NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome [ID1405]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

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3. **Patient group, professional group and NHS organisation submission** from:
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   b. British Association of Dermatologists
   c. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mogamulizumab for treating mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma [ID1405]

Document B

Company evidence submission

January 2020

File name	Version	Contains confidential information	Date
ID1405_mogamulizumab for treating MF or SS CTCL_Document B_FINAL_220420 Revised AIC-CIC_v2	**FINAL v2**	**Yes**	**22 April 2020**

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In this template any information that should be provided in an appendix is listed in a box.

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B.1. Decision problem, description of the technology and clinical care pathway

- The submission focuses on adults with advanced mycosis fungoides (MF) or Sézary syndrome (SS) cutaneous T-cell lymphoma (CTCL) (i.e. stage ≥IIB MF and all SS) following at least one prior systemic therapy who are clinically ineligible for, or refractory to, treatment with brentuximab vedotin (BV).
- CTCLs are a subset of NHLs that manifest in the skin, leading to rash-like skin redness, slightly raised or scaly patches on the skin and skin tumours.[1]
  - MF accounts for 55% of all CTCLs and is characterized by patches and plaques in the early stages.[2] Around 30% of patients develop advanced disease, characterized by tumours, ulceration, systemic involvement with lymph node or visceral spread, and is therefore linked with significant morbidity and mortality.[3]
  - SS accounts for 2.5% of all CTCLs and is a more aggressive, leukemic form of CTCL characterized by the presence of malignant lymphocytes called 'Sézary cells' in the peripheral blood.[3, 4] SS patients also experience erythroderma, lymphadenopathy and have thickened, scaly and fissured skin leading to opportunistic infections, sepsis and death.[5, 6]
- Between 2009 to 2013, 1,659 cases of diagnosed CTCL were recorded in England, of which 920 (55%) were MF and 42 (3%) were SS, thus representing an orphan sized population.[7]
- While patients in early stages of disease have a median survival of 21.5 years (stage IB), this dramatically reduces to under 5 years for patients with advanced disease (stage IIB onwards); for patients with stage IVB disease median survival is under 2 years.[8]
- Alongside the psychological distress of living with an incurable cancer, patients face a significant, disfiguring physical burden with the skin often oozing and infected; patients report discomfort, cracking and bleeding and skin '*like tin foil*'.[9] Importantly, pruritus has a significant impact on quality of life (QoL) with one patient quoted as saying '*you want to scratch yourself to pieces. You'd like to just rip your skin off*'.
- The disease also has a serious impact on patient's family life, can cause patients to miss work and due to its physical manifestation has a significant impact on social interactions such as participation in sports or hobbies.[9, 10]
- Caregivers face a substantial burden with psychologically and emotionally demanding responsibilities. In particular, the physical burden of practical care, such as regular changing of dressings is often time consuming and overwhelming[11], resulting in a more intensive caregiver burden compared with other cancer indications.
- First-line treatment of advanced stage MF and SS requires systemic treatments such as bexarotene, interferon (IFN), methotrexate, extracorporeal photopheresis (ECP) and electron beam radiotherapy (EBRT).
  - Within NHS England, methotrexate, bexarotene and IFN comprise the most commonly used treatments for advanced MF or SS patients who have received at least one prior systemic therapy and who are clinically ineligible for, or refractory to, treatment with BV; thus, these treatments make up the key comparators for this submission.
- As a result of the few treatment options available and the limitations of these, patients can cycle through multiple treatments that have previously failed, imposing a substantial burden on individuals and health care systems.[12]

- There is a clear unmet need for new treatment options for advanced MF and SS patients who are clinically ineligible for, or refractory to, treatment with BV and require systemic therapy that can target all disease compartments (skin, blood, lymph nodes and viscera) and provide a durable response in order to extend patients' disease-free interval and, subsequently, time to receiving next therapy, as well as meaningful survival benefit.
- Mogamulizumab (Poteligeo®) is a humanised IgG1 kappa immunoglobulin that selectively binds to CCR4, a G-protein-coupled-receptor involved in trafficking of lymphocytes to various organs including the skin.[13] CCR4 is expressed in high concentrations on the surface of some cancer cells including T cell malignancies, such as MF and SS in which CCR4 expression is inherent.
- Mogamulizumab addresses this unmet need by providing a novel immune-oncology agent which has provided improved efficacy and HRQL compared to an active comparator in both advanced MF and SS patients.
- Mogamulizumab is the only treatment available which specifically targets the malignant T cells in all four disease compartments; in particular the blood compartment, thus offering the potential for significant improvements in life expectancy for these patients.

B.1.1. Decision problem

The submission focuses on adults with advanced stage mycosis fungoides (MF) or Sézary syndrome (SS) cutaneous T-cell lymphoma (i.e. stage ≥IIB MF and all SS patients) following at least one prior systemic therapy who are clinically ineligible for, or refractory to, treatment with brentuximab vedotin (BV). This is narrower than the technology's marketing authorisation because it aligns with anticipated treatment placement in NHS clinical practice, and also represents the population with the greatest unmet need, thus reflecting where mogamulizumab (Poteligeo®) provides the most clinical benefit.

The decision problem is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma following at least one prior systemic therapy.	Adults with advanced mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma (i.e. stage ≥IIB MF and all SS) following at least one prior systemic therapy who are clinically ineligible for or refractory to treatment with brentuximab vedotin (BV).	In the pivotal MAVORIC study, approximately 80% of patients represented this subgroup. These patients have substantial reductions in OS and a greater burden of disease, hence represent a proportion of the total population with a great unmet need. Of these advanced patients, those who are ineligible for BV based on clinical judgement or who have previously received BV and have become refractory to this treatment represents patients with the greatest unmet need and the potential future clinical practice in the UK.
Intervention	Mogamulizumab	Mogamulizumab	N/A
Comparator(s)	Established clinical management without mogamulizumab	Established clinical management without mogamulizumab	N/A
Outcomes	• Overall survival • Progression-free survival • Response rates • Time to next treatment • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rates • Time to next treatment/ Next treatment-free survival • Adverse effects of treatment • Health-related quality of life	Time to next treatment was also analysed as next treatment-free survival. Next treatment-free survival is defined as time from randomisation to the start of next treatment or death, similar to progression-free survival. Time to next treatment and treatment-free survival includes both time spent on treatment and the treatment-free period. This is driven by symptoms,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			that in turn drives the changes in quality of life and resource use that determine the health states according to clinical experts. As a result, it is more appropriate to base the health states on treatment changes, rather than changes in progression status. In the MAVORIC trial, mogamulizumab increased the treatment-free period compared to vorinostat, due to its unique mechanism of action.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	The cost effectiveness of mogamulizumab is expressed in terms of incremental cost per quality-adjusted life year.	N/A
Subgroups to be considered	N/A	N/A	
Key: BV, brentuximab vedotin; MF, mycosis fungoides; N/A, not applicable; SS, Sézary syndrome.			

B.1.2. Description of the technology being appraised

A description of mogamulizumab is presented in Table 2. The full summary of product characteristics (SmPC) and the European Public Assessment Report (EPAR) is presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Mogamulizumab (Poteligeo®)
Mechanism of action	Mogamulizumab is a defucosylated, humanized IgG1 kappa immunoglobulin that selectively binds to C-C chemokine receptor type 4 (CCR4), a G-protein-coupled receptor for C-C 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.
Marketing authorisation	MA was issued on 22 November 2018, following a positive CHMP opinion, for the treatment of adults with MF or SS.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication of interest within this submission is: '*the treatment of adult patients with MF or SS who have received at least one prior systemic therapy*' This submission is specifically focused on advanced patients (i.e. stage ≥IIB MF and all SS) who are clinically ineligible for, or refractory to, treatment with BV.
Method of administration and dosage	The recommended dose of mogamulizumab is 1 mg/kg administered by 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 infusion every two weeks on Days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.
Additional tests or investigations	No additional tests or investigations required.
List price and average cost of a course of treatment	The list price is £1,329 per vial (20mg of mogamulizumab in 5ml, corresponding to 4mg/mL), the course of a treatment is £57,109.
Patient access scheme (if applicable)	Kyowa Kirin has offered a simple, [redacted] upfront with the 16th January submission.
Key: BV, brentuximab vedotin; CHMP, Committee for Medicinal Products for Human Use; MA, marketing authorization; MF, mycosis fungoides; SS, Sézary syndrome. **Source:** Kyowa Kirin, 2019.[13]	

B.1.3. Health condition and position of the technology in the treatment pathway

Disease background

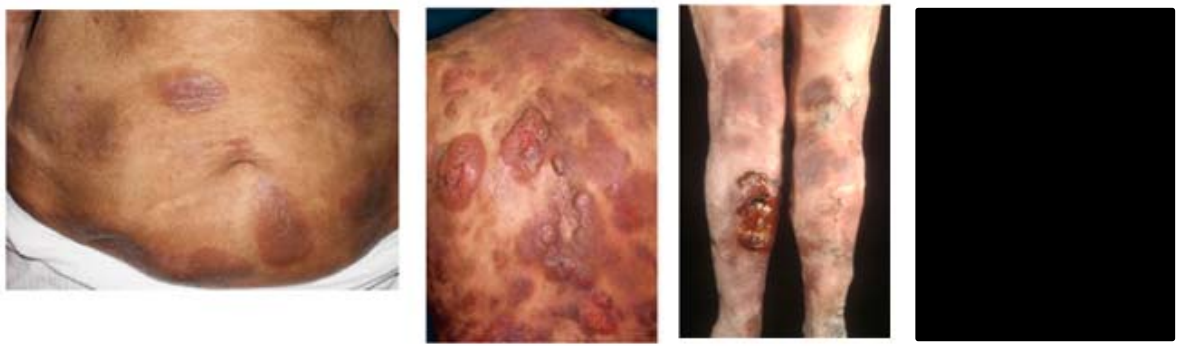
Lymphoma is a haematologic cancer of the lymphocytes, a type of white blood cell and can be classified as Hodgkin lymphoma or non-Hodgkin lymphoma (NHL); approximately 80% of lymphomas are NHL.[14] Cutaneous T-cell lymphomas (CTCLs) are a subset of NHLs that present with skin manifestations at diagnosis. In their normal state, T-cells can circulate from the peripheral blood into the dermis via a selective barrier of endothelial cells.[15] T-cells also function as an integral part of the body's defence system by initiating an immune response.[16] However, under abnormal circumstances T-cells that traffic between the peripheral blood and skin develop mutations resulting in a lymphoma that also manifests in the skin, leading to rash-like skin redness, slightly raised or scaly patches on the skin and skin tumours.[1]

Nearly two-thirds of CTCL can be categorized as either mycosis fungoides (MF), accounting for around 55% of cases, or Sézary syndrome (SS), which accounted for 2.5% of cases in England between 2009-2013.[7] Risk factors for MF and SS include smoking, obesity, eczema and occupation.[17] Importantly, MF and SS are not skin-only diseases, making them distinct from other CTCLs.[18] Instead, there are four potentially involved 'compartments': skin, blood, lymph nodes and viscera. All four compartments have prognostic significance in this disease.[2]

Classically, MF presents as slightly scaly, pruritic, erythematous patches, or thin plaques.[19] Around 30% of patients develop advanced disease, characterized by tumours, ulceration, systemic involvement and death.[2, 3] More advanced disease may also be characterized by more significant blood involvement with lymph node or visceral spread[3], as malignant T-cells may lose their skin-homing tendency, migrate back to blood and spread to other compartments, which is usually fatal.[19]

Examples of the visual disfigurement of more advanced MF are presented in Figure 1.

Figure 1: Visual representation of more advanced mycosis fungoides disease

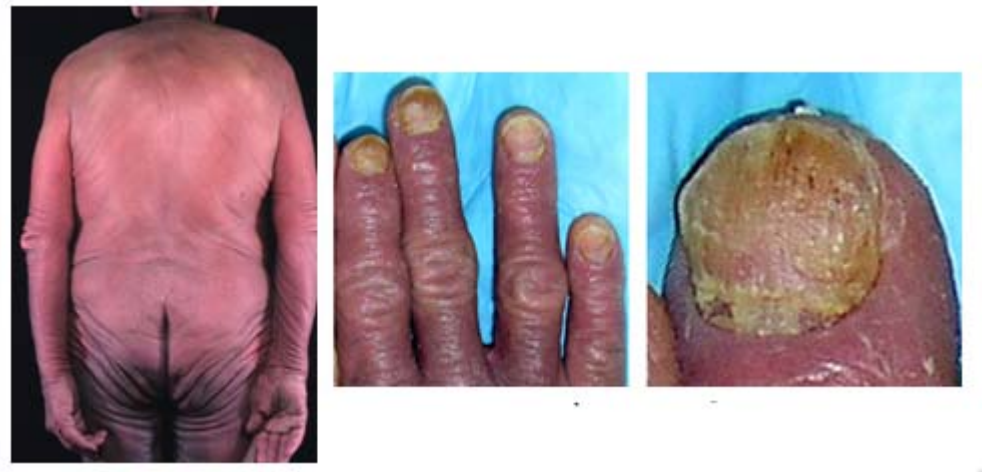


Source: Fujii, 2018.[20]

SS is a more aggressive, leukemic form of CTCL characterized by the presence of malignant lymphocytes called 'Sézary cells' in the peripheral blood.[3, 4] According to the International Society for Cutaneous Lymphoma (ISCL), SS is defined by the presence of widespread erythroderma (reddening of the skin), indicating blood involvement by malignant T-cells.[19] SS patients may also have lymphadenopathy (enlarged lymph nodes) and may also have thickened, scaly and fissured skin, especially on the palms and soles, causing clear disfigurement or experience changes in their nails or eyelids.[3, 21]

Visual examples of SS are presented in Figure 2.

Figure 2: Visual representation of Sézary syndrome disease



Source: Prince et al. 2009[22]; Damasco et al. 2018[23].

Diagnosis and staging of disease

Partly due to the absence of definitive diagnostic criteria and, particularly in the early stages, due to the non-specific nature of multiple clinical presentations similar to other chronic skin conditions (such as eczema and psoriasis), diagnosing CTCL is difficult and can take up to 6 years on average from the onset of cutaneous manifestations.[5, 19] Less advanced stage CTCL is typically indolent (slow growing) and most patients experience only skin symptoms with no serious complications. Indeed, for less advanced MF patients, the presentation of scaly plaques and patches are often initially mistaken for eczema or psoriasis.[3] Some patients may progress to advanced/aggressive disease, with the cancer spreading to lymph nodes and/or internal organs.[3] Identifying malignant cells in the peripheral blood of patients with CTCL is invaluable for detecting blood involvement in MF and confirming the diagnosis of SS, and therefore in determining prognosis.[5]

Recently there have been advances in the accurate diagnosis of CTCLs, with guidelines prepared by the National Comprehensive Cancer Network.[5] Observation and palpation of the skin by a physician are the mainstays in suspecting CTCLs with regular biopsies required to make definitive diagnoses using defined histopathological criteria.[5]

Staging of MF and SS was initially dependent on the type and extent of skin lesions and extracutaneous disease, first captured in the tumour, node, metastasis (TNM) classification published for CTCL in 1979. Suggested modifications published in 2007 for MF/SS revised the nodal classification, added blood involvement and removed the ambiguity surrounding variables critical to standardised staging and classification,[18] resulting in the adapted version of the TNM staging system (Table 3) which takes into account concurrent disease involvement of all four compartments: skin, lymph nodes, blood and viscera; each of these compartments has prognostic significance in MF and SS.[2] Advanced disease is defined as Stage IIB or above; as such, by definition, all SS patients are considered advanced.[24]

Table 3: Modified ISCL/EORTC proposed clinical staging

Subtype		Clinical stage	Skin	Node	Visceral	Blood
Mycosis fungoides		IA	T1	N0	M0	B0,1
		IB	T2	N0	M0	B0,1
		IIA	T1–2	N1, 2, X	M0	B0,1
		IIB	T3	N0–2, X	M0	B0,1
		IIIA	T4	N0–2, X	M0	B0
		IIIB	T4	N0–2, X	M0	B1
	Sézary syndrome	IVA1	T1–4	N0–2, X	M0	B2
		IVA2	T1-4	N3	M0	B0-2
		IVB	T1-4	N-3, X	1	B0-2

Key: EORTC, European Organisation for the Research and Treatment of Cancer; ISCL, International Society for Cutaneous Lymphomas; X, clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize histologic subcategories.
Note: Grey shading representing advanced stages. **Source:** Olsen et al., 2011[18]

Epidemiology

Due to a paucity of evidence in the literature, the epidemiology of MF and SS is not well defined. Most of the studies investigating the incidence and prevalence of CTCL are small registry analyses focused on the MF subtype.[25-27] SS has been largely unresearched, potentially related to the rarity of the disease.

Between 2009 to 2013, 1,659 cases of diagnosed CTCL were recorded in England, of which 920 (55%) were MF and 42 (3%) were SS, thus representing an orphan sized population.[7] Based on an assumed English population of 53,865,817,[28] the CTCL rate per 100,000 per 5 years was calculated as 3.08 which translated into an incidence rate per 100,000 per year of 0.616. Overall, CTCL is twice as common in males than females and most patients are diagnosed in the 50 to 74 age group.[7] Blacks/African Americans also have a significantly increased risk of being diagnosed with higher T-stage MF.[29]

Assuming 60% of MF patients are advanced[30] (i.e. stage ≥IIB), 629 advanced patients are predicted over the next 5 years. Advanced stage MF and SS are associated with substantial reductions in overall survival (OS) compared to less advanced stage disease.[8, 31] While patients with stage IB disease have a median

survival of 21.5 years, this dramatically reduces to under 5 years for patients with advanced disease (stage IIB onwards); for patients with stage IVB disease median survival is under 2 years.[8] Due to its more aggressive form, patients with SS have worse survival and higher risk of disease progression compared to MF patients. SS is associated with a median OS of 3 years and reduced 5-year survival rates. Survival by stage and population is presented in Table 4 and Table 5, respectively.[8]

Table 4: Survival rates from diagnosis by stage

Stage	Median survival (years)
IB	21.5
IIA	15.8
IIB	4.7
IIIA	4.7
IIIB	3.4
IVA1	3.8
IVA2	2.1
IVB	1.4

Source: Agar et al. 2010[8];
Note: Grey shading represents advanced stages.

Table 5: Survival rates for mycosis fungoides and Sézary syndrome populations

Disease type	Median survival, years	5-year OS, %	5-year DSS, %	5-year RDP, %
MF	20.01	78	84	24
SS	3.13	26	31	71

Key: DSS, disease specific survival; MF, mycosis fungoides, OS, overall survival; RDP, risk of disease progression; SS, Sézary syndrome.
Notes: Includes all disease stages.
Source: Agar et al. 2010[8]

Skin involvement is a prominent feature of all patients with MF and SS, regardless of stage, and is predictive of reduced survival rates; patients with MF and SS have an increased relative risk for death as levels of skin involvement increase.[32] MF patients that have extensive blood involvement and SS patients also have reduced survival. One-year survival reduced from 67% and 75% in patients with little or no detectable blood involvement (with 0% circulating Sézary cells) to 21% and 25% in patients with

the highest levels of involvement (>5% circulating Sézary cells and >10 billion absolute Sézary cells per litre).[33]

Patients with MF and SS are also at increased risk of death from other malignancies, chronic inflammatory conditions and infections.[4, 34-36] The breakdown of the immune system combined with the breakdown of the skin barrier increase the risk of infection, and lead to serious complications in over half of CTCL patients.[4] As infections continue and progress to systemic infection, they often become untreatable and increase the risk of death.[6] Furthermore, due to the extensive blood involvement in SS and MF (Stage IVA1 onwards), there is an increased risk of sepsis which can lead to death.[6] Indeed, in SS patients, immunosuppression and opportunistic infections due to the extensively compromised skin are the most common causes of disease-related death.[5]

Burden of disease

The diagnosis and management of MF and SS can be hugely burdensome on patients, caregivers and healthcare systems. Along with the psychological burden of being diagnosed with a life-shortening cancer, patients face a substantial physical burden due to the disfiguring nature of this condition which is associated with additional comorbidities and anxiety, particularly at advanced disease stage, leading to a significant negative impact on their quality of life.[34-39]

The symptoms of CTCL, specifically pain and itching, also have a major impact on health-related quality of life (HRQL).[40] Findings from interviews including 19 CTCL patients showed that patients mainly focused on the skin element of the disease, with reports including skin that was oozing and infected, intensely dry and '*like tin foil*', with discomfort, cracking and bleeding skin a major theme of the interviews.[9] One patient commented '*it affects the bottom of your feet…it will crack and bleed, so it hurts*'.[9] Pruritus often dominates the lives of patients with CTCL and can have a significant impact on quality of life.[9] Indeed, one patient interviewed was quoted as saying '*you want to scratch yourself to pieces. You'd like to just rip your skin off*'. Family members of patients described the disease as '*a very, very painful thing to have…you wouldn't really want to wish it on your worst, worst enemy*' and '*eighty percent of your skin open, ulcerated, a lot of pain, huge amount of pain*'.[11] Pruritus

can be intensified by excessive heat, due to lack of heat regulation caused by the disease itself (and thus a self-perpetuating issue), leading to sleep disturbance with one patient stating '*we had to change to single beds because I itch in the night*'.[9] Scratching due to pruritus can also leave further visible signs of the disease which have to be disguised with clothing or camouflage make-up or explained using pre-prepared phrases. In an attempt to alleviate the symptoms of skin discomfort and itching, patients often engage in time-consuming daily skin care routines; however, these often provide no improvement in pruritus.

