EU RISK MANAGEMENT PLAN

for

POTELIGEO® (mogamulizumab)

RMP version number: 1.1

Data lock point for this RMP: 29 Mar 2025

Date of final sign-off: 29 Sep 2025

Rationale for submitting an updated RMP:
- Update of PASS study milestones in line with PASS protocol

Summary of significant changes in this RMP:
- Part III: Update of PASS status, objectives and study milestones, in line with PASS protocol
- Part VII:
  - Annex 2: PASS details updated in line with PASS protocol
  - Annex 3: Inclusion of PASS protocol
  - Annex 4: Latest version of adverse drug reaction follow up form for Infusion-related reaction attached (editorial changes only)
- Editorial revisions made to align with EMA RMP template (Rev 2.0.1), and alignment of content with the updated DLP.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:
Version number: 1.0
Approved with procedure: EMEA/H/C/004232/0000
Date of approval: 22 Nov 2018

QPPV name: Beatriz Mengotti Fernandez de los Rios

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
ATL	Adult T-cell leukaemia-lymphoma
CCR4	CC chemokine receptor 4
CD4/CD8	Cluster of differentiation 4/ Cluster of differentiation 8
CTCL	Cutaneous T-cell lymphoma
DLP	Data lock point
DNA	Deoxyribonucleic acid
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GVHD	Graft versus host disease
HIV	Human immunodeficiency virus
HSCT	Haematopoietic stem cell transplant
HTLV-1	Human T-cell lymphotropic virus
IgE	Immunoglobulin E
INN	International Non-proprietary Name
KW-0761	Mogamulizumab or Poteligeo®
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis fungoides
NHL	Non-Hodgkins lymphoma
NRM	Non-relapse mortality
PASS	Post-authorisation safety study
PL	Package Leaflet
PT	Preferred Term
PTCL	Peripheral T-cell lymphoma
PY	Person-years/patient-years
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious adverse event
SmPC	Summary of Product Characteristics

SMQ	Standardised MedDRA Query
SS	Sézary syndrome
TEAE	Treatment-emergent adverse event
Th2	T helper cell
TLS	Tumour lysis syndrome
Treg	Regulatory T-cells
UK	United Kingdom
ULN	Upper limit of normal
US	United States

Part I: Product Overview

An overview of the product is provided in Table 1.

Table 1: Product Overview

Active substance(s) (INN or common name)	Mogamulizumab
Pharmacotherapeutic group(s) (ATC Code)	Humanized monoclonal antibodies L01FX09
Marketing Authorisation Holder	Kyowa Kirin Holdings B.V.
Medicinal products to which this RMP refers	POTELIGEO 4 mg/mL concentrate for solution for infusion
Invented name(s) in the European Economic Area (EEA)	POTELIGEO
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Recombinant, humanized monoclonal antibody of the immunoglobulin G subclass 1 kappa isotype.
	Summary of mode of action: Mogamulizumab is a defucosylated, humanized immunoglobulin G subclass 1 kappa monoclonal antibody that selectively binds to CC chemokine receptor 4 (CCR4). CCR4 is expressed on the surface of some cancer cells including T cell malignancies, such as cutaneous T-cell lymphoma (CTCL) and has limited expression on regulatory T (Treg) cells and a subset of type 2 T helper (Th2 T) cells. Non-clinical in vitro and in vivo studies demonstrate that mogamulizumab binding targets a cell for antibody-dependent cellular cytotoxicity, resulting in depletion of the target cells. As a defucosylated antibody, mogamulizumab has greater antibody-dependent cellular cytotoxicity activity against CCR4-expressing target cells compared with conventionally glycosylated antibodies.
	Important information about its composition: Each vial contains 20 mg of mogamulizumab in 5 mL, corresponding to 4 mg/mL. Mogamulizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information	Approved product information
Indication(s) in the EEA	Current: Treatment of mycosis fungoides (MF) or Sézary syndrome (SS) in adults who have received at least one prior systemic therapy.
	Proposed: Not applicable
Dosage in the EEA	Current: 1.0 mg/kg administered as an intravenous infusion over at least 60 minutes administered weekly on Days 1, 8, 15 and 22 of the first 28-day cycle, followed by infusions every two weeks on Days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 4 mg/mL concentrate for solution for infusion.
	Proposed: Not applicable
Is the product subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI – Epidemiology of the Indication and Target Population

Indication: Treatment of mycosis fungoides (MF) or Sézary syndrome (SS) in adults who have received at least one prior systemic therapy.

Cutaneous T-cell lymphomas are a heterogenous group of extra-nodal non-Hodgkin's lymphomas (NHLs) that are characterized by a cutaneous infiltration of the skin by malignant monoclonal T-lymphocytes (Bagherani, 2016). The major types of CTCL are mycosis fungoides (MF) and its leukemic variant, Sézary syndrome (SS) (Rodd, 2012).

Incidence

In 2017, the incidence of CTCL across Europe was estimated to be 0.63 per 100,000 persons per year (Zhang, 2019).

Mycosis fungoides represents nearly 50% of all CTCL cases (Burg, 2015) and SS represents 3 to 5% (Phan, 2016; Scarisbrick, 2015). The crude and age-standardized (European) incidence rates from 2004 to 2012 for MF were reported to be 0.16 and 0.12 per 100,000, respectively (Smith, 2015).

Prevalence

In 2017, 5-year prevalence, 10-year prevalence and 20-year prevalence of CTCL across Europe was 2.5, 4.4 and 6.9 per 100,000, respectively (Zhang, 2019).

The RARECARE project collected oncology data in Europe from 1995 to 2002. For the indication of "T cutaneous lymphoma (Sézary syndrome, mycosis fungoides)", a crude rate of 0.52/100,000/year (corresponding to 0.052/10,000/year) was reported. Considering the European population in 2002, this rate corresponded to 4.144 patients diagnosed per year in Europe overall; more recent data were not available (RARECARE, 2011).

The Orphanet database describes the prevalence of MF as unknown, and the annual incidence as estimated between 1/350,000 and 1/110,000 (Orphanet, 2009); these figures correspond to 0.29/10,000 and 0.09/10,000/year. The prevalence for SS is similarly listed as unknown; the incidence rate is listed as 1/10,000,000/year (corresponding to 0.001/10,000/year) (Orphanet, 2013).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Cutaneous T-cell lymphomas occur typically in adults with a median age of 55 to 60 years; men are more frequently affected than women (with a ratio of between 1.6:1 and 2.0:1) (Rodd, 2012; Willemze, 2003; Bradford, 2009). Mycosis fungoides is the most common type of cutaneous lymphoma (Paulli, 2004; Diamandidou, 1996) and mostly affects adults and the elderly (male/female ratio 2:1; average age ~50 years). Sporadic cases in young adults have been reported (Paulli, 2004; Crowley, 1998). Sézary syndrome occurs exclusively in adults and the elderly (Paulli, 2004; Vonderheid, 2002; Kim, 1999).

Based on 13 Surveillance Epidemiology and End Results (SEER) registries from 2004 to 2006 in the US population, black males and black females showed higher incidence rates of MF/SS than white males and females (Wang, 2013).

Several risk factors have been associated with NHL, including family history of hematopoietic malignancies, viral infections, occupational and environmental exposures, dietary intake, and personal exposures, such as use of hair dyes (Wang, 2013). Potential risk factors for extra-nodal NHL (including T-cell lymphomas) are immunosuppressive therapies and organ transplants (Wang, 2013). Proposed risk factors for CTCL include chronic cutaneous inflammation (Bagherani, 2016; Eklund, 2016), chronic or professional exposure to topical chemical agents, long-lasting psoriasis, and urticaria (Bagherani, 2016; Lebas, 2015). Risk factors for MF specifically, include advanced age, black race, and male sex (Bradford, 2009; Criscione, 2007). Genetic susceptibility (tumor necrosis factor G-308A) has also been hypothesized as a risk factor for MF (Wang, 2013).

The main existing treatment options

In patients with CTCL, the presence of extra-cutaneous disease, lymphadenopathy and peripheral blood involvement are all poor prognostic factors (Agar, 2010). Patients with early stage disease are treated with skin-directed therapies. As the disease progresses, systemic therapy becomes necessary. Mogamulizumab is indicated for patients who have received at least one prior systemic therapy. There is no standard therapy for subjects with later stage disease. Both approved and unapproved agents are used in these subjects, including immune modulators, single agent or combination chemotherapy and investigational agents.

The European Medicines Agency (EMA) granted marketing authorisation for bexarotene (a systemic retinoid) and brentuximab in refractory CTCL. Interferon-alpha is also approved nationally in some EU countries for patients with progressive CTCL disease. Denileukin diftitox (engineered protein combining interleukin-2 and diphtheria toxin) and romidepsin (histone deacetylase inhibitor) have been approved in the US for the treatment of CTCL. Vorinostat (another histone deacetylase inhibitor) methotrexate, bexarotene, are also approved in the US for the systemic treatment of CTCL. Vorinostat (also approved in Japan and Australia for CTCL treatment) is not currently approved by the EMA for the treatment of CTCL and is considered an investigational medicinal product within Europe. Chlormethine (a topical gel) is approved in the EU for MF-type CTCL (mechlorethamine is also approved in the US for MF-type CTCL).

Other unapproved therapeutic agents used in CTCLs include tazarotene (a topical retinoid; Besner Morin, 2016), acitretin and isotretinoin (systemic retinoids; Bagherani, 2016; Eklund, 2016), and anti-neoplastic agents such as imiquimod (Bagherani, 2016; Rook, 2015). Systemic chemotherapeutic agents for CTCL include methotrexate, chlorambucil, gemcitabine, and pegylated doxorubicin (Bagherani, 2016; Eklund, 2016). For relapsed or refractory CTCL, pralatrexate can be used (Bagherani, 2016; Chmielowska, 2015) and in advanced cases of CTCL cyclophosphamide, doxorubicin, vincristine, and prednisone have shown variable efficacy (Eklund, 2016; Chmielowska, 2015). Psoralen plus ultraviolet A/A1/B and excimer laser are common treatments in MF (Bagherani, 2016; Eklund, 2016; Olsen, 2016). Further therapeutic regimens include extracorporeal photopheresis (Bagherani, 2016; Zic, 2015), radiotherapy (Bagherani, 2016; Tandberg, 2015) and allogeneic hematopoietic stem cell

transplantations; the latter presenting an option for advanced stages of MF and SS (Bagherani, 2016; Väkevä, 2016; Virmani, 2015).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Unlike other forms of NHL, CTCL mainly affects the skin. It can present as patches, plaques, tumours, or erythroderma and may be associated with severe pruritus (Horwitz, 2008; Meyer, 2010). The type and extent of skin involvement, as well as the presence of extra-cutaneous disease, are significant prognostic factors in this subject population (Kim, 2003). Clinically, MF follows consecutive stages in most of the cases beginning with the initial patch stage followed by plaque- and tumour stage as well as erythroderma (affecting more than 90% of the body surface). At any stage, plaques can undergo blastic transformation which drastically worsens the prognosis. In Stage IA (patches and plaques affecting less than 10% of the body surface) life expectancy is not significantly reduced. When patches and plaques affect more than 10% of the body surface, approximately 20% of the patients die within the next 10 years. In tumor stage, the 10-year disease-specific survival is 42%, dropping to about 20% with lymph node involvement (Dugas-Breit, 2014; Willemze, 2005).

