▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

Australian Product Information – POTELIGEO (mogamulizumab) concentrated solution for intravenous infusion

1. NAME OF THE MEDICINE

Mogamulizumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of POTELIGEO contains 20 mg of mogamulizumab, a recombinant defucosylated humanised IgG_1 kappa monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Concentrated solution for intravenous infusion. Clear to slightly opalescent, colourless solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

POTELIGEO is indicated for the treatment of adult patients (≥ 18 years of age) with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer and should only be administered by healthcare professionals in an environment where resuscitation equipment is available.

Dosage

The recommended dose is 1 mg/kg mogamulizumab administered as an intravenous infusion over at least 60 minutes. Administration is 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.

POTELIGEO should be administered within 2 days of the scheduled day. If a dose is missed by more than 2 days, the next dose should be administered as soon as possible, after which the dosing schedule should be resumed with doses given based on the new scheduled days.

Pre-medication with anti-pyretic and anti-histamine is recommended for the first POTELIGEO infusion. If an infusion reaction occurs, administer pre-medication for subsequent POTELIGEO infusions.

Dose modification

Dermatologic reactions

Patients receiving mogamulizumab have experienced drug rash (drug eruption), some of which were severe and/or serious.

- In the event of a rash (drug related) with severity of Grade 2 or 3 (moderate or severe), treatment with mogamulizumab must be interrupted and the rash should be treated appropriately until rash improves to Grade 1 or less (mild severity), at which time mogamulizumab treatment may be resumed.
- POTELIGEO should be permanently discontinued for a life-threatening (Grade 4) rash (see section 4.4).

Infusion-related reactions

- The infusion of POTELIGEO should be temporarily interrupted for mild to severe (Grades 1-3) 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 reaction recurs, discontinuing the infusion should be considered (see section 4.4).
- POTELIGEO should be permanently discontinued for a life-threatening (Grade 4) infusion-related reaction (see section 4.4).

Preparation for Administration

- Visually inspect the medicinal product for particulate matter and discolouration prior to administration. POTELIGEO is a clear to slightly opalescent, colourless solution. Discard the vial if cloudiness, discolouration or particulates are observed.
- Calculate the required volume of POTELIGEO needed to prepare the infusion solution for the 1 mg/kg dosage based on patient weight. Aseptically withdraw the required volume of POTELIGEO into the syringe and transfer into an infusion bag containing 9 mg per mL (0.9%) sodium chloride solution for injection. Mix diluted solution by gentle inversion. Do not shake. The final concentration of the diluted solution should be between 0.1 mg/mL to 3.0 mg/mL.
- Product is for single use in one patient only. Discard any unused portion left in the vial in accordance with local requirements.

Administration

POTELIGEO is for intravenous use. It should be administered by intravenous infusion only, over at least 60 minutes. See above recommendations in case of infusion-related reaction.

For instructions on the dilution of the medicinal product before administration:

The diluted solution is compatible with polyvinyl chloride (PVC) or polyolefin (PO) infusion bags.

- Do not mix POTELIGEO with, or administer as an infusion with, other medicinal products.
- POTELIGEO is intended for intravenous use only, and should not be administered subcutaneously, intramuscularly, as a bolus dose or by rapid intravenous administration.
- Administer infusion solution over at least 60 minutes through an intravenous line containing a sterile, low protein binding 0.22 micron (or equivalent) in-line filter.

Special populations

Elderly (≥ 65 years of age)

No dose adjustment is required in elderly patients (see section 5.2).

Renal impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild to severe renal impairment (see section 5.2).

Hepatic impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild or moderate hepatic impairment. POTELIGEO has not been studied in patients with severe hepatic impairment (see section 5.2).