Using a dermatology-specific questionnaire in 95 patients with cutaneous lymphoma, SS patients were found to present with greater incidence and severity of symptoms than MF patients. Itching and sensitive skin, annoyance with disease, worries of disease worsening, effect of disease on interactions and impairments in sexual life were reported more frequently, compared to patients with MF.[39]

The significant physical symptom burden also has a far-reaching negative impact on patients' psychological and social well-being, particularly in relation to body image concerns. The visibility of the condition can cause patients to feel self-conscious, particularly when the condition affects exposed areas such as the face, hands or legs.[9] This was highlighted by one patient saying '*this takes your confidence completely away from you because of the way you look, and it's on your face and arms, face, skin, hair, hands, you can't hide that from people*' while another patient said '*it had become distressing and embarrassing…people do still shy away from people that have got skin disease*'.[9] Furthermore, the psychological impact of being diagnosed with a life-threatening disease is considerable; 94% of patients with CTCL reported worries of disease seriousness and 80% reported worries of dying from the disease.[10]

The physical and psychological symptoms of the disease have a serious impact on how patients function and have also been reported to affect the patient's everyday activities.[9, 10] Patients have difficulty with travel by public transport or car due to painful or sensitive skin.[9] The disease also affects patients' family life, as pain from physical contact restricts physical intimacy including cuddling, sleeping together and sexual intimacy.[41] The disease also interferes with work resulting in missed work

days, and has a significant impact on social interactions, such as participation in sports or hobbies.[9]

The burden of disease is also experienced by the patients' caregivers, including informal carers, who in addition to the physical burden of practical care, also face psychologically and emotionally demanding responsibilities such as regular changing of dressings.[11] Family members and/or informal caregivers face worries of disease worsening and anxiety over the eventual death of their relative. In advanced disease, the nature of the wounds can be distressing and leave caregivers overwhelmed by their responsibilities. Bereaved caregivers reported that looking after the skin of the patient, applying specialist dressings and providing skilled care was a major challenge with one spouse stating '*I did find it very difficult to do his dressings. There was an awful one on his leg and I just, I couldn't handle that, so the community nurses came in and did that one'*.[11] Many caregivers face anxiety over the disease prognosis and this impacts their own quality of life (QoL). In a study of 11 caregivers of patients with CTCL, the wife of one patient was quoted as saying '*because of his skin, people couldn't help him*'. Another stated: '*you go from being a wife to a carer*'. Living with someone with CTCL was described as being on a '*rollercoaster*', walking a '*daily tightrope*' and '*like treading on eggshells*' all of which has a profound psychological effect on caregivers.[41] Due to the severe dermatological symptoms and the knock on effect of these on physical intimacy, caregivers have also described the danger of causing pain or discomfort when patients and carers do share a bed, with one carer stating the disease was '*almost putting a gap between us*'.[41] The financial demands of CTCL were described as 'huge', particularly in relation to travel expenses, patients stopping work and carers having to work reduced hours.[41] The partner of a patient with CTCL summed up the disease as '*It's a traumatic illness, traumatic, traumatic to witness'*.

Additional work has been conducted to estimate the quality of life impact of caring for a partner with advanced CTCL.[42] Four health state vignettes were developed to describe the impact of caring for an individual with CTCL at different stages of their disease and treatment. One health state described the experience of caring for an individual who was receiving second-line treatment, and another described caring for an individual on third-line treatment. As the patient approaches the end of their life

(last three months) caregiver burden may change as patients receive palliative care and there may be a clear understanding of their prognosis. Therefore, an end of life state was developed to reflect this period. Finally, as the burden for a caregiver may continue after patient death due to a period of mourning and adjustment, a fourth state described the year immediately after a patient's death. Subsequent time trade-off interviews with 99 members of the UK public (mean age of 41 [SD: 15.3]; 52% female) were then used to generate utilities for each health state. The utility scores from the time trade-off (TTO) range from 0.52 (second-line treatment) to 0.39 (third-line treatment) and 0.37 (end of life care) and results showed a similar pattern across the three evaluation methods (VAS, TTO and EQ-5D-5L). Such low weights highlighted the substantial burden of caring for an individual with CTCL and demonstrated that treatments that can prevent the progression of CTCL and help manage its symptoms are likely to offer substantial benefits to patients and caregivers. Full details of the methodology of this study are presented in Appendix M. The utility difference between the second-line and third-line treatments have been used within some health states for the economic analyses, as described in Section B.3.4.4.

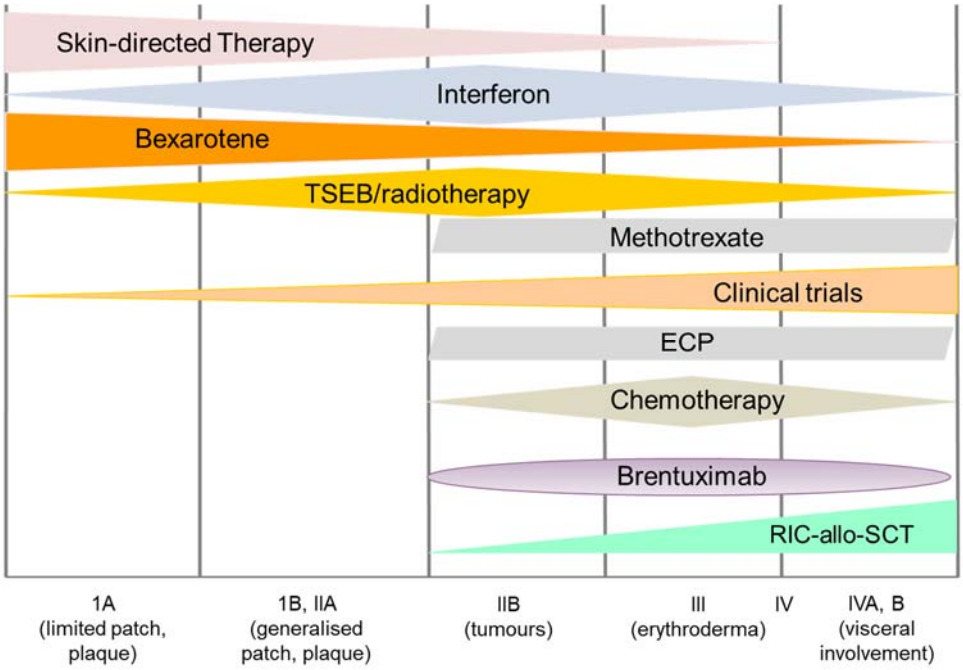
Additional management of comorbidities, treatment of patients and the management of adverse events (AEs) place substantial financial pressures on healthcare systems.[43-45] The high costs of MF and SS, particularly in advanced disease, are due mostly to laboratory tests and hospital visits necessary for administering multiple treatments and skin dressings which tend to have limited efficacy.[43, 45] Managing AEs associated with current treatments can also lead to substantial costs.[45, 46] A retrospective study has been conducted using the Hospital Episodes Statistics (HES) database containing details of all inpatient admissions, Accident and Emergency (A&E) attendances and outpatient appointments at NHS hospitals in England. Costs per patient per week ranged from £195 when in a state of disease control to close to £900 at end-stage care; costs increased the closer to death a patient was with the highest costs seen in the final six months prior to death (See Section B.3.5.2 for and Appendix Q further details).

Current pathway of care

Due to the rare and heterogenous nature of CTCL, and the lack of a standard of care for treatment, it is critical that patients have effective pathways of care that allow rapid access to centres with broad experience of primary cutaneous lymphomas (PCL), as defined in the NICE Improving Outcomes Guidance (IOG) for skin cancers.[47, 48] Notably, all patients with suspected or proven PCLs should be reviewed at regional specialist skin cancer multidisciplinary team (MDT) meetings with a close relationship between the specialist skin cancer and haemato-oncology MDTs critical. The NICE IOG also recommends that all patients with Stage IIB or higher MF, and all with SS, should be reviewed by the supra-network MDT to provide access to clinical trials, if required.

Figure 3 presents a summary of treatment options outlined in the British Association of Dermatologists (BAD) and UK Cutaneous Lymphoma Group (UKCLG) guidelines.[47]

Figure 3: Summary of treatment pathway



Key: ECP, extracorporeal photopheresis; RIC-allo-SCT, reduced intensity conditioning allogenic stem cell transplant; TSEB, total skin electron beam.
Source: Adapted from Gilson et al. 2018.[47]

For patients with advanced disease (i.e. stage ≥IIB MF and all SS patients), first-line treatment consists of systemic treatments such as bexarotene, interferon (IFN), methotrexate, extracorporeal photopheresis (ECP) and electron beam radiotherapy (EBRT). A key objective in MF and SS is to extend periods of remission allowing patients to remain free from treatment for longer.[49] In clinical practice, subsequent treatments are usually initiated following symptomatic progression.

Second-line treatment options remain similar and brentuximab vedotin (BV) is an option for advanced stage patients (stage ≥IIB MF and all SS) that are CD30-positive and who are clinically eligible; however, SS patients have minimal CD-30 positivity and the efficacy of BV has not been studied in this population specifically. Alemtuzumab may be used off-label at second line although clinicians have confirmed its' use in England is very infrequent.[50] Furthermore, due to reports of immune-mediated conditions (including autoimmune hepatitis) and problems with the heart and blood vessels, as well as a possible risk of progressive leukoencephalopathy caused by alemtuzumab, including fatal cases, use of the treatment has been restricted by the EMA, further limiting treatment options for CTCL patients.[51, 52]

Systemic chemotherapy (e.g. gemcitabine; cyclophosphamide plus doxorubicin, vincristine, prednisolone [CHOP] regimens) may also be used at first- or later-lines of treatment for patients with advanced disease, or disease refractory to SDT or immunobiological agents and is used as a palliative treatment, rather than curative. In addition, reduced intensity allogenic stem cell transplant (aSCT) is noted as a treatment option for SS patients or advanced stage MF patients after first-line therapy. Although this is potentially curative, this is only offered to certain patients, that is, young, well-performing patients with a low tumour burden at the time of transplant.[2] In England, it is thought that around 11% of patients will go on to receive an aSCT.[50]

For advanced MF or SS patients who have received at least one prior systemic therapy and who are clinically ineligible for, or refractory to, treatment with BV, current standard of care comprises a range of available therapies with choice dependent on clinical and patient preference; the most commonly used treatments are methotrexate, bexarotene and IFN and these comprise the key comparators for

this submission. All of the comparators are associated with a number of limitations. Firstly, limited trial or published data are available on the efficacy of the three treatments, both in general and on extracutaneous disease, and specifically within the SS population. Furthermore, the data that is available is focused to efficacy within the skin compartment only rather than taking into account the blood component of the disease, known to be a key prognostic factor.[53-56] Treatments are also associated with a substantial adverse event burden. Methotrexate is associated with a risk of toxicity to the gastrointestinal tract, bone marrow, liver and lungs[57] and bexarotene has been known to result in most patients requiring treatment for hyperlipidaemia and hyperthyroidism with oral doses.[58] Finally, interferon resistance has been reported[57] and, while side effects are dose dependent, these commonly include leukopenia, depression, flu-like symptoms, cardiac arrhythmias and thyroid dysfunction.[2] Such safety concerns can significantly impact a patient's quality of life.[2, 59]

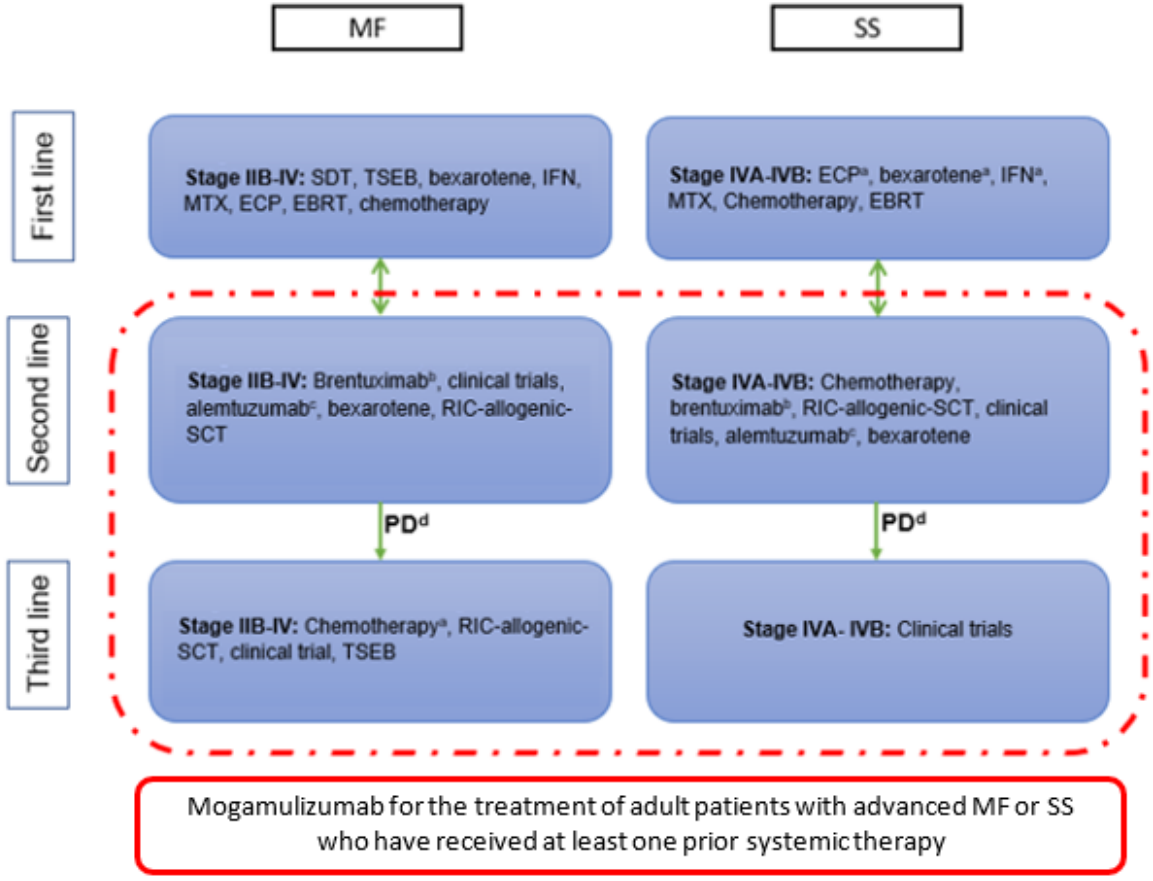
After progression from second-line treatment, third-line options are limited to entry into a clinical trial or a repeat of treatments previously received. For some well-performing patients reduced intensity aSCT is also an option after complete or good partial response to previous line of therapy. As a result of the few treatment options available and the limitations of these, patients may be re-challenged with multiple treatments that have previously failed, imposing a substantial burden on individuals and health care systems.[12] Of note, patients in the pivotal MAVORIC trial were heavily pre-treated, with a median of three prior systemic therapies.[60] Significantly, with each relapse, response to treatment becomes less complete and shorter in duration, and the disease-free interval, in which a patient can hope to be symptom free, is reduced. Additional work has been conducted to further understand the treatment pathway for patients who have progressed; methods and results for this are presented within Section B.3.5.2 and Appendix Q.

With exception to the small proportion of patients who may go on to receive aSCT, there is no cure for advanced MF or SS and patients often experience disease progression on therapy or become resistant to existing treatments. New treatment options are limited, with the European Medicines Agency (EMA) having approved only one other new systemic therapy (brentuximab vedotin in CD30-positive CTCL)

for the treatment of MF. There is a clear unmet need for new treatment options for advanced MF and SS patients who are clinically ineligible for or refractory to treatment with BV and require systemic therapy that can target all disease compartments (skin, blood, lymph nodes and viscera) and extend periods of remission and disease control (i.e. where symptoms are controlled) allowing patients to remain free from subsequent treatment for longer. Thus, extending time to next treatment (TTNT) is a key goal for these patients. There is also a clear unmet need for a therapy which provides a meaningful survival benefit and a tolerable safety profile.

Mogamulizumab is an orphan drug which addresses this unmet need by providing a novel immune-oncology agent which targets CCR4; its proposed place in the treatment pathway is presented in Figure 4, adapted from the British Association of Dermatologists (BAD) and UK Cutaneous Lymphoma Group (UKCLG) guidelines. Mogamulizumab has provided improved efficacy in all key areas of the disease including progression-free survival, overall survival (after cross-over adjustment), time to next treatment and HRQL, while also demonstrating a tolerable safety profile, compared to an active comparator in both advanced MF and SS patients who are clinically ineligible for, or refractory to, treatment with BV thus offering a treatment option for this population with the greatest unmet need. Importantly, mogamulizumab is the only treatment available which also targets the blood involvement aspect of the disease, thus offering significant improvements in life expectancy and HRQL for these patients. Such improvements offer the potential to reduce the overall burden on the healthcare system.

Figure 4: Placement of mogamulizumab in current treatment pathway for advanced stage patients (stage ≥IIB MF and all SS)



Key: EBRT, external beam radiotherapy; ECP, extracorporeal photopheresis; IFN, interferon; MF, mycosis fungoides; MTX, methotrexate; PD, progressed disease; RIC, reduced intensity; SCT, stem cell transplant; SDT, skin-directed therapy; SS, Sézary syndrome; TSEB, total skin electron beam therapy.
Notes: [a], chemotherapy as recommended by the supranetwork MDT; [b], brentuximab is available only for CD30-positive patients; [c], alemtuzumab is not licensed for use in Europe; [d], PD and exhausted first- and second-line options.
Source: Adapted from Gilson et al. 2019.[47]

B.1.4. Equality considerations

No equality issues have been identified or are foreseen.

B.2. Clinical effectiveness

- MAVORIC is the pivotal trial assessing the clinical effectiveness and tolerability of mogamulizumab compared to vorinostat in patients with stage IB to IVB MF or SS who have failed at least one prior therapy[60]
  - Vorinostat was chosen as the comparator, as an alternative to current NHS standard of care that patients were already refractory to, and was required to enable high recruitment of patients where re-challenge would have been inappropriate in a clinical trial setting and to ensure robust sample size for the MAVORIC study
- MAVORIC is the largest randomised Phase III study conducted in any CTCL subgroup to date, with 372 patients enrolled[60]
  - Almost 80% of patients had advanced disease (i.e. stage ≥IIB MF and all SS patients) and almost half (45%) of all patients recruited had SS; this is the largest number of SS patients to ever be recruited to a randomised trial
  - Patients were also heavily pre-treated with a median of 3 previous systemic treatments received including 58% of patients previously treated with bexarotene, 47% with interferon-alpha and 66% with chemotherapy; 5% of patients previously received BV
- Significantly greater improvements in PFS were seen in patients treated with mogamulizumab compared to those treated with vorinostat
  - In the advanced population, median PFS was 9.4 months with mogamulizumab compared to just 3.1 months with vorinostat, resulting in a HR of 0.43 (95% CI: 0.31, 0.58)[61]
  - This is consistent with the total population where median PFS was 7.7 months for mogamulizumab compared to 3.1 months for vorinostat resulting in a HR of 0.53 (95% CI: 0.41, 0.69; p<0.0001)[60]
  - Of note, the primary endpoint of PFS was investigator-assessed as this allowed the investigator to effectively assess the patients' skin in person (noting if response was a treatment or disease related effect), using both visualisation and palpation, which would not be possible with blinded independent review.
- A global composite response system was used to assess overall response rate which incorporates all four compartments of disease, skin, blood, lymph nodes and viscera, compared to historical assessments looking at the skin compartment only
  - Based on this more stringent assessment, mogamulizumab demonstrated an ORR of 30% compared to just 2.9% with vorinostat (p<0.0001) in the advanced population[60, 61]
- Median time to next treatment (TTNT) is an important measure for patients as it demonstrates the period a patients' symptoms are controlled and also potentially allows for a treatment-free period. In the advanced population, TTNT was 11.0 months with mogamulizumab compared to just 3.5 months with vorinostat (p<0.0001) [61, 62], providing patients with a period of symptom control more than double that reported historically in patients with MF and SS[63]
- The clinical benefits seen with mogamulizumab were demonstrated alongside a significant improvement in HRQL with patient-reported outcome data suggesting a patient's physical well-being, emotional life and overall impact on QoL were improved with mogamulizumab[64]
- OS was an exploratory endpoint, and median OS was not reached with mogamulizumab and was 43.9 months with vorinostat resulting in a HR of 0.93 (95% CI: 0.6, 1.4; p-value: 0.94)[60]

  - This data should be viewed with caution due to the immaturity of the data (only 23% of patients experienced an OS event) and the confounding due to high rates of crossover makes the interpretation of the results difficult without additional adjustment, which has been investigated and is discussed further in Section B 3.3.1
  - Adjusting for crossover, mogamulizumab led to an important survival benefit with both applicable crossover adjustment methods
- In addition, mogamulizumab was well tolerated with no new safety concerns identified and AEs generally mild or moderate in severity and easily managed[60]
- Historically, studies have used a skin only response assessment unlike the composite endpoint used in the MAVORIC study meaning historical comparisons are challenging as endpoints are not comparable. As such, the key strength of the evidence for mogamulizumab in this population is the MAVORIC study; the largest trial in CTCL and the most robust study resulting in the least uncertainty, which provides the best evidence on the clinical benefits of mogamulizumab compared to UK comparators
- Vorinostat can be considered a reasonable proxy for standard of care in England, as supported by naïve comparisons of PFS data for physician's choice in ALCANZA (bexarotene and methotrexate), comparisons of ORR seen with vorinostat in the MAVORIC trial to bexarotene in a Phase II study and the experience of clinical experts[49]; thus the results of the MAVORIC study are expected to translate to clinical practice
- Mogamulizumab is a novel treatment with an innovative mode of action which has demonstrated superior PFS and response in a highly burdensome orphan population, alongside significant improvements in HRQL and a well-tolerated safety profile

B.2.1. Identification and selection of relevant studies

An original systematic literature review (SLR) was conducted in February 2018 to identify and select evidence on the efficacy and safety of mogamulizumab and comparator treatments for patients with previously treated MF and SS. This was subsequently updated and expanded on 2 July 2019. See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2. List of relevant clinical effectiveness evidence

The clinical value of mogamulizumab was supported by results of a Phase I/II, open-label, multicentre, two-part trial conducted in the US (n= 42), assessing the safety, pharmacokinetics, dose and response of mogamulizumab in patients with CTCL.[65] Results of this study led to the development of the MAVORIC study, the only randomised controlled trial providing evidence on the clinical benefits of mogamulizumab in CTCL identified in the SLR. The MAVORIC study is summarized in Table 6.

MAVORIC, the largest randomised study in CTCL to compare systemic therapies, is a Phase III, international, randomised, open-label study designed to evaluate the effectiveness of mogamulizumab compared with vorinostat, a histone deacetylase inhibitor with a US license for CTCL, in patients with Stage IB-IVB MF and SS that had failed at least one prior course of systemic therapy.[60] The MAVORIC trial, enrolled a total of 372 patients across 61 sites in 11 countries (of which 16 were in Europe, including three in England), including 204 MF and 168 SS patients. Furthermore, 77% of all patients had advanced disease (i.e. stage ≥IIB MF and all SS patients) disease and were heavily pre-treated with a median of 3 previous systemic therapies. Of note, this is the first Phase III trial to include SS patients and the largest number of SS patients ever to be included in a randomised clinical trial, incorporating 45% of the trial population.

