.8)	1 (3.4)	**3 (1.7)**	4 (4.5)	3 (4.6)	1 (3.7)	**8 (4.4)**	1 (1.7)	1 (1.9)	2 (11.1)	**4 (3.1)**
Hospitalization	31 (31.3)	21 (40.4)	8 (27.6)	**60 (33.3)**	0	0	0	0	11 (18.6)	13 (24.1)	7 (38.9)	**31 (23.7)**
Life-threatening	4 (4.0)	4 (7.7)	1 (3.4)	**9 (5.0)**	5 (5.6)	5 (7.7)	0	**10 (5.5)**	0	0	2 (11.1)	**2 (1.5)**
Disability/incapacity	4 (4.0)	0	1 (3.4)	**5 (2.8)**	2 (2.2)	0	0	**2 (1.1)**	1 (1.7)	0	0	**1 (0.8)**
Medically significant	10 (10.1)	9 (17.3)	3 (10.3)	**22 (12.2)**	0	0	0	0	3 (5.1)	4 (7.4)	1 (5.6)	**8 (6.1)**
AEs leading to drop-out	12 (12.1)	8 (15.4)	5 (17.2)	**25 (13.9)**	0	0	0	0	8 (13.6)	9 (16.7)	4 (22.2)	**21 (16.0)**
Psychiatric disorders	18 (18.2)	10 (19.2)	3 (10.3)	**31 (17.2)**	15 (16.9)	9 (13.8)	4 (14.8)	**28 (15.5)**	5 (8.5)	4 (7.4)	2 (11.1)	**11 (8.4)**
Nervous system disorders	35 (35.4)	15 (28.8)	12 (41.4)	**62 (34.4)**	54 (60.7)	31 (47.7)	16 (59.3)	**101 (55.8)**	19 (32.2)	19 (35.2)	6 (33.3)	**44 (33.6)**
Injury, Poisoning and Procedural Complications	43 (43.4)	26 (50.0)	9 (31.0)	**78 (43.3)**	11 (12.4)	11 (16.9)	4 (14.8)	**26 (14.4)**	22 (37.3)	29 (53.7)	9 (50.0)	**60 (45.8)**
Cardiac disorders	4 (4.0)	8 (15.4)	3 (10.3)	**15 (8.3)**	7 (7.9)	4 (6.2)	2 (7.4)	**13 (7.2)**	2 (3.4)	4 (7.4)	3 (16.7)	**9 (6.9)**
Vascular disorders	14 (14.1)	7 (13.5)	6 (20.7)	**27 (15.0)**	21 (23.6)	10 (15.4)	7 (25.9)	**38 (21.0)**	2 (3.4)	3 (5.6)	1 (5.6)	**6 (4.6)**
Infections and Infestations	68 (68.7)	34 (65.4)	13 (44.8)	**115 (63.9)**	46 (51.7)	32 (49.2)	11 (40.7)	**89 (49.2)**	34 (57.6)	28 (51.9)	9 (50.0)	**71 (54.2)**
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	14 (14.1)	12 (23.1)	6 (20.7)	**32 (17.8)**	14 (15.7)	10 (15.4)	6 (22.2)	**30 (16.6)**	6 (10.2)	7 (13.0)	3 (16.7)	**16 (12.2)**
Baseline Skindex 29 Total Score												
n	93	51	26	**170**	87	62	27	**176**	59	54	18	**131**
Mean	55.48	49.87	56.43	**53.94**	51.21	47.27	41.456	**48.33**	50.19	48.97	47.27	**49.29**
SD	21.47	19.16	21.32	**20.83**	20.53	19.01	20.48	**20.18**	18.47	20.82	24.48	**20.21**
Min	6.55	8.31	20.14	**6.55**	14.94	3.41	0.00	**0.00**	13.77	11.90	0.00	**0.00**
Median	57.70	50.48	56.50	**52.84**	49.58	49.67	41.73	**49.02**	51.29	48.16	46.79	**48.85**
Max	94.17	95.28	92.85	**95.28**	92.18	88.51	72.30	**92.18**	93.33	100.00	85.62	**100.00**
Baseline ECOG Status (n [%])												
n	99	52	29	**180**	89	65	27	**181**	59	54	18	**131**
0	61 (61.6)	31 (59.6)	11 (37.9)	**103 (57.2)**	59 (66.3)	32 (49.2)	13 (48.1)	**104 (57.5)**	41 (69.5)	25 (46.3)	6 (33.3)	**72 (55.0)**
1	37 (37.4)	21 (40.4)	17 (58.6)	**75 (41.7)**	30 (33.7)	33 (50.8)	14 (51.9)	**77 (42.5)**	18 (30.5)	29 (53.7)	11 (61.1)	**58 (44.3)**
2	1 (1.0)	0	1 (3.4)	**2 (1.1)**	0	0	0	**0**	0	0	1 (5.6)	**1 (0.8)**
QoL Data Worsening (n [%])												
Skindex259 Score Worsening from Baseline	51 (54.8)	24 (47.1)	13 (50.0)	**88 (51.8)**	48 (55.2)	41 (66.1)	15 (55.6)	**104 (59.1)**	35 (59.3)	29 (53.7)	9 (50.0)	**73 (55.7)**
ECOG Status Worsening from Baseline	29 (29.3)	22 (42.3)	9 (31.0)	**60 (33.3)**	30 (33.7)	17 (26.2)	12 (44.4)	**59 (32.6)**	22 (37.3)	16 (29.6)	4 (22.2)	**42 (32.1)**

