Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Mogamulizumab

Proprietary Product Name: Poteligeo

Sponsor: Kyowa Kirin Australia Pty Ltd

April 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific annex
AST	Aspartate aminotransferase
ATL	Adult T-cell leukaemia
AUC	Area under the plasma concentration time curve
CCR4	C-C chemokine receptor type 4
CI	Confidence interval
C_{max}	Maximum plasma concentration
CMI	Consumer Medicines Information
COR	Comparable Overseas Regulator
COR-B	Comparable Overseas Regulator Report-based pathway B
CTCL	Cutaneous T-cell lymphoma
DLP	Data lock point
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency (European Union)
EOI	End of infusion
EOT	End of treatment
ER	Exposure-response
EU	European Union
GLP	Good Laboratory Practice
GVHD	Graft versus host disease
GVP	Good pharmacovigilance practices
HSCT	Haematopoietic stem cell transplantation
ICH	International Council for Harmonisation

Abbreviation	Meaning
IgG	Immunoglobulin G
ITT	Intent to treat
IV	Intravenous
KW-0761	Mogamulizumab drug development name
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis fungoides
NCA	Non compartmental analysis
ORR	Objective response rate
OS	Overall survival
PASS	Post-authorisation safety study
PBMC	Peripheral blood mononuclear cell
PFS	Progression-free survival
PI	Product Information
PK	Pharmacokinetic(s)
PPK	Population pharmacokinetic(s)
PSUR	Periodic safety update report
PTCL	Peripheral T cell lymphoma
QTc	Corrected QT interval
RMP	Risk management plan
SS	Sézary syndrome
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
TTNT	Time to next treatment
UV	Ultraviolet
US(A)	United States (of America)

Abbreviation	Meaning
VOR	Vorinostat

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	Poteligeo
Active ingredient:	Mogamulizumab
Decision:	Approved
Date of decision:	6 January 2021
Date of entry onto ARTG:	5 February 2021
ARTG number:	330232
▼ *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Kyowa Kirin Australia Pty Ltd Level 7, 68 York Street Sydney, NSW, 2000
Dose form:	Concentrate for solution for infusion
Strength:	4 mg/mL
Container:	10 mL glass vial
Pack size:	1
Approved therapeutic use:	*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.*
Route of administration:	Intravenous
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

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

	Days 1 and 15 of each subsequent 28 day cycle until disease progression or unacceptable toxicity. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	C Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Kyowa Kirin Australia Pty Ltd (the sponsor) to register Poteligeo (mogamulizumab) 4 mg / mL, 10 mL glass vial for the following proposed indication:

> *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.*

Mogamulizumab is an immunoglobulin G (IgG) antibody that targets the C-C chemokine receptor type 4 (CCR4) present on malignant T-cells typical of cutaneous T-cell lymphoma (CTCL). CCR4 is involved in targeting T-cells to the skin in CTCL but is also expressed in circulating cells. Binding of mogamulizumab to CCR4 induces cell cytotoxicity and death of the malignant T-cells targeted.

Mycosis fungoides (MF) and Sezary syndrome (SS) are the two most common forms of CTCL, yet both are rare forms of non-Hodgkins T-cell lymphoma, affecting approximately 1 in 100,000 persons. The early manifestations of disease include patches, plaques and tumours on the skin which increase in extent and severity as the malignancy progresses. In later stages, lymph nodes and visceral organs are involved. The prognosis of CTCL is variable. Early stage disease can be indolent for many years, but about 25% of patients will progress to later stage disease. Stages IIB, III and IV disease have median survivals of four to six years.

Early CTCL disease is typically managed with cutaneous therapies, such as topical steroids, ultraviolet (UV) light, and topical cytotoxic agents. Methotrexate and other systemic chemotherapies are used for more advanced systemic disease. Mogamulizumab offers a potentially targeted systemic therapy for CTCL which may be useful in advanced disease.

This application was submitted through the TGA's Comparable Overseas Regulator approach B (COR-B)[2] process, using evaluation reports from the European Medicines Agency (EMA). The full dossier was also submitted to the TGA.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, similar applications had been approved in the European Union (2018); USA (2018); and Japan (from 2012 onwards) as shown in Table 1, below.)

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	6 October 2017	Approved on 22 November 2018	*Poteligeo is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.*
United States of America	4 October 2017	Approved on 8 August 2018	*Poteligeo is a CC chemokine receptor type 4 (CCR4)-directed monoclonal antibody indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides or Sézary syndrome after at least one prior systemic therapy.*
Japan	30 November 2017	Approved on 21 August 2018	*Relapsed or refractory cutaneous T-cell lymphoma (CTCL) (Deleted CCR4 - positive)*
	30 June 2014	Approved on 18 December 2014	*Untreated adult CCR4 - positive adult T-cell leukemia lymphoma (ATL) in combination with other antineoplastic agents.*

[2] **COR-B (comparable overseas regulator pathway B):** The TGA makes use of assessments from comparable overseas regulators (CORs), where possible, in the evaluation of prescription medicines. Under the COR-B approach, the TGA regulatory decision will be mostly based on a critical review of the COR assessment reports. The COR-B process has a 175 working day evaluation and decision timeframe, allowing for TGA evaluation of certain data, in addition to the label, Product Information (PI) and Risk Management Plan (RMP).
The amount and type of additional data requiring evaluation will determine whether the application is best processed under the COR-B approach or as a Category 1 application.
Examples of additional data that may be considered under the COR-B process include updated stability data, validation data for an additional manufacturing site and updates to pivotal studies that support the proposed indication.