Cutaneous T-cell lymphoma can cause significant morbidity and adversely affect the subject's quality of life (Demierre, 2003; Demierre, 2005; Demierre, 2006). Cutaneous T-cell lymphoma is staged according to four anatomical compartments: involvement of skin (T), nodes (N), visceral metastases (M) and peripheral blood (B). Blood involvement is further divided into three categories: B0 (absence of significant blood involvement, where ≤5% of peripheral blood lymphocytes are atypical [Sézary] cells), B1 (low blood tumor burden, where >5% of peripheral blood lymphocytes are atypical [Sézary] cells without meeting the criteria of B2) and B2 (high blood tumor burden with >1,000/μL Sézary cells) (Olsen, 2011).

At presentation, up to 50% of subjects with MF will have limited disease, while only 10 to 20% present with erythrodermic involvement (Diamandidou, 1996). Survival, as would be expected, is related to stage. Subjects with early stage MF have median survivals in excess of 25 years; median survival of advanced disease is very variable, with some reporting median survival as low as 1.5 years (Kim, 2003).

As CTCL progresses and becomes refractory to treatment, the malignant cells may present a propensity to infiltrate lymph nodes and peripheral blood vessels. However, progression to the tumor stage where neoplastic cells spread to lymph nodes has been reported in less than 5% of cases with CTCL (Bagherani, 2016; Rodd, 2012). In CTCL cases with visceral involvement, skin lesions are severe and the risk of skin infection is high. Studies have shown that between 70 and 90% of MF patients die with visceral involvement (Bagherani, 2016; Gomez Venegas, 2015). Patients with MF present a chronic course lasting from years to decades; approximately 25% of them die of lymphoma (Bagherani, 2016; Eklund, 2016). Opportunistic infections and immunosuppression are the most common causes of disease-related death (Bagherani, 2016; Moyal, 2016).

Sézary syndrome is characterized by erythroderma, severe pruritus, generalized lymphadenopathy, and evidence of neoplastic T-cells in blood and skin. As in MF, opportunistic infections are the most common cause of death (Dugas-Breit, 2014). The SS prognosis is poor

with a median survival rate of 2 to 4 years (Rodd, 2012), and a 5-year survival rate of about 18 to 20% (Väkevä, 2016).

Important co-morbidities

Mycosis fungoides/SS-associated co-morbidities include secondary lymphomas, lung cancers, colon cancers, cancers of the urinary and biliary systems, vulva cancers, acute myeloid leukemias, and melanomas (Hodak, 2013; Brownell, 2008; Kantor, 1989; Huang, 2007). Mycosis fungoides was also found to be significantly associated with Hodgkin's lymphoma, anxiety and depression (Hodak, 2013).

Microbial colonization/infection (Bagherani, 2016; Eklund, 2016; Willerslev-Olsen, 2016) are also co-morbidities of MF, while infections and venous thromboembolism have been reported in SS patients (Booken, 2013). Opportunistic infections due to immunosuppression are the leading cause of death in SS (Dugas-Breit, 2014). In a study with 24 SS patients, 33% suffered from infectious diseases, including severe generalized cutaneous herpes simplex, generalized contagiosa, sepsis, and pneumonia (Booken, 2013).

Part II: Module SII – Non-clinical Part of the Safety Specification

A summary of key non-clinical findings and their relevance to humans is outlined in Table 2.

Table 2: Key non-clinical safety findings and relevance to human use

Findings	Relevance to human usage
Toxicity:	
• **Key issues identified from acute and repeat-dose toxicity studies**	
In the single-dose toxicity study in cynomolgus monkeys, mogamulizumab did not provoke a toxicological response or unanticipated immunological effect at single doses up to 100 mg/kg. In repeat-dose (once weekly) toxicity studies up to 26 weeks in cynomolgus monkeys, there were no findings suggesting systemic toxicity up to the maximum doses utilized, 40 mg/kg. Accordingly, the no-observed-adverse-effect-level was designated to be 40 mg/kg.	No safety concern was identified from administration of single doses of 100 times higher than the recommended human dose or weekly doses of 40 times higher than the recommended human dose.
• **Reproductive/developmental toxicity**	
In 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. In pregnant cynomolgus monkeys administered mogamulizumab during organogenesis (for 17 weeks, from Gestational Day 20 to 139 at 40 mg/kg weekly), there were no effects on dams and fetuses. The maximum dose used, 40 mg/kg, was designated the no-observed-adverse-effect-level of mogamulizumab for general toxicity and reproductive function in dams, and in terms of embryo-fetal development. Mogamulizumab was, however, detected in fetus plasma and a decrease in fetal CCR4+ lymphocytes was noted.	No safety concern was identified from weekly administrations to pregnant monkeys at 40 times higher than the recommended human dose; however, due to lack of clinical data on embryo-fetal development, the likelihood that mogamulizumab could cross the placenta and/or be excreted in milk, and the safety profile of the product in adults, use during pregnancy or lactation is considered missing information for mogamulizumab.
• **Genotoxicity**	
As described in the International Conference on Harmonisation S6 (R1) (Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals) guidance, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals since it is not expected that these substances would interact directly with DNA or other chromosomal material. Mogamulizumab is not expected to cause carcinogenicity via a genotoxic mechanism.	No non-clinical data are available. However, it is highly unlikely that mogamulizumab would react directly with DNA or other chromosomal material because mogamulizumab is a monoclonal antibody.
• **Carcinogenicity**	
Consistent with the International Conference on Harmonisation S6 (R1) and S9 guidance, no non-clinical studies were conducted for carcinogenic risk assessment. For small molecule therapeutics, 2-year carcinogenicity assays in mice and rats would be a	No non-clinical carcinogenicity study data are available. Mogamulizumab has potent cytolytic activity against CCR4-expressing target cells. No tumor incidence has been described in CCR4-knockout mice.

Findings	Relevance to human usage
standard approach to assess the risk of carcinogenesis; however, these bioassays are not feasible for mogamulizumab because mogamulizumab does not specifically bind to mouse and rat lymphocytes.	Although CCR4 expression has been 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, one of the endogenous ligands of CCR4. The relationship between tumorigenesis and CCR4 expressing T cells is difficult to establish. 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. Based on the clinical experience to date, there is no evidence of increased carcinogenic risk in subjects administered mogamulizumab. Although one case of follicular lymphoma was reported in a healthy subject who received mogamulizumab (0.001 mg/kg, single-dose, iv) in EU-001 study, experts in the field judged it as highly unlikely this was related to mogamulizumab given the indolent nature of follicular lymphoma and the advanced stage of disease when first detected. There were no proliferative or preneoplastic lesions observed in the 26-week repeat dose toxicity study. In addition, there was no evidence of general immunosuppression (lymphoid tissue organ weight and histopathology were normal and the humoral immune response to KLH or TT was not affected), indicating that elimination of CCR4-expressing target cells with mogamulizumab does not produce broad immunosuppressive activity. The sponsor considers that the overall body of evidence indicates that the risk of direct or indirect carcinogenicity by mogamulizumab is minimal.
• **Immunogenicity**	
The presence of mogamulizumab-specific antibodies was assessed in single- and repeat-dose toxicity studies, the reproductive and developmental toxicity study and the single-dose intravenous/subcutaneous bridging study. 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, and a 2.5 mg/kg repeat-dosed (once weekly for 26 weeks) animal, respectively. In a single-dose pharmacokinetics and pharmacodynamics study of mogamulizumab at doses from 0.0000725 to 1 mg/kg in male cynomolgus monkeys, anti-mogamulizumab antibodies were detected in 1 to 3 animals in all groups (n=3/group). There were, however, no immune-mediated reactions (immune complex-related, vasculitis, anaphylaxis, etc.).	Anti-mogamulizumab antibody production in animal studies was detected. No adverse reactions and no lack of efficacy concerns have been identified from immunogenicity during clinical experience with the product.

Findings	Relevance to human usage
Safety pharmacology:	
The potential for undesirable pharmacological activity of mogamulizumab was investigated in the single- and repeat-dose toxicity studies in male and female cynomolgus monkeys. No effects of mogamulizumab on the cardiovascular, respiratory, renal and central nervous system were observed.	No safety concern was identified.
Other information: • **Cytokine release in vitro**	
The effect of mogamulizumab on tumor necrosis factor alpha, interferon-gamma, and interleukin 6 production was evaluated using whole blood or peripheral blood mononuclear cells in vitro. Cytokine release from whole blood in a soluble phase assay after a relatively short, 4-hour incubation with mogamulizumab was only observed in the sample from 1 of 6 donors. Longer incubations of whole blood (24 hours) or peripheral blood mononuclear cells (24 or 48 hours) with mogamulizumab in soluble and solid phase assays, respectively, were notably characterized by cytokine release from all donor samples.	Theoretically, mogamulizumab could potentially lead to cytokine release in humans. Infusion-related reactions have been found to be very common (although usually mild or moderate in severity) with the majority occurring during the first infusion of mogamulizumab in clinical studies; infusion-related reactions are therefore classified as an important identified risk for the product.

No new safety concerns have been identified from non-clinical data, which would have relevance for human use, as of the Data Lock Point (DLP) for this RMP.