AE=adverse event; ECOG=Eastern Cooperative Oncology Group; N=population; n=sub-population; QoL=quality of life; SD=standard deviation.
Source: EMA_Q127_HMS, EMA_Q127_SUM, EMA_Q127_Summary_of_QoL_Data_Worsen

Gender

There were 223 male subjects and 176 female subjects in the overall Safety population. The overall incidence of TEAEs was similar between male subjects (97.3%) and female subjects (98.9%). Differences in the frequency of TEAEs between the genders were in the following PT: infusion related reactions, pyrexia, fatigue and chills

occurred more often in females than males (40% vs 29%, 31 vs 23%, 20 vs 14%, 17 vs 11% respectively), while drug eruption seems more common among males (22 vs 15%).

In Study 0761-010, the overall incidence of TEAEs was higher among male subjects (56.5%) than among female subjects (40.8%) receiving mogamulizumab. Differences in incidence of TEAEs by SOC and/or individual preferred terms were observed in Gastrointestinal Disorders (males, 29.9%; females, 20.7%); Infections and Infestations (males, 37.0%; females, 27.2%); Skin and Subcutaneous Tissue Disorders (males, 32.1%; females, 20.7%); Drug eruption (males, 14.7%; females, 9.2%); Respiratory, Thoracic and Mediastinal (males, 17.9%; females, 12.5%). Infusion-related reactions occurred with similar frequency in males (15.8%) and females (17.4%).

Race

The overall incidence of TEAEs was similar between subjects who were White (97.8%), Asian (100%), Black/African American (96.3%), or whose race was reported as Other (91.7%). Any observed differences were likely due to different study designs (i.e., inpatient monitoring, protocol-defined reporting of laboratory AEs, and protocol-defined assessments of infusion-related reactions; and protocol-mandated reporting of rashes as drug eruptions) of the studies in Japan. Due to the small number of subjects who were Black/African American (n=54) compared to subjects who were White (n=185), Asian (n=94), or Other (n=12), no meaningful conclusions can be made from these differences.

ECOG performance status

The majority of subjects had a baseline ECOG PS of 0 (213 subjects) or 1 (134 subjects); 43 subjects had a baseline ECOG PS of 2. Overall, the incidence of subjects with TEAEs and treatment-related TEAEs was similar between these groups. Treatment-emergent SAEs were more frequently reported in subjects with an ECOG PS of 2 (67.4%) than in subjects with an ECOG PS of 1 (41.8%) or 0 (26.3%), as were TEAEs leading to treatment discontinuation (27.9% vs. 20.9% vs. 11.3%, respectively), and TEAEs leading to death (27.9% vs. 3.7% vs. 1.9%).

Other subpopulations

Geographic locations: The geographic regions of the US (164[41.1%] subjects), Europe (121 [30.3%]), and the Rest of World (Japan, Australia, SA, and Caribbean; 106 [26.6%] were compared. Analysis by these geographic regions showed that no conclusions can be drawn based on the small numbers of subjects and reports of TEAEs.