4.3 CONTRAINDICATIONS

Known hypersensitivity to mogamulizumab or to any of the excipients listed in *section 6.1 List of Excipients*.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Dermatologic reactions

Fatal and life-threatening skin adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have occurred in recipients of mogamulizumab. Rash (drug eruption) is one of the most common adverse reactions associated with mogamulizumab. In Study 0761-010, 24% (44/184) of patients treated with mogamulizumab in the randomised phase of the study had an adverse reaction of drug eruption, with 4.3% of these cases being severe (Grade 3) and 95.7% of these cases being Grade 1 or 2. Of 528 patients treated with mogamulizumab in clinical trials, Grade 3 skin adverse reactions were reported in 3.6%, Grade 4 skin adverse reactions in <1%, and SJS in <1%.

The onset of drug eruption is variable, and the affected areas and appearance vary. In Study 0761-010, the median time to onset was 15 weeks, with 25% of cases occurring after 31 weeks. The more common presentations reported included papular or maculopapular rash, lichenoid, spongiotic or granulomatous dermatitis, and morbilliform rash. Other presentations included scaly plaques, pustular eruption, folliculitis, non-specific dermatitis, and psoriasiform dermatitis.

Monitor patients for rash throughout the treatment course. Management of dermatologic reactions includes topical corticosteroids and interruption or permanent cessation of mogamulizumab (see section 4.2). Consider skin biopsy to help distinguish drug eruption from disease progression.

Discontinue mogamulizumab permanently for SJS or TEN or for any life-threatening (Grade 4) reaction. For possible SJS or TEN, interrupt mogamulizumab and do not restart unless SJS or TEN is ruled out and the cutaneous reaction has resolved to Grade 1 or less.

Infusion related Reactions

Fatal and life-threatening infusion related reactions have been reported in patients treated with mogamulizumab. In Study 0761-010, infusion related reactions occurred in 33% (61/184) of patients treated with mogamulizumab in the randomised phase of the study, with 1.6% of these reactions being severe (Grade 3). In the crossover phase of the study, 37% (50/136) of the patients who switched to mogamulizumab treatment experienced infusion related reactions, with 4.4% being severe (Grade 3). Most reactions (approximately 90%) occur during or shortly after the first cycle of infusion (first four administrations). Infusion related reactions can also occur with subsequent infusions. The most commonly reported signs include chills, nausea, fever,

tachycardia, rigors, headache, and vomiting.

Consider premedication (such as anti-histamines and paracetamol) for the first infusion of mogamulizumab in all patients. Whether premedication reduces the risk or severity of these reactions is not established. In Study 0761-010, infusion related reactions occurred in 42% of patients without premedication and 32% of patients with premedication. Monitor patients closely for signs and symptoms of infusion related reactions and interrupt the infusion for any grade reaction and treat promptly (see section 4.2).

Infections

Fatal and life-threatening infections have occurred in patients treated with mogamulizumab, including sepsis, pneumonia, and skin infection. In Study 0761-010, 17% (32/184) of patients randomised to mogamulizumab had Grade 3 or higher infection or an infection-related serious adverse reaction. Monitor patients for signs and symptoms of infection and treat promptly.

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

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) after mogamulizumab

Increased risks of transplant complications have been reported in patients who receive allogeneic HSCT after mogamulizumab including severe (Grade 3 or 4) acute graft-versus-host disease (GVHD), steroid-refractory GVHD, and transplant-related death. Among recipients of pre-transplantation mogamulizumab, a higher risk of transplant complications has been reportedif mogamulizumab is given within a shorter time frame (approximately 50 days) before HSCT. Follow patients closely for early evidence of transplant-related complications.

Tumour lysis syndrome

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

Cardiac disorders

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

Large cell transformation (LCT)

There are limited data available on patients with LCT.

Other

Mogamulizumab should not be administered subcutaneously or intramuscularly, by rapid intravenous administration, or as an intravenous bolus.

Use in the Elderly

POTELIGEO may be administered to patients aged 65 years and over.

Paediatric Use

The safety and efficacy of POTELIGEO in children and adolescents aged below 18 years have not been established. No data are available.