Part II: Module SIII – Clinical Trial Exposure

Mogamulizumab has been studied in several oncologic indications. Exposure in haematologic clinical trials (CTCL, peripheral T-cell lymphoma [PTCL], and adult T-cell leukaemia-lymphoma [ATL]) are described in this section. Data from the development of the use of mogamulizumab in solid tumours is not discussed. A total of 391 subjects were exposed to mogamulizumab as initial treatment in the hematologic clinical trial development program[1], 233 of whom were CTCL patients. Details of study exposure are presented by duration of exposure (Table 3 and Table 4), age and sex (Table 5), dose (Table 6), and ethnic origin (Table 7).

Table 3: Duration of exposure to mogamulizumab given as initial treatment in hematologic clinical trials

Duration of exposure n (%)	All subjects, N (%)	CTCL subjects, N (%)
Total	**391 (100.0)**	**233 (100.0)**
≤4 weeks	98 (25.1)	23 (9.9)
>4 and ≤8 weeks	71 (18.2)	29 (12.4)
>8 weeks	222 (56.8)	181 (77.7)
Extent of exposure (days)		
n	391	233
Mean	158.8	223.8
SD	206.19	230.00
Median	70.7	135.1
Min, Max	1, 1379	1, 1379
Total number of infusions administered		
n	391	233
Mean	13.3	17.8
SD	13.84	15.41
Median	8.0	12.0
Min, Max	1, 90	1, 90

Note: Subjects who received any dose of mogamulizumab as initial treatment are included; subjects who were initially randomised to active comparator and received at least one dose of mogamulizumab after crossover are excluded.
Source: Tables 5.3.5.3.2.3.1.1 & 5.3.5.3.2.3.1.5.

Table 4 summarises the exposure in subjects who received mogamulizumab either from randomisation or following crossover from vorinostat in the pivotal Study 0761-010.

Table 4: Summary of duration of exposure to mogamulizumab in Study 0761-010

Duration of exposure	Crossover to mogamulizumab N=133 n (%)	Randomized to and received mogamulizumab N=184 n (%)	Total N=317 n (%)
<6 months	68 (51.1)	94 (51.1)	162 (51.1)
6 to 12 months	35 (26.3)	46 (25.0)	81 (25.6)
>12 months	30 (22.6)	44 (23.9)	74 (23.3)

Source: Table t2_oq111.

1 Five completed clinical studies (0761-0501, 0761-002, 0761-004, 0761-001, 0761-007) and 2 ongoing clinical studies (0761-009 [data cut-off of 31 Mar 2016] and Pivotal CTCL Study 0761-010 [data cut-off of 31 Dec 2016]); enrollment in the ongoing studies was complete at the time of the data cuts.

Table 5: Age group and sex in subjects treated with mogamulizumab as initial treatment (hematologic clinical trials)

Age group	All subjects, N (%)	CTCL subjects, N (%)
All subjects	391 (100)	233 (100)
Age category (years) n (%)		
<65	218 (55.8)	122 (52.4)
≥65	173 (44.2)	111 (47.6)
65 to 75	112 (28.6)	67 (28.8)
≥75	61 (15.6)	44 (18.9)
Sex		
Male	221 (56.5)	134 (57.5)
Female	170 (43.5)	99 (42.5)

Note: Subjects who received any dose of mogamulizumab as initial treatment are included; subjects who were initially randomized to active comparator and received at least one dose of mogamulizumab after crossover are excluded.
Source: Tables 5.3.5.3.2.2.1.1 & 5.3.5.3.2.2.1.5.

Table 6: Dose in subjects treated with mogamulizumab as initial treatment (hematologic clinical trials)

Dose of exposure	All subjects	CTCL subjects
All subjects	391	233
≤0.5 mg/kg	16	6
1.0 mg/kg	375	227

Note: Subjects who received any dose of mogamulizumab as initial treatment are included; subjects who were initially randomized to active comparator and received at least one dose of mogamulizumab after crossover are excluded.
Source: Tables 5.3.5.3.2.3.1.1 & 5.3.5.3.2.3.1.5.

Table 7: Ethnic origin of subjects treated with mogamulizumab as initial treatment (hematologic clinical trials)

Race	All subjects, N (%)	CTCL subjects, N (%)
All subjects	391 (100)	233 (100)
White	185 (47.3)	160 (68.7)
Asian	94 (24.0)	20 (8.6)
Black or African American	54 (13.8)	27 (11.6)
Not applicable	38 (9.7)	23 (9.9)
Other	12 (3.1)	1 (0.4)
Not specified	8 (2.0)	2 (0.9)
Ethnicity		
Hispanic or Latino	17 (4.3)	7 (3.0)
Not Hispanic or Latino	301 (77.0)	198 (85.0)
Unknown/not reported	73 (18.7)	28 (12.0)

Note: Subjects who received any dose of mogamulizumab as initial treatment are included; subjects who were initially randomized to active comparator and received at least one dose of mogamulizumab after crossover are excluded.
Source: Tables 5.3.5.3.2.2.1.1 & 5.3.5.3.2.2.1.5.

Part II: Module SIV – Populations Not Studied in Clinical Trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Important exclusion criteria in the pivotal CTCL clinical study (0761-010) are described in Table 8.

Table 8: Exclusion criteria in the pivotal clinical study

Criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale if not
Pregnancy and lactation	Standard clinical study exclusion criteria.	Yes
Clinically significant cardiac disease (New York Heart Association Class III or IV); Unstable angina pectoris; Angioplasty, stenting, or myocardial infarction within 6 months; Uncontrolled hypertension; Clinically significant cardiac arrhythmia	Significant uncontrolled intercurrent illness is a standard clinical study exclusion criterion.	No. Cardiac disorders (cardiomyopathy, acute myocardial infarction, and acute coronary syndrome) are categorised as important potential risks.
History of allogeneic transplant	Concerns over potential safety issues in patients with late stage disease who required transplant and who had recently been through the medically arduous process of transplant.	Yes. History of allogeneic or autologous transplant are considered missing information for mogamulizumab in CTCL.
Autologous hematopoietic stem cell transplant (HSCT) within 90 days of the Pre-treatment Visit		
Known or tests positive for human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV-1), herpes simplex, herpes zoster, or hepatitis B or C	Significant uncontrolled illness is a standard clinical study exclusion. In addition, patients with known prior history of certain viral infections have experienced viral reactivation (a known risk). In addition, the presence of HTLV-1 would indicate a possible alternative diagnosis (ATL).	No. Infections are listed as adverse drug reactions and hepatitis B reactivation is an important potential risk.
Uncontrolled infection requiring antibiotics	Significant uncontrolled intercurrent illness is a standard clinical study exclusion criterion.	No. Use of mogamulizumab, an immunomodulatory product, in these populations is not anticipated. Furthermore, it is not expected that the use of antibiotics would interfere with the efficacy or safety of mogamulizumab and therefore the benefit-risk balance would not be impacted.
Known active autoimmune disease	Mogamulizumab is known to affect the immune system.	No. Use of mogamulizumab, an immunomodulatory product, in these populations is not anticipated. Furthermore, it is not expected that autoimmune disease would interfere with the efficacy or safety of mogamulizumab.

Criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale if not
Subjects on any immunomodulatory drug for concomitant or intercurrent conditions other than T-cell lymphoma	Immunomodulatory drugs may affect the patient's disease.	No. A difference in the safety profile of mogamulizumab in this population is not anticipated.

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Limited exposure in special populations is summarised in Table 9.

Table 9: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the hematologic clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment	Subjects with bilirubin >1.5 times the specific institutional upper limit of normal (ULN; except for subjects with Gilbert's syndrome) and aspartate transaminase and alanine transaminase each >2.5xULN (or >5.0xULN in the presence of known hepatic involvement by CTCL), were excluded from pivotal Study 0761-010. Subjects with hepatitis B or C were excluded from trials 0761-001, 0761-007, 0761-009 and 0761-010. Subjects with acute or chronic hepatitis, hepatic cirrhosis, hepatic failure or hepatitis C were excluded from trial 0761-002. Subjects with hepatic failure, acute or chronic hepatitis, or hepatic cirrhosis were excluded from trial 0761-004. Subjects with hepatic failure, acute or chronic hepatitis, hepatic cirrhosis, hepatitis B or C were excluded from trial 0761-0501. Across the hematologic clinical development program, subjects were noted to have underlying hepatic conditions including, but not limited to, elevated liver enzymes, hepatic cysts, hepatic steatosis, and fatty liver.
• Patients with renal impairment	Subjects with serum creatinine >1.5 x ULN or creatinine clearance ≤50 mL/min were excluded from pivotal Study 0761-010. Subjects with renal failure were excluded from trials 0761-002, 0761-004, and 0761-0501. Across the hematologic clinical development program, subjects were noted to have underlying renal conditions including, but not limited to, renal cysts, chronic kidney disease, renal impairment, renal failure, and kidney stones.
• Patients with cardiovascular impairment	Subjects with clinically significant cardiac disease or myocardial infarction within 6 months were excluded from trials 0761-001, 0761-007, 0761-009, and 0761-010. Subjects with cardiac failure or myocardial infarction within 12 months before registration were excluded from trials 0761-002, 0761-004, and 0761-0501. Across the hematologic clinical development program, subjects were noted to have underlying cardiovascular conditions including, but not limited to, hypertension, arrhythmias, thrombosis, coronary artery disease, myocardial infarction, stroke, angioplasty/stenting, heart failure, heart disease, pacemaker use, heart block, venous insufficiency, and cardiac bypass.

Type of special population	Exposure
• Immunocompromised patients	Subjects with known HTLV-1, HIV, or using immunomodulatory drugs were excluded from pivotal Study 0761-010 and trial 0761-001. Subjects tested positive for HIV antibody were excluded from trials 0761-002, 0761-0501, and 0761-004. Subjects with known HIV antibody or using any immunomodulatory drugs were excluded from trial 0761-007, and those with detectable viral loads or using any immunomodulatory drugs were excluded from trial 0761-009. Across the hematologic clinical development program, subjects were noted to have underlying immune disorders including, but not limited to, HTLV-1 positive subjects with ATL, neutropenia, Bruton or sex-linked primary immunodeficiency, lymphopenia, and low CD4 count.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the hematologic clinical development program.
• Population with relevant different ethnic origin	No ethnicities were excluded from the hematologic clinical development program.
• Subpopulations carrying relevant genetic polymorphisms	Not included in the hematologic clinical development program.