The Applicant has not discussed the impact of renal impairment, hepatic impairment or CCR4 expression level on the safety profile of mogamulizumab.

The effect of ADA on safety was analysed from the pooled immunogenicity database of Study 0761-007, 0761-009, and 0761-010, that were similar for dose and dosing regimen and immunogenicity testing methodology, including the bioanalytical method used for measuring anti-mogamulizumab and neutralising antibody.

The overall percentage of samples with a status of “ADA-inconclusive” was 37.6% (790 of 2100 samples) because the concentration of mogamulizumab in the test sample exceeded the DLT for the neutralising assay.

Safety related to drug-drug interactions and other interactions

No adverse events due to interactions were noted.

Discontinuation due to adverse events

In pivotal Study 0761-010, 157 of the 184 subjects in the mogamulizumab group, 176 of the 186 vorinostat group (of which 136 subjects crossed over) and 105 of the 136 subjects in the cross-over group had discontinued treatment. The most frequent reasons for discontinuation were disease progression and AEs/intolerance of treatment. Discontinuation due to AE was reported for TEAEs leading to discontinuation of treatment occurred in 35 (19.0%) of subjects in the mogamulizumab group and 43 (23.1%) in the vorinostat group. For subjects randomized to mogamulizumab, the percentage of subjects discontinuing randomized therapy due to disease progression was slightly higher for subjects with the MF subtype compared to the SS Subtype (60/105 [57.2%] vs 38/81 [46.9%], respectively) and for subjects with stage IB/II compared to stage III/IV CTCL (40/68 [58.9%] vs 58/118 [49.2%], respectively). The number of subjects discontinuing due to adverse events was lower in subjects with the MF subtype compared to the SS Subtype (13/105 [12.4%] vs 15/81 [18.5%], respectively) and in subjects with stage IB/II compared to stage III/IV CTCL (8/68 [11.8%] vs 20/118 [16.9%], respectively). In contrast, in the control arm, the mean exposure was greater for subjects with MF than SS, and greater for subjects with stage IB/II compared to stage III/IV.

In the mogamulizumab group, drug eruption was the most frequent AE leading to discontinuation of treatment (13 subjects, 7.1%). In the vorinostat group, the most frequent AEs leading to discontinuation were fatigue (4.3%), diarrhoea (2.7%), and thrombocytopenia (2.7%).

During the crossover portion of study, treatment-related AEs leading to discontinuation were reported for 23 (16.9%) of 136 subjects, including 12 (8.8%) subjects with drug eruptions and 4 (2.9%) with infusion-related reactions.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

The safety database of mogamulizumab, administered as monotherapy is comprised of 7 clinical studies in patients with T-cell lymphoma (CTCL, PTCL, and ATL). The pivotal randomised controlled Phase 3 study 0761-010 is the main study used for safety assessment as it accounts for 79% of the total CTCL population exposed to mogamulizumab, supplemented by safety data from the other studies.

At the time of cut-off date for study 0761-010 (31 Dec 2016), the median number of 28 day-cycles during the randomized treatment period was 6 in the mogamulizumab arm (170 days), and 3 in the vorinostat arm (84 days). The median relative dose intensity was 97.49% for mogamulizumab, and 95.12% for vorinostat.

A difference in exposure between the disease subtypes and disease stages is seen in the mogamulizumab arm, with longer exposure time in subjects with more advanced/severe disease . Also the reasons for discontinuation seem to be different between subjects with less and more advanced/severe disease. In the less advanced/severe disease population discontinuations were more often due to disease progression, while in advanced disease population adverse events were more commonly noted as reason for discontinuation. These differences in exposure and discontinuation may suggests that in particular subjects with more advanced/severe disease experience a beneficial effect of mogamulizumab treatment, which is in line with the conclusion on efficacy.