Effects on laboratory tests

POTELIGEO may cause increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase or decreased lymphocyte count. Common or worsening laboratory abnormalities are summarised in Table 3.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMSOF INTERACTION

No interaction studies have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential / Contraception in males and females

Women of childbearing potential and males of reproductive potential should use effective contraception during treatment with POTELIGEO and for at least 3 months after treatment.

Effects on fertility

There are no clinical data available on the effect of POTELIGEO on human fertility. No specific studies in animals have been performed to evaluate the effect of mogamulizumab on fertility. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies in cynomolgus monkeys at intravenous doses up to 40 mg/kg/week for 26 weeks (yielding almost 80 times the systemic exposure in patients, based on AUC).

Use in pregnancy – Category C

There are no data from the use of POTELIGEO in pregnant women.

In a study in pregnant cynomolgus monkeys, mogamulizumab did not cause malformations, embryofetal lethality or growth retardation with administration at 40 mg/kg/week IV (yielding 27 times the systemic exposure in patients, based on AUC). However, mogamulizumab was shown to cross the placental barrier, and this resulted in pharmacological activity in the foetuses, evident as a decrease in CCR4-expressing lymphocytes. POTELIGEO is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.

Use in lactation

It is unknown whether mogamulizumab is excreted in human milk. Human IgGs are known to be excreted in breast milk. Consequently, a risk to the breast-fed child cannot be excluded. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for POTELIGEO and any potential adverse effects on the breastfed child from POTELIGEO.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Mogamulizumab has minor influence on the ability to drive and use machines. Fatigue may occur following administration of mogamulizumab (see section 4.8).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The most frequently reported serious adverse reactions were pneumonia, pyrexia, infusion related reaction and cellulitis.

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

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

Tabulated list of adverse reactions

The adverse reactions are presented by system organ class and frequency categories, defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions occurring in patients receiving POTELIGEO (N=184)

System organ class (SOC)	Adverse reaction
Blood and lymphatic system disorders	
Common:	Anaemia, neutropenia, leukopenia, thrombocytopenia
Endocrine disorders	
Common:	Hypothyroidism
Gastrointestinal disorders	
Very common:	Constipation, diarrhoea, nausea, stomatitis
Common:	Vomiting
General disorders and administration site conditions	
Very common:	Fatigue, oedema peripheral, pyrexia
Hepatobiliary disorders	
Uncommon:	Hepatitis acute, hepatitis
Infections and infestations	
Very common:	Infections[a]
Common:	Upper respiratory tract infection
Injury, poisoning and procedural complications	
Very common:	Infusion related reaction
Investigations	
Common:	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, lymphocyte count decreased

System organ class (SOC)	Adverse reaction
Metabolism and nutrition disorders	
Uncommon:	Tumour lysis syndrome
Nervous system disorders	
Very common:	Headache
Skin and subcutaneous tissue disorders	
Very common:	Drug eruption (including skin rash)

[a] Folliculitis, Cellulitis, Candidiasis, Pneumonia, Sepsis, Skin infection, Otitis externa, Herpes zoster, Staphylococcal skin infection, Urinary tract infection, Herpes simplex and cytomegalovirus

The most common adverse reactions (reported in ≥10% and having a ≥2% higher incidence with POTELIGEO than with vorinostat in Study 0761-010) are listed in Table 2.

Table 2: Common Adverse Reactions (≥10%) with ≥2% Higher Incidence in the POTELIGEO Arm (Study 0761-010)

Adverse Reactions by Body System [a, b]	POTELIGEO (N=184)		Vorinostat (N=186)	
	All Grades (%)	≥Grade 3 (%)	All Grades (%)	≥Grade 3 (%)
Skin and Subcutaneous Tissue Disorders				
Rash, Including Drug Eruption	35	5	11	2
Drug Eruption	24	5	<1	0
Procedural Complications				
Infusion Related Reaction	33	2	0	0
Infections				
Upper Respiratory Tract Infection	22	0	16	1
Skin Infection	19	3	13	4
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	22	<1	17	3
General Disorders				
Pyrexia	17	<1	7	0
Gastrointestinal				
Mucositis	12	1	6	0

[a] Adverse reactions include groupings of individual preferred terms.