Source: CSR medical history/concurrent conditions listings from Studies 0761-001, 0761-002, 0761-004, 0761-007, 0761-009, 0761-010, and 0761-0501.

Part II: Module SV – Post-authorisation Experience

Mogamulizumab has been approved in Japan since March 2012, where it is currently licensed for patient populations with CCR4-expressing T cell lymphomas, including CTCL, PTCL, and ATL. Marketing authorisation approval was granted in the EU on 22 November 2018, whereby mogamulizumab is indicated for the treatment of adult patients with MF or SS who have received at least one prior systemic therapy. As of the DLP, 29 March 2025, mogamulizumab has been approved in 17 countries/regions for the treatment of MF and SS (specific indication wording varies by country).

SV.1 Post-authorisation exposure

SV.1.1Method used to calculate exposure

Overall post-authorisation patient exposure has been estimated using the internal sales data of mogamulizumab vials divided by the average number of vials used per patient per month and/or direct feedback from healthcare professionals regarding the number of patients being treated with mogamulizumab from each region, including patient support programmes (PSPs). PSPs are established in countries where mogamulizumab has not been launched to help patients gain access to the product.
Since the sales data cannot be collected per indication, the patient exposure estimate applies to all indications.

SV.1.2 Exposure

As of 29 March 2025, the cumulative worldwide post-marketing exposure estimate for mogamulizumab is approximately 22,417 patients across all indications, based on the methods described in the section above. Within the EU, the cumulative patient exposure is 2,081 patients, with the remaining 20,336 patients deriving from non-EU countries.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

No significant potential for misuse for illegal purposes, e.g. as a recreational drug, is expected. Mogamulizumab does not have significant psychoactive properties. No effects of mogamulizumab on the central nervous system and no mogamulizumab neurobehavioral or electrophysiologic changes were observed in toxicity studies in monkeys. No case of misuse of the product for illegal purposes has been identified from clinical trials or post-marketing experience.

Part II: Module SVII – Identified and Potential Risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks which are considered to have minimal clinical impact on patients in relation to the severity of the life-threatening oncologic indication (adult patients with CTCL who have received at least one prior systemic therapy) are summarised in Table 10.

In addition, known risks that require no further characterisation and are followed-up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised), are presented in Table 11.

Table 10: Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

Risk not considered important	Comment
Infections[1]	A total of 151/233 (64.8%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced events under the SOC of Infections and infestations; 23.2% (35/151) were of ≥Grade 3 severity. Patients receiving mogamulizumab are at an increased risk of events pertaining to infections and infestations. Although 'infections' are listed as adverse drug reactions and 'Hepatitis B reactivation' is categorized as an important potential risk, to be managed with routine pharmacovigilance and routine risk minimization, i.e. description of events in the product information and advice to monitor patients and promptly treat infections, it should be noted that infections and viral reactivations are common in this patient population.
Fatigue	Although 50/233 (21.5%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced fatigue, 6% (3/50) were of ≥Grade 3 severity.
Diarrhoea	Although 48/233 (20.6%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced diarrhoea, 4% (2/48) were of ≥Grade 3 severity.
Nausea	Although 42/233 (18.0%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced nausea, 7% (3/42) were of ≥Grade 3 severity.
Pyrexia	Although 41/233 (17.6%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced pyrexia, 2% (1/41) was of ≥Grade 3 severity.
Headache	Although 33/233 (14.2%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced headache, no subject experienced headache to a severity of ≥Grade 3.
Thrombocytopenia	Although 22/233 (9.4%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced thrombocytopenia, no subject experienced thrombocytopenia to a severity of ≥Grade 3.
Leukopenia	One (1/233, 0.4%) subject administered mogamulizumab for CTCL as initial treatment in clinical studies experienced leukopenia; no subject experienced leukopenia to a severity of ≥Grade 3.
Anaemia	Although 22/233 (9.4%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced anemia, 14% (3/22) experienced the events to ≥Grade 3 severity.
Neutropenia	Eight (8/233, 3.4%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced neutropenia; 37.5% (3/8) experienced the events to ≥Grade 3 severity.
Oedema peripheral	Although 25/233 (10.7%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced oedema peripheral, no subjects experienced events to a severity of ≥Grade 3.
Constipation	Although 23/233 (9.9%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced constipation, 4.3% (1/23) subjects experienced the events to a severity of ≥Grade 3.
Stomatitis	A total of 11/233 (4.7%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced stomatitis; no subjects experienced events to a severity of ≥Grade 3.

Risk not considered important	Comment
Vomiting	A total of 16/233 (6.9%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced vomiting; 12.5% (2/16) subjects experienced the events to a severity of ≥Grade 3.
Alanine aminotransferase increased	A total of 12/233 (5.2%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced alanine aminotransferase increased; no subjects experienced events to a severity of ≥Grade 3.
Aspartate aminotransferase increased	A total of 10/233 (4.3%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced aspartate aminotransferase increased; 20% (2/10) subjects experienced events to a severity of ≥Grade 3.
Blood alkaline phosphatase increased	A total of 9/233 (3.9%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced blood alkaline phosphatase increased; no subjects experienced events to a severity of ≥Grade 3.
Lymphocyte count decreased	A total of 5/233 (2.1%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced lymphocyte count decreased; all of these 5 subjects experienced the events to a severity of ≥Grade 3.
Hypothyroidism	A total of 5/233 (2.1%) subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced hypothyroidism; no subjects experienced the events to a severity of ≥Grade 3.
Hepatitis acute	One (1/233, 0.4%) subject administered mogamulizumab for CTCL as initial treatment in clinical studies experienced an event coded to the PT of Hepatitis acute; the event was of Grade 3 severity.
Hepatitis	No subjects administered mogamulizumab for CTCL as initial treatment in clinical studies experienced events coded to the PT of Hepatitis.

Source: Tables 5.3.5.3.2.4.2.5 and 5.3.5.3.2.4.7.5.
[1] Infections include all infections within the SOC of Infections and infestations.

Table 11: Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised)

Risk not considered important	Comment
Rash (drug eruption)	Events of rash (drug eruption) occurred very commonly in patients treated with mogamulizumab and are described in Sections 4.2, 4.4, and 4.8 of the SmPC. The wording in the SmPC and Package Leaflet (PL) is considered sufficient and therefore further characterization and additional risk minimization measures are not considered necessary.
Stevens-Johnson Syndrome/toxic epidermal necrolysis	Stevens-Johnson Syndrome/toxic epidermal necrolysis has not been reported in CTCL, however, it has been reported in one study and 26 post-marketing cases for ATL. Stevens-Johnson Syndrome/toxic epidermal necrolysis is considered to be rare, but is life-threating with a high mortality rate. Characterization of this safety concern through a study is not considered feasible. The risk is already included in SmPC Section 4.4, and routine pharmacovigilance is considered sufficient to detect further cases from the post-marketing setting.
Tumor lysis syndrome	Tumor lysis syndrome occurred in <1% of the patients receiving mogamulizumab across all hematologic clinical studies. In the CTCL studies, tumor lysis syndrome occurred in two patients. At this point, there is insufficient data available to determine causal relationship. Considering the rarity of this event, characterization of this event by an additional study is not feasible. This event is included in SmPC Section 4.4 and routine pharmacovigilance is considered sufficient to detect further cases from the post-marketing setting.
Stress cardiomyopathy/acute myocardial infarction/acute coronary syndrome	Stress cardiomyopathy/acute myocardial infarction/acute coronary syndrome have occurred during or shortly after mogamulizumab infusions in <1% of T-cell lymphoma patients. One of 38 subjects experienced cardiomyopathy in Study 0761-007 (PTCL). Of [redacted] who have received mogamulizumab for the treatment of other hematological cancers in the post-marketing setting, four have experienced various forms of cardiomyopathy, including Tako-Tsubo cardiomyopathy. Considering the low frequency of these cardiac events and the fact that such events are confounded by previous oncolytic treatments and the patients' age and cardiac medical history, there is no evidence of a causal relationship for this safety concern. Based on the current data, this safety concern does not impact the benefit-risk balance of mogamulizumab. In addition, there is no additional pharmacovigilance activity proposed to further characterize this risk. It can be concluded that the risk can be sufficiently reviewed through routine pharmacovigilance activities.

Source: CHMP Day 180 List of Questions.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

The rationale for considering the important identified and potential risks and missing information to impact the risk-benefit balance of mogamulizumab is presented in Table 12, Table 13 and Table 14, respectively.

Table 12: Justification for risk-benefit impact of Important Identified Risks

Important Identified Risk	Justification for risk-benefit impact
1. Infusion-related reactions	Although usually mild or moderate in severity, infusion-related reactions are very common with the majority occurring during the first infusion of mogamulizumab.

Table 13: Justification for risk-benefit impact of Important Potential Risks

Important Potential Risk	Justification for risk-benefit impact
1. Hepatitis B reactivation	Hepatitis B reactivation has been reported in patients with ATL who were treated with mogamulizumab. There have been no cases of hepatitis B reactivation in the CTCL setting; however, these data are limited due to exclusion of subjects with a history of acute or chronic hepatitis from most of the CTCL clinical development studies.
2. Increased risk of severe GVHD after allogeneic HSCT	Allogeneic HSCT is a recognized treatment option for advanced CTCL, and theoretically prior treatment with mogamulizumab may be associated with an increased risk of severe refractory GVHD, as has been reported in the literature for ATL (see Table 26). There is insufficient clinical study data in CTCL to confirm or refute this risk, and therefore at the present time the impact on the risk-benefit assessment in CTCL is unknown.

Table 14: Justification for risk-benefit impact of Missing Information

Missing Information	Justification for risk-benefit impact
1. Use in patients with a history of autologous or allogeneic transplant	There are very limited data on the use of mogamulizumab in patients with a history of autologous or allogeneic HSCT. With the exception of Study 0761-001, subjects with a history of allogeneic HSCT were excluded. Across the hematologic clinical development program, 3 subjects in [redacted] Study 0761-004 (in subjects with CCR4+ relapsed PTCL and CTCL) received peripheral blood stem cell transplant (2 specified as autologous) prior to mogamulizumab (1.0 mg/kg iv weekly for 8 weeks). One of these patients experienced serious adverse events (SAEs), including Grade 3 toxic skin eruption, herpes esophagitis, oral candidiasis, and psoriasis. Review of case reports from marketing experience in Japan revealed a small number of cases in this population. Additional data on product use and adverse events in patients treated with mogamulizumab after HSCT for CTCL are required to further evaluate the risk.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable – No new safety concerns or modifications to the current risks have been identified.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Information on the important identified risk for mogamulizumab is summarised in Table 15 (Infusion-related reactions).