It should also be noted that MAVORIC is the first pivotal trial in CTCL to compare systemic therapies using progression-free survival (PFS) as a primary endpoint.[60] Conversely, the majority of studies identified in the SLR used response rate as a primary outcome, most of which were based on skin only responses thus not accounting for the full impact of the treatment on the disease. MAVORIC was among one of the first studies to use the updated international global composite response scoring system that accounted for all four potential disease compartments: skin, blood, lymph nodes, and viscera.[18] Radiological cross-sectional imaging is based on lymph nodes and viscera and is therefore inappropriate for CTCL as it does not take into account skin and blood disease, which are key for CTCL. Furthermore, historically, progression assessments have been based on skin response only; as such, historical comparisons are often inappropriate, as discussed in Section B.2.9.

Table 6: Clinical effectiveness evidence

Study	MAVORIC				
Study design	Phase III, multicentre, open-label, randomised study.				
Population	Patients aged ≥18 years with stage IB-IVB relapsed or refractory MF or SS.				
Intervention(s)	Mogamulizumab 1.0 mg/kg IV on Days 1, 8, 15 and 22 of the first cycle, and Days 1 and 15 on subsequent cycles.				
Comparator(s)	Vorinostat 400 mg orally once daily.				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X
	No			No	

Study	MAVORIC
Rationale for use/non-use in the model	Pivotal study supporting this indication.
Reported outcomes specified in the decision problem	• **PFS as assessed by the investigator according to global composite response** • Response including ORR, DOR and TTR according to global composite response • **Time to next treatment/ Next treatment-free survival[a] (*post-hoc* analysis)** • QoL as assessed by: – Skindex-29 – FACT-G – **EQ-5D-3L** – Pruritus Likert scale – ItchyQoL • Safety • **OS**
All other reported outcomes	• TTF • PFS and ORR by independent review **Post-hoc analyses**: • PFS, ORR and TTNT in patients with advanced disease (stage ≥IIB MF and all SS patients) • ORR by disease compartment (skin, blood, lymph nodes, viscera) • Skindex-29 and FACT-G – assessment of individual items • PFS and ORR by number of prior therapies • PFS, ORR and DOR by type of prior systemic therapy • ORR and safety after >351 days exposure to mogamulizumab • ORR and TTNT in patients with Stage IB-IIA disease

Key: DOR, duration of response; EQ-5D-3L, EuroQol five-dimensional questionnaire (three-level version); FACT-G, Functional Assessment of Cancer Therapy – General; IV, intravenous; ORR, overall response rate; PFS, progression-free survival; TTF, time to treatment failure; TTNT, time to next treatment; TTR, time to response; QoL, quality of life.
Note: [a], presented in economic analyses only.
Source: Kim et al. 2018.[60]

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

MAVORIC is the pivotal trial supporting this indication and was the key trial used in the EMA regulatory submission. To be eligible for inclusion in the study, patients had

to have stage IB–IVB histologically confirmed relapsed or refractory MF or SS and be aged ≥18 years (in Japan, ≥20 years). Furthermore, patients had to have failed at least one previous systemic therapy, have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1 and adequate haematological, hepatic, and renal function.

Patients who did not qualify to be included in the study were those with large cell transformation at study entry, previous mogamulizumab or vorinostat treatment (brief exposure without evidence of progression or toxicity on treatment was allowed with sponsor approval), central nervous system metastasis, active autoimmune disease, clinically significant uncontrolled intercurrent illness, and previous allogeneic transplant. Eligible patients were randomised in a 1:1 ratio to the following:[60]

- Mogamulizumab (1.0 mg/kg) administered as an intravenous (IV) infusion over at least 1 hour on Days 1, 8, 15 and 22 of the first cycle and on Days 1 and 15 of subsequent cycles
- Vorinostat (400 mg) administered orally once daily with food beginning on Day 1

The study drug was administered until disease progression, drug intolerance or unacceptable toxicity. Due to the rarity of the disease, study stratification for all clinical stages was not feasible. As such, randomization was stratified by disease type (MF or SS) and disease stage (IB/II or III/IV.)[60] As previously discussed, this submission defines advanced patients as Stage ≥IIB in accordance with published guidelines and NICE TA577.[24, 30]

MAVORIC had a one-way crossover design, allowing patients who progressed after at least two full treatment cycles of vorinostat, or who were unable to tolerate vorinostat despite dose reduction, to cross over to treatment with mogamulizumab.[60] This ensured patients receiving vorinostat were not discontinued prematurely, which also reduced the number of patient dropouts from the control arm (discussed further in Section B.2.13).

Although vorinostat is considered standard of care in the US, Canada, Australia and Japan, it is not currently licensed in Europe. Therefore, in order to enable a robust sample size for the MAVORIC study, alternatives to current NHS standard of care had to be available, as the majority of European patients were likely to have received

most currently available treatments (as shown in Table 8) and re-challenge in a clinical trial setting would be inappropriate by introducing selection bias into the study. As such, the MAVORIC trial provided an attractive option to recruit patients by providing one new promising therapy option (mogamulizumab), and one previously unattainable therapy option (vorinostat), for which promising Phase II data are available (discussed further in Section B.2.13). This allowed for high patient recruitment during MAVORIC, resulting in the largest randomised study investigating a systemic therapy in CTCL to date.

Vorinostat can be considered a reasonable proxy for current standard of care in the NHS, based on a naïve comparison of results from the vorinostat arm of the MAVORIC study and the physician's choice arm (methotrexate or bexarotene i.e. UK standard treatments) of the ALCANZA study as well as comparison to Phase II bexarotene data (discussed in Section B.2.9).[55] It is also supported by clinical expert opinion,[49] and the EMA accepted this comparison when granting marketing authorisation for mogamulizumab. Thus, the results of the MAVORIC study should be considered to translate to English clinical practice. Furthermore, vorinostat is the only drug with data in the SS population.

The primary endpoint of the study was investigator-assessed PFS, defined as time from randomization until progressive disease (PD) according to the global composite response or death due to any cause.[60] Investigator-assessed results were chosen as the primary endpoint over blinded independent review because the investigator was able to physically examine the patient. Specifically, the investigator could examine the patient's skin disease and any potential treatment related rashes; this could not be as effectively undertaken by a blinded independent reviewer as they were unable to physically examine the patient or be made aware of the source cause of a rash (i.e. treatment or disease related), as this would effectively unblind the reviewer (see Section B.2.13). Recognizing that this is an open label trial, a blinded independent review of PFS (secondary endpoint) was also performed to assess response and validate the date of progression.

Other key secondary endpoints included overall response rate (ORR), best overall response, duration of response (DOR), time to response (TTR), health-related quality of life (HRQL) and safety. The MAVORIC study was not powered for survival

and overall survival (OS) was considered an exploratory endpoint (discussed further in Section B.2.13).

MAVORIC was among one of the first studies to use the updated international global composite response scoring system that accounted for all four potential disease compartments: skin, blood, lymph nodes, and viscera.[18] This more recent and recommended scoring system is based on complete and partial responses in each disease compartment, and response scores in these four compartments were used to determine disease progression for the primary endpoint (PFS), as well as the key secondary endpoints (ORR, best overall response, DOR and TTR).[60] The proportion of patients who achieved an overall response included only those patients with confirmed global response in all four compartments at two (or more) successive evaluations at least 8 weeks apart. Historically, CTCL studies have largely focused their study outcomes on progression in the skin compartment only as a measure of efficacy and the systematic literature review (SLR) (conducted in July 2019 and reported in Appendix D) found that prior to 2017, only one study reported results in line with updated compartment-based response criteria.[66] Due to these discrepancies in endpoint assessments, efficacy comparisons between MAVORIC and previous studies are extremely difficult, particularly when considering the efficacy of the drug in patients with blood involvement (a key feature in advanced MF and SS).

Quality of life (QoL) was assessed through the Skindex-29, Functional Assessment of Cancer Therapy – General (FACT-G) and the EuroQol five-dimensional questionnaire (three-level version; EQ-5D-3L).[60] In addition, pruritus was assessed through the Pruritus Likert scale and the Itchy Quality of Life questionnaire. A post-hoc analysis of QoL was also conducted assessing individual symptom items from Skindex-29 and FACT-G in order to identify any significant differences between treatment arms over the course of treatment.

A number of post-hoc analyses were also conducted including, among others, TTNT and response rate (ORR, DOR and TTR) by individual disease compartment.

Table 7 presents a summary of the trial methodology for MAVORIC.

Table 7: Summary of MAVORIC trial methodology

Trial name	MAVORIC
Location	Patients were recruited across 61 sites in Australia, Denmark, France, Germany, Italy, Japan, the Netherlands, Spain, Switzerland, the UK, and the US
Trial design	• An open-label, multicentre, randomised Phase III study • Patients were randomised in a 1:1 ratio through CTIVRS • Randomization was stratified by disease type (MF or SS) and disease stage (IB/II or III/IV)
Eligibility criteria for participants	**Inclusion criteria**: • Written informed consent • Aged ≥18 years of age in all countries except Japan, where patients had to be ≥20 years of age • Histologically confirmed diagnosis of MF or SS • Stage IB, II-A, II-B, III or IV disease • Failed at least one prior course of systemic therapy (e.g. interferon, denileukin diftitox, bexarotene, photopheresis, anti-neoplastic chemotherapy, etc.). Psoralen plus ultraviolet light therapy (PUVA) was not considered a systemic therapy • ECOG performance status of ≤1 • Adequate haematological function – ANC ≥1,500 cells/μL (≥1,500/mm^3) – Platelets ≥100,000 cells/μL (≥100,000/mm^3) – In patients with known bone marrow involvement, ANC ≥1,000 cells/μL (≥1,000/mm^3) and platelets ≥75,000 cells/μL (≥75,000/mm^3) • Adequate hepatic function – Bilirubin ≤1.5 times the specific institutional ULN, except for patients with Gilbert's syndrome – Aspartate transaminase (AST) and alanine transaminase (ALT) each ≤2.5 x ULN or ≤5.0 x ULN in the presence of known hepatic involvement by CTCL • Adequate renal function – Serum creatinine ≤1.5 x ULN or calculated creatinine clearance >50 mL/min using the Cockcroft-Gault formula • CD4+ cell count >200/mm^3 • Patients with MF and a known history of non-complicated staphylococcus colonization/infection were eligible provided they continued to receive stable doses of prophylactic antibiotics • Women of childbearing potential must have had a negative pregnancy test within 7 days of receiving study medication • Willing to use appropriate method of contraception **Exclusion criteria**: • Current evidence of large cell transformation • Diagnosed with a malignancy in the past 2 years • Clinical evidence of central nervous system metastasis

Trial name	MAVORIC
	• Psychiatric illness, disability or social situation that would compromise the patient's safety or ability to provide consent, or limit compliance with study requirements • Significant uncontrolled intercurrent illness including, but not limited to – Uncontrolled infection requiring antibiotics – Clinically significant cardiac disease (class III or IV of the New York Heart Association [NYHA]) – Unstable angina pectoris – Angioplasty, stenting, or myocardial infarction within 6 months – Uncontrolled hypertension (systolic blood pressure (BP) >160 mmHg or diastolic BP >100 mmHg, found on two consecutive measurements separated by a 1-week period) despite two anti-hypertensive medications – Clinically significant cardiac arrhythmia or uncontrolled diabetes • Known or tests positive for HIV, HTLV-1, hepatitis B or hepatitis C disease • Active herpes simplex or herpes zoster • Experienced allergic reactions to monoclonal antibodies or other therapeutic proteins • Known active autoimmune disease (e.g. Graves' disease; systemic lupus erythematosus; rheumatoid arthritis; Crohn's disease; psoriasis) • Pregnant or lactating • Prior treatment with mogamulizumab • Prior treatment with vorinostat. Patients who were exposed to vorinostat for a short time, did not progress while on treatment, and did not have intolerable toxicity but were discontinued for another reason (e.g. comorbidity) were permitted to enter the study after discussion with the Medical Monitor • Had any cancer therapy within four weeks of randomization • Systemic corticosteroid use, except to treat an infusion reaction • Topical corticosteroid use, except to treat acute rash • History of allogeneic or autologous transplant • Receiving any immunomodulatory drug for concomitant or intercurrent conditions other than T-cell lymphoma within 4 weeks of treatment
Settings and locations where the data were collected	A DSMB was responsible for overseeing patient safety in the trial; DSMB meetings were held approximately every 6 months.
Trial drugs	• 1.0 mg/kg of mogamulizumab as an IV infusion over at least 1 hour on Days 1, 8, 15 and 22 of the first cycle and on Days 1 and 15 of subsequent cycles (each treatment cycle was 28 days) • 400 mg of vorinostat orally once daily with food, beginning on Day 1

Trial name	MAVORIC
Permitted and disallowed concomitant medication	The following medications are prohibited during the study: • systemic steroids or increase in dose except to treat an infusion reaction. • topical corticosteroids except to treat an acute rash • Any experimental therapy or anticancer therapy including radiation and phototherapy other than the study medications • Any live or live attenuated vaccine • Alternative medicines, particularly use of St. John's Wort • Immunomodulatory agents such as methotrexate; azathioprine; iv immunoglobulin; cyclophosphamide; cyclosporine; mycophenolate; infliximab; etanercept; leflunomide; adalimumab; lenalidomide; abatacept; rituximab; anakinra; interferon-α; interferon-β; IL-2 and natalizumab • Other concurrent HDAC inhibitors including valproic acid • Whenever possible, concomitant use of drugs that may cause a prolongation of the QTc interval were to be avoided
Primary outcomes (including scoring methods and timings of assessments)	PFS (investigator assessed), defined as the time from the day of randomization to a treatment arm until documented PD or death due to any cause. PFS was assessed by the investigator using a stratified Log-rank test at the one-sided 2.5% significance level.
Other outcomes used in the economic model/specified in the scope	**Secondary endpoints**: • ORR (investigator assessed), defined as the proportion of patients who had a confirmed CR or PR. A CR or PR per Global Composite Response Score that was confirmed by two (or more) successive evaluations at least 8 weeks apart • Best overall response (investigator assessed), defined as the best response (CR + PR) recorded across all time points from the start of treatment until disease progression/recurrence or end of treatment • DOR (investigator assessed), defined as time from the date that of first CR or PR until first documented PD or death • TTR (investigator assessed), defined as time from randomization to first confirmed CR or PR • Change in Skindex-29 score from baseline through the 6-month assessment • Change in FACT-G total score from baseline through the 6-month assessment • Change in EQ-5D-3L index score from baseline through the 6-month assessment • PFS as assessed by independent review • ORR as assessed by independent review • ORR in the crossover portion of the trial only

Trial name	MAVORIC
	• Changes from baseline in Skindex-29, FACT-G, and EQ-5D-3L at other timepoints • Changes from baseline in Pruritus Evaluation (Likert scale and Itchy QoL) • Safety, as assessed by reported AEs, changes in physical examinations, vital sign measurements, ECGs and laboratory analyses **Exploratory endpoints**: • OS, defined as time from randomization until death by any cause • TTF, defined as time from randomization until discontinuation of randomised treatment due to any reason **Post-hoc analyses** • PFS, ORR and TTNT in patients with advanced disease (stage ≥IIB MF and all SS patients) • TTNT • ORR by disease compartment (skin, blood, lymph nodes, viscera). • Skindex-29 and FACT-G – assessment of individual items • PFS and ORR by number of prior therapies • PFS, ORR and DOR by type of prior systemic therapy • ORR and safety after >351 days exposure to mogamulizumab • ORR and TTNT in patients with stage IB-IIA disease
Pre-planned subgroups	Efficacy analyses were performed within the following patient populations: • Disease type (MF, SS) • Disease stage (IB/II, III/ IV) • Blood involvement (yes, no) • Region (US, Japan, Rest of World) • Age group (<65 years, ≥65 years) • Gender (male, female) • Race category (Black or African American, White, Other) • Lactate dehydrogenase (LDH) (normal, elevated)
Key: ANC, absolute neutrophil count; CR, complete response; CTCL, cutaneous T cell lymphoma; CTIVRS, ClinTrak Interactive Voice/Web Response System; DOR, duration of response; DSMB, data safety monitoring board; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EQ-5D-3L, EuroQol five-dimensional questionnaire (three-level version); FACT-G, functional Assessment of Cancer Therapy – General; HDAC, histone deacetylase; MF, mycosis fungoides; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QoL, quality of life; SS, Sézary syndrome; TTF, time to treatment failure; TTNT, time to next treatment; TTR, time to treatment response; ULN, upper limit of normal **Notes**: [a], for patients who were continuing to receive study treatment as of protocol Amendment 8, the period of contraceptive use was extended to 6 months after the last dose of mogamulizumab **Source**: Kim et al. 2018[60]; MAVORIC CSR, 2017.[67]	

Baseline characteristics

Patient demographic and disease characteristics were generally well balanced between treatment arms, as were the distributions in previous CTCL therapies.[60] In total, 58% of patients were male and 70% were white. The median time from initial diagnosis was 37.6 months (3.1 years; range: 1–30 months). Patients with advanced disease (Stage ≥IIB) accounted for 77% of the population and measurable blood involvement (defined as stage B1 or B2, based on central flow cytometry) was present in 66% of patients. It should also be noted that almost half (45.2%) of the total population were SS patients.

Patients in the MAVORIC trial were heavily pre-treated before enrolment. All randomised patients had received prior CTCL therapies including topical or systemic, with the majority of patients receiving three or more prior systemic therapies (median: 3; interquartile range [IQR]: 2-5).[60] All except one patient (in the vorinostat arm) had failed at least one prior systemic therapy (the patient was included following a protocol deviation), and the majority of randomised patients ([redacted]) did not respond to their most immediate prior therapy.[67]

Table 8 presents a summary of the baseline demographic and disease characteristics of patients in the MAVORIC study.

Table 8: Baseline demographic and disease characteristics of patients in MAVORIC

	Mogamulizumab (n=186)	**Vorinostat (n=186)**
Median age, years (range)	63.5 ([redacted])	65.0 ([redacted])
<65 years, n (%)	99 (53.2)	89 (47.8)
Male, n (%)	109 (58.6)	107 (57.5)
Race, n (%)		
White	125 (67.2)	135 (72.6)
Black or African American	[redacted]	[redacted]
Other	[redacted]	[redacted]
Not reported	24 (12.9)	25 (13.4)
ECOG performance status[a], n (%)		
0	106 (57.0)	104 (55.9)
1	78 (41.9)	82 (44.1)

	Mogamulizumab (n=186)	**Vorinostat (n=186)**
Time from initial diagnosis (months), median (IQR)	41.0 (17.4–78.8)	35.4 (16.2–68.2)
Current clinical stage, n (%)		
IB–IIA	36 (19.4)	49 (26.3
IIB	32 (17.2)	23 (12.4)
IIIA-IIIB	22 (11.8)	16 (8.6)
IVA_1	73 (39.2)	82 (44.1)
IVA_2	19 (10.2)	12 (6.5)
IVB[b]	4 (2.2)	4 (2.2)
Current sites of disease, n (%)		
Skin	[redacted]	[redacted]
Nodes	[redacted]	[redacted]
Viscera	[redacted]	[redacted]
Blood	[redacted]	[redacted]
Other (including bone marrow)	[redacted]	[redacted]
Blood involvement, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Previous CTCL therapies[c], n (%)		
Skin-directed therapies		
PUVA	[redacted]	[redacted]
Topical steroid	[redacted]	[redacted]
Bexarotene-topical	[redacted]	[redacted]
Systemic therapies		
Bexarotene-oral	107 (57.5)	110 (59.1)
Interferon-alpha	81 (43.5)	94 (50.5)
Methotrexate	[redacted]	[redacted]
ECP	[redacted]	[redacted]
Romidepsin	45 (24.2)	32 (17.2)
Nitrogen mustard	[redacted]	[redacted]
Doxorubicin HCL liposome	[redacted]	[redacted]
Pralatrexate	14 (7.5)	13 (7.0)
Carmustine	[redacted]	[redacted]
Brentuximab vedotin	16 (8.6)	4 (2.2)
Denileukin diftitox	[redacted]	[redacted]
Chlorambucil	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]
IL-12	[redacted]	[redacted]
Other (skin-directed and systemic)	[redacted]	[redacted]
Median prior systemic therapies (IQR)	3.0 (2–5)	3.0 (2–5)

	Mogamulizumab (n=186)	Vorinostat (n=186)
CR or PR to last prior CTCL therapy	[redacted]	[redacted]

Key: CCR4, C-C chemokine receptor type 4; CR, complete response; CTCL, cutaneous T cell lymphoma; ECOG, Eastern Cooperative Oncology Group; ECP, extracorporeal photopheresis; HCL, hydrochloride; IQR, interquartile range; NR, not reported; PR, partial response; PUVA, psoralen plus ultraviolet light therapy
Notes: [a], two patients had ECOG=1 at pre-treatment but ECOG=2 on Cycle 1, Day 1; [b], two patients (one in each treatment group) were noted to have stage IVB disease at baseline but did not have measurable visceral disease at baseline; [c], all patients in the ITT population had received at least one prior CTCL therapy.
Source: Kim et al. 2018[60]; Kyowa Kirin, 2019[68]; MAVORIC CSR, 2017.[67]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Unless otherwise stated, the MAVORIC data presented in this submission is based on a data cut-off of 31 December 2016, where the median follow-up was 17.0 months.[60] An updated data cut (2 March 2019) which focused on safety outcomes and collected only limited efficacy data (OS and time to discontinuation [TTD]) and thus this is not presented within Section B.2; updated OS data is presented in Appendix O.3.

Table 9 presents the hypothesis and associated statistical analysis methods adopted in MAVORIC. A total of 372 patients were randomised (mogamulizumab, n=186; vorinostat, n=186), comprising the ITT population.[60] Patient disposition in the MAVORIC trial is summarized in Appendix D.2, alongside a Consolidated Standards of Reporting Trials (CONSORT) diagram of participant flow. Four patient analysis populations were evaluated during the study:[60]

- Intention-to-treat (ITT) population (n=372), which included all randomised patients
- Safety population (n=370), which included all patients who received at least one dose of study treatment (mogamulizumab or vorinostat)
- Efficacy evaluable population (n=361), which included all patients who received the first cycle of treatment (at least one dose), had a baseline tumour assessment and at least one post-baseline assessment for response

  - Patients that had a baseline tumour assessment but experienced PD during the study without any post-baseline tumour assessment were considered efficacy evaluable
- Pharmacokinetic (PK) analysis population, which included all patients who provided at least one post-dose mogamulizumab concentration measurement[67]
  - Of note, the results of analyses conducted in this population are not presented in this submission

The primary analysis of all efficacy endpoints was based on the ITT population.[60] Primary and key secondary efficacy endpoints were also analysed for the efficacy evaluable population. Safety analyses were conducted on the safety analysis population.