[b] Includes adverse reactions reported up to 90 days after randomised treatment.

Rash/Drug Eruption includes: dermatitis (allergic, atopic, bullous, contact, exfoliative, infected), drug eruption, palmoplantar keratoderma, rash (generalized, macular, maculopapular, papular, pruritic, pustular), skin reaction, toxic skin eruption

Upper Respiratory Tract Infection includes: laryngitis viral, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection

Skin Infection includes: cellulitis, dermatitis infected, erysipelas, impetigo, infected skin ulcer, periorbital cellulitis, skin bacterial infection, skin infection, staphylococcal skin infection

Musculoskeletal Pain includes: back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity

Mucositis includes: aphthous stomatitis, mouth ulceration, mucosal inflammation, oral discomfort, oral pain, oropharyngeal pain, stomatitis

Table 3 summarises common treatment-emergent laboratory abnormalities having a ≥2% higher incidence with POTELIGEO than with vorinostat in Study 0761-010.

Table 3: Common New or Worsening Laboratory Abnormalities (≥10%) with ≥2% Higher Incidence in the POTELIGEO Arm (Study 0761-010)

Laboratory Test [a]	POTELIGEO (N=184)		Vorinostat (N=186)	
	All Grades (%)	≥Grade 3 (%)	All Grades (%)	≥Grade 3 (%)
Chemistry				
Albumin Decreased	34	2	27	3
Calcium Decreased	30	3	20	2
Uric Acid Increased	29	29	11	11
Phosphate Decreased	27	5	26	5
Magnesium Decreased	17	<1	8	<1
Glucose Decreased	14	0	8	<1
Calcium Increased	12	<1	8	<1
Haematology				
CD4 Lymphocytes Decreased [b]	63	43	17	8
Lymphocytes Decreased	31	16	12	4
White Blood Cells Decreased	33	2	18	2

[a] Includes laboratory abnormalities, reported up to 90 days after treatment, that are new or worsening in grade or with worsening from baseline unknown.

[b] Out of 99 evaluable recipients of POTELIGEO and 36 evaluable recipients of vorinostat.

Description of selected adverse events

Dermatologic reactions

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

Infusion-related reactions

Infusion-related reactions have been observed in 33% of patients treated with POTELIGEO. The majority of treatment-related infusion-related reactions were Grade 1 or 2 and occurred during or shortly after the first infusion. Severe reactions (Grade 3) were experienced by 1.6% of the patients in the randomised phase of the study and 4.4% of patients in the crossover phase of the study.

The incidence of infusion related reactions was highest after the first infusion (28.8% of patients), reducing to ≤ 3.8% of patients after two or more infusions.

Infusion interruptions occurred in approximately 6% of patients, most of which (approximately 90%) occurred within the first cycle of treatment with mogamulizumab.

Less than 1% of patients treated in Study 0761-010 discontinued treatment due to infusion-related reactions.

Serious infections

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

Immune-mediated events

Fatal and life-threatening immune-mediated complications have been reported in recipients of mogamulizumab. Grade 3 or higher immune-mediated or possibly immune-mediated reactions have included myositis, myocarditis, polymyositis, hepatitis, pneumonitis, and a variant of Guillain-Barré syndrome. Use of systemic immunosuppressants for immune-mediated reactions was reported in 1.9% (6/319) of recipients of mogamulizumab in Study 0761-010, including for a case of Grade 2 polymyalgia rheumatica. New-onset hypothyroidism (Grade 1 or 2) was reported in 1.3% of patients and managed with observation or levothyroxine. Interrupt or permanently discontinue mogamulizumab as appropriate for suspected immune-mediated adverse reactions. Consider the benefit/risk of mogamulizumab in patients with a history of autoimmune disease.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. A small percentage of patients receiving POTELIGEO tested positive for treatment emergent (treatment induced or treatment boosted) anti mogamulizumab antibodies. There were no positive neutralising antibody responses.