Region	Submission date	Status	Approved indications
	19 July 2013	Approved on 17 March 2014	*Relapsed or refractory CCR4 -positive peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL)*
	26 April 2011	Approved on 30 March 2012	*Relapsed or refractory CCR4 -positive adult T-cell leukemia lymphoma (ATL)*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for submission PM-2020-00700-1-6

Description	Date
Positive Designation (Orphan)[3]	11 December 2019
Submission dossier accepted and first round evaluation commenced	1 April 2020
First round evaluation completed	31 July 2020
Sponsor provides responses on questions raised in first round evaluation	1 September 2020
Second round evaluation completed	9 October 2020
Delegate's Overall benefit-risk assessment	20 October 2020
Registration decision (Outcome)	6 January 2021

[3] **Orphan** drugs are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related orphan designation is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

Description	Date
Completion of administrative activities and registration on the ARTG	5 February 2021
Number of working days from submission dossier acceptance to registration decision*	167

* The COR-B process has a 175 working day evaluation and decision timeframe.

III. Submission overview and risk/benefit assessment

This section is a TGA summary of wording used in TGA's evaluation reports, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

The quality evaluator has raised no outstanding issues for registration of mogamulizumab.

Poteligeo (mogamulizumab), also known as KW-0761;[4] is a defucosylated humanised IgG subclass 1 kappa monoclonal antibody that selectively binds to chemokine (C-C motif) receptor 4 (CCR4): a G protein coupled receptor for C-C chemokines. In healthy individuals, CCR4 is known to be selectively expressed on a subset of T cells, including type 2 helper-T cells and regulatory-T cells.

The drug substance is manufactured using a Chinese hamster ovary cell line.

The drug product is formulated at [information redacted]. Each single use glass vial delivers 5 mL of solution. The formulation was developed to stabilise the monoclonal antibody and provide a clear to slightly opalescent, colourless, preservative free, sterile solution.

The drug product is presented as a sterile, single use, ready to use, preservative free, practically free of particles, and clear to slightly opalescent, colourless solution for intravenous (IV) administration. Each 10 mL vial contains 5 mL deliverable volume of mogamulizumab (20 mg) at a concentration of 4 mg / mL. Each vial contains 0.5 mL of overfill, thus the total filled volume of mogamulizumab solution is 5.5 mL.

The drug product is provided in a 10 mL, Type I clear borosilicate tubing glass vial, sealed with a fluoropolymer laminated butyl rubber stopper, and clamped with an aluminium seal with a polypropylene flip off cap.

Nonclinical

The nonclinical evaluator has raised no issues for the registration of mogamulizumab.

The nonclinical evaluator has noted the following:

- The sponsor's nonclinical data contained an adequate set of studies conducted in general accordance with relevant guidelines for the nonclinical assessment of

[4] KW-0761 is the sponsor's drug development name for mogamulizumab (Poteligeo)

anticancer pharmaceuticals and biological medicines (ICH S9 and ICH S6 (R1)).[5,6] The nonclinical dossier was of good overall quality, and all pivotal safety related studies were Good Laboratory Practice (GLP) compliant.[7]

- *In vitro* studies established that CCR4 was expressed on numerous human T cell lymphoma and T cell leukaemia cell lines. Mogamulizumab was shown to bind to human CCR4, and to induce antibody dependent cellular cytotoxicity, depleting CCR4-expressing target cells. Mogamulizumab additionally recognised the cynomolgus monkey form of CCR4, but not CCR4 of other routine laboratory animal species (mouse, rat and dog). *In vivo*, mogamulizumab decreased $CD4^+/CCR4^+$ lymphocytes in cynomolgus monkey peripheral blood and showed anti tumour activity in immunodeficient mice bearing human CTCL and adult T cell leukaemia/lymphoma (ATL) xenografts. These pharmacology studies offer support for efficacy for the proposed indication.
- No off-target binding was evident for mogamulizumab in immunohistochemical assays, conducted using a panel of human and cynomolgus monkey tissues.
- *In vitro,* mogamulizumab induced cytokine release from human whole blood and isolated peripheral blood mononuclear cells (PBMCs). This is considered a notable finding of clinical relevance.
- Examination of safety pharmacology endpoints in monkeys indicated no clinically relevant effects on central nervous, cardiovascular or respiratory function.
- The pharmacokinetic profile of mogamulizumab was typical of an immunoglobulin G (IgG) antibody, and similar in cynomolgus monkeys and humans. This was characterised by a long elimination half life, leading to accumulation with repeat dosing, and a low volume of distribution, indicative of confinement largely to the vascular compartment.
- Mogamulizumab displayed a low order of acute toxicity by the IV route in cynomolgus monkeys.
- Repeat dose toxicity studies, involving weekly IV administration for up to 26 weeks, were conducted in cynomolgus monkeys. Doses of mogamulizumab producing high multiples of the clinical systemic exposure were well tolerated, with no target organs for toxicity identified. Treatment caused reductions in CCR4-expressing T-helper cells and cytotoxic/suppressor-T lymphocytes, representing the primary pharmacological action of the drug.
- Genotoxicity and carcinogenicity studies were not conducted, in line with ICH guidelines.[8]
- No impairment of fertility is predicted in patients, based on the absence on histopathological findings in the male and female reproductive tissues in treated monkeys. No malformations, embryofetal lethality or fetal growth retardation were observed with mogamulizumab in an embryofetal development study in monkeys.

[5] EMA, ICH Topic S9, Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals, EMEA/CHMP/ICH/646107/2008, December 2008. Available from the EMA website.
[6] EMA, ICH Topic S6(R1), Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals – Step 5, CPMP/ICH/302/95, July 2011 (Revision 1). Available from the EMA website
[7] **GLP**: **Good Laboratory Practice** is a code of standards following the International Council for Harmonisation (ICH) guidance relevant to testing of medicines in laboratories during drug development.
[8] **ICH**: The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together regulatory authorities and the pharmaceutical industry. It makes recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration.

However, placental transfer was evident and resulted in pharmacological activity (decreased CCR4-positive lymphocytes) in the fetuses, carrying the potential for impaired immune function following *in utero* exposure. Accordingly, assignment to Pregnancy Category C[9] is warranted (rather than Category B2[10] as the sponsor proposes).