During the randomized treatment period in Study 0761-010, almost all patients experienced at least one TEAE: 97.3% in the mogamulizumab arm and 99.5% in the vorinostat arm. While the incidence of Grade ≥3 TEAEs was similar between the two treatment groups (42.4% vs 45.7%), a higher incidence of SAEs including deaths was seen in the mogamulizumab group (37.5% vs 24.7%). The incidence of TEAEs that led to death was 1.6% (3 subjects) in the mogamulizumab group and 4.8% (9 subjects) in the vorinostat group.

The incidence of treatment-related TEAEs and treatment-related grade ≥3 TEAE was lower for mogamulizumab (84.8%, and 25.5%) compared to vorinostat (95.7% and 34.9%). As this is an open label study, this might reflect the physicians perception of the safety of mogamulizumab vs vorinostat rather than a real difference in treatment-attributable TEAEs.

The most frequently reported serious adverse reactions were pneumonia, pyrexia, infusion related reaction and cellulitis. The most frequently reported adverse reactions were infusion-related reaction and rash (drug eruption); most of these reactions were non-serious and Grades 1 or 2.

Severe adverse reactions included Grade 4 respiratory failure (1.1%) and Grade 5 reactions were polymyositis and sepsis (0.5% each).

No major differences are noted between the profile of treatment-related TEAEs or SAEs compared to that of all TEAEs and SAEs irrespective of causality.

The reporting of the effects of laboratory analysis consisted only of an analysis of shifts in laboratory parameters. In this analysis a shift to ≥ grade 3 lymphocyte decreased was more frequently noted in mogamulizumab treated patients (44% vs 10.3%). Similarly, neutropenia and neutrophil count decrease were also considered related to treatment in some cases (2.7% and 1.6%, respectively), and are included in table of section 4.8 of the SmPC.

More frequent TEAEs (by SOC or PT) in the vorinostat group included GI symptoms (diarrhoea, nausea, vomiting constipation), constitutional symptoms (fatigue, asthenia), thrombocytopenia and taste disorders (dysgeusia, dry mouth) and correspond to the most common adverse reactions described in the (FDA) label of vorinostat.

The majority of subjects experienced a TEAE early during treatment, the frequency of late onset TEAE was lower, but still occurred regularly, in approximately 25% of the subjects treated for longer duration. Of note the number of subjects with long term treatment is rather limited (n=102 for > 24 weeks and n=51 for >48 weeks). The majority of infusion-related reactions and pyrexia occurred within the first weeks of treatment (<4 weeks), while infections and infestations and skin and subcutaneous tissue disorders also occurred later on (>8 weeks).

Acute infusion-related reactions (IRRs) have been observed in patients treated with mogamulizumab. The IRRs were mostly mild or moderate in severity, although there have been a few reports of severe reactions (Grade 3). The majority of IRRs occur during or shortly after the first infusion (all within 24 hours of administration), with the incidence decreasing over subsequent treatments. During the first month of treatment a higher frequency of TLS-related events is apparent, therefore routine monitoring of clinical laboratory parameters, including renal function test and electrolytes, for all patients at least during this time frame are recommended (see SmPC section 4.4).

The number of subjects with a TEAEs leading to discontinuation of treatment were 35 (19.0%) in the mogamulizumab group and 43 (23.1%) in the vorinostat group. For a substantial number of subjects (35%) a dose of mogamulizumab was withheld or not administered. The AEs recorded as reason for withholding a dose (drug eruption, thrombocytopenia/platelet count decreased, neutrophil count decreased/neutropenia, infusion

related reaction) are among the most commonly observed AEs. Notably, drug eruption was the most frequent AE leading to discontinuation of treatment.

When mogamulizumab has been administered to patients with T-cell lymphomas other than MF or SS, serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in less than 1% of patients during clinical trials, and also reported during the post-marketing period; some of these cases were reported with fatal outcomes. Patients should be closely monitored for symptoms or signs that suggest SJS or TEN. If they occur, mogamulizumab should be interrupted and treatment should not restart unless SJS or TEN is ruled out and cutaneous reaction has resolved to Grade 1 or less. If SJS/TEN occur, appropriate medical therapy should be administered. (see SmPC section 4.4).