Safety post last dose

Of the 320 subjects exposed to mogamulizumab in Study 0761-010, 21 (6.6%), experienced at least one serious adverse drug reaction (SADR) that occurred within 90 days from the date of last study drug administration.

Of these, SADRs that were reported in more than one patient were coded under the SOCs Infections and infestations (7 [2.2%] patients), General disorders and administration site conditions (5 [1.6%] patients), Respiratory, thoracic and mediastinal disorders (4 [1.3%] patients), Musculoskeletal and connective tissue disorders (3 [0.9%] patients), Hepatobiliary disorders (2 [0.6%] patients), and Injury, poisoning and procedural complications (2 [0.6%] patients). All remaining SOCs reported SADRs in one patient (0.3%).

The safety profile observed in the 90 days following the last dose of mogamulizumab is consistent with the safety profile observed during the study treatment period.

Elderly population

The safety profile in elderly patients (≥ 65 years) was generally consistent with that of adult patients, except for dermatologic reactions and infusion related reactions which were seen more often in older subjects.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdose with mogamulizumab. In case of overdose, the patient, including their vital signs, should be closely monitored (for at least 1 hour) and supportive treatment should be administered if required.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Mogamulizumab is a defucosylated, humanised IgG1 kappa monoclonal antibody that selectively binds to CCR4, a G protein-coupled receptor for CC chemokines that is involved in the trafficking of lymphocytes to various organs including the skin. CCR4 is expressed on the surface of some T cell malignancies, such as MF and SS as well as Type 2 T helper (Th2) T cells and regulatory T cells (T_{regs}). Binding of mogamulizumab to CCR4 induces antibody-dependent cellular cytotoxicity (ADCC), resulting in the depletion of target cells.

Clinical trials

The efficacy of mogamulizumab in the treatment of patients with mycosis fungoides (MF) or Sézary syndrome (SS) was established in a Phase 3, multicentre, open-label, study (0761-010) of 372 adult patients randomised 1:1 to treatment with either mogamulizumab or vorinostat. Each arm enrolled 186 patients. Mogamulizumab infusion was administered at a dose of 1 mg/kg once weekly for the first 28-day cycle (on Days 1, 8, 15 and 22), and on days 1 and 15 of subsequent 28-day cycles. Vorinostat was administered at a starting dose of 400 mg orally, once daily beginning on day 1 for 28-day cycles. Vorinostat patients with disease progression or unacceptable toxicities were permitted to cross over to mogamulizumab therapy. Crossover patients received up to 46 months of mogamulizumab therapy, as of December 2016 data cut.

Treatment with mogamulizumab continued until disease progression or unacceptable toxicity. The trial excluded patients with active autoimmune diseases, central nervous system metastasis, and medical conditions that required systemic corticosteroids or other immunosuppressive medicinal products, or an active infection requiring therapy, including HIV, or hepatitis B or C. Patients with ECOG performance status ≥2 were also excluded. At study baseline, 38% had stage IB-II disease, 10% stage III, 52% stage IV. This study included patients regardless of their baseline level of CCR4 expression in skin biopsy.

The primary efficacy endpoint was progression-free survival (PFS) based on investigator assessment using a global composite response criteria that took into account all potentially affected disease compartments (skin, blood, lymph nodes and viscera). Response in skin and blood was evaluated every 4 weeks. Response in lymph nodes and viscera was evaluated at 4 weeks, then every 8 weeks in the first year, and then every 16 weeks thereafter.