Information on the important potential risks for mogamulizumab is summarised in Table 16 (Hepatitis B reactivation) and Table 17 (Increased risk of severe GVHD after allogeneic HSCT).

Table 15: Important Identified Risk: Infusion-related reaction

Potential mechanisms	The cause(s) of infusion reactions associated with the use of mogamulizumab are not known. Infusion reactions in general may have a hypersensitivity basis, in which the molecular structure of the anticancer drug or a component of the drug formulation is recognised as an antigen by the immune system. Type 1 hypersensitivity (or immediate hypersensitivity) reactions are mediated by immunoglobulin E (IgE). When an anticancer drug binds to cell-bound IgE histamine, leukotrienes, and prostaglandins are released inducing smooth muscle contraction, capillary dilation, and vascular permeability, leading to the development of urticaria, rash, angioedema, bronchospasm, and hypotension. Anaphylactoid reactions present with symptoms similar to those of anaphylaxis, but occur in the absence of IgE. Monoclonal antibodies may also interact with their molecular targets on circulating blood cells to release inflammatory cytokines. When released into the circulation, cytokines can produce a wide range of symptoms characteristic of infusion reactions, including fever, chills, nausea, vomiting, hypotension, and dyspnoea (Chung, 2008; Breslin, 2007).
Evidence source(s) and strength of evidence	Infusion-related reaction occurred in approximately a third of patients treated with mogamulizumab in hematologic clinical studies. However, severe (Grade ≥3) infusion-related reaction occurred infrequently, i.e. in approximately 2.9% of patients treated with mogamulizumab. Nearly all infusion-related reaction occurred in the first 4 weeks of treatment. Based on the frequency, the clinical importance, and the potential for severe events, infusion-related reaction is considered to be an important identified risk for mogamulizumab.

Table 15: Important Identified Risk: Infusion-related reaction

Characterisation of the risk	At the time of marketing authorisation, available clinical trial data showed the following: The incidence of the PT of Infusion-related reaction in all pooled hematologic clinical studies (n=391) was 33.8%, the incidence in the pooled CTCL studies (n=233) was 29.6%. The incidence of severe (Grade ≥3) events coded to the PT of Infusion-related reaction in all pooled hematologic clinical studies was 2.3%, the incidence in the pooled CTCL studies was 1.3%. No deaths associated with the PT of Infusion-related reaction occurred in all pooled hematologic clinical studies. The incidence of serious PTs of infusion-related reaction in all pooled hematologic clinical studies (n=391) was 1.5% and the incidence in the pooled CTCL studies (n=233) was 1.3%. Discontinuation of mogamulizumab due to PT of Infusion-related reaction occurred in 2 subjects (0.5%) in all pooled hematologic clinical studies. Nearly all infusion-related reactions occurred in the first 4 weeks of treatment (130/132 in the all pooled hematologic clinical studies). Other infusion-related reactions reported were Cytokine release syndrome (2 [0.5%] subjects) and Anaphylactic reaction (1 [0.3%] subject). Both events of Cytokine release syndrome were reported for subjects with T-cell lymphoma other than CTCL and were considered related to mogamulizumab but not serious. The event of Anaphylactic reaction was Grade 4 severity, serious, related to mogamulizumab, led to treatment discontinuation and was reported as resolving. A medical review of the remaining PTs within the search criteria described above did not reveal any other reports which could be considered as undiagnosed infusion-related reactions. <u>Post-marketing data</u> Cumulatively, from post-marketing sources under the CTCL indication (including T-cell lymphoma), there have been 93 case reports describing 97 events (28 serious, 69 non-serious) pertaining to infusion-related reactions. Reported PTs were Infusion related reaction (81), Anaphylactic reaction (5), Cytokine release syndrome (4), Infusion related hypersensitivity reaction (3), Circulatory collapse (2), Shock (1), and Anaphylactoid reaction (1). Of the SAEs, event outcome was recovered (20), recovering (4), unknown (3) and fatal (1). The fatal event reported was Circulatory collapse, which was assessed by the MAH and reporter as not related to mogamulizumab, but instead due to the underlying condition. Additionally, a total of 369 events (from 321 cases) pertaining to infusion-related reactions have been reported globally from post-marketing sources in which mogamulizumab was used for an unknown indication or a non-CTCL indication (e.g. ATL, PTCL, hypereosinophilic syndrome). ATL and PTCL are both approved indications for mogamulizumab in Japan.
Risk factors and risk groups	Infusion-related reactions have been observed in patients treated with mogamulizumab with the majority occurring during or shortly after the first infusion with the incidence decreasing over time (EU SmPC Section 4.4).
Preventability	Predictability of this risk is limited to treatment-naïve patients, with the incidence decreasing over time. Mogamulizumab is administered by staff familiar with the recognition and treatment of such reactions. Premedication is recommended for the first infusion. If an infusion-related reaction occurs, administer premedication for subsequent infusions (SmPC Section 4.2). The infusion of mogamulizumab should be temporarily interrupted for mild to severe (Grades 1 to 3) infusion-related reactions and symptoms treated. The infusion rate should be reduced by at least 50% when re-starting the infusion after symptoms resolve. If

Table 15: Important Identified Risk: Infusion-related reaction

	reaction recurs, discontinuing the infusion should be considered (SmPC Section 4.2). Mogamulizumab should be permanently discontinued for a life-threatening (Grade 4) infusion-related reaction (SmPC Section 4.2). In addition, the infusion of mogamulizumab should only be administered when staff trained to evaluate and manage anaphylactic reactions are immediately available, in an environment where full resuscitation facilities can be assured (SmPC Section 4.2).
Impact on the risk-benefit balance of the product	Infusion-related reaction is very common with the first or second infusion of mogamulizumab but are usually mild or moderate in severity and can be adequately managed by staff that are familiar with the recognition and treatment of such reactions. Life-threatening reactions such as anaphylaxis are uncommon, as is discontinuation of mogamulizumab due to infusion-related reaction. Considering the seriousness of the oncologic indication, the impact of this risk on the benefit-risk balance is acceptable compared to the expected benefit. No significant change to the risk is anticipated during post-marketing use.
Public health impact	Severe infusion-related reaction may require supportive care and specific therapy but are infrequently reported. In addition, CTCL is a rare condition. No significant impact to public health is therefore anticipated.

Sources: Tables 5.3.5.3.2.4.19.1, 5.3.5.3.2.4.19.5, 5.3.5.3.2.4.19.7, 5.3.5.3.2.4.7.1, 5.3.5.3.2.4.7.5, 5.3.5.3.2.4.11.1, 5.3.5.3.2.4.11.5, 5.3.5.3.2.4.14.1, 5.3.5.3.2.4.15.1, 5.3.5.3.2.4.15.5, 5.3.5.3.2.4.17.1, 5.3.5.3.2.4.9.1, & 5.3.5.3.2.4.2.6

No new information that would significantly affect the characterisation of this risk has been identified as of the DLP for this RMP.

Table 16: Important Potential Risk: Hepatitis B reactivation

Potential mechanisms	Mogamulizumab targets T-cells and Treg cells of the immune system for destruction.
Evidence source(s) and strength of evidence	Patients with CTCL are at increased risk of infection, particularly with advanced disease and when using combination therapies (Thursky, 2006; Akpek, 1999); patients frequently display evidence of immunosuppression, in particular at the later stages of the lymphoma (Zhang, 2014; Kim, 2005) and the risk is also increased by compromised skin integrity (Foss, 2014; Tsambiras, 2001). Axelrod (1992) retrospectively studied 356 patients with CTCL in the era predating monoclonal antibodies and identified 478 infective episodes. Cutaneous bacterial infection was most common (17.0 infections per 100 PY), followed by cutaneous herpes simplex virus and herpes zoster virus infection (3.8 infections per 100 PY), bacteremia (2.1 infections per 100 PY), bacterial pneumonia (1.7 infections per 100 PY), and urinary tract infection (1.4 infections per 100 PY). Viral reactivation is a known complication of chemotherapy, especially for malignant lymphoma, and the increased risk in lymphoma patients parallels the potency of the immunosuppressive treatments (Phipps, 2016). Review of available data for mogamulizumab revealed no evidence of increased risk of hepatitis B reactivation in the CTCL setting, although the data are limited due to exclusion of subjects with a history of acute or chronic hepatitis (including hepatitis B and C) from most of the clinical development studies. Reported cases of hepatitis B occurred in the ATL setting against a confounding immunosuppressive background of prior/concomitant ablative cytotoxic therapy.
Characterisation of the risk	At the time of marketing authorisation, available clinical trials data showed the following: • No cases of hepatitis B reactivation have been reported in CTCL study subjects; however, these data are limited due to exclusion of subjects with a history of acute or chronic hepatitis from most of the clinical development studies. • In the clinical non-CTCL patients, hepatitis B or hepatitis B virus DNA was detected in 2 subjects receiving mogamulizumab after the start of study treatment. The first subject (Study 0761-003) experienced the event on Day 76, when the last dose of mogamulizumab was administered, and recovered after 66 days. The second subject (Study 0761 0501J Re-administration) experienced a first event of hepatitis B on Day 18, which lasted up to Day 36, and a second event of hepatitis B on an unknown date, which had resolved by Day 318. Both subjects had no medical history suggestive of hepatitis B infection prior study entry. Post-marketing data Cumulatively, from post-marketing sources under the CTCL indication (including T-cell lymphoma), there was 1 case which reported PT Hepatitis B reactivation. This was a serious case in which the event outcome was reported as not recovered. Both the company and reporter assessed this case as related to mogamulizumab. Additionally, a total of 7 events (from 7 cases) pertaining to hepatitis B reactivation have been reported globally from post-marketing sources in which mogamulizumab was used for a non-CTCL indication (ATL and PTCL). ATL and PTCL are both approved indications for mogamulizumab in Japan.
Risk factors and risk groups	Patients with CTCL are at increased risk of serious infections. No risk factors for increased susceptibility to hepatitis B reactivation subsequent to mogamulizumab administration have been identified.
Preventability	Other than standard sanitary and clinical practices, no method by which hepatitis B reactivation can be prevented has been determined. The EU SmPC advises that patients should be tested for hepatitis B infection before initiating treatment with

Table 16: Important Potential Risk: Hepatitis B reactivation

	mogamulizumab, and provides comprehensive advice to both physician and patient concerning the risk of hepatitis B reactivation.
Impact on the risk-benefit balance of the product	Patients with CTCL are at risk of serious infections including hepatitis B reactivation; the level by which mogamulizumab increases this risk is not known. Considering the seriousness of the oncologic indication and the lack of evidence that mogamulizumab dramatically increases the risk of hepatitis B reactivation, the risk-benefit balance is considered acceptable.
Public health impact	These events are serious, however due to the rarity of CTCL, no significant impact to public health is anticipated.