Subjects with MF or SS treated with mogamulizumab are at increased risk of serious infection and/or viral reactivation. The combination of mogamulizumab with systemic immune modulating medicinal products or with other licensed therapies for MF or SS has not been studied and is, therefore, not recommended, especially in consideration of the risk of severe infections in patients treated with mogamulizumab. Topical steroids or low doses of systemic corticosteroids may be used during treatment with mogamulizumab; however, the risk of serious infection and/or viral reactivation may be higher in case of concomitant administration with systemic immunosuppressive agents. Patients should be monitored for signs and symptoms of infection and treated promptly.

Patients should be tested for hepatitis B infection before initiating treatment with mogamulizumab. For patients who test positive for current/previous hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended for advice concerning appropriate measures against hepatitis B reactivation (see section 4.4 of the SmPC).

Complications, including severe graft versus host disease (GVHD), have been reported in patients with T-cell lymphomas other than MF or SS who received allogeneic HSCT after mogamulizumab.

A higher risk of transplant complications has been reported if mogamulizumab is given within a short time frame (approximately 50 days) before HSCT. Follow patients closely for early evidence of transplant-related complications. The safety of treatment with mogamulizumab after autologous or allogeneic HSCT has not been studied.

Increased severity of GVHD, including post-HSCT NCTL subjects, is considered as a potential risk associated with the use of mogamulizumab. A post-Authorisation Safety Study to Characterise the Safety of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in Patients with Cutaneous T-Cell Lymphoma (CTCL) treated with Mogamulizumab is agreed (see RMP).

Tumour lysis syndrome (TLS) has been observed in patients receiving mogamulizumab. TLS was observed most frequently during the first month of treatment. Patients with rapidly proliferating tumour and high tumour burden are at risk of TLS. Patients should be monitored closely by appropriate laboratory and clinical tests for electrolyte status, hydration and renal function, particularly in the first month of treatment, and managed according to best medical practice. Management of TLS may include aggressive hydration, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care (see section 4.4 of the SmPC).

One case of acute myocardial infarction has been observed in a clinical trial patient with MF / SS receiving mogamulizumab. In clinical trial patients with other T-cell lymphomas there have been reports of stress cardiomyopathy (one case) and acute myocardial infarction (one case). The subjects had a medical history including various risk factors. Patients who have risk factors associated with cardiac disease should be monitored and appropriate precautions taken (see section 4.4 of the SmPC).

The review of the updated safety data on SAEs and AEs leading to death across study 0761-010 and pooled CTCL and other lymphoma studies did not change the picture in the CTCL patient population.

Further, the type and frequency of adverse events was compared between MF stage I/II, MF stage III/IV, and SS patients. The study population with SS had primarily advanced stage disease, and included a substantial larger proportion of patients ≥65 years of age compared to the MF subcategories. Some differences in safety profile between the three subcategories were observed: in particular, an increased incidence of some infections (mainly cellulitis and pneumonia), drug-related thrombocytopenia, and increased incidence of ALT increased and AST increased in patients with SS compared to the MF subtypes. It seems that the longer exposure to treatment in the SS/stage III-IV populations, as well as the higher proportion of elderly and more severe disease in the SS subpopulation might have confounded safety subgroup analyses. It is reassuring that exposure adjusted frequencies showed smaller differences for most AEs between the disease subcategories.

AEs in the SOCs of cardiac disorders and Vascular diseases, and rash and infusion-related reactions as AEs of special interest occurred with a higher frequency in older (≥65 years) patients receiving mogamulizumab, but not in those randomized to vorinostat. However, only for rash and IRR the difference was considered indicative of age being a potential risk factor for the occurrence of these adverse events. This as the incidence for treatment related rash was 29% vs 18% for ≥ 65 years and < 65 years, respectively, and for IRR (anaphylactic reaction, CRS) was 60.0% vs 50.5% for ≥ 65 years and < 65 years, respectively.

Some differences in frequency of TEAEs were noted between the genders. Overall it appears that females were more likely to have general disorders and administration site conditions (pyrexia/chills, pain), infusion related reactions, blood and lymphatic system disorders (lymphopenia, anaemia and neutropenia) and insomnia, while males were more prone to have skin and cutaneous disorders (drug eruption, alopecia). No gender specific AE was observed, and no consistent gender difference in grade 3/4 AE across the T cell lymphoma population and study 0761-010 population and in serious AE was noted. It was concluded that the difference in frequency between AE as PT is relatively small, and not clinically relevant, meaning that there is insufficient data to justify inclusion in the SmPC.