All patients had a histologically confirmed diagnosis of mycosis fungoides (MF), 56.5%, 53.2%, or Sézary Syndrome (SS), 43.5%, 46.8%, in the mogamulizumab and vorinostat groups, respectively, and had received at least one prior systemic therapy. The most common prior systemic therapies used by subjects in Europe were bexarotene (70%), interferon (59%), methotrexate (49%), extracorporeal photopheresis (ECP) (31%) and gemcitabine/gemcitabine regimens (28%).

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

received mogamulizumab for at least 12 cycles.

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

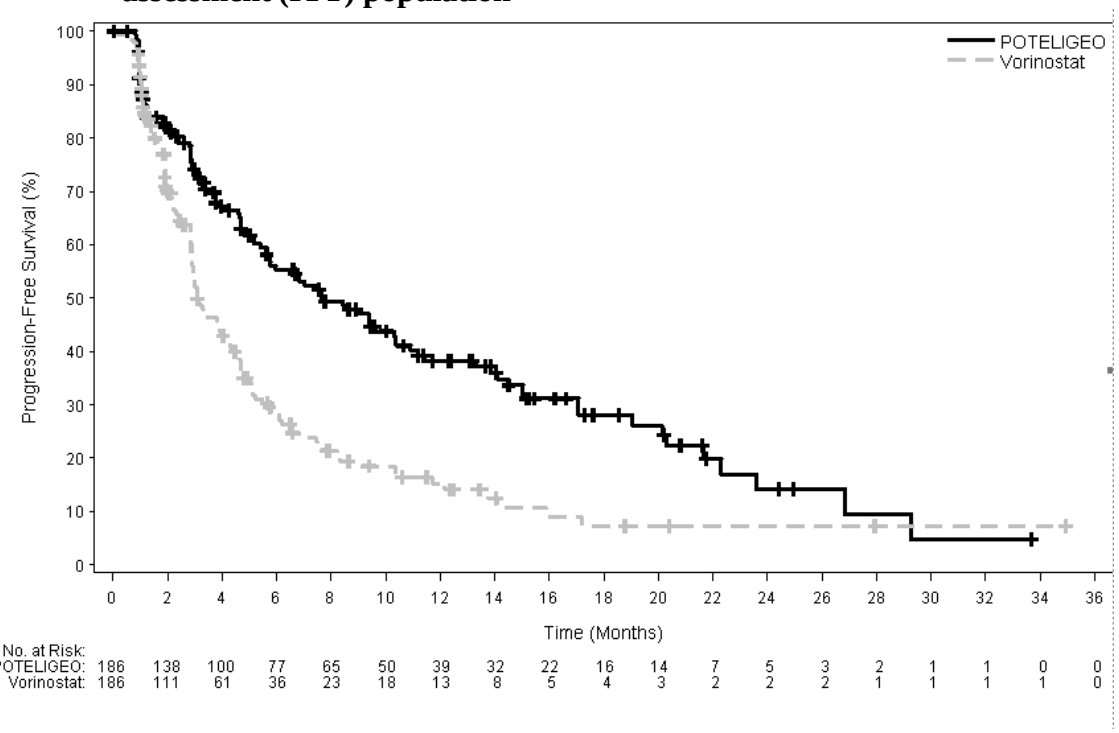
CCR4 expression was assessed retrospectively on pre-treatment skin biopsies (formalin fixed paraffin embedded) using immunohistochemistry. In the mogamulizumab arm, baseline CCR4 expression levels were available in 75% of patients (N=140). CCR4 was detected on ≥1% of lymphocytes in 100% of patients,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

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

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

The Kaplan-Meier curve for PFS is shown Figure 1.

Figure 1: Plot of Kaplan-Meier curve of progression-free survival by investigator's assessment (ITT) population



Key secondary endpoints were overall response rate (ORR), ORR after crossover, duration of response (DOR), and changes from baseline of the Skindex-29 Symptoms and Functional Scales, and Functional Assessment of Cancer Therapy-General (FACT-G) Physical and Functional Well-being domains.

