ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

POTELIGEO 4 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 20 mg of mogamulizumab in 5 mL, corresponding to 4 mg/mL.

Mogamulizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology 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.

Posology
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).

Special populations

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

Elderly
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).

Method of 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, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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

When mogamulizumab has been administered to patients with T-cell lymphomas other than MF or SS, serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in less than 1% of patients during clinical trials, and also reported during the post-marketing period; some of these cases were reported with fatal outcomes. Patients should be closely monitored for symptoms or signs that suggest SJS or TEN. If they occur, POTELIGEO should be interrupted and treatment should not restart unless SJS or TEN is ruled out and cutaneous reaction has resolved to Grade 1 or less. If SJS/TEN occur, appropriate medical therapy should be administered. See section 4.2 for dose modification information.

Infusion-related reactions
Acute infusion-related reactions (IRRs) have been observed in patients treated with mogamulizumab. The IRRs were mostly mild or moderate in severity, although there have been a few reports of severe reactions (Grade 3). The majority of IRRs occur during or shortly after the first infusion (all within 24 hours of administration), with the incidence decreasing over subsequent treatments.

Patients should be carefully monitored during and after infusion. If an anaphylactic reaction occurs, administration of mogamulizumab should be immediately and permanently discontinued and appropriate medical therapy should be administered.

If an IRR occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. See section 4.2 for pre-medication and dose modification information.

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

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

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

A higher risk of transplant complications has been reported if mogamulizumab is given within a short time frame (approximately 50 days) before HSCT. Follow patients closely for early evidence of transplant-related complications.

The safety of treatment with mogamulizumab after autologous or allogeneic HSCT has not been studied.

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.

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

This medicine contains 1 mg of polysorbate 80 in each vial which is equivalent to 0.2mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females
Women of childbearing potential should use effective contraception during treatment with POTELIGEO and for at least 6 months after treatment.

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

Breast-feeding
It is unknown whether mogamulizumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed child cannot be excluded during this short period. Afterwards POTELIGEO could be used during breast-feeding if clinically needed.

Fertility
There are no clinical data available on the effect of mogamulizumab on human fertility. No specific studies in animals have been performed to evaluate the effect of mogamulizumab on fertility. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies in cynomolgus monkeys (see section 5.3).

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 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 identified with POTELIGEO

System organ class (SOC)	Frequency	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
	Common	Colitis
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
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)
	Not known	Granuloma[b]

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

[b] Including cases of granuloma of the skin (scalp, periauricular area, and trunk) and bone (sternum, skull, spine, costa, and pelvis).

Description of selected adverse reactions

Dermatologic reactions

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

Infusion-related reactions

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

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

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

Less than 1% of patients treated in Clinical Trial 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.

Immunogenicity
Following infusion of POTELIGEO during clinical trials of the use of POTELIGEO in patients with adult T-cell leukaemia-lymphoma or cutaneous T-cell lymphoma, approximately 14% of patients (44 out of 313 evaluable patients) tested positive for treatment emergent anti-mogamulizumab antibodies. There were no patients identified to have positive neutralising antibody responses.

Gastrointestinal disorders
Colitis was mainly characterized by watery diarrhoea, in some cases excessive.

Safety post last dose
Of the 320 subjects exposed to mogamulizumab in Clinical Trial 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
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 reactions
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 via the national reporting system listed in Appendix V.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, monoclonal antibodies
ATC code: L01FX09

Mechanism of action
Mogamulizumab is a defucosylated, humanised IgG1 kappa immunoglobulin 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, resulting in depletion of the target cells. CCR4 is expressed on the surface of some cancer cells including T cell malignancies, such as MF and SS in which CCR4 expression is inherent.