Women of childbearing potential and males of reproductive potential should use effective contraception during treatment with POTELIGEO and for at least 6 months after treatment.

There are no data from the use of mogamulizumab in pregnant women. Although mogamulizumab crosses the placental barrier in cynomolgous monkey, apart from the pharmacological effect in foetuses, animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of mogamulizumab during pregnancy.

It is unknown whether mogamulizumab is excreted in human milk. There is no data on the excretion of mogamulizumab in milk from animal studies with mogamulizumab. In humans, during the first few days after birth IgG1 antibodies may be excreted in milk and through the milk transferred to newborns. In this short period, a risk to the breast-fed child cannot be excluded.

There are no clinical data available on the effect of mogamulizumab on human fertility. No specific studies in animals have been performed to evaluate the effect of mogamulizumab on fertility. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies in cynomolgus monkeys (see section 4.6).

As only a few subjects were considered ADA-positive, no conclusion can be drawn on the effect of ADA on the safety profile.

The effect of differences in the % of CCR4 positive cells on the safety of mogamulizumab treatment was analysed. The frequency of reported AEs fluctuated across the 4 analysed subcategories with CCR4 expression levels between 1-90%. It is nevertheless agreed that no substantial difference in the safety profile of mogamulizumab in patients with different CCR4 expression levels has been observed.
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of mogamulizumab has been characterised in a sufficient number of subjects. Overall, main risks associated with mogamulizumab treatment are infusion-related reactions, drug eruption and infections – which were in general mild or moderate in severity, therefore the safety profile appears to be manageable. The MAH should closely monitor in the PSURs the immune-related adverse events.

The CHMP considers the following measures necessary to address issues related to safety:

- Post-Authorisation Safety Study to Characterise the Safety of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in Patients with Cutaneous T-Cell Lymphoma (CTCL) treated with Mogamulizumab.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Infusion-related reaction
Important potential risks	Hepatitis B reactivation Increased risk of severe GVHD after allogeneic HSCT
Missing information	Use in patients with a history of autologous or allogeneic transplant

Pharmacovigilance plan

Study title and status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Post-Authorisation Safety Study to Characterise the Safety of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in Patients with Cutaneous T-Cell Lymphoma (CTCL) treated with Mogamulizumab. Planned	To include treatment-related mortality, non-relapse mortality and cause, and incidence and characterization of GVHD and graft failure.	Increased risk of severe GVHD after allogeneic HSCT	Finalization of protocol	Q1 2019
			Date of interim report	Jul 2021
			End of data collection	Feb 2024

Study title and status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Final Clinical Study Report	Jul 2024

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified Risk		
Infusion-related reaction	Routine risk minimization measures: SmPC Section 4.2; 4.4; 4.8 PL Section 2 and 4 SmPC Section Legal status. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: A questionnaire to obtain further information on infusion-related reactions. Additional pharmacovigilance activities: None.
Important Potential Risks		
Hepatitis B reactivation	Routine risk minimization measures: SmPC Section 4.4 and 4.8 PL Section 2 and 4 Legal status. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Increased risk of severe GVHD after allogeneic HSCT	Routine risk minimization measures: PL Section 2 and 4 SmPC Section 4.4 Legal status. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS to characterize the safety of allogeneic HSCT in patients with CTCL treated with mogamulizumab.
Missing Information		
Use in patients with history of autologous or allogeneic transplant	Routine risk minimization measures: Section 2 of the PL Legal status. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 30.03.2012. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. New Active Substance

The applicant declared that mogamulizumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on a review of the available data, considers mogamulizumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, POTELIGEO (mogamulizumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The initial proposed indication was CTCL, but no data had been provided in other subtypes than MF or SS in the pivotal trial; the indication was later revised to include MF and SS patients.

Further to the CHMP review, the proposed indication is 'the treatment of mycosis fungoides (MF) or Sézary syndrome (SS) in adults who have received at least one prior systemic therapy. These conditions are the most frequently observed subsets of Cutaneous T-cell lymphoma (CTCL) a group of primary cutaneous lymphomas (PCL).