Overall response was reported as a composite score from measures in each compartment, and a response had to be demonstrated at two successive overall disease assessments (at least 8 weeks apart during the first year and 16 weeks apart thereafter) in order to be confirmed. Patients were included in the analysis for a specific compartment if they had presence of disease in that compartment at baseline, or had any post-baseline response assessment for that compartment.

Table 4 summarises ORR and DOR, and response by compartment. The study demonstrated statistically significant improvements in ORR and response by compartment in the blood, skin, and lymph nodes as compared to vorinostat. Response in the viscera could not be evaluated due to limited efficacy data in subjects with visceral involvement; the benefit-risk of mogamulizumab in subjects with visceral involvement is currently undetermined due to lack of data.

Table 4: Response during randomised treatment period in study 0761-010 (intent-to-treat)

	Mogamulizumab N=186	**Vorinostat N=186**
Overall response rate (confirmed CR + PR, %)	28.0	4.8
95% CI	(21.6, 35.0)	(2.2, 9.0)
P-value[a]	<.0001	
Duration of response (months)		
Median (95% CI)	14.1 (9.4, 19.2)	9.13 (4.7, -)
Response by compartment		
Blood	n=124	n=125
Response rate (confirmed CR + PR, %)	66.9	18.4
95% CI	(57.9, 75.1)	(12.0, 26.3)
P-value[a]	<0.0001	
Skin	n=186	n=186
Overall response rate (confirmed CR + PR, %)	41.9	15.6
95% CI	(34.8, 49.4)	(10.7, 21.6)
P-value[a]	<.0001	
Lymph nodes	n=136	n=133
Overall response rate (confirmed CR + PR, %)	15.4	3.8
95% CI	(9.8, 22.6)	(1.2, 8.6)
P-value[a]	0.0008	
Viscera	n=6	n=4
Overall response rate (confirmed CR + PR, %)	0	0
95% CI	(0.0, 45.9)	(0.0, 60.2)

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

[a]: P-value was obtained from Cochran-Mantel-Haenszel test adjusting for disease type, disease stage, and region.

CI=confidence interval; CR=complete response; PR=partial response

Treatment with mogamulizumab resulted in 8 confirmed complete responses (complete clearing of all affected compartments) compared with 0 patients on vorinostat: 4 of these 8 patients were initially randomised to mogamulizumab and 4 had crossed over to mogamulizumab during the study. Forty-one of the 136 cross-over patients (30.1%) responded with either partial or complete response with mogamulizumab.

There are limited efficacy data in patients with low (<10%) CCR4 expression in the skin. In Study 0761-010 there were 10/290 evaluable patients with CCR4 expression <10%, of which 6 were randomised to mogamulizumab, and 4 were randomised to vorinostat and subsequently crossed over to mogamulizumab. No confirmed responses were observed in these 10 subjects with low (<10%) CCR4 expression. Compartmental responses were seen in 3 of 10 evaluable subjects treated with mogamulizumab in the randomised or cross over phase.

Patients with stage IB/II disease treated with mogamulizumab had confirmed ORR of 17.6% compared to 8.3% for vorinostat, and compartment level (blood, skin, lymph node) response rates that were higher than those for vorinostat treated patients (Table 5). Overall, the median period of progression free survival for stage IB/II subjects treated with mogamulizumab was 4.7 months compared to 3.9 months for vorinostat-treated patients (Table 6). In patients with stage IB/II disease, given the limited number of subjects with a response and immaturity of the data, no conclusion on duration of response can be made.

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

Table 5: Overall and Compartmental Response Rate in Early Disease Stages

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

M=mogamulizumab. V= vorinostat

Table 6: Progression Free Survival (PFS) by Treatment Group and Disease Stage (Randomised Treatment Period)

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

ITT=intent to treat

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

Mogamulizumab is dosed via intravenous route and therefore is immediately and completely bioavailable.