Sources: Tables 5.3.5.3.2.4.15.1, 5.3.5.3.2.4.15.5, 5.3.5.3.2.4.2.5, 5.3.5.3.2.4.3.1, 5.3.5.3.2.4.3.5, 5.3.5.3.2.4.7.1, 5.3.5.3.2.4.7.5, 5.3.5.3.2.4.9.1, 5.3.5.3.2.4.9.5, 5.3.5.3.2.4.11.1, 5.3.5.3.2.4.11.5, 5.3.5.3.2.4.13.5, 5.3.5.3.2.4.13.1, 5.3.5.3.2.4.15.1, 5.3.5.3.2.4.15.5 & Listings 5.3.5.3.2.4.3 & 5.3.5.3.2.4.4

No new information that would significantly affect the characterisation of this risk has been identified as of DLP for this RMP.

Table 17: Important Potential Risk: Increased risk of severe GVHD after allogeneic HSCT

Potential mechanisms	Regulatory T cells (Tregs) express CCR4 and may be affected by the administration of mogamulizumab. Regulatory T cells reduce GVHD severity; therefore, mogamulizumab administered as an induction therapy prior to allogeneic HSCT might deplete the graft of Treg cells, and cause severe refractory GVHD (Koreth, 2011).
Evidence source(s) and strength of evidence	Allogeneic HSCT is a recognized treatment option for advanced refractory CTCL (Paralkar, 2012; Duarte, 2008), although experience is limited and not well defined. Retrospective studies of outcomes after allogeneic HSCT (transplant from another person) for ATL suggest that prior treatment with mogamulizumab may increase the risk of moderate to severe acute GVHD and be associated with increased non-relapse mortality (NRM) and reduced overall survival (Fuji, 2016; Inoue, 2016; Sugio, 2016). However, a prolonged interval between mogamulizumab treatment and allogeneic HSCT may reduce the risk of moderate to severe acute GVHD. The retrospective nature of these reports, possible confounding factors, and the inherent risks of allogeneic HSCT mean that this potential risk requires further evaluation before a definitive assessment is possible. Whilst the same potential risk that prior treatment with mogamulizumab may increase the risk of moderate to severe GVHD after allogeneic HSCT for advanced refractory CTCL, very limited data are currently available, and a definitive assessment is not possible (Fuji, 2016). A review of the 456 patients who had received mogamulizumab (as initial or cross-over therapy) in Western clinical trials for hematologic indications was conducted to a DLP of 20 Jul 2017. Data on 32 of the 35 subjects reported to have undergone transplant are available, including 24 CTCL subjects. Twelve of 32 subjects developed acute GVHD after transplant (10 CTCL; 2 non-CTCL subjects). Due to the small subject numbers, no conclusions could be drawn concerning the effect of mogamulizumab treatment on the eventual outcome of HSCT as a treatment for T-cell lymphoma. Review of post-marketing data pertaining to this risk showed findings consistent with those recorded from clinical studies.
Characterisation of the risk	Acute GVHD describes a distinctive syndrome of dermatitis, hepatitis, and/or enteritis developing within 100 days after allogeneic HSCT. Chronic GVHD describes a more diverse syndrome developing after 100 days from HSCT (Mandanas, 2017). In acute GVHD, the skin, liver and/or gastrointestinal tract may be affected. Organs affected in chronic GVHD are typically the skin, mouth, joints, liver, eyes,

Table 17: Important Potential Risk: Increased risk of severe GVHD after allogeneic HSCT

	gastrointestinal tract and occasionally the lungs. Immune dysfunction is associated with GVHD and the majority of deaths from GVHD are due to infections (Jacobsohn, 2007). At the time of marketing authorisation, available clinical trial data showed the following: <u>GVHD in patients with ATL</u> A retrospective analysis of data from the Fukuoka Blood and Marrow Transplant Group in Japan included a total of 23 patients with ATL who were treated with mogamulizumab prior to allogeneic HSCT. The cumulative incidences of acute GVHD at 100 days were 60.9% Grade 2 to 4 and 37.9% Grade 3 to 4. The cumulative incidence of transplant-related mortality was high with 53.3% at 1 year. At the last follow-up, 5 patients were alive and 18 were deceased; GVHD was the leading cause of death in 6 patients (Sugio, 2015). A retrospective analysis of the transplant outcomes of 91 patients with ATL included 11 patients who received mogamulizumab before allogeneic HSCT. The cumulative incidence of Grade 2 to 4 acute GVHD at day 100 after allogeneic HSCT was significantly higher in the mogamulizumab group than in 80 controls who did not receive mogamulizumab (81.8% vs 41.3%, P = 0.002). There was no significant difference in the incidence of chronic GVHD at 6 months between the mogamulizumab and control groups (21.2% vs 31.7%, respectively). The cumulative incidences of NRM at 6 months after allogeneic HSCT were 58.2% in the mogamulizumab group and 12.7% in the control group (P=0.001) (Inoue, 2016). The same research group expanded the retrospective analysis to a total of 996 allogeneic HSCT recipients age 70 years or younger with aggressive ATL. Eighty-two patients received mogamulizumab prior to HSCT. Grade 3 to 4 acute GVHD occurred in 25 (30.9%) in the mogamulizumab group compared to 150 (17.2%) patients in the control group (P<0.01). Use of systemic corticosteroids for acute GVHD was significantly greater in the mogamulizumab group compared to the control group (47/64 [73.4%] vs 341/570 [59.8%]; P=0.03). In these patients, refractoriness to systemic corticosteroids for acute GVHD was observed in 23 of 47 (48.9%) in the mogamulizumab group compared to 80 of 341 (23.5%) patients in the control group (P <0.01). One-year cumulative incidence of NRM was 43.7% in the mogamulizumab group compared to 25.1% in the control group (P <0.01). The probability of one-year overall survival (OS) was also significantly inferior in the mogamulizumab group compared to the control group (32.3% vs 49.4% P <0.01). Multivariate analyses showed that mogamulizumab administered <50 days prior to HSCT was associated with increased risk of NRM and inferior OS (Fuji, 2016). Since marketing authorisation, an additional study supported the recommendation of maintaining an adequate interval between mogamulizumab administration and allo-HSCT, except the authors suggested a higher risk of acute GVHD and NRM when mogamulizumab was administered ≤ 66 days before allo-HSCT (Fuji, 2025). <u>Post-marketing data</u> Cumulatively, from post-marketing sources under the CTCL indication, 6 events of GVHD (from 6 cases) have been reported. Of these 6 cases, 3 cases reported transplant 50 days or more after mogamulizumab administration. Of the remaining 3 cases, 1 did not report the interval between mogamulizumab administration and transplant and 2 cases did not report any details regarding the transplant. There was 1 fatal GVHD event reported in the CTCL indication, however the timeframe between drug administration and transplant was unknown.

Table 17: Important Potential Risk: Increased risk of severe GVHD after allogeneic HSCT

	There were 3 events of GVHD (from 3 cases) in which mogamulizumab was used for an unknown indication. Of these, 1 case reported transplant >50 days after mogamulizumab administration. Of the remaining cases, 1 case reported medical history of ATLL and 1 case did not report the date of transplant.
Risk factors and risk groups	The predominant determinants of acute GVHD risk after allogeneic HSCT for hematologic malignancies are the degree of human leukocyte antigen match, intensity of conditioning (higher risk with total body irradiation), source of graft (higher risk with peripheral blood than bone marrow, and in female human leukocyte antigen identical sibling donors to male recipients) and GVHD prophylaxis regimen (higher risk with cyclosporine than tacrolimus) (Jagasia, 2012). It is currently unclear whether the same risk factors of acute GVHD after allogeneic HSCT are applicable for CTCL, due to the limited experience of this treatment option. The risk of moderate to severe acute GVHD after allogeneic HSCT for ATL may be increased after prior mogamulizumab administration, although longer periods between mogamulizumab administration to allogeneic HSCT may reduce the risk. However, this requires confirmation, particularly regarding use of the product for the treatment of CTCL.
Preventability	Given the observation that mogamulizumab administered <50 days prior to HSCT was associated with increased NRM and inferior OS (Fuji, 2016), a prolonged interval between mogamulizumab treatment and allogeneic HSCT may reduce the risk of moderate to severe acute GVHD and be associated with improved survival. The product label includes a warning regarding safety of mogamulizumab treatment after HSCT stating that a higher risk of transplant complications has been reported if mogamulizumab is given within a short time frame (approximately 50 days) before HSCT. Patients should be monitored closely for early evidence of transplant-related complications.
Impact on the risk-benefit balance of the product	Allogeneic HSCT is a recognized treatment option for advanced refractory CTCL (Paralkar, 2012; Duarte, 2008) although experience is limited and not well defined. Retrospective studies of outcomes after allogeneic HSCT for ATL suggest that prior treatment with mogamulizumab may increase the risk of moderate to severe acute GVHD and be associated with increase in NRM and reduced overall survival. However, a prolonged interval between mogamulizumab treatment and allogeneic HSCT may reduce the risk of moderate to severe acute GVHD and be associated with improved survival. Whilst the same potential risk that prior treatment with mogamulizumab may increase the risk of moderate to severe GVHD after allogeneic HSCT for advanced refractory CTCL, very limited data are currently available. Despite the uncertainties concerning this potential risk, the proposed risk minimisation through inclusion of a warning in the product label is considered appropriate. The Company is conducting a post-authorisation safety study (PASS), which is expected to generate data on the nature and magnitude of the risk.
Public health impact	Allogeneic HSCT is a recognized treatment option for advanced refractory CTCL although experience is limited and not well defined. There is a potential risk that prior treatment with mogamulizumab may increase the risk of moderate to severe GVHD after allogeneic HSCT for advanced refractory CTCL, however this has not been confirmed, and the numbers of patients at risk is unknown but likely to be small. As CTCL is a rare condition no significant impact to public health is anticipated.