- Mogamulizumab was shown to be well tolerated locally in monkeys.

There are no nonclinical objections to the registration of Poteligeo for the proposed indication. There are no outstanding issues in relation to the PI.

Clinical

The clinical dossier contained the following:

- Two Phase III pivotal safety and efficacy studies
- One Phase I-II supportive study and one Phase II extension study
- Five Phase II studies
- One Phase I study.

Pharmacology

Pharmacokinetics

A summary of clinical pharmacokinetic studies are listed in Table 3 below.

[9] **Pregnancy Category C**: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
[10] **Pregnancy Category B2**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Table 3: Summary of clinical pharmacokinetic studies

Study No. (Region)	Design	Dose/ route schedule	Study population; population size for PK analysis	PK sampling point	Assessment
0761-0501 (Japan)	Phase I, open label	0.01, 0.1, 0.5 and 1.0 mg/kg IV weekly for 4 weeks	Subjects with CCR4-positive relapsed ATL and PTCL[a] 16 subjects: 0.01 mg/kg: n = 3; 0.1 mg/kg, n = 4; 0.5 mg/kg, n = 3; 1.0 mg/kg, n = 6	Dose 1: Pre-dose, 0.5, 2, 4, 24 and 72 hrs. Dose 2-3: Pre-dose and EOI; Dose 4: Pre-dose, 0.5, 2, 4, 24 and 72 hrs and 7, 14, 21 and 28 days after dosing	Single-dose PK. (NCA), Multiple-dose PK (NCA), PPK
0761-002 (Japan)	Phase II, open label	1.0 mg/kg IV weekly for 8 weeks	Subjects with CCR4-positive relapsed ATL 27 subjects	Dose 1: Pre-dose, 0.5, 2, 4, 24 and 72 hrs; Dose 2-7: Pre-dose and EOI; Dose 8: Pre-dose, 0.5, 2, 4, 24 and 72 hrs and 7, 14, 21 and 28 days after dosing	Multiple-dose PK (NCA), PPK
0761-003 (Japan)	Phase II, multicentre, randomised, open label, parallel group study	mLSG15[c] or 1.0 mg/kg, mogamulizumab + mLSG15; mogamulizumab given IV every two weeks for 16 weeks; randomised 1:1	Subjects with CCR4-positive ATL (untreated primary disease) 29 subjects [b]	Dose 1-7: Pre-dose and EOI; Dose 8: Pre-dose, EOI and 14 days after dosing	PPK
0761-004 (Japan)	Phase II, open-label	1.0 mg/kg IV weekly for 8 weeks	Subjects with CCR4-positive relapsed PTCL[b] and CTCL 37 subjects	Dose 1: Pre-dose; Dose 4: EOI; Dose 5: Pre-dose; Dose 8:EOI and 7 and 28 days after dosing	PPK

Study No. (Region)	Design	Dose/ route schedule	Study population; population size for PK analysis	PK sampling point	Assessment
0761-009 (US, EU, South America)	Phase II, open label, multicentre, randomised	Mogamulizumab 1.0 mg/kg IV weekly (Day 1, 8. 15 and 22) in Cycle 1, then biweekly (Day 1 and 15) in subsequent cycles. Investigator's choice of (pralatrexate, GemOx or DHAP) until progression; randomised 2:1	Subjects with relapsed/ refractory ATL 59 subjects (including subjects who were initially assigned to the investigator's choice and then crossed over into mogamulizumab)	Cycle 1: Day 1: Pre-dose and EOI; Days 8, 15, 22: Pre-dose. Cycles 2-3: Days 1 and 15; Pre-dose, EOT	PPK, ER (Conc. effect on QTc)[11]
0761-010 (US, EU, Japan, and Australia)	Phase III, open label, multicentre, randomised	Mogamulizumab 1.0 mg/kg iv weekly for 4 weeks, then every other week or vorinostat until progression; randomised 1:1	Subjects with relapsed/ refractory CTCL 298 subjects (including subjects who were initially assigned to vorinostat and then then crossed over into mogamulizumab)	Cycle 1: Day 1: Pre-dose and EOI; Days 8, 15, 22; Pre-dose. Cycles 2-3: Days 1 and 15; Pre-dose, EOT	PPK, ER

IV: intravenous ATL; adult T-cell leukaemia-lymphoma; PTCL: peripheral T-cell lymphoma; EOI: End of infusion; NCA; Non compartmental analysis; PPK: Population Pharmacokinetics; ER: Exposure-response; EOT: End of Treatment; CTCL: cutaneous T-cell lymphoma; DHAP: Dexamethasone, cisplatin and cytarabine; GemOx: Gemcitabine and Oxaliplatin; conc = Concentration; US: United States; EU: European Union.
(a) 2 subjects with PTCL were not included in the PPK analysis
(b) 29 subjects with PTCL were not included in the PPK analysis
(c) Mogamulizumab administered in combination with mLSG15 regimen i.e., intrathecal Ara-C (Cytarabine), MTX (Methotrexate) and PSL (Prednisolone sodiumsuccinate) in addition to the VCAP (Vincristine sulfate, Cyclophosphamide hydrate, Doxorubicin hydrochloride, Prednisolone or prednisolone sodium succinate), AMP (Doxorubicin hydrochloride, Ranimustine, Prednisolone or prednisolone sodium succinate), and VECP (Vindesine sulfate, Etoposide, Carboplatin)

Mogamulizumab is 100% bioavailable as it is intravenously administered. Based on population pharmacokinetic (PK) analysis, the volume of distribution is 3.57 L. Clearance is 12.0 mL / hour with a mean elimination half life of 17 days. PK data has demonstrated

[11] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The **corrected QT interval (QTc)** estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

dose-proportionality for maximum plasma concentration (C_{max}) and area under the plasma concentration time curve (AUC). Mogamulizumab accumulates slightly over several days of administration, with an accumulation factor of 2 to 3. Pathways of elimination have not been specifically investigated.