Distribution

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

Metabolism

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

Excretion

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

Linearity and accumulation

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

Renal impairment

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

Hepatic impairment

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

Other special populations

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

Pharmacokinetic/pharmacodynamic relationship(s)

Efficacy

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been conducted to assess the genotoxic potential of mogamulizumab.

As a large protein molecule, mogamulizumab is not expected to interact with DNA or other chromosomal material.

Carcinogenicity

No studies have been conducted to assess the carcinogenic potential of mogamulizumab.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Citric acid monohydrate

Glycine

Polysorbate 80

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injections

This medicinal product contains less than 1 mmol sodium per dose, that is to say essentially 'sodium free'.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Mogamulizumab should not be infused concomitantly in the same intravenous line with other medicinal products.

6.3 SHELF LIFE

Unopened vial

3 years

After opening

POTELIGEO does not contain a preservative. Once opened, the medicinal product should be diluted and infused immediately (see section 4.2).

After preparation of infusion

Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (at 25°C) under ambient room light. These time limits include storage of the infusion solution in the infusion bag through the duration of infusion. From a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not be longer than a total of 4 hours at 2°C - 8°C provided that dilution has taken place under controlled and validated aseptic conditions.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Must be stored in a refrigerator (2ºC to 8ºC).

Do not freeze.

Do not shake.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3

6.5 NATURE AND CONTENTS OF CONTAINER

5 mL solution in a 10 mL glass vial (type I glass) with a rubber stopper, an aluminium seal and a polypropylene flip-off cap.

Pack of one vial.

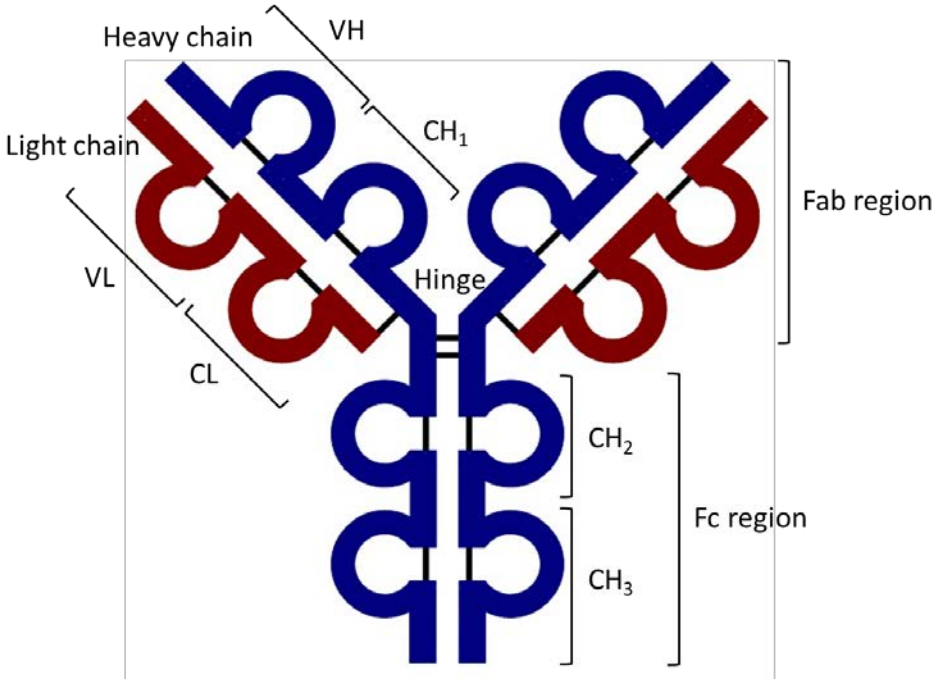
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Product is for single use only. Discard any residue.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



CAS Number

CAS registry number: 1159266-37-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

6 January 2021