Sources: Tables 5.3.5.3.2.4.5.5, 5.3.5.3.2.4.5.1, 5.3.5.3.2.5.6.1 & 5.3.5.3.2.6.5.

As of the DLP, no new information that would significantly affect the characterisation of this risk has been identified.

SVII.3.2. Presentation of the missing information

Missing information that is considered a safety concern for mogamulizumab is described in Table 18 (Use in patients with a history of autologous or allogeneic transplant).

Table 18: Missing Information: Use in patients with a history of autologous or allogeneic transplant

Evidence source	There is very limited data on the use of mogamulizumab in patients with a history of autologous or allogeneic HSCT. Three subjects in [redacted] Study 0761-004 (in subjects with CCR4+ relapsed PTCL and CTCL) received peripheral blood stem cell transplant (2 specified as autologous) prior to mogamulizumab (1.0 mg/kg iv weekly for 8 weeks). One of these patients experienced SAEs, including Grade 3 toxic skin eruption, herpes esophagitis, oral candidiasis, and psoriasis. Review of post-marketing experience globally revealed a very small number of cases in the CTCL population.
Population in need of further characterisation	Additional data on product use and adverse events in patients treated with mogamulizumab after HSCT for CTCL are required to further evaluate the risk.

Part II: Module SVIII - Summary of the Safety Concerns

A summary of the safety concerns for mogamulizumab is presented in Table 19.

Table 19: Summary of 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

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection includes a specific adverse reaction follow-up questionnaire for the identified risk of infusion-related reaction. The purpose of this questionnaire is to allow for the collection of more comprehensive data when infusion-related reactions are reported (Annex 4).

III.2 Additional Pharmacovigilance Activities

For the potential risk of increased risk of severe GVHD after allogeneic HSCT, the Company is conducting a Post-Authorisation Safety Study (PASS) (Annex 2). A summary of the PASS is provided below.

Study title:
Post-authorisation safety study of allogeneic hematopoietic cell transplantation in patients treated with Mogamulizumab.

Rationale and study objectives:

The purpose of this study is to assess the potential risks of allogeneic hematopoietic cell transplantation (alloHCT) in patients with CTCL or ATLL who have received mogamulizumab either within 1 year before or within 18 months after transplantation. This study will help to characterise and address the safety concern of "Increased risk of severe GVHD after allo-HSCT".

The primary objective of the study is to assess treatment-related mortality and non-relapse mortality (death without prior relapse or progression) among patients who were either treated with mogamulizumab, (alone as a single agent or in combination with other therapies) within one year prior to alloHCT, or treated with mogamulizumab, (alone as a single agent or in combination with other therapies), within 18 months after alloHCT.

Study design:
Non-interventional cohort study evaluating treatment-related mortality, non-relapse mortality and cause, and incidence and characterisation of GVHD and graft failure in patients with CTCL or ATLL treated with mogamulizumab pre- or post-alloHCT.

Study population:
At least 50 patients with CTCL or ATLL (of which at least 40 patients have been diagnosed with CTCL and at least 33 patients should have received mogamulizumab as last therapy line before alloHCT) who received mogamulizumab within 1 year prior to alloHCT. Information on patients receiving mogamulizumab within 18 months after alloHCT will also be collected.

Milestones:
Study milestones are summarised in the below section (Table 20).

III.3 Summary Table of Additional Pharmacovigilance Activities

One Category 3 PASS is ongoing and details are summarised in Table 20.

Table 20: Ongoing additional pharmacovigilance activities

Study title and status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities *(by the competent authority)*				
Post-authorisation safety study of allogeneic hematopoietic cell transplantation in patients treated with mogamulizumab. Ongoing	The primary objective of the study is to assess treatment-related mortality and non-relapse mortality (death without prior relapse or progression) among patients who were either treated with mogamulizumab, (alone as a single agent or in combination with other therapies) within one year prior to alloHCT, or treated with mogamulizumab, (alone as a single agent or in combination with other therapies), within 18 months after alloHCT.	Increased risk of severe GVHD after allogeneic HSCT	Finalisation of protocol	Q1 2019
			Start of data collection	Jan 2019
			Registration of study in EU-PAS register	Sep 2019
			Date of interim report	Jul 2021
			Study completion	Sep 2028
			End of data collection	Sep 2028
			Final report of study results	Mar 2029

Part IV: Plans For Post-Authorisation Efficacy Studies

No post-authorisation efficacy studies are planned for mogamulizumab.

Part V: Risk Minimisation Measures

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Routine risk minimisation measures for mogamulizumab are summarised in Table 21.

Table 21: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important Identified Risk	
Infusion-related reaction	Routine risk communication: SmPC Sections 4.2, 4.4 and 4.8. PL Sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Monitoring of patients for signs and symptoms of infusion-related reactions is included in Section 4.4 of the SmPC, which also refers to Section 4.2 stating that pre-medication with anti-pyretic and anti-histamine is recommended for the first POTELIGEO infusion and if an infusion reaction occurs, pre-medication for subsequent POTELIGEO infusions is to be administered. • A recommendation that POTELIGEO should be interrupted and treatment of the symptoms initiated for mild to severe infusion-related reactions and that POTELIGEO should be permanently discontinued in the event of a life-threatening reaction is included in SmPC Section 4.2. It is also noted that patients with mild, moderate, or severe reactions, the infusion rate should be reduced by at least 50% when re-starting the infusion. • Management in the case of an anaphylactic reaction is included in SmPC Section 4.4. In addition, a recommendation that infusion of POTELIGEO should only be administered when staff trained to evaluate and manage anaphylactic reactions are immediately available, in an environment where full resuscitation facilities can be assured, is included in SmPC Section 4.2. • Section 2 of the PL notes that patients should talk to their doctor or nurse if they have ever had an infusion reaction during or after previously using POTELIGEO and Sections 2 and 4 note that they should tell the person giving the infusion or tell their doctor immediately if they experience symptoms of an infusion reaction. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription.
Important Potential Risks	
Hepatitis B reactivation	Routine risk communication: SmPC Sections 4.4 and 4.8. PL Sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation measures
	• Testing of patients for hepatitis B infection before initiation of treatment with mogamulizumab is recommended in SmPC Section 4.4, where prompt treatment is also recommended. • Section 2 of the PL notes that patients should talk to their doctor or nurse if they have hepatitis B virus. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription.
Increased risk of severe GVHD after allogeneic HSCT	Routine risk communication: SmPC Section 4.4. PL Section 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • A recommendation for patients to be closely followed for early evidence of transplant-related complications is included in SmPC Section 4.4. Section 4.4 of the SmPC states that GVHD has been reported in patients with T-cell lymphomas other than MF and SS who received allogeneic HSCT after POTELIGEO. Section 4.4 includes a warning stating that a higher risk of transplant complications has been reported if mogamulizumab is given within a short time frame (approximately 50 days) before HSCT. • Section 2 of the PL notes that patients should talk to their doctor or nurse if they have undergone or plan to have a stem cell transplant and Section 4 notes that they should tell their doctor immediately if they experience GVHD symptoms. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription.
Missing Information	
Use in patients with a history of autologous or allogeneic transplant	Routine risk communication: SmPC Section 4.4 PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Section 2 of the PL notes that patients should talk to their doctor or nurse if they have undergone stem cell transplant and Section 4 notes that they should tell their doctor immediately if they experience GVHD symptoms. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription.

V.2 Additional Risk Minimisation Measures

The routine risk minimisation activities described in Part V.1 are considered sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Risk minimisation activities and pharmacovigilance activities for all safety concerns are summarised in Table 22.

Table 22: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk		
Infusion-related reaction	Routine risk minimisation measures: SmPC Section 4.8 SmPC Section 4.2 and 4.4, where advice is given on the medical management of infusion-related reactions. PL Section 2 and 4 Legal status. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: A specific adverse reaction follow-up questionnaire to obtain further information on infusion-related reactions. Additional pharmacovigilance activities: None.
Important Potential Risks		
Hepatitis B reactivation	Routine risk minimisation measures: SmPC Section 4.8 SmPC Section 4.4, where testing of patients for hepatitis B infection before initiation of treatment with mogamulizumab is advised. PL Section 2 and 4 Legal status. Additional risk minimisation 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 minimisation measures: SmPC Section 4.4, where a recommendation for patients to be closely followed for early evidence of transplant-related complications is included. PL Section 2 and 4 Legal status. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS of allogeneic HCT in patients treated with mogamulizumab.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
Use in patients with history of autologous or allogeneic transplant	Routine risk minimisation measures: SmPC Section 4.4 mentions that treatment with mogamulizumab after autologous or allogeneic transplant has not been studied. PL Sections 2 and 4. Legal status. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Part VI: Summary Of The Risk Management Plan

Summary of Risk Management Plan for Poteligeo (mogamulizumab)

This is a summary of the Risk Management Plan (RMP) for POTELIGEO. The RMP details important risks of POTELIGEO, how these risks can be minimised, and how more information will be obtained about this product's risks and uncertainties (missing information).

POTELIGEO's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how POTELIGEO should be used.

This summary of the RMP for POTELIGEO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of POTELIGEO's RMP.

I. The Medicine and What it is Used For

POTELIGEO is authorised for the treatment of mycosis fungoides (MF) or Sézary syndrome (SS) in adults who have received at least one prior systemic therapy. It contains mogamulizumab as the active substance and it is given by infusion.

Further information about the evaluation of POTELIGEO's benefits can be found in POTELIGEO's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: Poteligeo | European Medicines Agency (EMA).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of POTELIGEO, together with measures to minimise such risks and the proposed studies for learning more about POTELIGEO's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of POTELIGEO is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of POTELIGEO are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of POTELIGEO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

A summary of the important risks and missing information for POTELIGEO is provided in Table 23.