3.1.2. Available therapies and unmet medical need

Most CTCL subtypes are characterized by frequent recurrences. The early stages of MF and pcALCL have an excellent prognosis, while the advanced stages of MF have a poor prognosis. In contrast to patch/plaque MF, SS is much more symptomatic, has a lower potential for remission, and lower expected survival. At present, there are no standard therapies for patients with higher stage treatment resistant disease. Systemic options bexarotene and methotrexate are frequently used in second line MF (both RR 30-50%). With Sézary's syndrome (SS), low dose methotrexate, bexarotene, denileukin difitox, alemtuzumab (low-dose) and multi-agent chemotherapy have been recommended as second-line treatment.

3.1.3. Main clinical studies

Main evidence to support this application is obtained from pivotal Phase 3, randomized, open-label Study 0761-010. This study evaluated the efficacy and safety of mogamulizumab (n=186) versus vorinostat (n=186) in patients with previously treated relapsed or refractory CTCL (~54% MF and ~45% SS).

3.2. Favourable effects

The primary endpoint PFS per Investigator based on the ITT population, as reported after 241 PFS events at the data cut-off (31 Dec 2016), showed a statistically significant improvement for mogamulizumab compared with vorinostat with a HR of 0.53 (95% CI: 0.41, 0.69, 2-sided p<0.0001) and a gain in median PFS of 4.6 months in favour of mogamulizumab (median PFS 7.7 months vs 3.1 months, respectively).

The results of several secondary endpoints supported the primary endpoint. PFS by Independent Review as reported after 232 PFS events, showed a statistically significant improvement for mogamulizumab with a HR of 0.64 (95% CI: 0.49, 0.84, 2-sided p=0.0007), and a gain in median PFS of 2.87 months (6.70 months mogamulizumab vs. 3.83 months vorinostat). The ORR per investigator was significantly higher for mogamulizumab (28%) vs. vorinostat (4.8%) in the ITT, and in all the analysed subpopulations.

Confirmed compartmental response rates in skin, blood and lymph nodes based on investigator assessment as well as independent review were all significantly larger for mogamulizumab than for vorinostat in the ITT, and in all the analysed subpopulations.

The median DOR was 14.07 months vs. 9.13 months, in favour of mogamulizumab; The median TTR was 3.32 months vs. 5.10 months, in favour of mogamulizumab. A post-hoc analysis of Time to Next Treatment (TTNT)

indicated a significant increase in median TTNT for mogamulizumab compared to vorinostat in the ITT (11.00 months; 95% CI: 8.80, 12.63 vs 3.47 months; 95% CI; 3.10, 4.27), and in all the analysed subpopulations. The exploratory endpoint of TTF was 5.8 months with mogamulizumab vs. 2.87 months with vorinostat.

The median OS was 43.93 months (43.57,-) in the vorinostat arm, and not estimable for the mogamulizumab arm (HR=0.93, 95% CI 0.61, 1.43); however the interpretation of this result is hindered by the cross-over design of the trial.

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties in the favourable effects of mogamulizumab in the treatment of MF and SS.

3.4. Unfavourable effects

Almost all patients (97.3%) experienced at least one TEAE upon mogamulizumab treatment, with 42% grade ≥ 3 TEAEs, 38% of the subjects experiencing SEA, and 3 subjects (1.6%) were reported to have a TEAE that led to death. In the pivotal study 35 (19%) subjects randomised to mogamulizumab discontinued treatment due to adverse events.

The most frequently reported adverse reactions were infusion related reaction and rash (drug eruption); most of these reactions were non serious and Grades 1 or 2. Severe adverse reactions included Grade 4 respiratory failure (1.1%) and Grade 5 reactions were polymyositis and sepsis (0.5% each). The most frequently reported serious adverse reactions were pneumonia, pyrexia, infusion related reaction and cellulitis.

A shift to ≥ grade 3 lymphocyte decreased was more frequently noted in mogamulizumab treated patients (44% vs 10.3%). The reduction of lymphocytes is linked to the mechanism of action of mogamulizumab treatment. Flow cytometry analysis showed that the target subset of lymphocytes specifically expected to be reduced by the treatment with mogamulizumab were CD26- and CD7- populations of CD4+ cells.