The global composite response scoring system was used to analyse the individual disease compartments.[60] Compartmental disease was evaluated by the modified Severity Weighted Assessment Tool (mSWAT), CT scans, and flow cytometry. Clinical response to treatment in skin and blood was assessed every 4 weeks using mSWAT. Response in the blood compartment was assessed by flow cytometry; lymph nodes and visceral disease were identified by size criteria and evaluated by CT at 4 weeks, then every 8 weeks for the first year, and every 16 weeks thereafter.

As with many studies investigating rare diseases, the MAVORIC study was not powered for survival; OS was assessed on an exploratory basis. Within the study, 73.1% of patients from the vorinostat arm crossed over to mogamulizumab treatment;[60] therefore, the comparator OS data is highly confounded by cross-over. To investigate the impact of cross-over on survival a number of analyses were carried out, including the inverse probability of censoring weighting (IPCW) model, the rank-preserving structural failure time (RPSFT) model and a two-stage approach (discussed further in Section B.3.3.1). These analyses were conducted in accordance with the NICE Decision Support Unit technical support document 18.[69]

Table 9: Summary of statistical analyses, MAVORIC

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
The primary objective of the study was to compare the efficacy of mogamulizumab to vorinostat. Efficacy determination was based on PFS as the primary endpoint. The MAVORIC study was considered positive if the mogamulizumab group was significantly superior to the vorinostat group for the primary endpoint.	A Cox proportional hazard model with treatment, disease type, disease stage, and region (US, Japan, and Rest of World) as covariates were used to assess the magnitude of the treatment difference in PFS. The HR along with the 95% CI obtained from the Cox proportional hazard model was presented. The median PFS and the 2-sided 95% CI for each treatment was estimated using the Kaplan–Meier survival analysis methods. Kaplan–Meier estimate of PFS rates and the corresponding 95% CI were also provided for each treatment arm by 6 months intervals. Investigator assessed ORR was compared between the two treatment arms using Cochran-Mantel-Haenszel (CMH) test adjusted for disease type, disease stage, and region). The exact 95% CIs for ORR were calculated for each treatment arm along with the difference in response rates between the two treatment arms.	Unless otherwise specified, all efficacy and safety analyses were done on the basis of the first assigned (randomised) treatment. The original protocol was time-driven and powered at 80% to detect a 50% increase in PFS, using a reference median PFS around 10% to account for patients lost to follow-up before documented progression, resulting in a projected enrolment of 317 patients. The primary analysis was to be conducted when 255 total PFS events had been observed in order to ensure 90% power in the primary analysis, or 24 months after the last randomised patients' first dose (whichever occurred first).	For the PFS analysis, any patients still receiving treatment as of the cut-off date (31 December 2016) that had not progressed were censored at that date. Patients that withdrew from the study for any reason before documented progression were censored at the time of their last post-baseline tumour assessment from any compartment. Randomised patients with an unspecified baseline disease compartment were censored at randomization if there was no post-baseline tumour assessment for that compartment or if there was any evidence of lymphoma in that compartment at post-baseline evaluation. Randomised patients who withdrew from treatment prior to the first post-baseline tumour assessment for any reason other than disease progression were censored at the last documented visit. Patients who initiated a new anti-cancer therapy (including crossover to mogamulizumab) in the absence of a PFS event were censored at the

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	All 95% CIs on individual rates were computed using exact computational methods.		last tumour assessment (from any compartment) prior to the start of the new anticancer therapy.
Key: CI, confidence interval; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival. **Source**: Kim et al. 2018[60]; MAVORIC CSR, 2017.[67]			

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

Table 10 provides a summary of the quality assessment of the MAVORIC trial. The MAVORIC protocol and informed consent form were reviewed and approved by an Institutional Review Board or Independent Ethics Committee at each study centre according to national or local regulations and in accordance with the US Food and Drug Administration (FDA). The trial was also conducted under the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation and applicable local regulatory requirements.

In each country and study site, the investigator agreed to conduct and administer the study according to the protocol and this was documented by the sponsor, as required by each country's national authority.

Every patient gave written informed consent before any study-specific procedures were performed. Furthermore, a Data Safety Monitoring Board was responsible for overseeing patient safety in the trial.

Baseline demographics and disease characteristics were generally well-balanced between treatment arms. For patients in both arms, per protocol design, disease progression was the primary reason for study withdrawal. MAVORIC was an open-label study, and unblinded investigators assessed response and progression based on face-to-face assessments with patients; as discussed in Section B.2.3, investigator-assessed PFS was deemed to be the most reliable assessment method and was therefore chosen as the primary endpoint. A blinded independent review of PFS (secondary endpoint) was also performed to assess response and validate the date of progression.

Table 10: Quality assessment, MAVORIC

Was randomisation carried out appropriately?	Yes. Randomization was conducted in a 1:1 ratio and was stratified by disease type (MF or SS) and disease stage (IB/II or III/IV).
Was the concealment of treatment allocation adequate?	Yes. Randomization was performed using a CTIVRS.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Patient demographics were generally similar between treatment arms.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No. Open-label study design. Blinded independent review was also carried out to account for any potential bias.
Were there any unexpected imbalances in dropouts between groups?	No.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the ITT population was used for the primary analysis. Standard censoring methods were used for the primary analysis.
Key: CTIVRS, ClinTrak Interactive Voice/Web Response System; MF, mycosis fungoides; N/A, not applicable; SS, Sézary syndrome; ITT, intention-to-treat. **Source**: Kim et al. 2018.[60]	

B.2.6. Clinical effectiveness results of the MAVORIC trial

Unless otherwise stated, the data in this section is based on the 31 December 2016 data cut-off and results in this section are presented for the total ITT population, results for the advanced population (i.e. stage ≥IIB MF and all SS patients) are highlighted in the subgroup analysis section (Section B.2.7).

The clinical effectiveness results for patients who received vorinostat and crossed over to receive mogamulizumab (n=133) are presented in Appendix O.1. In summary, these results indicate that the use of mogamulizumab at later lines of treatment has no detrimental impact on its efficacy.

B.2.6.1. Primary endpoint: Progression-free survival (as assessed by investigator)

At the time of data cut-off, a total of 241 PFS events had been observed across the total population: 110 (59%) occurred in the mogamulizumab arm and 131 (70%) in the vorinostat arm.[60]

As presented in Table 11, mogamulizumab demonstrated significantly greater PFS compared to vorinostat, with a median PFS of 7.7 months versus 3.1 months, respectively, resulting in a HR of 0.53 (95% confidence interval [CI]: 0.4, 0.7; p<0.0001).[60] After 75% of patients had progressed or died, PFS was approximately three times longer for the mogamulizumab arm (20.1 months) compared to the vorinostat arm (6.6 months).[60] These results indicate that there is a proportion of patients who respond well to treatment with mogamulizumab and subsequently have a long period of progression-free disease. It should also be noted that at 6, 12, 18 and 24 months, the proportion of patients alive and without progression was consistently higher in the mogamulizumab arm ([redacted], respectively) compared with the vorinostat arm ([redacted], respectively).[67]

Table 11: Summary of investigator-assessed progression-free survival: ITT population

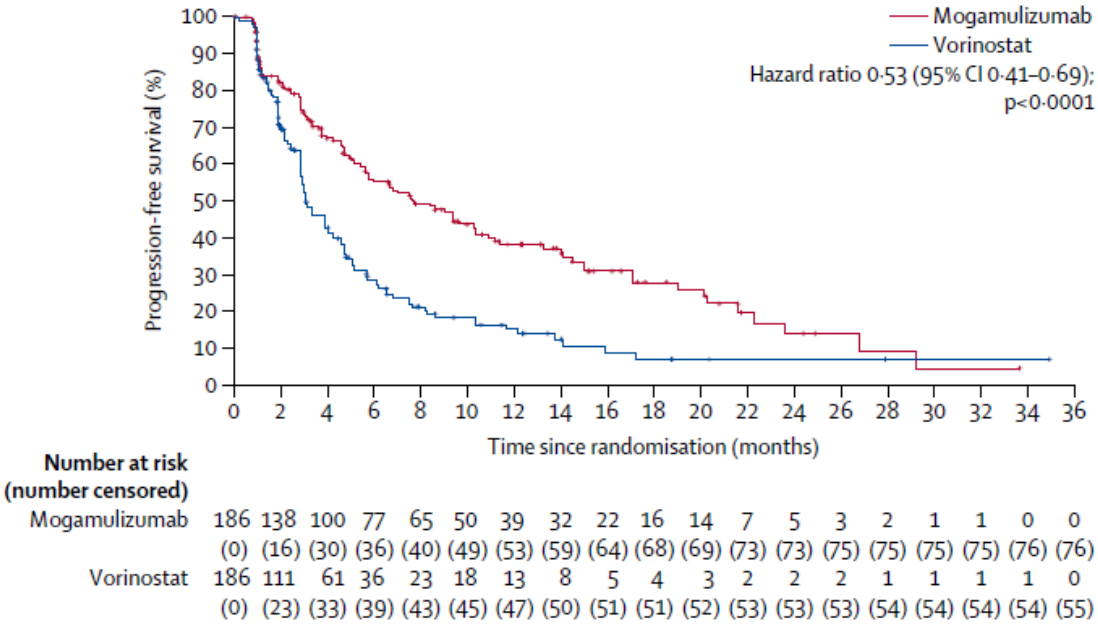
	Mogamulizumab (n=186)	**Vorinostat (n=186)**
Patients with PFS event, n (%)	110 (59.1)	131 (70.4)
Progressive disease	104 (55.9)	128 (68.8)
Death	6 (3.2)	3 (1.6)
Patients censored, n (%)	76 (40.9)	55 (29.6)
PFS (months)		
Median (95% CI)	7.70 (5.67, 10.33)	3.10 (2.87, 4.07)
HR (95% CI)	0.53 (0.41, 0.69)	
Log rank p-value	<0.0001	
Q1[a]	2.9	1.9
Q3[a]	20.1	6.6
Proportion of patients alive without PD at each 6-month interval, % (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]

	Mogamulizumab (n=186)	Vorinostat (n=186)
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PD, progression of disease; PFS, progression-free survival.
Notes: [a], Q1 is after 25% of patients had progressed or died, Q3 is after 75% of patients had progressed or died.
Source: Kim, et al. 2018[60]; MAVORIC CSR, 2017.[67]

Figure 5 presents a Kaplan–Meier (KM) plot of PFS for the ITT population. The curves for the mogamulizumab and vorinostat treatment arms begin to separate within the second cycle of treatment, and the separation is maintained through approximately 28 months.[60]

Figure 5: Kaplan–Meier plot of investigator-assessed progression-free survival: ITT population



Key: CI, confidence interval; ITT, intention-to-treat.
Source: Kim, et al. 2018.[60]

PFS results for the efficacy evaluable population were [redacted], with a HR of [redacted] (95% CI[redacted]; [redacted]).[67] PFS as assessed by independent review (a secondary outcome) was also conducted to assess response and validate the date of progression and are presented in Appendix O.2.

B.2.6.2. Secondary endpoints

Response rates (as assessed by investigator)

Table 12 presents a summary of response rate, including ORR, best overall response, DOR and TTR, which were calculated by combining the scores of each individual disease compartment.

The confirmed ORR was significantly higher for mogamulizumab (28.0%) than for vorinostat (4.8%) resulting in a risk ratio of 23.1 (95% CI: 12.8, 33.1; p<0.0001),[60] suggesting the potential for more patients to become eligible for aSCT with mogamulizumab. Overall there were five CRs in the mogamulizumab group and no CRs in the vorinostat group (Table 12). This ORR benefit was confirmed by blinded independent review with 43 (23%; 95% CI: 17.3, 29.8) patients assigned to mogamulizumab compared to seven (4%; 95% CI: 1.5, 7.6) patients assigned to vorinostat responding according to blinded independent review (risk difference: 19.4 [95% CI: 9.0, 29.4]; p<0.0001). In addition, the median DOR was 14.1 months in the mogamulizumab arm compared with 9.1 months in the vorinostat arm while median TTR was 3.3 months and 5.1 months respectively, indicating that a larger proportion of patients in the mogamulizumab arm respond to treatment quicker and maintained this response for longer, compared to patients receiving vorinostat.

Table 12: Summary of response rate: ITT population

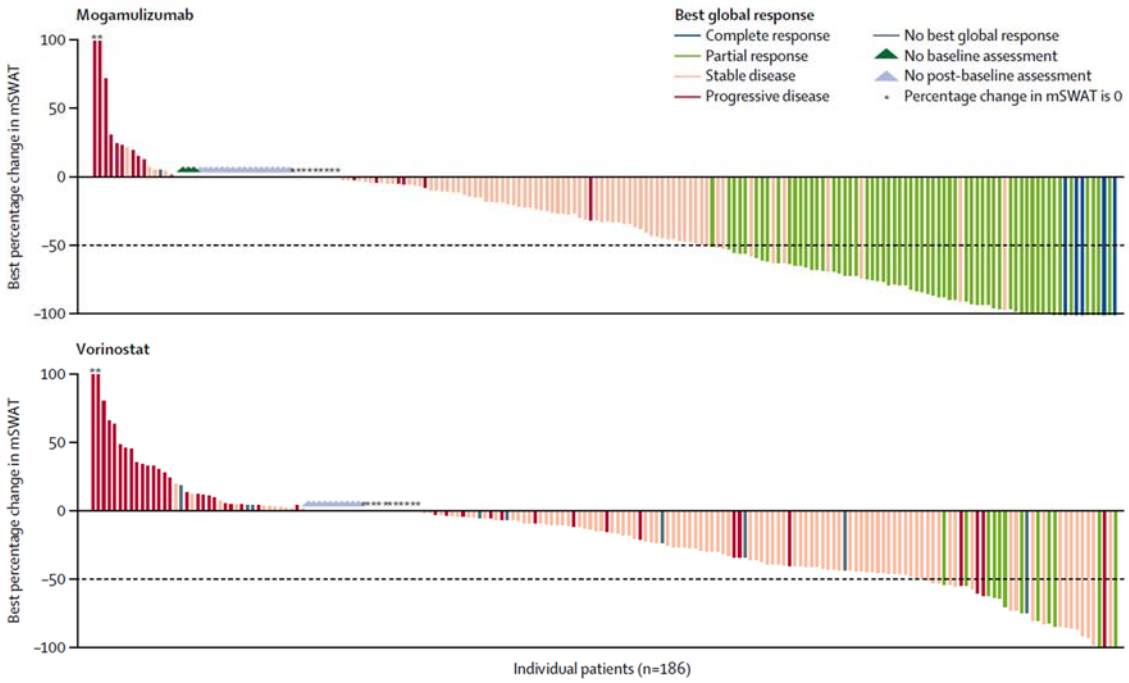
	Mogamulizumab (n=186)	**Vorinostat (n=186)**
ORR (confirmed CR + PR), n (% [95% CI])	52 (28.0 [21.6, 35.0])	9 (4.8 [2.2, 9.0])
Risk ratio (95% CI)	23.1 (12.8, 33.1)	
p-value	<0.0001	
Best overall response (CR + PR), n (%)	65 (34.9)	12 (6.5)
Confirmed CR, n (%)	[redacted]	[redacted]
CR, n (%)	5 (2.7)	0
Confirmed PR, n (%)	[redacted]	[redacted]
PR, n (%)	[redacted]	[redacted]
Stable disease, n (%)	80 (43.0)	115 (61.8)
Progressive disease, n (%)	1 (0.5)	6 (3.2)
Not accessible, n (%)	40 (21.5)	53 (28.5)

	Mogamulizumab (n=186)	Vorinostat (n=186)
DOR (months), median (IQR)	14.1 (8.4–19.2)	9.1 (5.6–NE)
MF patients, median (IQR)	13.1 (4.7–18.0)	9.1 (5.6–NE)
SS patients, median (IQR)	17.3 (9.4–19.9)	6.9 (6.9–6.9)
TTR (months), median (IQR)	3.3 (2.0–6.4)	5.1 (2.9–8.5)
MF patients, median (range)	[redacted]	[redacted]
SS patients, median (range)	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete response; DOR, duration of response; ITT, intention-to-treat; IQR, interquartile range; MF, mycosis fungoides; NE, not estimable; ORR, overall response rate; PR, partial response; SS, Sézary syndrome; TTR, time to response.
Source: Kim et al. 2018[60]; MAVORIC CSR, 2017.[67]

In addition, 44% of patients receiving mogamulizumab had at least a 50% improvement in skin response compared to only 22% in the vorinostat arm, as presented in Figure 6.

Figure 6: Best global and skin responses

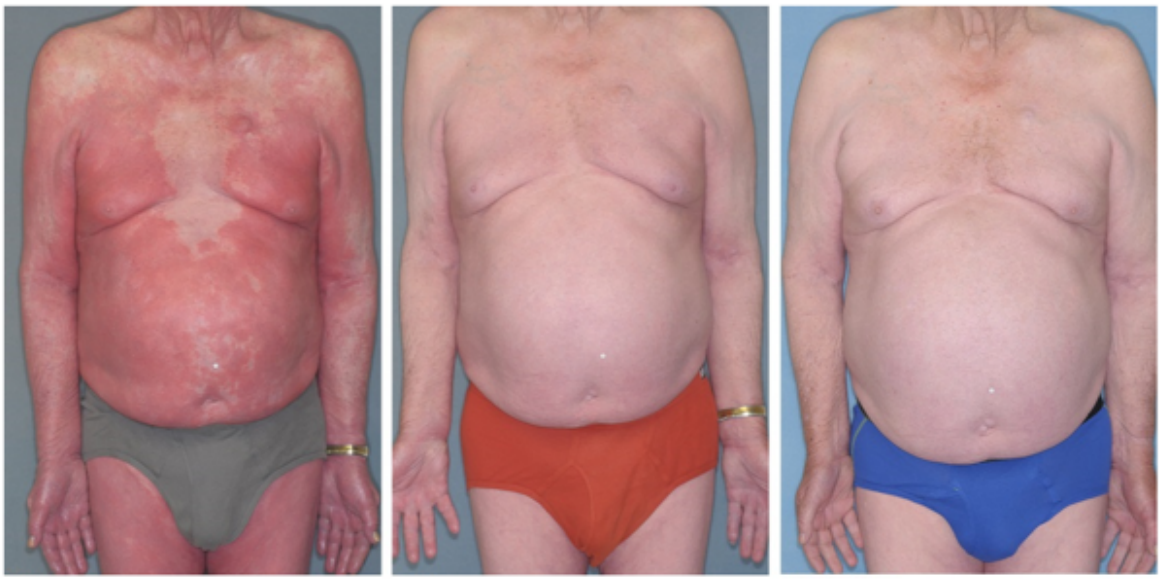


Key: mSWAT, modified Severity Weighted Assessment Tool.
Source: Kim et al. 2018.[60]

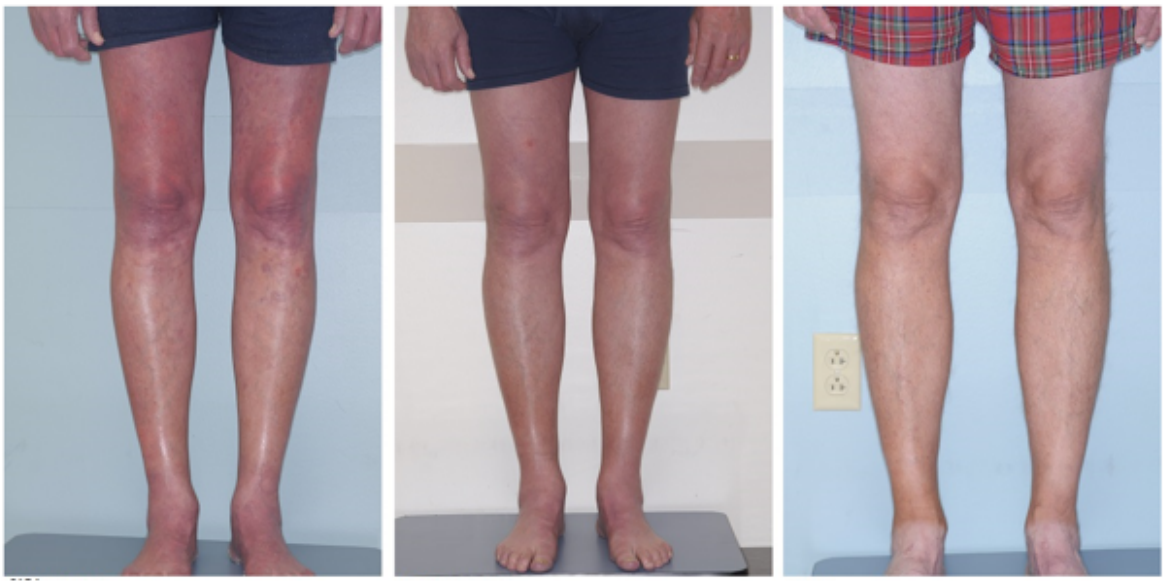
Visual depictions of the response to mogamulizumab in advanced patients is presented in Figure 7 depicting partial response (Figure 7A and C) and complete response (Figure 7B); [redacted].