Studies in patients with renal impairment were not performed as these were considered unnecessary due to mogamulizumab being a macromolecule and hence not renally excreted. Population PK analysis of the effect of hepatic impairment indicated that hepatic function, albumin and aspartate aminotransferase (AST) influenced mogamulizumab pharmacokinetics. AUC was 61% and 129% of normal for patients with low or high albumin concentrations; 119% and 77% of normal for patients with low or high AST; and 12% less for patients with mild to moderate hepatic impairment. The evaluator noted that these differences were not of clinical significance and did not require dose modification.

No pharmacokinetic interaction studies were performed.

A summary of PK parameters from Study 0761-002 is shown in Table 4 below.

Table 4: Study 0761-002 Pharmacokinetic parameters for mogamulizumab (non-compartmental model)

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

Reproduced from the European Public Assessment Report (EPAR): Study 0761-002 is a Phase II multiple dose study of 27 Japanese patients with CCR4 positive relapsed ATL. They received 1.0 mg / kg IV mogamulizumab weekly for 8 weeks. Serial plasma samples for PK analysis were collected after the first and eighth doses; additional samples were collected pre-dose and at the end of infusion of the second through seventh doses.

EMA, European Public Assessment Report (EPAR), Poteligeo (mogamulizumab), EMA/698539/2018, 20 September 2018. Available from the EMA website.

There was no apparent relationship between mogamulizumab exposure and degree of efficacy by means of progression-free survival (PFS) or objective response rate (ORR).

Pharmacodynamics

Ligand expression

The expression of CCR4 was examined in 372 patients enrolled in the pivotal Study 0761-010. The median percentage expression level of 290 evaluable patients was 80%, with a range between 1% and 100%. Approximately 97% of patients had > 10% CCR4 expression.

Low expression of CCR4 (< 10%) was associated with a reduced response to mogamulizumab (KW-0761 in Figure 1 below).

Figure 1: Study 0761-010 CCR4 expression (as a percentage) in responders and non-responders in the vorinostat and KW-0761 (mogamulizumab) arms of pivotal trial (Intent to treat population)

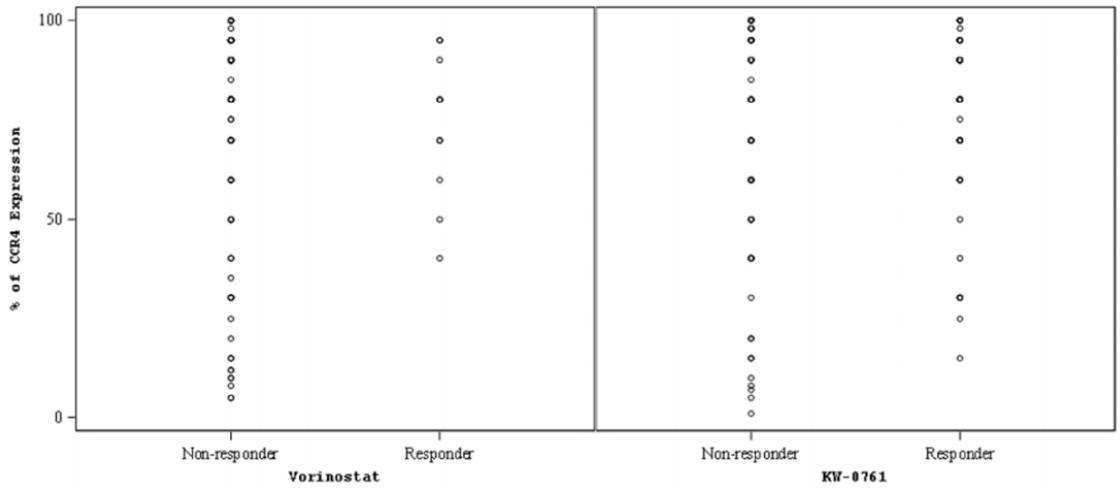

Figure reproduced from the European Public Assessment Report (EPAR), Poteligeo (mogamulizumab), EMA/698539/2018, 20 September 2018. Available from the EMA website.

The EPAR comments that a literature search was conducted to investigate the expression of CCR4 in CTCL, which reviewed 19 articles. Expression of CCR4 was reported in 79% to 100% of MF patients and percentage of CCR4 positive lymphocytes ranged from 1 to 90%. Expression of CCR4 was reported in 83% to 100% of SS patients, with expression in between 0 to 100% of lymphocytes. CCR4 was considered inherent in MF and SS and as such there was no need to limit the indication to pre-tested CCR4+ patients.

Efficacy

The main efficacy study supporting this application was Study 0761-010, which was an open label, randomised study comparting mogamulizumab with vorinostat (VOR) in patients with CTCL who had not responded to at least one prior course of systemic therapy.

Figure 2 (reproduced from the EPAR) below shows a graphical summary of the patient disposition in this pivotal trial.