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

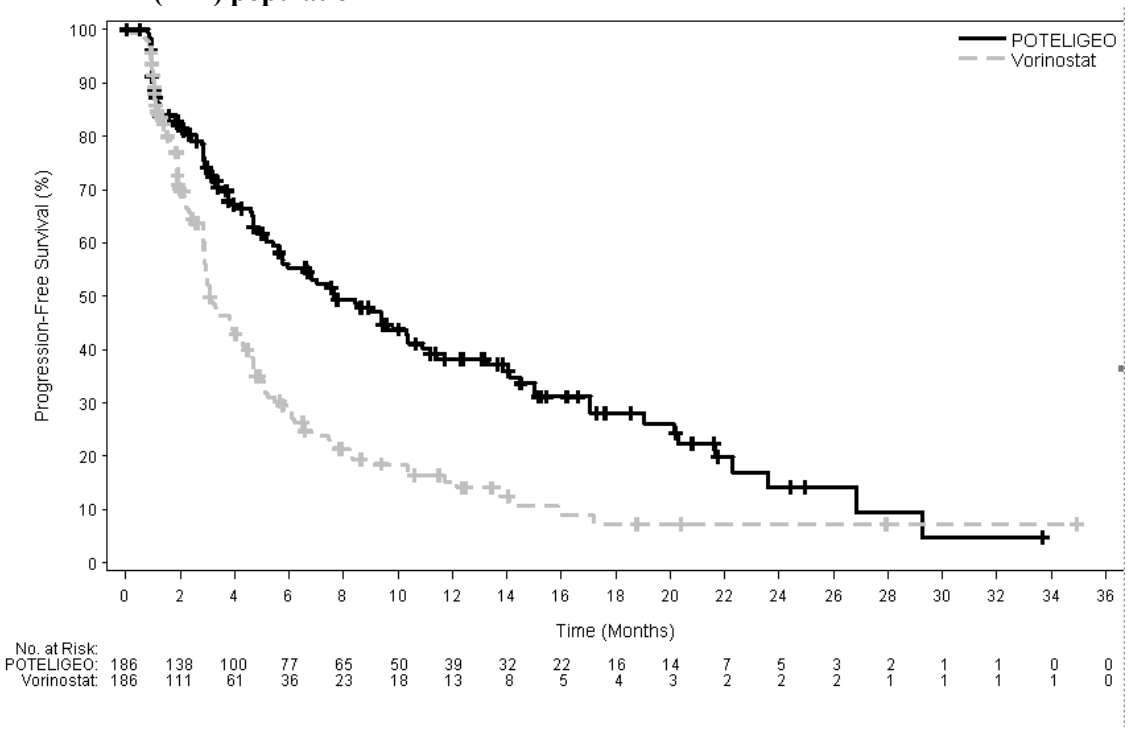
Of the patients randomised to vorinostat, 136 patients (73.1%) crossed over to mogamulizumab during the study. Reasons for crossover to mogamulizumab were disease progression (109 patients) and

treatment intolerance (27 patients). The number of infusions of mogamulizumab administered to crossover patients ranged from 1 to 94 (up to 46 months of treatment) as of the December 2016 datacut.

At 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 2 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 2: Response during randomised treatment period in clinical trial 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]	< 0.0001	
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]	< 0.0001	
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 randomized 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 Clinical Trial 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 3). 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 4). 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 3: 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 4: 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

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with mogamulizumab in all subsets of the paediatric population in cutaneous T-cell lymphoma (CTCL) (MF and SS are subtypes of CTCL). See section 4.2 for information on paediatric use.

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%).

Biotransformation
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.

Elimination
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 $\geq$ 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

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity. Carcinogenicity or genotoxicity studies have not been conducted with mogamulizumab. No specific studies have been conducted to evaluate potential effects on fertility.

No mogamulizumab-related toxic effects in the male and female reproductive organs were observed in repeat-dose toxicology studies in sexually mature monkeys up to 26 weeks.

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

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

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 6.6).

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 24 hours at 2 °C - 8 °C provided that dilution has taken place under controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
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 1 vial.

6.6 Special precautions for disposal and other handling

Preparation
- 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 dose based on patient weight (see section 4.2). 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.
- Each vial is for single use only. Discard any unused portion left in the vial in accordance with local requirements.

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.

7. MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
Netherlands
medinfo@kyowakirin.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1335/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2018
Date of latest renewal: 01 September 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Kyowa Kirin Co., Ltd.
Takasaki Plant
100-1 Hagiwara-machi, Takasaki-shi,
Gunma, 370-0013, Japan

Name and address of the manufacturer responsible for batch release

allphamed PHARBIL Arzneimittel GmbH
Hildebrandstr. 10-12
37081 Göttingen
Germany

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

POTELIGEO 4 mg/mL concentrate for solution for infusion
mogamulizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One mL of concentrate contains 4 mg of mogamulizumab.
Each vial of 5 mL contains 20 mg of mogamulizumab.

3. LIST OF EXCIPIENTS

Citric acid monohydrate, glycine, polysorbate 80, sodium hydroxide, hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
20 mg/5 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
For single use only.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1335/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

POTELIGEO 4 mg/mL concentrate for solution for infusion
mogamulizumab
Intravenous use after dilution

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mg/5 mL

6. OTHER

For single use only.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

POTELIGEO 4 mg/mL concentrate for solution for infusion
mogamulizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What POTELIGEO is and what it is used for

POTELIGEO contains the active substance mogamulizumab, which belongs to a group of medicines called monoclonal antibodies. Mogamulizumab targets cancer cells which are then destroyed by the immune system (the body's defence).

This medicine is used to treat adults with mycosis fungoides and Sézary syndrome, which are types of cancers called cutaneous T-cell lymphomas. The medicine is for use in patients who have received at least one medicine given by mouth or by injection.

2. What you need to know before you use POTELIGEO

Do not use POTELIGEO:
- if you are allergic to mogamulizumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or nurse before using POTELIGEO if you:
- ever had a severe skin reaction with this medicine.
- ever had an infusion reaction with this medicine (possible symptoms of an infusion reaction are listed in section 4).
- have human immunodeficiency virus (HIV), herpes, cytomegalovirus (CMV), or hepatitis B or C infection, or other on-going infections.
- have had or plan to have a stem cell transplant, either using your own cells or a donor's.
- have had tumour lysis syndrome (a complication involving the destruction of cancer cells) after a previous treatment.
- have heart problems.

Tell the person giving you the infusion or get medical help straight away if you experience a reaction during or after any POTELIGEO infusion.

Tell your doctor immediately if you experience any of the serious side effects listed in Section 4 after starting POTELIGEO treatment.

Other medicines and POTELIGEO
Tell your doctor if you are taking, have recently taken,or might take any other medicines.

Children and adolescents
This medicine should not be used in children and adolescents below 18 years of age.

Pregnancy and breast-feeding
The effects of POTELIGEO in pregnancy and breast-feeding are not known. Due to the mechanism of action of the medicine, it may harm your baby if it is administered when you are pregnant or breast-feeding.

If you can get pregnant, you will need to use effective contraception during and for at least six months after receiving this treatment.

If you are breast-feeding, you should discuss with your doctor whether you can breast-feed during or after treatment with POTELIGEO.

You must tell your doctor or nurse if you are pregnant, breast-feeding, think you may be pregnant, or are planning to have a baby.

Driving and using machines
POTELIGEO is unlikely to affect your ability to drive and use machines. However, the medicine can cause tiredness in some people, so take particular care when driving and using machines until you are certain that this medicine does not affect you.

POTELIGEO contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

POTELIGEO contains polysorbate
This medicine contains 1 mg of polysorbate 80 in each vial which is equivalent to 0.2 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How POTELIGEO is given

The amount of POTELIGEO you will receive is calculated by your doctor based on your body weight. The recommended dose is 1 mg POTELIGEO for each kg of body weight.
POTELIGEO will be given to you through a vein (intravenous infusion) over at least 60 minutes.
To start with, the infusions will be given once a week for the first 5 doses, then once every 2 weeks.
Treatment should be continued unless you get serious side effects or the cutaneous T-cell lymphoma starts to get worse.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Tell your doctor or nurse or get medical help immediately if you have any of the following signs and symptoms after starting POTELIGEO:

Very common side effects: may affect more than 1 in 10 people
- chills, nausea or vomiting, headache, wheezing, itching, flushing, rash, dizziness or feeling faint, difficulty breathing and fever, which may be signs of an infusion reaction. If this happens, the infusion may need to be stopped and you may require additional treatment. When the symptoms go away, POTELIGEO can normally continue to be given, but more slowly. Your doctor may stop POTELIGEO treatment if your reaction is severe.