Figure 7: Images of response to mogamulizumab in advanced MF and SS patients (movement over time from left to right)

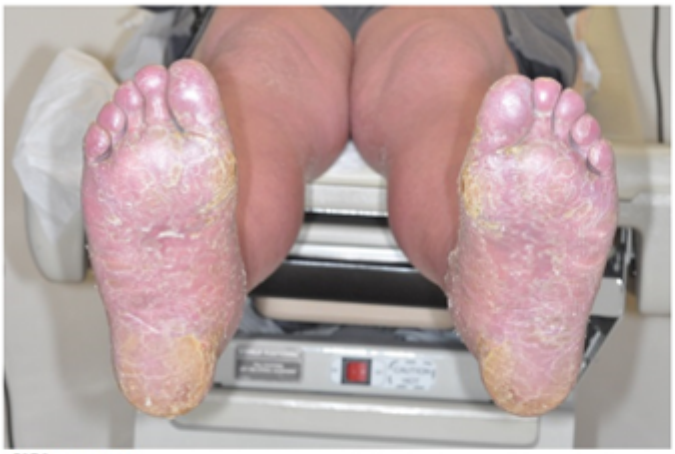
A: 74-year-old white male with Stage IVA_1 SS



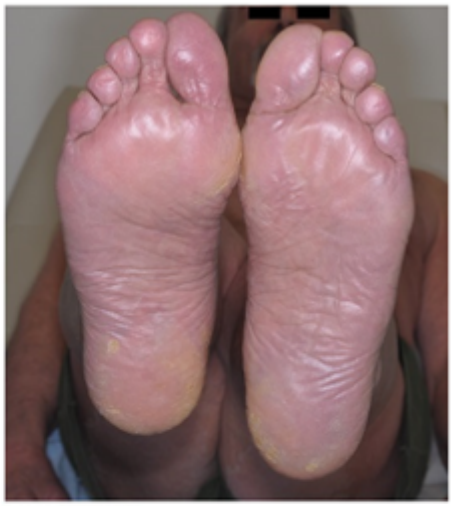
B: 62-year-old white male with Stage IVA1 MF



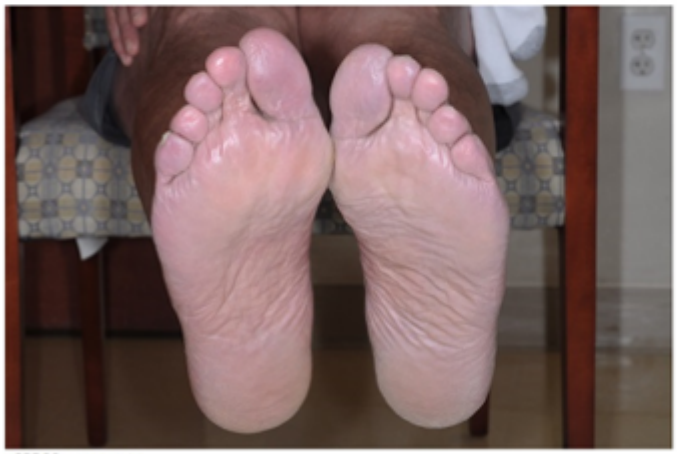
C: 68-year old white male with Stage IIIA MF



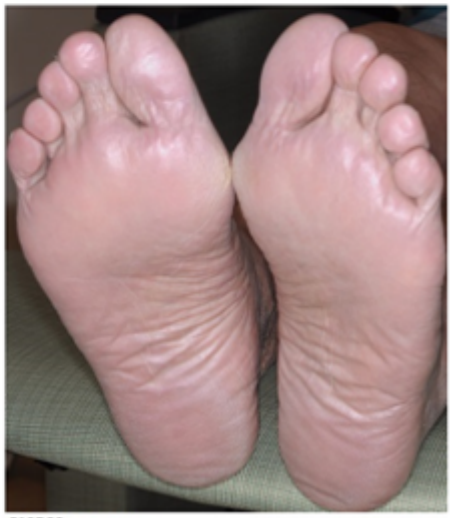
C1D1 crossover



C2D28 crossover



C5D28 crossover



C10D28 crossover

Key: C, cycle; D, day; MF, mycosis fungoides; SS, Sézary syndrome.
Notes: A, progression of response through 51 cycles of mogamulizumab from 3 December 2014 to December 2016; B, progression of response through 36 cycles of mogamulizumab from 19 Dec 2013 to 20 October 2016; C, progression of response through 20 cycles of mogamulizumab from 13 October 2015 to December 2016.
Source: Kyowa Kirin, 2018.[70]

The median DOR was 14.1 months in the mogamulizumab arm compared with 9.1 months in the vorinostat arm.[60] The median TTR was 3.3 months with mogamulizumab compared to 5.1 months with vorinostat.[60] Overall, results from the response rate analyses indicate that a larger proportion of patients in the mogamulizumab arm responded to treatment compared with those treated with vorinostat. Furthermore, patients treated with mogamulizumab responded quicker to

treatment overall, and maintained the response for longer compared to those treated with vorinostat.

Response rate by disease compartment (as assessed by investigator; post-hoc analysis)

A post-hoc analysis was conducted, analysing ORR, DOR and TTR individually for each disease compartment (blood, skin, lymph nodes and viscera), to assist in the interpretation of the key secondary response rate endpoints. Table 13 presents a summary of response rate by individual disease compartments.

Table 13: Summary of response rate by disease compartment: ITT population

Response by compartment	Mogamulizumab (n=186)	Vorinostat (n=186)
Overall ORR (confirmed CR + PR), n (% [95% CI])[a]	52 (28.0 [21.6, 35.0])	9 (4.8 [2.2, 9.0])
Skin	**(n=186)**	**(n=186)**
ORR (confirmed CR + PR), n (%)	78 (41.9)	29 (15.6)
p-value	[redacted]	
DOR (months), median (range)	20.6 (11.2–NE)	10.7 (4.8–NE)
TTR (months), median (range)	3.0 (1.9–4.7)	2.7 (1.1–5.6)
Blood	**(n=122)**	**(n=123)**
ORR (confirmed CR + PR), n (%)	83 (68.0)	23 (18.7)
p-value	[redacted]	
DOR (months), median (range)	25.5 (15.9–NE)	NE
TTR (months), median (range)	1.1 (1.0–1.2)	1.9 (1.0–2.1)
Lymph nodes	**(n=124)**	**(n=122)**
ORR (confirmed CR + PR), n (%)	21 (16.9)	5 (4.1)
p-value	[redacted]	
DOR (months), median (range)	15.5 (15.5–15.5)	NE
TTR (months), median (range)	3.3 (2.8–6.8)	2.9 (1.1–8.5)
Viscera	**(n=3)**	**(n=3)**
ORR (confirmed CR + PR), n (%)	0 (0)	0 (0)

Key: CI, confidence interval; CR, complete response; DOR, duration of response; ITT, intention-to-treat; NE, not estimable; ORR, overall response rate; PR, partial response; TTR, time to response.
Source: Kim et al. 2018[60]; MAVORIC CSR, 2017.[67]

ORR was significantly greater with mogamulizumab treatment compared with vorinostat for patients in both the skin (42% versus 16%; [redacted]) and blood (68% versus 19%; [redacted]) compartments, both of which have been linked to reduced life

expectancy[2, 19], as well as the lymph node (17% versus 4%; [redacted]) compartments.[60, 67] Only a very small number of patients had visceral involvement at baseline (vorinostat, n=3; mogamulizumab, n=3), so these results are not informative.[60]

The median DOR for patients in the skin compartment was greater for mogamulizumab (20.6 months) compared with vorinostat (10.7 months).[60] For patients in the blood and lymph node compartments, the median DOR for mogamulizumab was 25.5 months and 15.5 months, respectively; whereas for vorinostat, median DOR was not reached for patients in these compartments.

Across the skin, blood and lymph node compartments, median TTR was similar between the mogamulizumab and vorinostat treatment groups.[60] Median TTR for patients in the skin and lymph node compartments was slightly longer for mogamulizumab compared with vorinostat (3.0 versus 2.7 months; and 3.3 versus 2.9 months, respectively). Median TTR for patients in the blood compartment was slightly longer with vorinostat compared to mogamulizumab (1.9 versus 1.1 months).

Health-related quality of life

Assessments of HRQL during MAVORIC were carried out using three patient reported outcome (PRO) instruments: the Skindex-29, the FACT-G, and the EQ-5D-3L. Evaluation of pruritus was assessed using the ItchyQoL and the Pruritus Likert scale. A brief description of each instrument is provided below their respective sub-headings; further information on the scoring systems used and interpretation of results for each instrument is provided in Appendix N.

All PRO measures had high completion rates of over [redacted] % throughout the MAVORIC study. Similarly, by domain, the overall percentage of patients who completed each scale was high (>[redacted] %) and comparable for each measure. Baseline scores for all domains in each instrument were similar between the mogamulizumab and vorinostat treatment arms.[65] Over the course of the MAVORIC study, results become less interpretable due to study size attrition. As the number of patients declined, the variability observed for each of the PRO measures' domains increased, reducing the interpretability of the results. Therefore, only the results at Cycles 1, 3, 5, 7, 9, and 11 are summarized in this section.

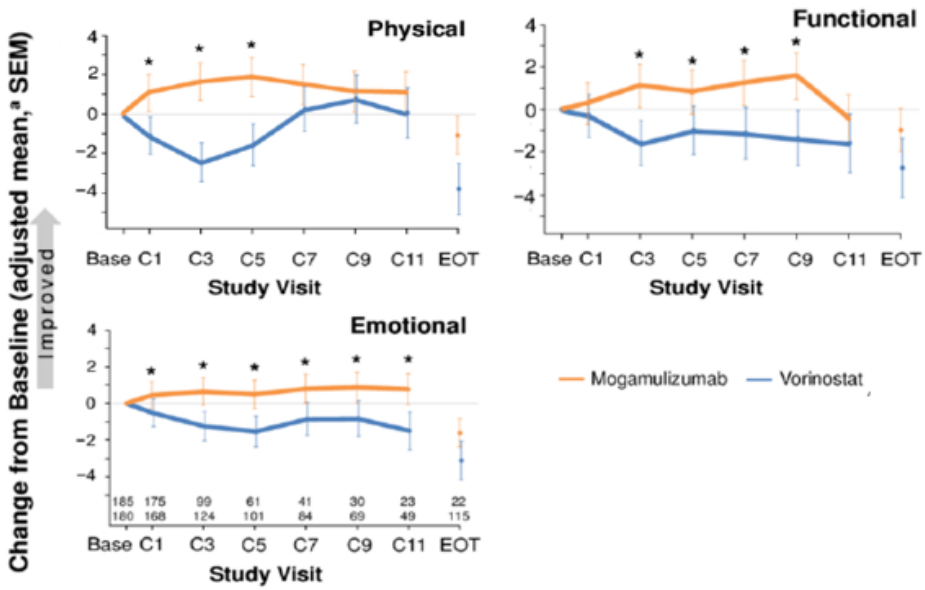
Overall, across both generic and disease-specific instruments used in the MAVORIC study patients' HRQL was improved more when treated with mogamulizumab compared to treatment with vorinostat.

FACT-G

The FACT-G is used to assess HRQL in patients with cancer; it consists of 27 items assessing four domains: physical well-being, social/family well-being, emotional well-being and functional well-being. Higher scores indicate better QoL. Minimally important differences (MIDs) for the FACT-G range from 3 to 7, with a mean MID of 5.[71]

The results of the FACT-G indicate that mogamulizumab led to significant benefits in physical, emotional and functional well-being compared with vorinostat.[72] As seen in Figure 8, significant improvements in the social domain were seen at Cycles 3 and 5 while improvements in the physical and emotional domains were seen as early as Cycle 1. All effects remained until the end of treatment visit.

Figure 8: Treatment effects in the FACT-G



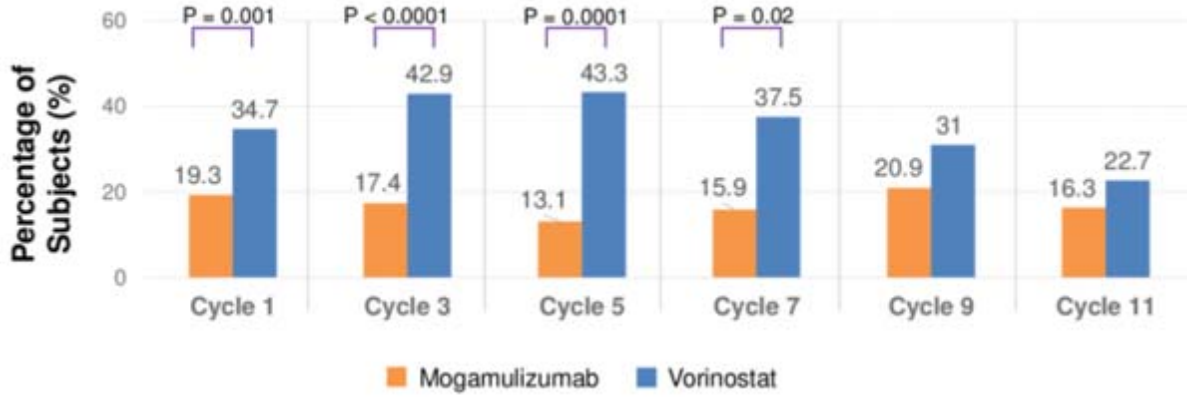
Key: EOT, end of treatment; FACT-G, Functional Assessment of Cancer Therapy – General; SEM, standard error of mean.
Note: [a], $p<0.05$
Source: Quaglino et al. 2018.[72]

[redacted].[65] [redacted]

[redacted].

In addition, significantly more patients treated with vorinostat reported a clinically meaningful decline in physical well-being through Cycles 1 to 7 compared with patients treated with mogamulizumab (Figure 9).[72]

Figure 9: Proportion of patients with clinically meaningful decline in the FACT-G physical well-being domain



Key: FACT-G, Functional Assessment of Cancer Therapy – General.
Source: Quaglino, et al. 2018.[72]

These data suggest that cancer-specific symptoms associated with a patient's physical well-being (e.g. lack of energy, nausea, pain and feeling ill), emotional life (feeling sad, nervous and losing hope), and overall impact on QoL were improved in patients treated with mogamulizumab compared to those treated with vorinostat.

EQ-5D-3L

The EQ-5D-3L is a generic QoL questionnaire consisting of five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression with a higher score indicating greater QoL. The EQ-5D-3L also utilizes a visual analogue scale

(VAS), which records a patient's self-rated health on a scale of 0-100 with higher scores indicating greater QoL. A change of 8-12 in VAS scores related to a MID for self-rated health status among cancer patients.[73]

[redacted].[65]

[redacted] (Figure 10).[65]

Figure 10: Proportion of patients with clinically meaningful improvements in the MAVORIC study as measured by EQ-5D-3L

[redacted]

Key: EQ-5D-3L, EuroQol 5 dimensions 3 level questionnaire.
Source: Kyowa Kirin data on file, 2019.

These results indicate that [redacted]. Similar to that seen in Figure 11, Table 14 [redacted]

Table 14: Change in EQ-5D HUI scores

	Baseline		Randomised treatment period[a]		
	Mean	**95% CI**	**Mean difference**	**95% CI**	**p-value**
Mogamulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vorinostat	[redacted]	[redacted]			

Key: EQ-5D, EuroQol 5-Dimension; HUI, health utility index.
Note: [a], six-month average.
Source: Data on file.

Please, note that additional EQ-5D analyses can be found in full analysis report.[74]

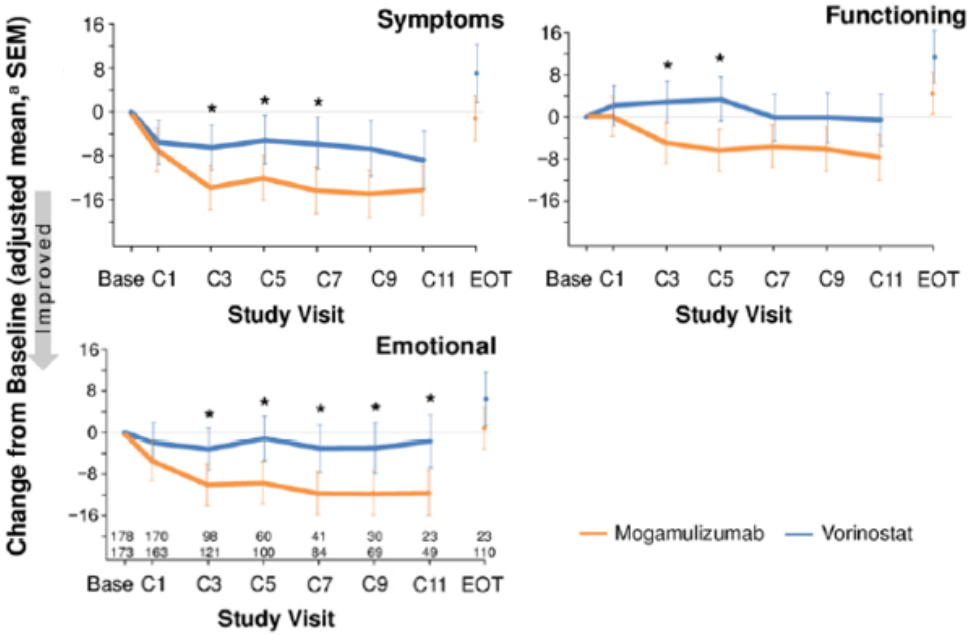
Skindex-29

The Skindex-29 is used to measure the effect of skin disease on HRQL; it consists of 29 items assessing three domains: emotions, symptoms, and functioning. Higher scores indicate a higher impact of skin disease. MIDs for the Skindex-29 symptom domain were estimated to be 9 to 12.3 using distribution based methods.[75]

Results from Skindex-29 indicated significant HRQL improvements following treatment with mogamulizumab compared with vorinostat.[72] These findings were further supported by analyses of individual emotional, functional and symptoms domain scores, where mogamulizumab demonstrated significant improvements.[72]

As demonstrated in Figure 11, improvements in all three domains were seen in patients in both treatment arms however greater improvements were observed with mogamulizumab treatment compared with vorinostat.

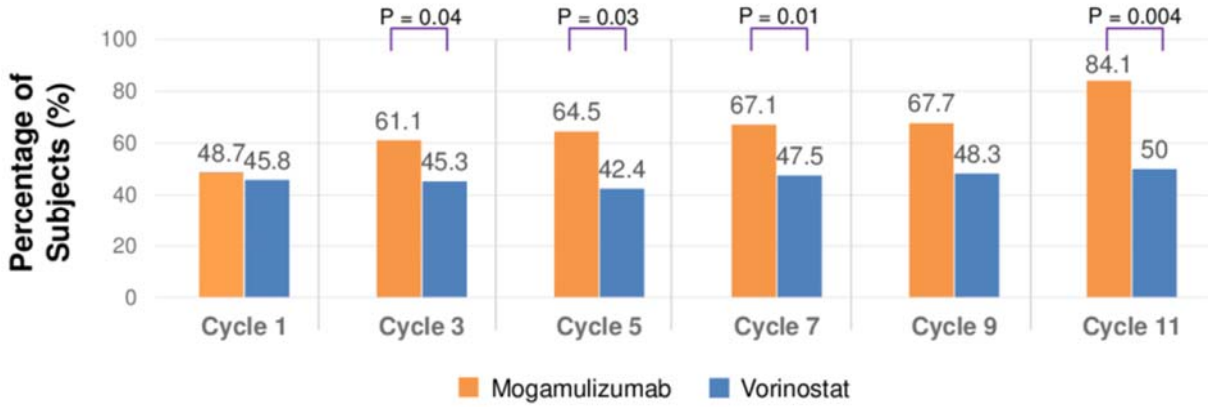
Figure 11: Treatment effects in the Skindex-29



Key: EOT, end of treatment; SEM, standard error of mean.
Note: [a], p<0.05.
Source: Quaglino, et al. 2018.[72]

When assessing the proportion of patients reporting clinically meaningful improvements in the individual Skindex-29 domains, statistically significant differences in favour of mogamulizumab were observed at cycle 5 for the functioning domain (54.3% vs. 28.8%; p=0.0068)[64], and at cycles 3, 5, 7 and 11 for the symptoms domain, as presented in Figure 12.[72] At least 60% of patients randomised to mogamulizumab reported clinically meaningful improvements in symptoms beginning at Cycle 3 and lasting throughout treatment.

Figure 12: Patients with clinically meaningful improvements in the Skindex-29 symptoms domain

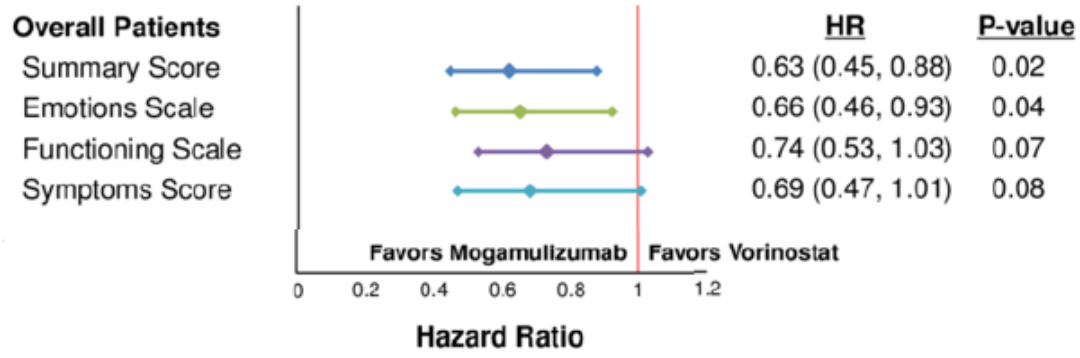


Source: Quaglino, et al. 2018.[72]

Treatment with mogamulizumab also resulted in numerically longer times to clinically meaningful worsening in Skindex-29 domains compared with vorinostat, as presented in Figure 13.[72] The median time to worsening of symptoms was significantly longer for patients treated with mogamulizumab compared to those treated with vorinostat (27.4 versus 6.6 months; p=0.08).

These data indicate that mogamulizumab improves both disease-specific symptoms (e.g. skin pain, burning, stinging, bleeding and itching) and patient functioning (e.g. fatigue, ability to work and sex-life) in addition to preserving HRQL for substantial periods of time compared to vorinostat.

Figure 13: Time to clinically meaningful worsening across all Skindex-29 domains



Key: HR, hazard ratio.
Source: Quaglino, et al. 2018.[72]

ItchyQoL and pruritus Likert scale

The ItchyQoL is a pruritus-specific QoL instrument that includes 22 items covering three domains: symptoms, functioning, and emotions. The overall score is the average of the responses to all items with higher scores indicating worse QoL. The pruritus Likert scale specifically measures the level of itching associated with pruritus and uses a numbered scale from 0 to 10 with 10 indicating worse itch imaginable and 0 indicating no itch.

Treatment with mogamulizumab [redacted].[65] As presented in Figure 14, [redacted]. As previously discussed in Section B.1.3, itching is a key aspect of disease which causes significant burden to patients. Therefore, the improvement seen with mogamulizumab can be reasonably assumed to have a significant effect on patients' life.