Figure 2: Study 0761-010 Disposition of patients in pivotal trial

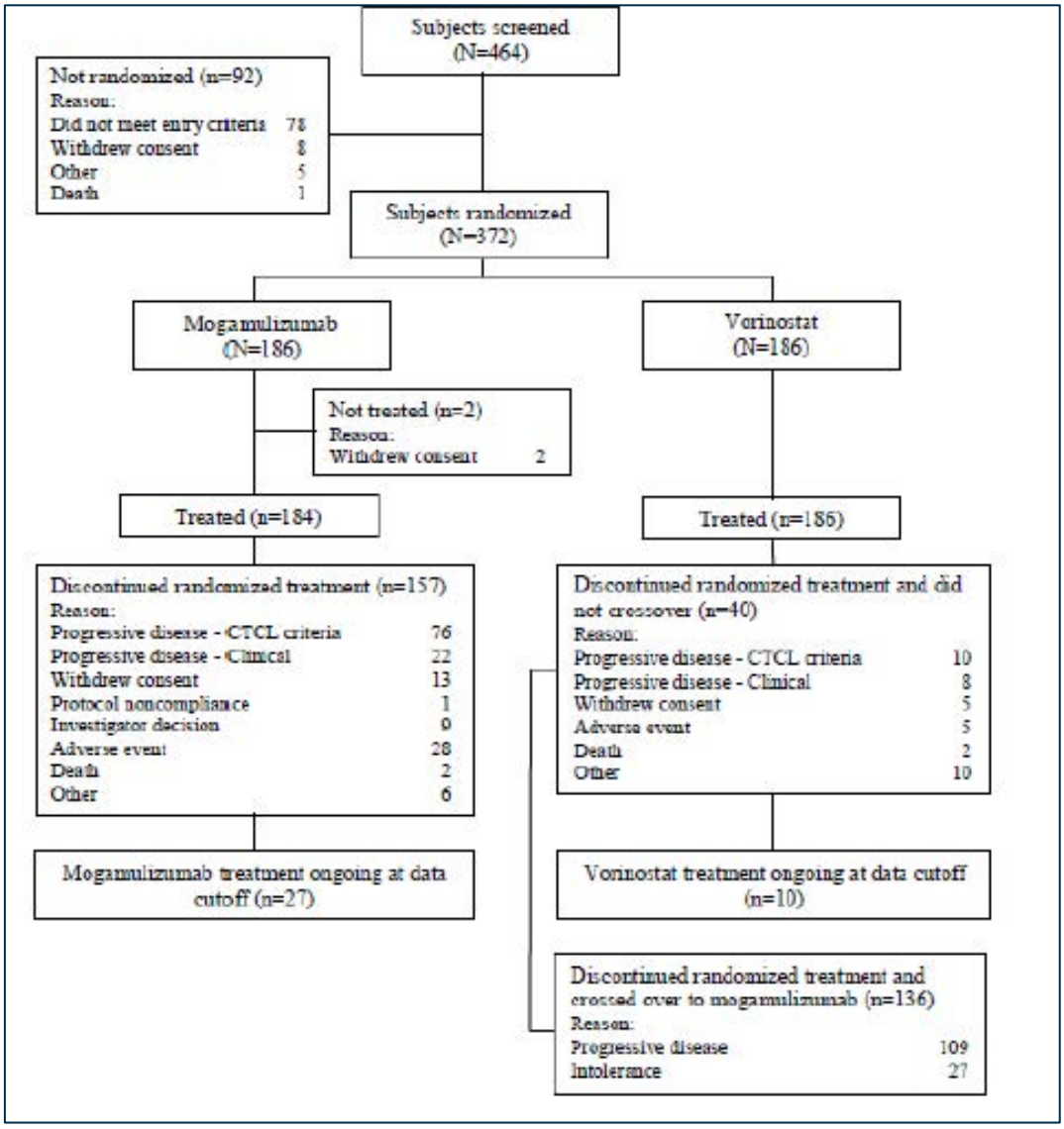

Figure reproduced from the European Public Assessment Report (EPAR), Poteligeo (mogamulizumab), EMA/698539/2018, 20 September 2018. Available from the EMA website.

The patients included in the study were all adults with an ECOG performance status ≤ 1.[12]. They had early (Stage 1B) to advanced (Stage IV) MF or SS.

Patients with a history of autologous stem cell transplant within the previous 90 days were excluded from the study.

[12] **ECOG Performance Status**: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

Patients were randomised to receive either a) mogamulizumab 1 mg / kg weekly for the first 28 day cycle, and then twice weekly for the remainder of the study or b) vorinostat 400 mg on Day 1 and then daily of each 28 day cycle.

Patients randomised to the vorinostat treatment arm who received two full treatment cycles and had disease progression, or were unable to tolerate VOR despite dose reduction, were allowed to cross over to the mogamulizumab arm.

The primary endpoint of this study was progression-free survival (PFS).

Of the patients randomised to receive vorinostat, 73.1% crossed over to receive mogamulizumab during the trial.

Table 5 (reproduced from the EPAR) summarises the demographic characteristics of the intent to treat population of both the vorinostat arm and the mogamulizumab arm in the pivotal trial.

Table 5: Study 0761-010 Baseline demographic characteristics in the pivotal trial (intent to treat population)

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

a = Baseline is defined as the last measurement obtained prior to the first dose of study drug.
b = two subjects had ECOR = 1 at Pre-treatment, but ECOG = 2 on Cycle 1 of Day 1.
c = time from initial diagnosis (months) is calculated as (date of first dose of study medication – date on initial diagnosis + 1) divided by 30. If the month and year of the diagnosis are provided by the day is missing, the missing day is imputed as 15. If only the year is provided, then the missing month and day are imputed as July 1 for the calculation.

CCR4 = CC Chemokine Receptor 4; ECOG[12] = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase.

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As shown in Table 5, most patients had Stage III or IV disease (62.4%) and the median time since diagnosis was 3.1 years. CCR4 expression was > 10% in 75.3% of patients and an assessment was missing in 22% of patients.

Table 6, shown below, concentrates on the prior CTCL therapy statistics of the intent to treat population of both the vorinostat arm and the mogamulizumab arm in the pivotal trial.

Table 6: Study 0761-010 Prior cutaneous T cell lymphoma therapy at Baseline (intent to treat population)

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

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

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As shown in Table 6, the most common prior systemic therapies patients had received before enrolment in Study 0761-010 was bexarotene (58.3%), interferon-alpha (47%), methotrexate (38.2%) and extra-corporeal photophoresis (36.6%). The majority of patients had failed more than one line of previous therapy before commencing the study.

Patients were well balanced for number of prior therapies and stage of disease between the two arms of Study 0761-010.