Infusion-related reaction, infections, and rash (drug eruption) are considered as identified risks associated with the use of mogamulizumab. Furthermore tumour lysis syndrome and severe cutaneous adverse reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) were identified as potential risks associated with mogamulizumab treatment. Also increased severity of GVHD upon HSCT after mogamulizumab treatment has been noted as a potential risk associated with the use of mogamulizumab.

3.5. Uncertainties and limitations about unfavourable effects

As subjects with a history of allo-HSCT were excluded from the pivotal clinical study and allo-HSCT was not included as a treatment option, only a few CTCL patients underwent allo-HSCT after mogamulizumab treatment. Increased severity of GVHD, including post-HSCT NCTL subjects, has been reported in the literature is considered as a potential risk associated with the use of mogamulizumab. A PASS study is agreed to characterise safety of HSCT- including treatment-related mortality, non-relapse mortality and cause, and incidence and characterization of GVHD and graft failure, in CTCL patients treated with mogamulizumab (see RMP).

3.6. Effects Table

Table 47. Effects Table for mogamulizumab in the treatment of CTCL in adults who have received at least one prior systemic therapy (efficacy data cut-off: 31 Dec 2016).

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Time from randomization to PD or death.	Median months	7.7	3.1	HR of 0.53 (95% CI: 0.41, 0.69, 2-sided p<0.0001)	CSR
ORR	CR or PR, confirmed 4 weeks later (Inv).	n (%)	28%	4.8%	95% CI (21.6, 35.0) vs (2.2, 9.0)	0761-010
DOR	Time from CR/PR to PD or death.	Median months	14.07	9.13	(by Inv: 95% CI = (9.43, 19.17; n=52)	
TTF	Time from randomization until discontinuation due to any reason.	Median months	5.8	2.87		
Unfavourable Effects						
Grade 3-4 TEAEs		%	42.4	45.7		
SAE (including deaths)		%	37.5	24.7		
Deaths due to AE		% (n)	1.6% (n=3)	4.8% (n=9)		
Discontinuations due to AE		% (n)	19.0 (n=35)	23.1 (n=43)		
TEAE profile: most common TEAEs	IRR (pt) Drug eruption (pt) Infections (SOC	% % %	33.2 23.9 64.1	0.5 0.5 50.0		

Abbreviations: *CR: complete response, DOR: duration of response ORR: Objective Response Rate, OS: Overall survival, PD: progressive disease, PFS: progression free survival, PR: partial response, QoL: Quality of Life, TTF: Time to treatment failure, TTR: time to response.PT: preferred term, SOC: system of organ class, AE: adverse event, TEAE: treatment emergent adverse event, SAE: serious adverse event, IRR: infusion-related reaction.*

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The difference in median PFS of 4.6 months (HR 0.53; 95% CI: 0.41, 0.69; p<0.0001) is considered clinically relevant for the target population. The PFS results were supported by secondary endpoints ORR (28 vs 5%) +DoR (14 months) and time to next line therapy (TTNT, 11 months vs 3.5 months). The response rates of 28%

with a median DoR of 14 months in the ITT, obtained using a stringent global composite assessment, is clinically meaningful to the patient in terms of reduction of disease related symptoms which limit the quality of life.

The safety profile of mogamulizumab has been characterised in a sufficient number of subjects, main risks associated with mogamulizumab treatment are infusion-related reactions, drug eruption and infections. As the majority of these events were mild or moderate in severity, the safety profile appears to be manageable.

3.7.2. Balance of benefits and risks

Taken together it is considered that the outcomes of PFS, supported by the ORR+DoR, can be viewed as clinically relevant in the context of a relapse/remitting disease where patients continue through therapies, which makes this product with a new mode of action a valuable additional treatment option in MF/SS. The overall safety profile appears manageable. As the target population MF and SS is inherently CCR4 positive, there is no need to specify the molecular target in the indication.

3.8. Conclusions

The overall benefit-risk of POTELIGEO in the treatment of MF and SS who have previously received at least one prior systemic therapy, is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Poteligeo is not similar to Ledaga and Adcetris within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of POTELIGEO is favourable in the following indication:

POTELIGEO is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any

subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that mogamulizumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

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