Figure 14: Change in ItchyQoL LS score from baseline through 6 months

Key: LS, least squares.
Source: Kyowa Kirin data on file, 2019.[65]

B.2.6.3. Exploratory endpoints

Overall survival

The median OS was not reached with mogamulizumab and was 43.9 months with vorinostat resulting in a HR of 0.93 (95% CI: 0.6, 1.4; p-value: 0.94).[60] This data should be viewed with caution due to the immaturity of the data (only 23% of patients experienced an OS event) and the confounding due to high rates of crossover (72.6% of patients switched to mogamulizumab from the vorinostat arm) makes the interpretation of the results difficult without additional adjustment. Nevertheless, mogamulizumab demonstrated significantly improved response in all four compartments of disease (Table 13), including the blood and skin compartments which are known to be key prognostic factors and are predictors of reduced survival.[2, 32, 33, 76] Such improvements in response can logically be assumed to translate into improved survival for patients and thus mogamulizumab can be seen to provide an OS benefit. This is supported by clinical opinion which notes that the OS predicted with mogamulizumab is reasonable based on the superior efficacy demonstrated via other endpoints and the crossover adjusted OS results, that show an important improvement in OS with mogamulizumab compared to vorinostat. This further discussed in Section B.2.13.

A summary of OS is presented in Table 15, and a KM plot for OS is presented in Figure 15.

Table 15: Summary of overall survival: ITT population

	Mogamulizumab (n=186)	**Vorinostat (n=186)**
OS (months), median (95% CI)	NE (NE, NE)	43.93 (43.57, NE)
Hazard ratio (95% CI)	0.93 (0.61, 1.43)	
Log rank p-value	0.9439	
Q1	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Patients died, n (%)	[redacted]	[redacted]
Patients censored, n (%)	[redacted]	[redacted]

Key: CI, confidence interval; ITT, intention-to-treat; NE, not estimable; OS, overall survival.
Notes: [a], Kaplan–Meier estimate.
Source: Kim et al. 2018[60]; MAVORIC CSR, 2017.[67]

Figure 15: Kaplan–Meier curve of overall survival: ITT population

Key: KW/KW-076, mogamulizumab; VOR, vorinostat.
Source: MAVORIC CSR, 2017.[67]

Of note, OS based on an updated data cut of 2 March 2019 was incorporated into the economic model; a KM curve for this data is presented in Appendix O.3.

Time to treatment failure

Time to treatment failure (TTF) was defined as time from randomization until discontinuation of treatment due to any reason, except for patients who discontinued treatment after 1 year on treatment post-achieving a CR (achieved by).[77] Overall, patients failed on treatment with vorinostat compared with those receiving mogamulizumab (% versus %, respectively).[67] The median TTF was for mogamulizumab treatment (months) than with vorinostat treatment (months) resulting in a HR of (95% CI: , ;).

As breaks from receiving treatment are often positive goals for patients with CTCL, TTF is not considered a particularly relevant endpoint as it is not fully reflective of a successful CTCL patient journey. Furthermore, failure of treatment does not always

coincide with disease progression. As such, TTF was considered an exploratory endpoint.

B.2.6.4. Additional endpoints

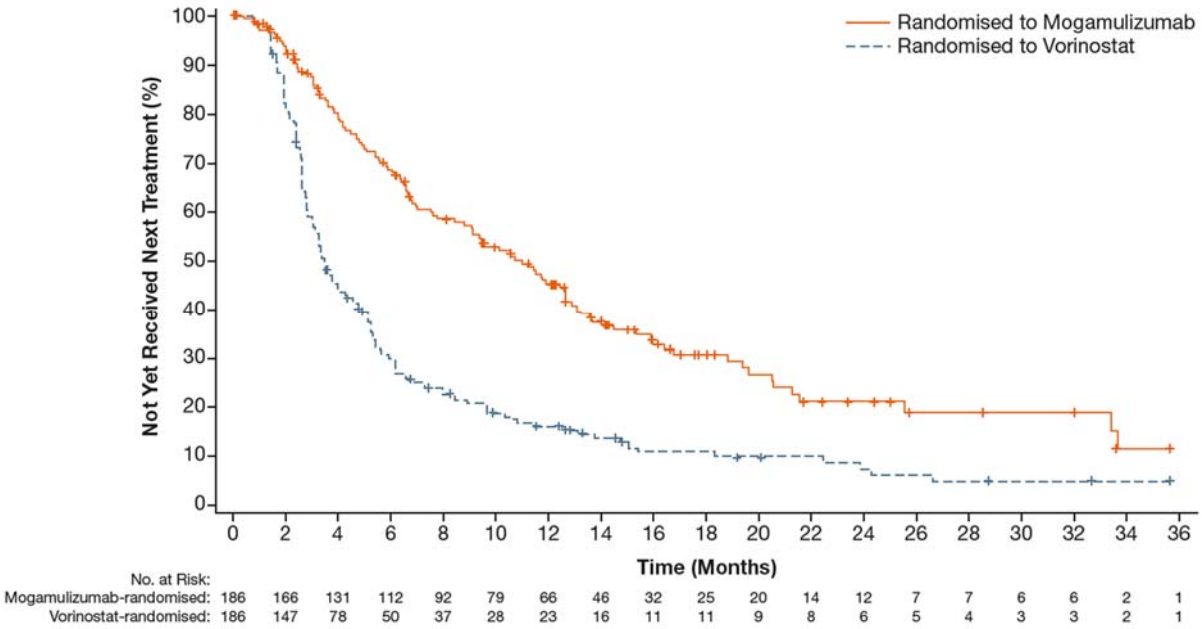
Time to next treatment (post-hoc analysis)

As previously noted, TTNT is an important measure for CTCL patients as, unlike TTF, it is more closely aligned with symptoms and disease control.

For this analysis, the median follow-up time was defined as time from end date of randomised treatment (including end date of mogamulizumab treatment for crossover patients) to next systemic treatment.[62] All patients were followed to monitor survival and to document any new treatments every 3 months (+/- 14 days).

In the ITT population, median TTNT was significantly longer for mogamulizumab treatment compared with vorinostat (11.0 [95% CI: 8.8, 12.6] versus 3.2 [3.1, 4.3] months; p<0.0001).[62] It should also be noted that the median TTNT for mogamulizumab is more than double that reported historically for systemic treatments (11.0 versus 5.4 months, respectively).[63] Figure 16 presents a Kaplan–Meier curve of TTNT for the ITT population.

Figure 16: Kaplan–Meier plot of TTNT: ITT population



Key: ITT, intention-to-treat; TTNT, time to next treatment.
Source: Kim, et al. 2019.[62]

Clinicians experienced with mogamulizumab expressed the potential effect for mogamulizumab to slow the disease progression, and allow for longer response even on subsequent treatments.[49] In order to investigate if mogamulizumab has any 'spill-over' effect on the subsequent treatments, the time on subsequent treatments (based on an updated data cut of 2 March 2019 and defined in terms of the length of time between subsequent treatments which as noted is of key clinical measurement for CTCL) was assessed. Data was analysed on patients that fulfilled the following criteria of having had at least two subsequent treatments following:

- The discontinuation of mogamulizumab in patients randomised to mogamulizumab
- The discontinuation of mogamulizumab in patients randomised to vorinostat
- The discontinuation of vorinostat in patients randomised to vorinostat

Subsequent treatment was defined in the same way as above, that is, systemic or significant skin-directed therapy, not aimed at treating a limited area of disease. TTNT was defined as time from the start date of first subsequent treatment to the start date of second subsequent therapy.

[redacted].[78] These data suggest that the use of mogamulizumab has the potential to change the natural course of the disease by delaying the need for subsequent treatments, a key outcome of importance for patients.

Additional post-hoc analyses

Additional post-hoc analyses include PFS and ORR by number of prior therapies, PFS, ORR and DOR by type of prior systemic therapy, long-term clinical benefit of mogamulizumab, and ORR and TTNT in less advanced MF; these are presented in Appendix O.

B.2.7. Subgroup analysis

Subgroup analyses of PFS, ORR and TTNT in patients with advanced disease (≥Stage IIB MF and all SS patients) are presented below; these represent patients with the highest unmet need. Subgroup analyses of PFS in the ITT population are presented in Appendix E.

In patients with advanced disease, the efficacy results were consistent with those of the total ITT population, and in some cases further improved, confirming the benefit of mogamulizumab in this subgroup of high unmet need.

In patients with stage ≥IIB disease, the median PFS was greater for mogamulizumab compared with vorinostat (9.4 versus 3.1 months), with a HR of 0.43 (95% CI: 0.31, 0.58; p<0.0001).[61] ORR was also greater for patients treated with mogamulizumab compared with vorinostat (30% versus 3%, respectively; p<0.0001). Furthermore, TTNT was significantly longer for patients treated with mogamulizumab compared with vorinostat (11.0 versus 3.5 months; p<0.0001). Table 16 presents a summary of investigator assessed PFS, ORR and TTNT in patients with advanced disease in the ITT population.

Table 16: Summary of investigator-assessed progression-free survival, overall response rate and time to next treatment: ITT population (stage ≥IIB patients)

	Stage ≥IIB (n=287)	
	Mogamulizumab (n=150)	**Vorinostat (n=137)**
Patients with PFS event, n (%)	86 (57.3)	101 (73.7)
Median PFS, months (95% CI)	9.40 (5.73, 14.03)	3.07 (2.87, 3.90)
HR (95% CI)	0.43 (0.31, 0.58)	
p-value	<0.0001	
ORR, n (% [95% CI])	45 (30.0 [22.8, 38.0])	4 (2.9 [0.8, 7.3])
Rate difference (95% CI)	27.1 (19.1, 35.5)	
p-value	<0.0001	
Median TTNT, months (95% CI)	11.00 (7.73, 13.63)	3.47 (2.87, 4.53)
HR (95% CI)	0.36 (0.27, 0.48)	
p-value	<0.0001	

Key: CI, confidence interval; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; TTNT, time to next treatment.
Source: Leoni, et al. 2019.[61]

B.2.8. Meta-analysis

Meta-analysis has not been performed because a single RCT provides comparative evidence supporting the use of mogamulizumab for the treatment of MF or SS following at least one prior systemic therapy in patients who are clinically ineligible for, or refractory, to treatment with BV.

B.2.9. Indirect and mixed treatment comparisons

MAVORIC is the pivotal trial assessing the clinical effectiveness and tolerability of mogamulizumab compared to vorinostat in patients with Stage IB to IVB MF or SS who have failed at least one prior therapy.[60] MAVORIC is the largest randomised Phase III study conducted in CTCL to date, with 372 patients enrolled. Furthermore, almost 80% of patients had advanced stage disease and almost half (45%) of patients had SS; this represents both the only Phase III study to include SS patients and the largest number of SS patients to ever be recruited to a randomised trial.

As the MAVORIC study compares mogamulizumab to vorinostat, a treatment not current standard of care within England, an indirect treatment comparison (ITC) was considered to allow comparisons to treatments used within the NHS. The clinical SLR (presented in Appendix D) identified 34 unique studies. These were then re-reviewed to identify studies which are fully representative of the decision problem. This included identifying the appropriate patient population, as the SLR was designed to be fully inclusive and therefore included studies which are outside of the decision problem for this submission. Similarly, studies were re-reviewed to identify only those treatment regimens applicable to the UK setting, including combination therapies and dosages reflective of NHS clinical practice, based on clinical consultation.[49] Finally, studies were restricted by relevant outcomes, namely OS, PFS and ORR. This resulted in the identification of seven single-arm studies. As only evidence from single arm studies was available, it was not possible to form a network of the MAVORIC study to the evidence to other comparative treatments. Population adjusted indirect treatment comparisons as per NICE TSD 18 was considered;[69] however, was deemed inappropriate due to a variety of reasons presented in Table 17. In addition, the identified vorinostat studies were not

considered further given that direct comparative atrial data were available in MAVORIC, which is performed in the population of interest.

Table 17: Reasons population adjustment methods were not applied to studies identified within the clinical SLR

Study	Treatment arms	Reason not considered for population adjustment
Wada 2012[79]	• Vorinostat (n=6): 400 mg once daily	• Vorinostat study • Very low patient numbers • Japanese population • Limited survival data reported (no OS data, only median PFS reported)
Duvic 2007[80]	• Vorinostat (n=13): 400 mg daily • Vorinostat (n=11): 300 mg twice daily, three days a week for 4 weeks, then 5 days every week. • Vorinostat (n=9): Induction: 300 mg twice daily for 14 days followed by 7 days' rest. Maintenance: 200 mg twice daily •	• Vorinostat study • Very low patient numbers per arm • Limited survival data reported (no OS data, only median PFS reported)
Olsen 2007[81]	• Vorinostat 400 mg daily (n=74)	• Vorinostat study • Limited survival data reported (no OS data, only median TTP reported)
Duvic 2017[82]	• Bexarotene (150 or 300 mg/day) + pralatrexate (N=34)	• Low patient numbers (only 3 SS patients) • Limited survival data reported (no OS data, only median PFS reported)
Rupoli 2016[83]	• Bexarotene (150 – 300 mg/day) + PUVA (n=21)	• Low patient numbers • Disease type not reported – assumption of no unmeasured confounders does not hold given disease type is prognostic.
Ilidge 2013[84]	• Bexarotene (150-300 mg/day) + gemcitabine (n=35)	• Low patient numbers • Disease type not reported – assumption of no unmeasured confounders does not hold given disease type is prognostic.
Talpur 2014[85]	• Bexarotene 300 mg + pralatrexate (n=3) • Bexarotene 150 mg + pralatrexate (n=11)	• Very low patient numbers • No SS patients

		• Limited survival data reported (no OS data, only median time to response reported)

Key: OS, overall survival; PFS, progression-free survival; PUVA, Psoralen and Ultraviolet A; SS, Sezary syndrome; TTP, time to progression.

Note: Criteria for screening were 1) matching to MAVORIC study population* AND 2) Study investigating either vorinostat or a treatment regimen reflective of UK clinical practice** AND 3) study reporting OS/PFS/ORR/TTNT

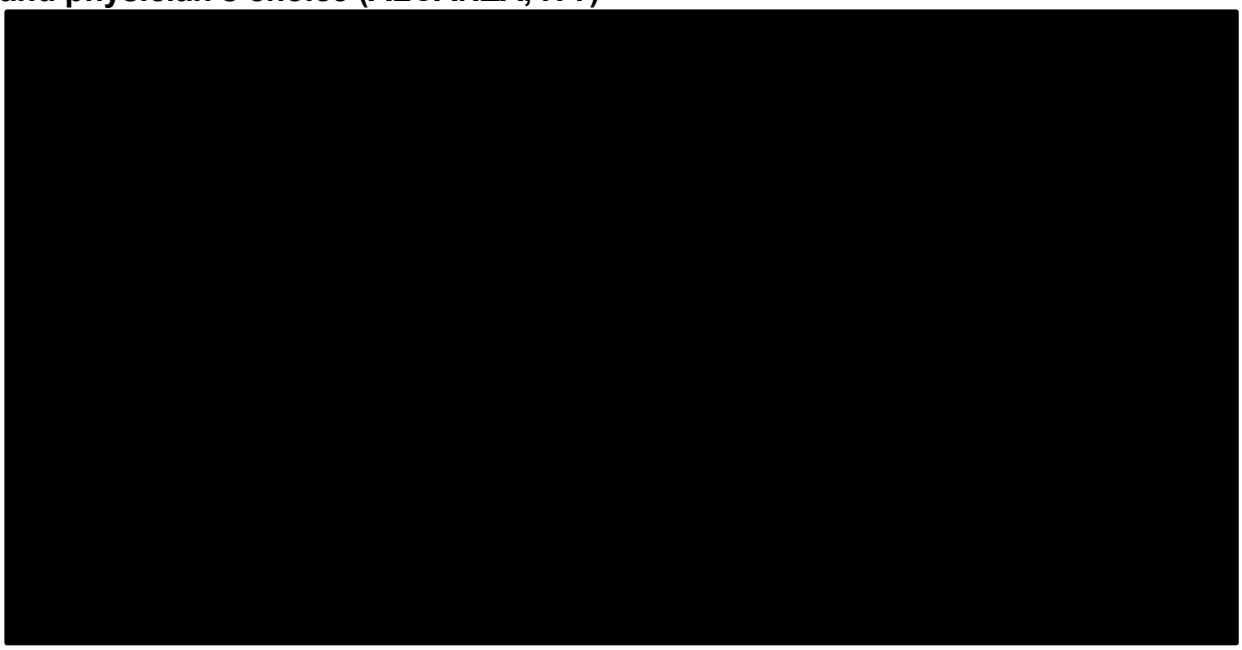
*patients had to have stage IB–IVB histologically confirmed relapsed or refractory MF or SS and be aged ≥18 years (in Japan, ≥20 years), and to have failed at least one previous systemic therapy, have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1 and adequate haematological, hepatic, and renal function

**Methotrexate (oral) 20-30mg once weekly OR Bexarotene (oral) up to 300mg/m^2 OR Interferon alpha-2a 3 MIU/day

Vorinostat is considered a reasonable proxy for standard of care currently used in the NHS supported by clinical opinion[49], as well as evidence in the literature. The approval of bexarotene, a key comparator for this submission, was based on a Phase II study of 193 CTCL patients; of these patients 93 had advanced stage disease refractory to prior systemic therapy.[55] The efficacy data in this study showed an ORR in the skin of 31%; this is similar to the ORR of 29.7% seen in the skin compartment in the vorinostat arm of the MAVORIC study.

The use of vorinostat as a proxy for standard of care is further supported when considering the PFS curves for vorinostat from the MAVORIC study and the physician's choice arm (i.e. methotrexate or bexarotene) from the ALCANZA study. The ALCANZA study is the most recent Phase III RCT conducted in CTCL and is the next largest study after MAVORIC. Importantly, NICE accepted the physician's choice arm as standard UK clinical practice in TA577.[30] As shown in Figure 17, the PFS curves from the ITT population of these studies overlap thus confirming clinicians' comments that vorinostat should be considered a proxy for English standard of care. Of note, of the patients receiving physician's choice in ALCANZA, 63% were classed as having advanced disease compared to 74% of patients receiving vorinostat in MAVORIC. Furthermore, no SS patients were included in the ALCANZA study. A full table of baseline characteristics of patients in each arm of the two studies is presented in Appendix L.

Figure 17: KM investigator-assessed PFS curves for vorinostat (MAVORIC, ITT) and physician's choice (ALCANZA, ITT)



Key: ITT, intent-to-treat; KM, Kaplan–Meier; PFS, progression-free survival.

As such, the key strength of the evidence for mogamulizumab in this population is the Phase III active controlled RCT, MAVORIC; the largest trial in CTCL and the most robust study resulting in the least uncertainty, which provides the best evidence on the clinical benefits of mogamulizumab compared to UK comparators.

B.2.10. Adverse reactions

B.2.10.1. Treatment exposure

Table 18 presents a summary of the treatment exposure during MAVORIC and further details are presented in Appendix F.1. Of particular note, the median duration of exposure was approximately twice as long for mogamulizumab (170 days) compared with vorinostat (84 days).[60]

Table 18: Summary of treatment exposure

	Randomised Treatment Period		Crossover
	Mogamulizumab (n=186)	**Vorinostat (n=186)**	**Mogamulizumab (n=136)[a]**
Extent of exposure (days)[b]			
Median (range)	170.0 ([redacted])	84.0 ([redacted])	[redacted]
Mean (SD)	245.2 (234.48)	144.3 (172.48)	[redacted]
Number of cycles initiated[c], n (%)			
Median (range)	[redacted]	[redacted]	[redacted]
1 cycle	[redacted]	[redacted]	[redacted]
2 cycles	[redacted]	[redacted]	[redacted]
3 cycles	[redacted]	[redacted]	[redacted]
4 cycles	[redacted]	[redacted]	[redacted]
5 cycles	[redacted]	[redacted]	[redacted]
6 cycles	[redacted]	[redacted]	[redacted]
7 cycles	[redacted]	[redacted]	[redacted]
8 cycles	[redacted]	[redacted]	[redacted]
9 cycles	[redacted]	[redacted]	[redacted]
10 cycles	[redacted]	[redacted]	[redacted]
11 cycles	[redacted]	[redacted]	[redacted]
12 cycles	[redacted]	[redacted]	[redacted]
13 cycles	[redacted]	[redacted]	[redacted]
Mogamulizumab infusions administered, median (range)	[redacted]	[redacted]	[redacted]
Dose intensity[d] (%), median (range)	97.49 ([redacted])	95.12 ([redacted])	[redacted]

Key: IQR, inter-quartile range; N/A, not applicable; SD, standard deviation.
Notes: [a], exposure results are based on 133 patients who crossed over to mogamulizumab and were treated; [b], 10 patients randomised to vorinostat were ongoing at data cut-off and had missing last dose date for vorinostat during the randomised treatment period. The last dose date has been imputed using the patient's last visit date during randomised treatment period; [c], a patient is considered to have initiated treatment for a cycle if the patient received any assigned study drug for that cycle; [d], % dose intensity of mogamulizumab was calculated as 100*(total actual dose/total duration of treatment/7)/(total planned dose/total planned weeks). % dose intensity of vorinostat was calculated as 100*(sum of [patient's actual dosage per dosing interval*actual days exposed per dosing interval])/(400*expected dose days), where expected dose days is last dose date - first dose date + 1.
Source: Kim et al. 2018[60]; MAVORIC CSR, 2017.[67]

B.2.10.2. Adverse events

Summary of treatment-emergent adverse events

During the randomised treatment period, the incidence of treatment-emergent adverse events (TEAEs) was similar between the mogamulizumab and vorinostat treatment groups ([redacted]% and [redacted]%, respectively), while the incidence of drug-related TEAEs was somewhat lower for mogamulizumab ([redacted]%) compared with vorinostat ([redacted]%).[67] The incidence of Grade 3, 4 or 5 TEAEs was also similar for the two groups (42.4% and 45.7%, respectively), while the incidence of drug-related Grade 3, 4 or 5 TEAEs was again lower for mogamulizumab (25.5%) compared to vorinostat (34.9%). Of note, the incidence of TEAEs observed for patients receiving mogamulizumab after crossover was similar to that observed for patients randomised to mogamulizumab.

A total of 12 (3%) patients died as a result of AEs.[60] Of these, nine occurred in the vorinostat arm and three occurred in the mogamulizumab arm. Of the three mogamulizumab patients who died from an AE, two were possibly related to treatment (sepsis and polymyositis), and one to unrelated disease progression. Of the nine vorinostat patients who died due to an AE, three were possibly related to treatment (two cases of pulmonary embolism and one of bronchopneumonia) and six were considered unrelated to treatment (one each of disease progression; intestinal obstruction, sepsis, or septic shock; endocarditis; pneumonia; depressed level of consciousness; and skin disorder).