Table 7 and Figure 3 below present the results of the primary endpoint in the pivotal trial.

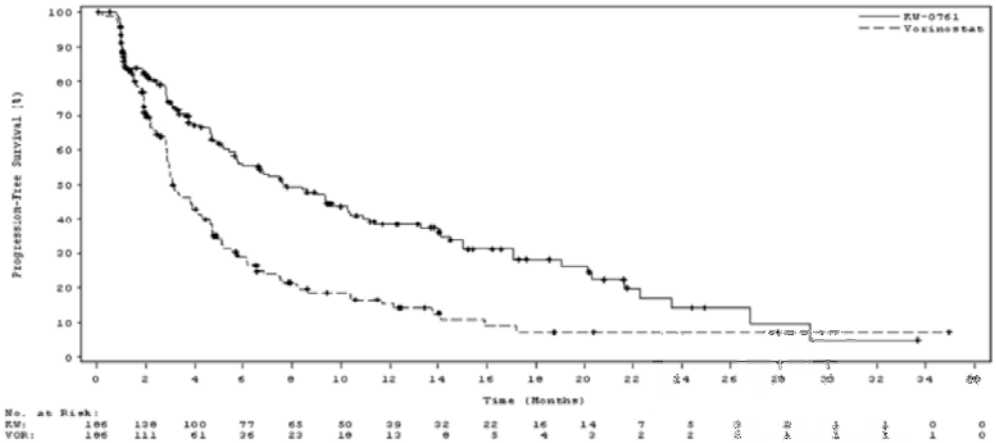
Table 7: Study 0761-010 Summary of progression-free survival statistics (intent to treat population)

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

a = 95% CIs are obtained from SAS Proc Lifetest using loglog transformation.
b = Hazard ratio and 95% CI are based on Cox proportional hazards model with treatment, disease type, disease stage, and region and covariates. P-value (two-sided) was obtained from a stratified log rank test (one-sided test at 0.025 level or equivalently two-sided test at 0.05 level) with disease type, disease stage, and region as stratification factors.
c = Kaplan-Meier estimate
CI = Confidence interval; PFS = Progression-free Survival

Table reproduced from the European Public Assessment Report (EPAR), Poteligeo (mogamulizumab), EMA/698539/2018, 20 September 2018. Available from the EMA website.

Figure 3: Study 0761-010 Kaplan-Meier curve of progression-free survival (intent to treat population)



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

Figure reproduced from the European Public Assessment Report (EPAR), Poteligeo (mogamulizumab), EMA/698539/2018, 20 September 2018. Available from the EMA website.

At the data cut off point, 70.4% of vorinostat and 59.1% of mogamulizumab patients had suffered a progression event, a hazard ratio of 0.53 that was a statistically significant difference. The median time to treatment failure was 5.8 months for mogamulizumab and 2.87 months for vorinostat, which was a statistically significant difference.

At the time of data cut off, 23.4% of patients had died, 47 in the vorinostat arm and 40 in the mogamulizumab arm.

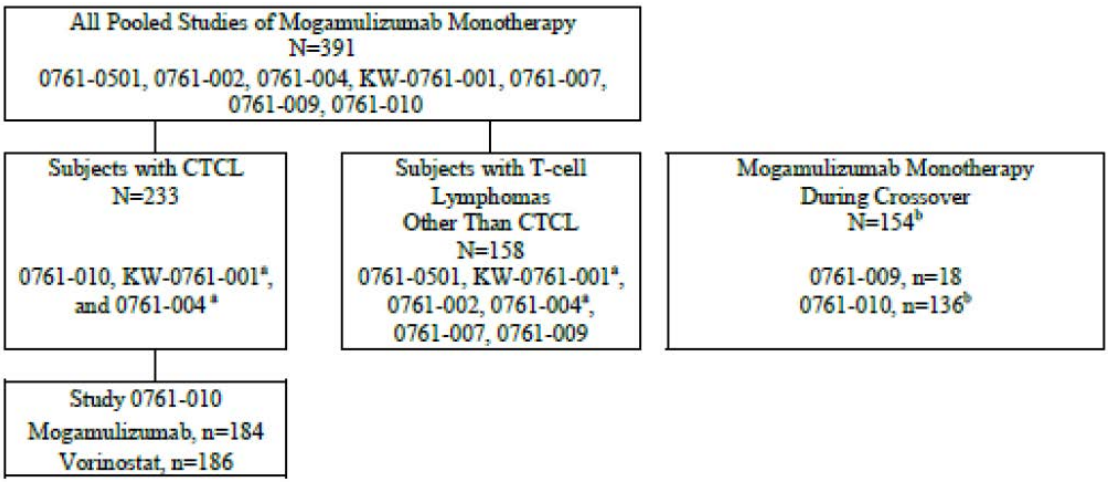
As per the EPAR, the PFS effect size was not consistent between subgroups; subgroup analyses indicate that the effect size of PFS depends on the stage of disease. The PFS effect size between mogamulizumab and vorinostat varied across all stages of disease. The main advantage of mogamulizumab compared to vorinostat was seen in patients with SS (PFS of 13.3 months compared to 3.3 months respectively), and stage III or IV disease (FPS of 10.9 months compared to 3 months respectively). The odds ratio in favour of mogamulizumab was less favourable in patients with early stage (IB or II) disease.

The crossover design, which involved the majority of vorinostat randomised patients, complicates the assessment of the scale of difference between the two therapies. The PFS was similar between patients with one or more previous lines of therapy.

Safety

Safety data was available from seven clinical studies involving mogamulizumab in the treatment of CTCL, PTCL and ATL. This provided a total of 542 patients who had received at least one dose of mogamulizumab.