Table 23: Summary of important risks and missing information for POTELIGEO

List of important risks and missing information	
Important identified risks	• Infusion-related reaction
Important potential risks	• Hepatitis B reactivation • Increased risk of severe graft versus host disease (GVHD) after allogeneic hematopoietic stem cell transplant (HSCT)
Missing information	• Use in patients with history of autologous or allogeneic transplant

II.B Summary of Important Risks

Further information about the important risks and missing information for POTELIGEO is provided in Table 24, Table 25, Table 26 and Table 27.

Table 24: Important identified risk of infusion-related reaction

Important identified risk: Infusion-related reaction	
Evidence for linking the risk to the medicine	Infusion-related reaction occurred in approximately a third of patients treated with mogamulizumab in hematologic clinical studies. However, severe (Grade ≥3) infusion-related reaction occurred infrequently, i.e. in approximately 2.9% of patients treated with mogamulizumab. Nearly all infusion-related reaction occurred in the first 4 weeks of treatment. Based on the frequency, the clinical importance, and the potential for severe events, infusion-related reaction is considered to be an important identified risk for mogamulizumab.
Risk factors and risk groups	Infusion-related reactions have been observed in patients treated with mogamulizumab with the majority occurring during or shortly after the first infusion with the incidence decreasing over time (EU SmPC Section 4.4).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 SmPC Section 4.2 and 4.4, where advice is given on the medical management of infusion-related reactions. PL Section 2 and 4 Additional risk minimisation measures: None.

Table 25: Important potential risk of hepatitis B reactivation

Important potential risk: Hepatitis B reactivation	
Evidence for linking the risk to the medicine	Patients with CTCL are at increased risk of infection, particularly with advanced disease and when using combination therapies (Thursky, 2006); patients frequently display evidence of immunosuppression, in particular at the later stages of the lymphoma (Zhang, 2014; Kim, 2005) and the risk is also increased by compromised skin integrity (Foss, 2014; Tsambiras, 2001). Axelrod (1992) retrospectively studied 356 patients with CTCL in the era predating monoclonal antibodies, and identified 478 infective episodes. Cutaneous bacterial infection was most common (17.0 infections per 100 PY), followed by cutaneous herpes simplex virus and herpes zoster virus infection (3.8 infections per 100 PY), bacteremia (2.1 infections per 100 PY), bacterial pneumonia (1.7 infections per 100 PY), and urinary tract infection (1.4 infections per 100 PY). Viral reactivation is a known complication of chemotherapy, especially for malignant lymphoma, and the increased risk in lymphoma patients parallels the potency of the immunosuppressive treatments (Phipps, 2016). Review of available data for mogamulizumab revealed no evidence of increased hepatitis B reactivation in the CTCL setting, although the data are limited due to exclusion of subjects with a history of acute or chronic hepatitis (including hepatitis B and C) from most of the clinical development studies). Reported cases of hepatitis B occurred in the ATL setting against a confounding immunosuppressive background of prior/concomitant ablative cytotoxic therapy.

Risk factors and risk groups	Patients with CTCL are at increased risk of serious infections. No risk factors for increased susceptibility to hepatitis B reactivation subsequent to mogamulizumab administration have been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 SmPC Section 4.4, where testing of patients for hepatitis B infection before initiation of treatment with mogamulizumab is advised. PL Section 2 and 4 Additional risk minimisation measures: None.

Table 26: Important potential risk of increased risk of severe GVHD after allogeneic HSCT

Important potential risk: Increased risk of severe GVHD after allogeneic HSCT	
Evidence for linking the risk to the medicine	Allogeneic HSCT is a recognized treatment option for advanced refractory CTCL (Paralkar, 2012; Duarte, 2008), although experience is limited and not well defined. Retrospective studies of outcomes after allogeneic HSCT (transplant from another person) for ATL suggest that prior treatment with mogamulizumab may increase the risk of moderate to severe acute GVHD and be associated with increased non-relapse mortality (NRM) and reduced overall survival (Fuji, 2016; Inoue, 2016; Sugio, 2016). However, a prolonged interval between mogamulizumab treatment and allogeneic HSCT may reduce the risk of moderate to severe acute GVHD. The retrospective nature of these reports, possible confounding factors, and the inherent risks of allogeneic HSCT mean that this potential risk requires further evaluation before a definitive assessment is possible. Whilst the same potential risk that prior treatment with mogamulizumab may increase the risk of moderate to severe GVHD after allogeneic HSCT for advanced refractory CTCL, very limited data are currently available, and a definitive assessment is not possible (Fuji, 2016). A review of the 456 patients who had received mogamulizumab (as initial or cross-over therapy) in Western clinical trials for hematologic indications was conducted to a DLP of 20 Jul 2017. Data on 32 of the 35 subjects reported to have undergone transplant are available, including 24 CTCL subjects. Twelve of 32 subjects developed acute GVHD after transplant (10 CTCL; 2 non-CTCL subjects). Due to the small subject numbers, no conclusions could be drawn concerning the effect of mogamulizumab treatment on the eventual outcome of HSCT as a treatment for T-cell lymphoma. Review of post-marketing data pertaining to this risk showed findings consistent with those recorded from clinical studies.
Risk factors and risk groups	The predominant determinants of acute GVHD risk after allogeneic HSCT for hematologic malignancies are the degree of human leukocyte antigen (HLA) match, intensity of conditioning (higher risk with total body irradiation), source of graft (higher risk with peripheral blood than bone marrow, and in female HLA identical sibling donors to male recipients) and GVHD prophylaxis regimen (higher risk with cyclosporine than tacrolimus) (Jagasia, 2012). It is currently unclear whether the same risk factors of acute GVHD after allogeneic HSCT are applicable for CTCL, due to the limited experience of this treatment option. The risk of moderate to severe acute GVHD after allogeneic HSCT for ATL may be increased after prior mogamulizumab administration, although longer periods between mogamulizumab

	administration to allogeneic HSCT may reduce the risk. However, this requires confirmation, particularly regarding use of the product for the treatment of CTCL.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, where a recommendation for patients to be closely followed for early evidence of transplant-related complications is included. PL Section 2 and 4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS of allogeneic HCT in patients treated with mogamulizumab. See section II.C of this summary for an overview of the post-authorisation development plan.

Table 27: Missing information of use in patients with a history of autologous or allogeneic transplant

Missing information: Use in patients with a history of autologous or allogeneic transplant	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 mentions that treatment with mogamulizumab after autologous or allogeneic transplant has not been studied. PL Sections 2 and 4 Additional risk minimisation measures: None

II.C Post-authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of POTELIGEO.

II.C.2 Other studies in post-authorisation development plan

One Category 3 post-authorisation safety study is ongoing to further investigate the potential risk of increased risk of severe GVHD after allogeneic HSCT.

Study title:
Post-authorisation safety study of allogeneic hematopoietic cell transplantation in patients treated with Mogamulizumab.

Purpose of the study:
The purpose of this study is to assess the potential risks of allogeneic hematopoietic cell transplantation (alloHCT) in patients with CTCL or ATLL who have received mogamulizumab either within 1 year before or within 18 months after transplantation. This study will help to characterise and address the safety concern of “Increased risk of severe GVHD after allo-HSCT”.

The primary objective of the study is to assess treatment-related mortality and non-relapse mortality (death without prior relapse or progression) among patients who were either treated with mogamulizumab, (alone as a single agent or in combination with other therapies) within one year prior to alloHCT, or treated with mogamulizumab, (alone as a single agent or in combination with other therapies), within 18 months after alloHCT.

Annex 4 Specific adverse drug reaction follow-up forms

Infusion related reaction (IRR) follow-up form

Date of report			
PATIENT INFORMATION			
Patient ID (Initials)		Age / Date of birth:	
Gender:	☐ Male ☐ Female	Weight (Kgs):	
CTCL: ☐ Yes ☐ No	Subtype: ☐ Mycosis fungoides ☐ Sézary Syndrome ☐ Other (please specify)	Disease Stage: ☐ IB ☐ II ☐ III ☐ IV	
INFUSION DETAILS			
Batch number:	Cycle/Infusion dose (please specify e.g. Cycle 1/first dose)	Dose administered/Infusion rate:	
REACTION DETAILS			
Did the patient experience any of the following? ☐ Pruritus ☐ Flushing ☐ Chest discomfort ☐ Hypotension ☐ Myalgia ☐ Nausea ☐ Urticaria ☐ Headache ☐ Rash ☐ Dizziness ☐ Chills ☐ Rigors ☐ Circulatory collapse ☐ Anaphylaxis ☐ Other(s), please specify		Do you consider the IRR to be serious? ☐ Yes ☐ No If yes, please tick as applicable ☐ Patient died due to IRR ☐ Life threatening ☐ Involved or prolonged hospitalisation ☐ Significant clinical sequelae (i.e., incapacity or disability)	
Was IRR of early onset (<24 hours from start of infusion)? ☐ Yes ..... (minutes/hours) ☐ No		Was IRR of late onset (>24 hours from start of infusion)? ☐ Yes ..... (days) ☐ No If yes, what was the duration of IRR? Start date: ..... Stop date:	
Was infusion rate slowed down after onset of IRR? ☐ Yes, please specify ..... ☐ No If yes, did IRR resolve following rate modification? ☐ Yes ☐ No		Was infusion interrupted? ☐ Yes ☐ No If yes, what was the duration of interruption? ☐ <15 minutes ☐ 15 – 30 minutes ☐ 30 – 60 minutes ☐ >60 minutes	
Was infusion completed? ☐ Yes		What was the outcome of IRR? ☐ Recovered	

☐ No Was infusion discontinued? ☐ Yes ☐ No		☐ Recovering ☐ Ongoing ☐ Fatal
Did patient receive premedication prior to infusion? ☐ Yes ☐ No If yes, please specify ☐ Antipyretic ..... ☐ Antihistamine ..... ☐ Corticosteroid	Did IRR require additional clinical intervention? ☐ Yes ☐ No If yes, please specify	Has patient had any prior IRRs to Poteligeo? ☐ Yes ☐ No If yes, please specify cycle(s) and which infusion does(s) ....
RELEVANT MEDICAL HISTORY		
Does the patient have past history of allergy/hypersensitivity?		Please provide details of any relevant investigations (e.g. antidrug antibody screening) ....
REPORTER DETAILS		
Name:		
Job title/Occupation:		
Address:		
Phone number:		
Email address:		

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable

Annex 7 Other supporting data (including referenced material)

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