During the crossover portion, [redacted]additional patients receiving mogamulizumab experienced AEs leading to death.[67] The incidence of treatment emergent serious adverse events (SAEs) was higher in the mogamulizumab group (37.5%) than the vorinostat group (24.7%); the incidence of drug-related SAEs was 19.6% in the mogamulizumab group compared with 16.1% in the vorinostat group.[60]

Discontinuation of treatment due to AEs was reported for 19.0% of patients randomised to mogamulizumab, and 23.1% of patients randomised to vorinostat.[60] Table 19 presents a summary of the adverse events during MAVORIC.

Table 19: Overview of adverse events: Safety population

	Pre-treatment and randomised treatment period		Crossover portion
	Mogamulizumab (n=184)	**Vorinostat (n=186)**	**Mogamulizumab (n=136)**
Adverse Events (AEs), n (%)			
Any AEs	[redacted]	[redacted]	[redacted]
Any TEAEs	[redacted]	[redacted]	[redacted]
Drug-related TEAEs	[redacted]	[redacted]	[redacted]
NCI/CTCAE Grade 3, 4, 5 AEs, n (%)			
Any Grade 3, 4, 5 AEs	[redacted]	[redacted]	[redacted]
Any Grade 3, 4, 5 TEAEs	[redacted]	[redacted]	[redacted]
Drug-related Grade 3, 4, 5 TEAEs	[redacted]	[redacted]	[redacted]
AEs with Outcome of Death	[redacted]	[redacted]	[redacted]
Serious Adverse Events, n (%)			
Any SAEs	[redacted]	[redacted]	[redacted]
Treatment-emergent SAEs	69 (37.5)	46 (24.7)	[redacted]
Drug-related Treatment-emergent SAEs	36 (19.6)	30 (16.1)	[redacted]
Discontinuation due to AEs, n (%)			
Any AEs	[redacted]	[redacted]	[redacted]
Any TEAEs	35 (19.0)	43 (23.1)	[redacted]
Drug-related TEAEs	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event;
Notes: [a], includes one patient with TEAE with outcome of death that occurred during crossover and >30 days after the last dose of vorinostat, but was related to vorinostat; [b], includes two patients with non-TEAEs with outcome of death.
Source: Kim et al. 2018[60]; MAVORIC CSR, 2017.[67]

Most common treatment-emergent adverse events

A summary of the most common Grade 1–2 TEAEs, occurring in ≥10% of patients and most common Grade 3–5 TEAEs, occurring in ≥2% of patients (in either treatment group) is presented in Appendix F.3. In the mogamulizumab arm, the most common TEAEs were infusion-related reactions (34%), drug eruption (24%), diarrhoea (24%), and fatigue (24%) while in the vorinostat arm the most common

TEAEs were diarrhoea (62%), nausea (43%), thrombocytopenia (40%) and fatigue (38%).[60]

While infusion-related reactions and drug eruption were more frequent in the mogamulizumab arm than in the vorinostat arm, most of these events were mild or moderate in severity with only three Grade ≥3 infusion-related reactions and eight Grade ≥3 drug eruption events recorded.[60] It should also be noted that both of these events are known to occur with mogamulizumab therapy due to its mode of action and were therefore expected (discussed further in Section B.2.13).

Serious treatment-emergent adverse events

Appendix F.2 presents a summary of the most common SAEs. In the mogamulizumab arm, the most frequently reported SAEs of any cause were pyrexia in eight (4%) and cellulitis in five (3%) patients.[60] In the vorinostat arm, the most frequently reported SAEs were cellulitis in six (3%), pulmonary embolism in six (3%), and sepsis in five (3%) patients.

For mogamulizumab the most common treatment-related SAEs were pneumonia in four (2%) patients and pyrexia in four (2%) patients and for vorinostat pulmonary embolism in five (3%) patients and thrombocytopenia in three (2%) patients.

Safety overview

Results from the MAVORIC trial reveal that mogamulizumab was generally well tolerated in previously treated patients with MF and SS, with AEs generally mild or moderate in severity and easily managed, and no new safety concerns were identified. As mentioned, the most frequently reported TEAE for patients in the mogamulizumab group was infusion-related reaction (34%);[60] this was most often associated with the first infusion, with serious infusion-related reactions reported in only three patients. It should also be noted that for patients that crossed over to mogamulizumab treatment, the type and incidence of TEAEs observed in these patients were similar to that observed for patients initially randomised to mogamulizumab.

The incidence of Grade 3, 4 or 5 TEAEs was similar between patients treated with mogamulizumab and those treated with vorinostat ([redacted]% and [redacted]%,

respectively), while the incidence of drug-related Grade 3, 4 or 5 TEAEs was lower for mogamulizumab ([redacted]%) compared to vorinostat ([redacted]%).[67] Furthermore, more deaths occurred in the vorinostat arm than in the mogamulizumab arm (nine versus three, respectively), and of these, three were related to vorinostat treatment compared to two with mogamulizumab.[60]

In summary, the results suggest that the potential clinical benefit of mogamulizumab outweighs the potential burden of the reported AEs. It should also be noted that treatment exposure was much greater for mogamulizumab patients compared to those treated with vorinostat. Despite this, the overall incidence and severity of TEAEs were comparable between treatment arms. Furthermore, the incidence and severity of TEAEs did not vary with increasing levels of mogamulizumab exposure, allowing patients to safely remain on treatment for longer (post-hoc safety analysis presented in Appendix F.4). These findings are in line with the EMA regulatory approval for mogamulizumab, which was granted based on its positive risk/benefit ratio profile (discussed further in Section B.2.13).

B.2.11. Ongoing studies

The MAVORIC study is expected to reach completion in December 2020; at present, 10 patients are currently ongoing with treatment.

B.2.12. Innovation

Mogamulizumab represents a significant innovation in the management of adult patients advanced stage disease (stage ≥IIB MF and all SS patients) who have received at least one prior systemic therapy and who are clinically ineligible for, or refractory, to treatment with BV as evidenced by the granting of 'Breakthrough Therapy Designation' by the US Food and Drug Administration[86], as well as 'Promising Innovative Medicine' designation by the Medicines and Healthcare products Regulatory Agency.[87]

Mogamulizumab is the first approved immune oncology treatment that specifically targets CCR4, a specific chemokine that is expressed highly on T-cells in MF and SS, and elicits anti-tumour activity mediated by antibody-dependent cellular cytotoxicity (ADCC), thus enables the body's own immune system to destroy the

cancer cells.[13] Compared to currently available treatments, this represents an innovative mechanism of action thus providing patients with a novel targeted treatment and an alternative to the current cycling of treatments which commonly occurs in advanced disease. The added psychological benefit that accompanies a therapy with a novel mechanism should also be noted; one which patients and clinicians will welcome given the limited treatment options in this disease area (as discussed in Section B.1.3).

The pivotal trial supporting this indication, MAVORIC, is the largest clinical trial of systemic treatment conducted in MF and SS patients to date.[60] In particular, MAVORIC provides the only compelling evidence from a Phase III trial for SS patients, who constituted >40% of the total patient population. MAVORIC is also the first pivotal trial in CTCL to use PFS as the primary endpoint, which was assessed according to the criteria described by Olsen et al., capturing PFS duration based on the composite global response assessment of each disease compartment (skin, blood, lymph nodes and viscera).[18] Importantly, this allows for assessment of the highly leukemic aspect of the disease in SS patients, which would otherwise not be considered. Furthermore, by incorporating the individual results from the various aspects of the disease, the MAVORIC study results may more broadly reflect the overall impact of new therapies compared with results from previous clinical trials, which have primarily focused on assessment of skin alone, and do not take into account the impact on systemic disease (blood, lymph nodes and viscera).

In a disease that causes disfiguring lesions, debilitating pruritus and the psychological distress of living with an incurable cancer, the ability to positively affect a patient's quality of life is of great importance. During MAVORIC, mogamulizumab demonstrated greater improvements in quality of life compared with vorinostat[60], providing a beneficial impact on the symptoms and functioning of patients suffering from this debilitating orphan disease as well as wider effects on family members and caregivers, who are often affected by a significant impairment in quality of life due to the disease. Furthermore, mogamulizumab provides hope to patients and caregivers by offering an effective treatment option with a tolerable safety profile.

B.2.13. Interpretation of clinical effectiveness and safety evidence

Patients with advanced MF and SS represent an orphan population with a substantial disease burden and limited treatment options. The efficacy of mogamulizumab in patients with MF or SS who have previously received at least one prior therapy has been demonstrated in the pivotal Phase III RCT, MAVORIC, the largest trial in CTCL with a high proportion of advanced, heavily pre-treated patients.[60] Post-hoc analysis of PFS was more than tripled with mogamulizumab compared to vorinostat (9.4 versus 3.1 months, respectively) resulting in a HR of 0.43 (95% CI: 0.31, 0.58; p<0.0001).[61] Similar results were observed in the ITT population with PFS more than doubling from 7.7 months with mogamulizumab to 3.1 months with vorinostat (HR: 0.53; p<0.0001).[60]

In the advanced population, the analysis of response rate results favoured mogamulizumab over vorinostat.[61] The overall ORR for mogamulizumab was ten-times greater than that observed for vorinostat (30% versus 2.9%; p<0.0001). Furthermore, the response to mogamulizumab remained high despite the heavily pre-treated nature of patients in the MAVORIC trial, the majority of whom had failed two or more prior therapies. It should also be noted that the clinical response to mogamulizumab was consistently high regardless of the number or type of prior systemic therapies received.[88, 89]

In the total population, the ORR for mogamulizumab was almost six-times greater than for vorinostat (28.0% versus 4.8%; p<0.0001), time to response for mogamulizumab was nearly 2 months shorter than that observed for vorinostat (3.3 versus 5.1 months, respectively), and the DOR was 5 months longer overall (14.1 versus 9.1 months, respectively).[60] The overall results suggest that not only did a greater proportion of patients respond to mogamulizumab compared with vorinostat, but also that these patients benefitted from a faster and more sustained response.

Disease in the skin and blood compartments have been linked to reduced life expectancy for patients with CTCL.[2, 19] When focusing on the response in these individual compartments, ORR for mogamulizumab in both the skin and blood compartments was significantly greater than vorinostat in the total population ([redacted]).[67] It is important not to underestimate the importance of an effective

treatment which can target these aspects of the disease, in particular the leukemic aspect of advanced and SS patients due to malignant T-cell circulating between the blood and skin.

Although OS data in MAVORIC is immature and heavily confounded, it is plausible to suggest an OS benefit with mogamulizumab given the extent of the response results and the implications to the patient's survival. As significant improvement was seen in the blood and skin compartments, it is logical to assume this would translate into improved survival for these patients. This is supported by clinical opinion which notes that the OS predicted with mogamulizumab (presented in Section B.3.3.1) is logical due to the higher response rate and longer duration of response,[49] and the crossover adjusted OS results, that show an important improvement in OS with mogamulizumab compared to vorinostat (Section B.3.3.1). Furthermore, the breakdown of the skin barrier increases the risk of infections which can become untreatable and lead to death.[6] Indeed, for SS patients and advanced MF patients, opportunistic infections due to the compromised skin are the most common causes of disease-related death.[5] Therefore, it is expected that mogamulizumab is not only able to improve OS through the improved skin and blood responses, but also by reducing sepsis infections which can lead to death.[5, 6]

TTNT represents an important endpoint in assessing the direct benefit to a patient beyond survival outcomes by representing a period of remission in which a patient can expect to have symptoms controlled while still receiving treatment. Furthermore, TTNT implies a durability of response that is particularly meaningful in diseases such as MF and SS, where progression may be subtle and driven by development of symptoms.[63]

A post-hoc analysis revealed that TTNT was almost three times longer with mogamulizumab treatment compared with vorinostat (11.0 versus 3.5 months; $p<0.0001$) in the advanced population.[61] In addition, the median TTNT for mogamulizumab reported in MAVORIC was more than double that reported historically for systemic therapies in MF and SS patients (11.0 versus 5.4 months, respectively).[63] The trend for mogamulizumab to extend time to between treatments was also seen in the time to subsequent treatments suggesting that the use of mogamulizumab is able to change the natural course of the disease by delaying the

need for subsequent treatments, a key outcome of importance for patients. Mogamulizumab is therefore able to reduce the burden on patients, carers and healthcare systems as patients can expect to be free of symptoms and potentially able to return to normal living and daily activities.

Treatment with mogamulizumab also improved QoL relative to vorinostat across a range of physiological and psychological domains in the total population.[65, 72] Cancer-specific symptoms associated with a patients' physical well-being (e.g. lack of energy, nausea, pain and feeling ill) and emotional life (feeling sad, nervous and losing hope) were improved significantly with mogamulizumab compared to vorinostat.[72] Mogamulizumab patients also reported [redacted] in mobility, self-care, usual activities, and anxiety compared to those treated with vorinostat.[65] Importantly, treatment with mogamulizumab significantly improved disease-specific skin related symptoms (skin pain, burning, stinging and bleeding and itching) compared to vorinostat;[72] these symptoms are key areas of burden and poor QoL for patients and thus improvements in these areas are of primary importance to patients. Along with reducing the physical burden, the visual improvement of the skin (as depicted in Figure 7) can reduce the emotional burden associated with the disease, greatly improving the QoL of patients.

Mogamulizumab demonstrated a tolerable and manageable safety profile in patients with MF and SS, and despite the duration of mogamulizumab therapy being double that of vorinostat, mogamulizumab demonstrated a comparable safety profile. Furthermore, the incidence and severity of TEAEs in patients treated with mogamulizumab did not vary with increasing levels of mogamulizumab exposure, allowing patients to safely remain on treatment for longer. The most frequently reported TEAEs seen with mogamulizumab were infusion-related reactions, infection and drug skin eruption, which are all known to be associated with mogamulizumab or the underlying disease.[60]

Overall, mogamulizumab treatment resulted in a clinically and statistically superior effect on PFS, ORR, and TTNT in patients with advanced stage MF and SS who have previously received at least one prior therapy. Importantly, this superior efficacy response with mogamulizumab treatment was observed in patients whose disease failed or ceased to respond to other available treatments. In addition,

mogamulizumab is a well-tolerated treatment option, demonstrating a predictable, manageable and acceptable safety profile with no detriment to quality of life.

B.2.13.1. Strengths and limitations of clinical evidence base

The MAVORIC study is the largest clinical trial conducted in patients with CTCL to date, enrolling a total of 372 patients. MAVORIC is the only Phase III CTCL study to include SS patients (45% of the trial population) and also includes a substantial proportion (77%) of advanced stage patients. MAVORIC is a head-to-head RCT versus an active comparator, vorinostat, the only available drug with data for the SS population.

Vorinostat is not licensed for use in Europe, therefore its use as a comparator in MAVORIC meant that patients recruited to the study were given access to a previously unavailable therapy option, resulting in the large patient numbers attained in this trial. The comparison of the vorinostat arm of the MAVORIC study and the physician's choice arm (methotrexate or bexarotene i.e. UK standard treatments) of the ALCANZA study, which showed overlapping PFS curves, and similar ORR rates in the skin compartment for vorinostat in the MAVORIC study and bexarotene in its pivotal phase II trial suggests that vorinostat is suitable proxy for current standard of care in England (presented in Section B.2.9). This has also been confirmed by clinical expert opinion.[49] It should be noted that not using vorinostat as a comparator would have presented a number of challenges in this heavily pre-treated population who had become refractory to the UK standard of care therapy options. Blinded assignment using UK standard of care would have resulted in patients being re-treated with therapies they had previously relapsed on, which may have deterred patient entry into the study. Furthermore, using an unlicensed comparator and/or re-challenging with agents used previously may have presented ethical challenges. EMA has accepted vorinostat also as a comparator. The MAVORIC study assessed patients using a global composite response criterion that takes into account all potentially affected disease compartments;[18] whereas historically, response rates were based on responses in the skin only. Assessment of all compartments has prognostic utility in CTCL as blood, lymph node and viscera involvement result in additional morbidity beyond the observable skin disease and reduced survival. Therefore, although mogamulizumab response rates were consistent with those

reported for current systemic therapies (approximately 30%),[50] this is not an accurate comparison as response results have historically been based on a far less rigorous method of assessment. Results from the SLR (conducted in July 2019) found that prior to 2017, only one study reported results in line with updated compartment-based response criteria.[66] As such, any comparison between mogamulizumab and current treatments are highly likely to be incomplete and underestimate the benefits of mogamulizumab, particularly when considering the efficacy of mogamulizumab in patients with blood involvement (advanced MF and SS patients).

Importantly, MAVORIC was the first trial in CTCL in which PFS was the primary outcome. In addition, PFS assessment was based on the above-mentioned global composite response, thus providing a more comprehensive assessment than used in previous CTCL trials. As discussed earlier, investigator assessed PFS was chosen as the primary endpoint over PFS by independent review, which was assessed as a secondary endpoint. Although investigators were not blinded, they were able to physically examine the patient, which was not the case for the blinded independent reviewers. Treatment with mogamulizumab is associated with a rash which can be mistaken for worsening of the skin condition due to the disease; this is not the case for vorinostat. Blinded independent reviewers could not be told the nature of any changes in skin measures (mSWAT), so they were not able to determine the source cause of a rash (i.e. treatment or disease related); revealing this information would have nullified the blinded review. As such, the independent review is not considered a reliable an assessment of PFS and therefore was not chosen as the primary endpoint. Instead, the review was carried out to ascertain any potential bias in the assessment of the primary endpoint; however, based upon outcome, none was detected.

Furthermore, OS was not pre-specified as a primary objective within the trial and thus the study was not powered to detect differences in OS. This is due to several factors confounding the assessment of OS, notably the need for one-way crossover, and the relatively long overall life span of the patient population, during which many events unrelated to CTCL disease can occur. As such, OS was pre-specified as an exploratory endpoint only. Nevertheless, due to the highly positive results seen for both PFS and ORR, particularly in the blood and skin response, and as previously

noted, a survival benefit seen after cross-over adjustment with mogamulizumab is logical; this is further discussed in Section B.3.3.1.

The response to vorinostat during MAVORIC was lower than previously reported.[90] As patients randomised to the vorinostat arm received a median of 84 days exposure with a dose intensity >95%, and considering the median time to response in registration trials was 56 days, insufficient exposure was not deemed to be the cause. In the MAVORIC study, response rate was based upon the global composite response assessment criteria whereas vorinostat activity reported in the registration trials was measured primarily in the skin compartment only. In the MAVORIC study, the skin only response rate for vorinostat was 12.4%, around half that reported in the registrational trial. Potential reasons include advances in, and increasing familiarity with, skin assessment techniques, changes in assessment criteria, and very large differences in size and number of sites and design of the Phase III versus Phase II studies. Of note, studies of vorinostat identified in the SLR suggest a similarly high proportion of advanced patients, so disease stage is not thought to affect levels of response in MAVORIC.

Finally, patients in the MAVORIC study were generally reflective of patients presenting for treatments expected to receive mogamulizumab in NHS clinical practice. Although three NHS sites in England were included in MAVORIC, it was important to assess generalizability of the overall population compared to UK clinical practice. Therefore, to further validate the generalizability of the MAVORIC trial population to English clinical practice, comparisons were made to the **PRO**spective **C**utaneous **L**ymphoma **I**nternational **P**rognostic **I**ndex (PROCLIPI) dataset.[91] The PROCLIPI study is a web-based observational data collection system which aims to develop a prognostic index in cutaneous lymphoma by collecting MF and SS data worldwide at diagnosis and measuring against survival.[91] It has been ongoing since 2015 and aims to develop a prognostic index for MF and SS. To date it has recruited over 1,000 patients from 44 specialist centres worldwide, representing the largest database in this disease area, a feat which should not be underestimated considering the rarity of the disease.[76] Each centre has collected prospective data at diagnosis, annually, and at stage progression, and these will be used to determine the prognostic significance of mSWAT, alongside other potentially important factors,

with the aim of developing a prognostic index to preselect patients with a worse prognosis who require more aggressive therapies.[76]

The first step in using the PROCLIPI database was to understand if there was a sizeable group of patients in PROCLIPI who are demographically and prognostically similar to the patients in MAVORIC. To this end, the eligibility criteria of the MAVORIC study was applied to the PROCLIPI cohort by the PROCLIPI analysts. As some of the inclusion/exclusion criteria variables from the MAVORIC study were not captured by the PROCLIPI dataset, judgement was needed in some cases.

After this was completed, the PROCLIPI analysts summarized the baseline characteristics of these patients. From an initial sample of the 1,350 patients currently in the PROCLIPI database, 178 patients met MAVORIC's eligibility criteria. Baseline characteristics of these patients are presented in Appendix P alongside the baseline characteristics of the MAVORIC population. As shown in Appendix P, the MAVORIC patients are generally comparable to the PROCLIPI population, supporting the view that the MAVORIC population is generalizable to UK clinical practice. In addition, the PROCLIPI dataset also provides a potential ongoing source of comparative evidence that may be useful for future work within CTCL.

In addition to the PROCLIPI dataset, the Haematological Malignancy Research Network (HMRN) dataset was also assessed for relevance in comparing MAVORIC patients to those patients with MF and SS who present in UK clinical practice. The HMRN is a population-based cohort comprising a total of 3.8 million people and was established in 2004 to provide robust, generalizable data to inform clinical practice and research. The HMRN is a collaboration between researchers in the Epidemiology & Statistics Group (ECSG) at the University of York, a unified Clinical Network operating across 14 hospitals, and an integrated Haematological Malignancy Diagnostic Service (HMDS) at St James's Hospital in Leeds (https://www.hmrn.org/about/info). The HMRN dataset holds records from 2004 onwards and currently documents 120 CTCL patients and all their treatments. Unfortunately, a number of legal and ethical issues prevented the dataset from being used within this submission: the progression data available in HMRN is very different to that in the MAVORIC study, a sharing agreement is not in place between HMRN and the manufacturer making data-sharing complicated and, as HMRN is an

academic institution, non-commercial priorities meant the relevant data was not available in time.

In addition, the Dutch Cutaneous Lymphoma Working Group (DCLWG) database was also assessed for feasibility of conducting a matched cohort analysis to serve as historic control for MAVORIC. When assessing the plausibility of this approach it was found that time to death analyses would be possible although most endpoints, such as time to progressive disease, time to next systemic therapy and next systemic therapy received, required additional, manual, medical record review. Also, no information on quality of life was available in the current dataset or through medical records and would thus require prospective data collection. Importantly, a breakdown of patient characteristics was not available to the level required to match patients to the MAVORIC cohort and so this analysis was not deemed feasible.