Figure 4: Summary of studies pooled in safety analysis



a = Studies KW-0761-001 and 0761-004 contributed data from subjects with CTCL and subject with T-cell lymphomas other than CTCL.
b= 136 subjects crossed over. 133 subjects were treated with mogamulizumab.
CTCL =cutaneous T-cell lymphoma, N = number of subjects treated with mogamulizumab, n = number of subjects who received a specific treatment.

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Table 8 below describes events which led to dose modification in patients receiving mogamulizumab in the pivotal trial, Study 0761-010.

Table 8: Study 0761-010 Adverse events leading to dose modification in the pivotal trial

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

Subjects with multiple reasons were counted in each applicable category.
a = non-compliance is based on investigator assessment
(-) = not applicable

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Table 9, shown below, summarises all adverse events (all grades, and all adverse of Grade 3 and above) reported in the pivotal trial according to System Organ Class, and Preferred Term.

Table 9: Study 0761-010 Adverse events (all grades and severe (≥ Grade 3)) reported in pivotal trial

System Organ Class/Preferred Term	Vorinostat (n=186)		Mogamulizumab (n=184)	
	All Grades n(%)	Grades ≥ 3 n(%)	All Grades n(%)	Grades ≥ 3 n(%)
Subjects with any TEAEs	185 (99.5)	85 (45.7)	179 (97.3)	78 (42.4)
Gastrointestinal Disorders	152 (81.7)	17 (9.1)	93 (50.5)	4 (2.2)
Diarrhoea	115 (61.8)	9 (4.8)	43 (23.4)	1 (0.5)
Nausea	79 (42.5)	3 (1.6)	28 (15.2)	1 (0.5)
Constipation	34 (18.3)	2 (1.1)	21 (11.4)	1 (0.5)
Vomiting	24 (12.9)	1 (0.5)	11 (6.0)	0
Abdominal Pain	21 (11.3)	0	7 (3.8)	0

System Organ Class/Preferred Term	Vorinostat (n=186)		Mogamulizumab (n=184)	
Dry Mouth	17 (9.1)	0	4 (2.2)	0
Abdominal pain upper	11 (5.9)	1 (0.5)	1 (0.5)	0
Dyspepsia	11 (5.9)	0	1 (0.5)	0
General Disorders and Administration Site Conditions	126 (67.7)	17 (9.1)	106 (57.6)	8 (4.3) [b]
Fatigue	70 (30.6)	11 (5.9)	43 (23.4)	3 (1.6)
Oedema peripheral	27 (14.5)	1 (0.5)	27 (14.7)	0
Pyrexia	11 (5.9)	0	31 (16.8)	1 (0.5)
Asthenia	27 (14.5)	4 (2.2)	10 (5.4)	0
Chills	14 (7.5)	0	13 (7.1)	0
Infections and Infestations	93 (50.0)	19 (10.2)	118 (64.1)	32 (17.4) [c]
Skin infection	13 (7.0)	3 (1.6)	17 (9.2)	0
Upper respiratory tract infection	9 (4.8)	2 (1.1)	19 (10.3)	0
Nasopharyngitis	15 (8.1)	0	12 (6.5)	0
Urinary tract infection	15 (8.1)	0	12 (6.5)	0
Folliculitis	4 (2.2)	1 (0.5)	13 (7.1)	0
Cellulitis	10 (5.4)	4 (2.2)	6 (3.3)	4 (2.2)
Oral candidiasis	1 (0.5)	0	10 (5.4)	0
Skin and Subcutaneous Tissue disorders	78 (41.9)	9 (4.8)	97 (52.7)	10 (5.4)
Alopecia	36 (19.4)	0	13 (7.1)	0
Drug eruption	1 (0.5)	0	44 (23.9)	8 (4.3)
Nervous System Disorders	101 (54.3)	7 (3.8)	65 (35.3)	2 (1.1)
Dysgeusia	54 (29.0)	1 (0.5)	6 (3.3)	0
Headache	29 (15.6)	1 (0.5)	23 (12.5)	0
Dizziness	19 (10.2)	0	12 (6.5)	0
Paraesthesia	14 (7.5)	0	5 (2.7)	0

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

System Organ Class/Preferred Term	Vorinostat (n=186)		Mogamulizumab (n=184)	
Respiratory, Thoracic and Mediastinal Disorders	42 (22.6)	7 (3.8)	56 (30.4)	7 (3.8)
Cough	15 (8.1)	0	18 (9.8)	0
Oropharyngeal pain	5 (2.7)	0	10 (5.4)	1(0.5)
Vascular Disorders	38 (20.4)	13 (7.0)	29 (15.8)	12 (6.5)
Hypertension	25 (13.4)	12 (6.5)	17 (9.2)	8 (4.3)
Eye disorders	32 (17.2)	0	34 (18.5)	3 (1.6)
Vision blurred	12 (6.5)	0	8 (4.3)	0
Dry eye	11 (5.9)	0	7 (3.8)	0
Psychiatric Disorders	28 (15.1)	2 (1.1)	32 (17.4)	2 (1.1)
Insomnia	14 (7.5)	0	16 (8.7)	0
Depression	6 (3.2)	0	11 (6.0)	2 (1.1)

TEAE: Treatment emergent adverse effect. MedDRA = Medical Dictionary for Regulatory Activities.
a = MedDRA version 15.1 was used for coding.
b = includes one grade 5 TEAE (disease progression)
c = Grade ≥3 infections and infestations TEAEs reported for subjects in the mogamulizumab group but not shown in the table (that is, reported by less than 5.0% of subjects in either group) include pneumonia (n=4), sepsis (n=3, one grade 5), bacteraemia (n=2), herpes simplex (n=2), osteomyelitis (n=2); all other events occurred in one subject each, including Grade 5 pneumonia pneumococcal.
d = includes one Grade 5 TEAE (polymyositis)
e = One subject [ID redacted] had an infusion reaction on Day 1 of crossover to mogamulizumab treatment (17 days after the last dose of vorinostat) that was indicated as possibly related to vorinostat (and mogamulizumab).