- signs of infection, which may include a fever, sweats or chills, flu-like symptoms, sore throat or difficulty swallowing, cough, shortness of breath, stomach pain, nausea or vomiting, diarrhoea and feeling very unwell.
- skin rash (which may become severe), or sore mouth. In some people receiving POTELIGEO for other types of cancers, skin pain/burning sensation, itching, skin blisters/peeling, ulcers in the mouth or on the lips or genitals occurred, which are possible signs of a severe skin reaction, such as Stevens-Johnson syndrome or toxic epidermal necrolysis (which affected up to 1 in 100 people).

Common side effects: may affect up to 1 in 10 people
- Watery diarrhoea, more bowel movements than usual, severe abdominal pain or tenderness which are possible signs of inflammation of the large bowel (colitis).

Uncommon side effects: may affect up to 1 in 100 people
- fever, chills, nausea, vomiting, confusion, shortness of breath, seizures, irregular heartbeat, dark or cloudy urine, unusual tiredness and/or muscle or joint pain. The destruction of cancer cells and the body's reaction to it can very occasionally lead to a problem called tumour lysis syndrome.
- chest pain, shortness of breath, fast or slow heartbeat, sweating, dizziness, nausea or vomiting, weakness, feeling faint and feeling unwell. Although unlikely to be caused by this medicine, these may be signs of a heart disorder.

Not known: frequency cannot be estimated from the available data
- if you go on to have a stem cell transplant, it is possible that you could then develop complications (graft versus host disease) that are difficult to manage. Symptoms may include skin rashes or blistering, nausea or diarrhoea that doesn't go away, stomach pain or vomiting, joint pain or stiffness, dry or irritated eyes or blurred vision, mouth sores, irritation or pain, a cough that does not go away or difficulty breathing, sensitive genitals, jaundice (turning yellow), dark urine, and any swelling.

Other side effects

Talk to your doctor if you get any other side effects. These can include:

Very common side effects: may affect more than 1 in 10 people
- Lack of energy (fatigue)
- Constipation
- Swollen legs or ankles
- Headache

Common side effects: may affect up to 1 in 10 people
- Anaemia (reduced red blood cells)
- Reduced blood platelets (thrombocytopenia)
- Reduced white blood cells (neutropenia and leucopenia) or reduced lymphocytes
- Blood tests showing raised liver enzyme levels
- Underactive thyroid

Uncommon side effects: may affect up to 1 in 100 people
- Inflammation of the liver (hepatitis)

Not Known: frequency cannot be estimated from the available data
- Small lumps of the skin, bone or other tissues caused by accumulation of immune cells as a response to inflammation (granuloma)

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in

Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store POTELIGEO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vial: Store in a refrigerator (2 °C - 8 °C). Do not freeze.

Store in the original carton in order to protect from light

Reconstituted/diluted solution: Use immediately or store in a refrigerator (2 °C - 8 °C) and use within 24 hours.

Do not use this medicine if you notice signs of deterioration, such as particulate matter or discolouration.

Do not throw away any medicines via wastewater or household waste. These measures will help protect the environment.

6. Contents of the pack and other information

What POTELIGEO contains
- Each vial contains 20 mg of mogamulizumab in 5 mL of concentrate, corresponding to 4 mg/mL.
- The other excipients are citric acid monohydrate, glycine, polysorbate 80, sodium hydroxide, hydrochloric acid, and water for injections. See section 2 "POTELIGEO contains sodium".

What POTELIGEO looks like and contents of the pack
POTELIGEO is a clear, colourless solution. The pack contains a glass vial containing 5 mL concentrate for solution for infusion.

Marketing Authorisation Holder
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This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.