Treatment emergent adverse events that occurred more frequently in the mogamulizumab than the vorinostat arm included infusion-related reactions, drug eruption and pyrexia. There was also a higher rate of infections in the mogamulizumab arm than the vorinostat arm of the pooled safety population (64.1% compared to 50% respectively).

Adverse events (AE) typically occurred within the first four weeks of mogamulizumab therapy (88.4% of all AEs and 65.2% of treatment related AEs).

Infusion-related reactions was the most frequently reported treatment emergent adverse event in the mogamulizumab group, being highest after the first infusion (28.8% of subjects) and reducing to < 3.8% of subjects after two or more infusions The majority of these were low grade in severity, with serious adverse events from infusion reactions being reported in 1.6% of cases.

Infections were reported as an adverse event in 24.7% of mogamulizumab patients, the most commonly reported sites being upper respiratory tract infection and cough (10.3% and 9.8% respectively). Overall 4.9% of mogamulizumab patients had treatment emergent infections which led to treatment discontinuation. Serious infections including sepsis, pneumonia and skin infections were reported in 14.3% of patients receiving mogamulizumab, and the majority recovered. There were two reports of fatal pneumonia

in mogamulizumab patients in the pivotal trial. The evaluator notes that patients with CTCL are vulnerable to skin infections and secondary sepsis as a result of impaired immunity and disruption of skin integrity.

Tumour lysis syndrome was reported in two mogamulizumab patients, an incidence of 1.1%.

The EPAR refers to a recent publications suggesting that patients who had undergone haematopoietic stem cell transplantation (HSCT) following mogamulizumab therapy, mainly in the ATL group, and reported that this may be associated with an increased severity of graft versus host disease (GVHD). There is remaining uncertainty of the effect of mogamulizumab on the success of subsequent HSCT since patients with a history of allogeneic HSCT were excluded from the pivotal trial, and a post-authorisation safety study (PASS) is being conducted to characterise any potential safety issue related to the use of mogamulizumab in this context.

Patients who received mogamulizumab reported drug rash (drug eruption) at an incidence of 23.9% (Grade ≥ 3 severity, 4.3%). These occurred both early and late in therapy.

Risk management plan

The sponsor has submitted approved EU-risk management plan (RMP) version 1.0 (dated 17 September 2018; data lock point (DLP): 31 December 2016) and Australian specific annex (ASA) version 1.0 (dated 6 February 2020) in support of this application. At the second round of RMP evaluation, an updated ASA was provided (version 1.1, dated 31 August 2020).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 10.[13]

Table 10: Summary of safety concerns

Summary of Safety Concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important Identified Risks	Infusion related reaction	✓*	-	✓	-
Important Potential Risks	Hepatitis B reactivation	✓	-	✓	-
	Increased risk of severe GVHD after HSCT	✓	✓†	✓	✓‡

[13] *Routine risk minimisation activities* may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of Safety Concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Missing Information	Use in patients with history of autologous or allogenic HSCT	✓	✓†	✓	-

(*) = follow-up questionnaire
† = Post authorisation safety study
‡ = Dear Healthcare Professional Letter

The RMP evaluator has noted that the pharmacovigilance plan is acceptable. They have noted a PASS study in HSCT patients (see Delegate's Considerations), which will be completed in 2025.

Risk-benefit analysis

Delegate's considerations

The evidence from the pivotal trial indicates a significant increase in PFS for mogamulizumab compared to vorinostat of a mean of 4.6 months. This was associated with a significant increase in median time to next treatment for mogamulizumab compared to vorinostat of a mean of 11.00 versus 3.47 months. The median overall survival (OS) was 43.93 months in the vorinostat arm and had not been reached in the mogamulizumab arm. The Delegate feels that, in the context of a chronic but frequently fatal condition, this represents sufficient demonstration of clinical benefit to warrant registration.

The main adverse effect of mogamulizumab compared to vorinostat is toxicity, mostly associated with infusion related reactions. Lymphocyte depletion, tumour lysis syndrome and severe cutaneous reactions are also noted as potential risks associated with mogamulizumab treatment.

The EU evaluation noted that patients with a history of allogenic HSCT were excluded from the pivotal trial and only a few patients underwent HSCT after mogamulizumab treatment. It was noted that increased severity of GVHD has been reported in the literature and is considered a potential risk of mogamulizumab treatment. The EU has required a PASS study to characterise the safety of mogamulizumab in the allogenic HSCT population.

The Delegate notes that the draft Product Information contains significantly less descriptive information than the US PI and in some cases (see Dermatological Reactions section of the PI) conveys a less severe degree of reaction. The Delegate intends to replace the entire Special Warnings and Precautions for Use section of the draft Australian PI with the Warnings and Precautions Section of the US PI. The sponsor should note that this will include quantitative tables comparing rates of adverse events with vorinostat in the pivotal trial.

Proposed action

The Delegate intends to register mogamulizumab for the indication:

> *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.*

With a Product Information document amended to:[14]

- replace the entire Special Warnings and Precautions for Use section of the draft Australian PI with the Warnings and Precautions Section of the US PI; and
- include amendments as requested in the Toxicology evaluation.

Advisory Committee considerations[15]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Poteligeo (mogamulizumab) 4 mg/mL, concentrate for solution for infusion, in 10 mL glass vial, indicated for:

> *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.*

Specific conditions of registration applying to these goods

- Poteligeo (mogamulizumab) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Poteligeo must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The mogamulizumab EU-Risk Management Plan (RMP) (version 1.0, dated 17 September 2018; data lock point 31 December 2016), with Australian Specific Annex (version 1.1, dated 31 August 2020), included with submission PM-2020-00700-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes.

[14] All Delegate requests to amend the PI were made by the time of approval.
[15] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Note that submission of a PSUR does not constitute an application to vary the registration.

- Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Poteligeo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au