MF and SS represent an orphan disease which causes disfiguring lesions, debilitating pruritus and psychological stress that dramatically affects the QoL of these patients.[10] There is a substantial medical need to develop new therapies for CTCL (including MF and SS) that can target all disease compartments and provide a durable response in the treatment of this orphan disease. The treatment landscape for MF and SS patients has been static for some time, with patients commonly cycling between therapies, which results in a shortened disease-free period each time. The MAVORIC study provides an appropriate base to inform the assessment of clinical and cost-effectiveness of mogamulizumab and highlights the potential of this treatment to significantly delay disease progression, reduce disease burden and improve the overall QoL in previously treated MF and SS patients who are clinically ineligible for or refractory to treatment with BV.

B.3. Cost effectiveness

- Due to the lack of published data, a de novo cost-utility model was developed comparing mogamulizumab to Established Clinical Management (ECM) for adults with advanced MF or SS cutaneous T-cell lymphoma following at least one prior systemic therapy who are ineligible for, or refractory to, treatment with BV
- The model structure is based on the standard partitioned survival analysis approach, with the possibility of patients receiving aSCT, the only potentially curative treatment. Due to its unique mechanism of action, disease control or time to next treatment was used in place of progression determining the health states, i.e. next-treatment-free survival (NTFS) instead of PFS
- Efficacy and safety results with the vorinostat arm of the MAVORIC trial were used as a proxy for ECM, based on comparison with the physician's choice arm (methotrexate or bexarotene i.e. UK standard treatments) of the ALCANZA study, the bexarotene Phase II study of 193 CTCL patients and expert opinion
- The analyses below include the simple upfront [redacted] offered by Kyowa Kirin
- Efficacy and safety data were based on the MAVORIC trial
  - Time to event data was extrapolated where follow-up was not complete according to the recommendation in the NICE Technical Support Document 14
  - As the OS data in the MAVORIC trial are also heavily confounded by crossover design (72.6% of patients switched to mogamulizumab from the vorinostat arm), crossover adjustment was conducted with all appropriate methods
  - Clinical plausibility was assessed using published observational data, UK Hospital Episode Statistics data and leading NHS consultants experienced with the treatment and care of MF and SS patients in an NHS England setting
  - Proportion of patients receiving aSCT after subsequent treatments were from MAVORIC trial, however as it did not allow for aSCT after current treatment as is used in current clinical practice, it was supplemented with data from a short clinician survey
- Patient utilities were estimated from the EQ-5D data from the MAVORIC trial for the main health states and were taken from the NICE TA577 for additional health states.
- The intense schedule of dressings, the visible nature of the disease places a longer and higher burden on the carers. As a result, it is important to incorporate carers' burden in the model. A vignette study was conducted by Kyowa Kirin to assess carers' utilities, and to avoid conferring survival benefit on to carers too, a conservative assumption was used to accrue benefit in only the Disease control health state
- Treatment costs were based on publicly available databases. For mogamulizumab, a [redacted] offered by Kyowa Kirin and wastage with dose banding was used. A 24-month stopping rule was assumed for mogamulizumab based on clinical input and benefits determined from MAVORIC trial
- To reduce the uncertainty of the expert opinion-based heath state costs from NICE TA577, Kyowa Kirin has conducted a retrospective study in the HES database following all UK MF/SS patient for 10 years to estimate inpatient/outpatient costs. Community based costs were not available from the database and therefore, were based on the NICE TA577 using ERG's preferred scenario. Additional costs were taken from the literature
- Model structure, assumptions and inputs were all validated through in-depth clinical interviews

- Using the submitted [redacted] for mogamulizumab, mogamulizumab led to a QALY gain of 2.83 and a discounted incremental cost of £95,577. Most of the incremental costs were:
  - [redacted] due to ECM including mostly cheaper generic treatments or short-term interventions and
  - [redacted] due to the high cost of MF/SS in the community setting due to the intense schedule of dressings and other wound care.
- This resulted in an incremental cost-effectiveness ratio (ICER) of £33,819/QALY with an [redacted] on mogamulizumab
- While there are important uncertainties in the analyses, the results were stable with the ICERs of almost all of the scenarios and one-way sensitivity analyses falling between £30,000-£40,000 per QALY. The only scenarios that have ICERs outside this range (£40,000-£50,000 per QALY) and are clinically implausible. The probabilistic analyses showed the probability of mogamulizumab being cost-effective at the £30,000/QALY threshold is 21.8%, while at the £50,000/QALY threshold 97.8%
- In an orphan disease with a high unmet need, with a [redacted] offered, the ICER for mogamulizumab is around the NICE threshold in all plausible scenarios

B.3.1. Published cost-effectiveness studies

A systematic search in June 2019 for economic evaluations of treatments for relapsed or refractory CTCL, documented in Appendix G, identified no published cost-effectiveness analyses of mogamulizumab to treat MF or SS.

The cost-effectiveness analysis of BV for previously treated, advanced CTCL supporting the TA577 company submission, is summarised in Table 20. Though as described in Section 1.3, the proposed position of mogamulizumab in the treatment pathway does not overlap that of BV; it should be noted that when on treatment, patient pathways are similar including the use of aSCT.

A review of the TA577 analysis highlights the unavoidable limitations of contemporary lifetime cost-effectiveness analyses in CTCL. Due to rare nature of the disease, available data is based on smaller studies with the associated limitations; the lack of treatment options for these patients leads to the ethical need for cross-over within the study design that leads to issues in the interpretation of the survival directly from clinical trial; there is uncertainty in disease management costs for these patient as there is a lack of well reported data within the literature; there is a lack of data on carers' utilities despite the recognised high carers' burden.

For BV, a partitioned survival model structure was developed, based on patient's movement between pre-progression with the option (based on response) for aSCT in

appropriate patients, post-progression and death. Though redacted, lifetime cost and QALY estimations were clearly highly uncertain from advanced patient subgroup data of the pivotal ALCANZA study, in which (i) OS, was not prespecified , (ii) treatment crossover was permitted within the study, and the cross-over analyses was criticised as it 'may have been conducted incorrectly' and (iii) a key proposed benefit in allowing subsequent allogenic STC (aSCT) was not captured. Additional uncertainties included treatment duration when eligible for aSCT, quality of life implications for patients and carers, modelling of overall survival for people not having aSCT and the disease management costs.

The routine-use recommendations for BV in CD30-positive CTCL patients were made despite, and in the context of, substantial decision uncertainty in particular cost of treatment in the post-progression health state, rate of aSCT following BV, the long-term survival benefits with BV and despite the lack of data for BV in SS patients. For those high unmet need CTCL patients who have since benefitted from BV, this recommendation was vital.

Table 20: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA577[30]	2018–19	A cohort-level, discrete-time model described as a 5-state partitioned survival model by the company, using a 1-week cycle length and 45-year time horizon.	Adult patients with 'advanced' CTCL [MF stage ≥IIB, SS, and all pcALCL]; clinical effectiveness data from n=95 patients with MF stage ≥IIB or pcALCL from the total n=131 enrolled. (n=49 BV patients median baseline age 62 years, range 31-82 years; n=46 PC patients median baseline age 54 years, range 25-83 years).	Redacted information	Redacted information	Results from ERG sensitivity analyses ranged from an ICER BV of £58,516 per QALY gained, to brentuximab vedotin being dominant (less costly and more effective). (FAD 3.25). The committee recalled that the assumptions which best reflected clinical practice [produced an ICER for BV versus current care of] £29,613 per QALY gained. [On balance, the committee] concluded that the most plausible ICER for brentuximab vedotin compared with methotrexate or bexarotene was less than £30,000 per QALY gained, which is within the range normally considered an acceptable use of NHS resources. (FAD 3.26)

Key: BV, brentuximab vedotin; CTCL, cutaneous T-cell lymphoma; ERG, Evidence Review Group; FAD, Final Appraisal Determination; ICER, incremental cost-effectiveness ratio; MF, mycosis fungoides; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PC, physician's choice; pcALCL, primary cutaneous anaplastic large cell lymphoma; QALY, quality-adjusted life year; SS, Sézary syndrome; TA, Technology Appraisal.

B.3.2. Economic analysis

The following section describe the de novo economic model developed in line with the NICE Reference case and the decision problem described in Section B.1.1. The analyses below include the simple [redacted] offered by Kyowa Kirin.

B.3.2.1. Patient population

As described in Section B.1.2, the EMA marketing authorisation for mogamulizumab, in line with the inclusion/exclusion criteria of the MAVORIC trial,[60] is 'for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy'.

The advanced patients (stage ≥IIB MF and all SS patients), as the analysis of the MAVORIC trial has shown stand to benefit relatively more from treatment with mogamulizumab, are in line with the NICE TA577 and would reflect better to future clinical practice (See Section B.2.7),[30] the patient population in the economic evaluation was restricted to those with advanced disease in the base case. Since all SS patients are, by definition, advanced (See Section B.1.3), this includes from the MAVORIC trial all SS patients and MF patients with stage IIb disease or higher. Approximately, 80% of the patients in MAVORIC had advanced stage ≥IIB disease (including blood involvement). This definition is in line with clinical practice,[49] and with the definition used for advanced patients in the NICE TA577 for brentuximab vedotin.[30] The intention to treat (ITT) population was included in a scenario analysis.

Based on in-depth interviews with clinical experts, for the population BV is used (high grade, bulky, transformed, CD30 positive MF) mogamulizumab would not be used.[49] Mogamulizumab would be used for patient's clinically ineligible for, or refractory to, BV. Thus, the patient population for this cost-effectiveness analyses is:

- Adults with advanced MF or SS cutaneous T-cell lymphoma following at least one prior systemic therapy who are ineligible for, or refractory to, treatment with BV

This population represents the marketing authorisation, the pivotal trial, the clinical practice in the UK and also the patients with the greatest unmet need.

B.3.2.2. Model structure

Due to the lack of published economic analyses evaluating mogamulizumab, a de novo economic model was developed to assess the cost-effectiveness of mogamulizumab in the treatment of adult patients with advanced MF and SS who have received at least one prior systemic therapy and are ineligible for, or refractory to, treatment with BV. The model was developed based on:

- The MAVORIC trial,[60] which the trial conducted in MF and SS and includes patients from the UK (see Section B.2.3),
- An economic systematic literature review (see Section B.3.1 and Appendix G),
- Data from the UK Hospital Episodes Statistics (HES) database for patients with at least one diagnosis code for SS and MF (see Section B.3.5.20),
- Extensive consultation with clinical experts through a short survey, five in depth interviews and one Advisory board meeting (see Appendix U).

The model structure is based on the partitioned survival analysis (PartSA) approach, similarly to TA577. This technique is commonly used in modelling oncology, and is appropriate for capturing progressive, chronic conditions which are described with clinical outcomes requiring an ongoing, time-dependent risk, such as progression and death.[92, 93] This approach is also in line with prior NICE TA in MF/SS.[30]

However, in line with the previous NICE TA in MF/SS and given the novel mechanism of action, two changes were made to the traditional PartSA approach:

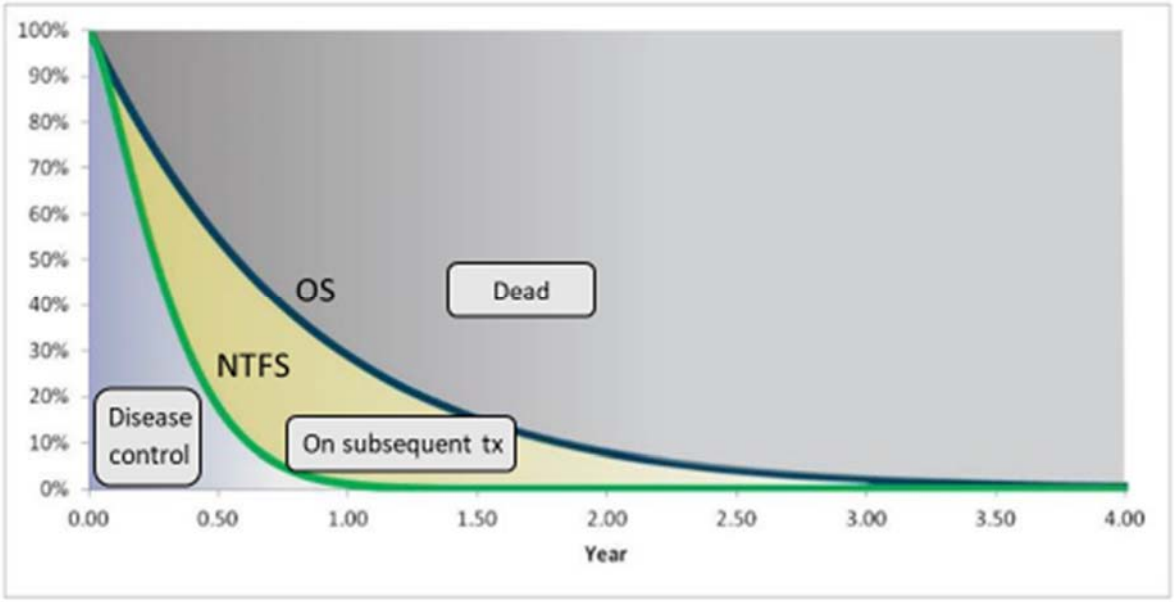
- Inclusion of the potential for patients to receive the potentially curative treatment of allogeneic stem cell transplant (aSCT) as seen in the NICE TA577,[30] and
- The use of disease control or time to next treatment (TTNT) in place of progression determining the health states

Due to its mechanism of action (see Section B.1.2), patients can experience benefit from mogamulizumab after stopping treatment and after progression as defined by the trial protocol as described in Section B.2.3. This can be seen in the analyses of the treatment-free period in the MAVORIC trial using TTNT (see Section B.2.6.4).

In MF and SS, disease control is crucial, as the symptoms drive the changes in patients' quality of life, resource utilisation and the changes in treatments. PFS, an

important clinical outcome, is measured using a complex, rigorous definition of response, a global composite response score, based on responses (complete and partial) in each of four compartments (skin, blood, lymph nodes, and viscera). It is very useful to determine treatment success in clinical trials; however, it is less useful to track changes in quality of life and costs.[49] TTNT, another measure of clinical benefit, is more closely aligned with symptoms and disease control, and as a result is a better proxy not only for treatment changes, but also for quality of life and resource utilisation, thereby, for determining health states. Therefore, health states in the model were defined based on disease control and the need for new treatments, i.e. instead of PFS, next-treatment-free survival (NTFS) defined as time to next treatment or death was used (Figure 18). In scenario analyses, the effect of using the more traditional PFS was explored.

Figure 18. Partitioned survival analysis (PartSA) approach

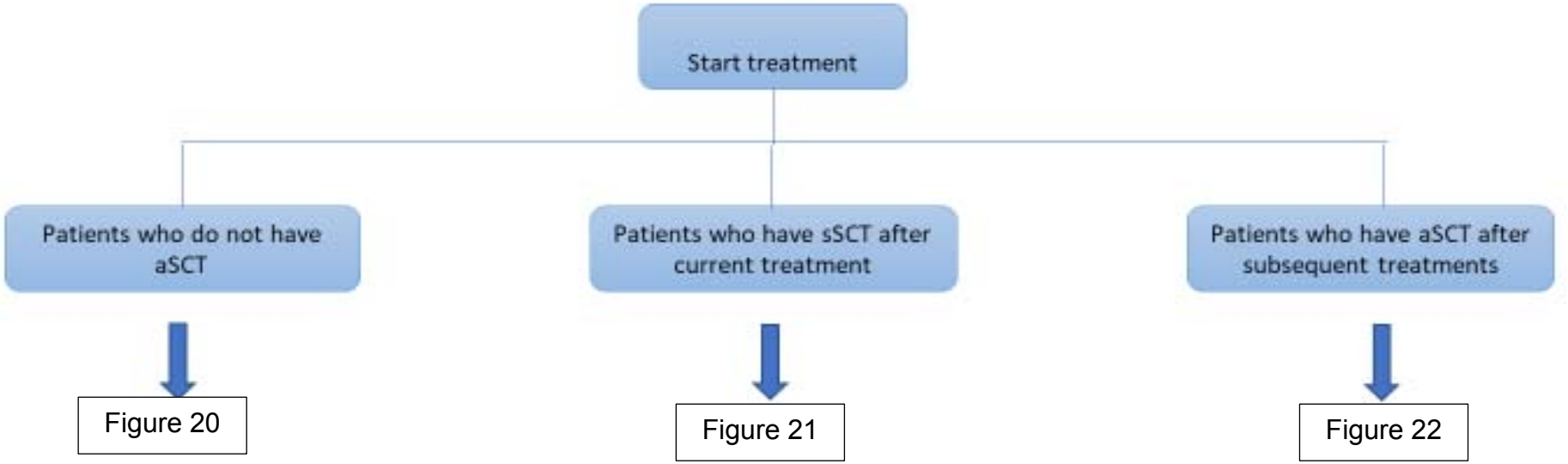


While currently available treatment options are aimed at disease control, BV (recommended by NICE TA577 in 24 April 2019)[30] can be used to bridge to aSCT which can result in prolonged remission, and even potential cure. Mogamulizumab similarly can result in bridging to aSCT in a smaller, but important portion of patients. Bridging to aSCT can happen after good partial response (PR) or complete response (CR) in any line of treatment, if the patients are eligible. That means, patients have the potential to receive aSCT after achieving CR or good PR on mogamulizumab or established clinical management after the required washout period, but also after

achieving CR or good PR on subsequent treatments. Since aSCT is an important part of the patients' pathway and it has a very important effect on both costs and health outcomes, it is important to include in the cost-effectiveness modelling, similarly to NICE TA577.[30] To take into account differences between these patient pathways, the economic evaluation comprises of three separate patient pathways represented by three PartSA models running in parallel (see Figure 19):

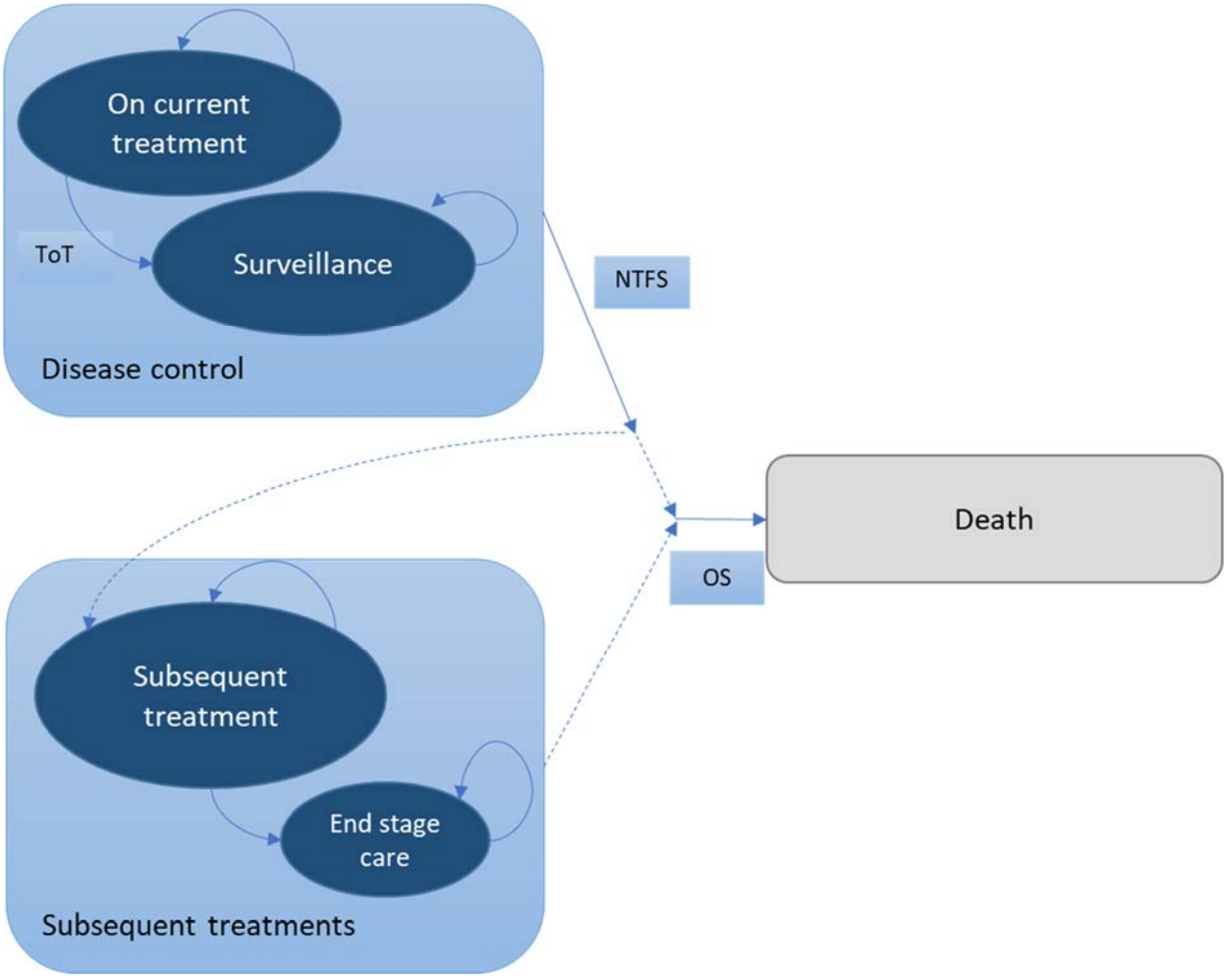
- patients who do not undergo aSCT,
- patients who undergo aSCT after the current treatment, and
- patients who undergo aSCT after subsequent treatments.

Figure 19: Three parallel model structures for three patient pathways



The model structure for patient who do not have aSCT is presented in Figure 20. All patients start in the 'Disease control' health state receiving their current treatment. In any cycle, patients may stop treatment. If their symptoms do not necessitate starting a new treatment immediately, they may remain in the 'Disease control' health state and enter a treatment-free period, i.e. 'Surveillance' health state. Eventually patients require subsequent therapies including symptomatic care and increased monitoring due to the progression of their disease. The last 6 months of life, similarly to the NICE TA577,[30] were also tracked separately to account for the increase in resource utilisation and reduction in quality of life. Patients may die at any time point. This structure represents the standard PartSA with disease control instead of progression.

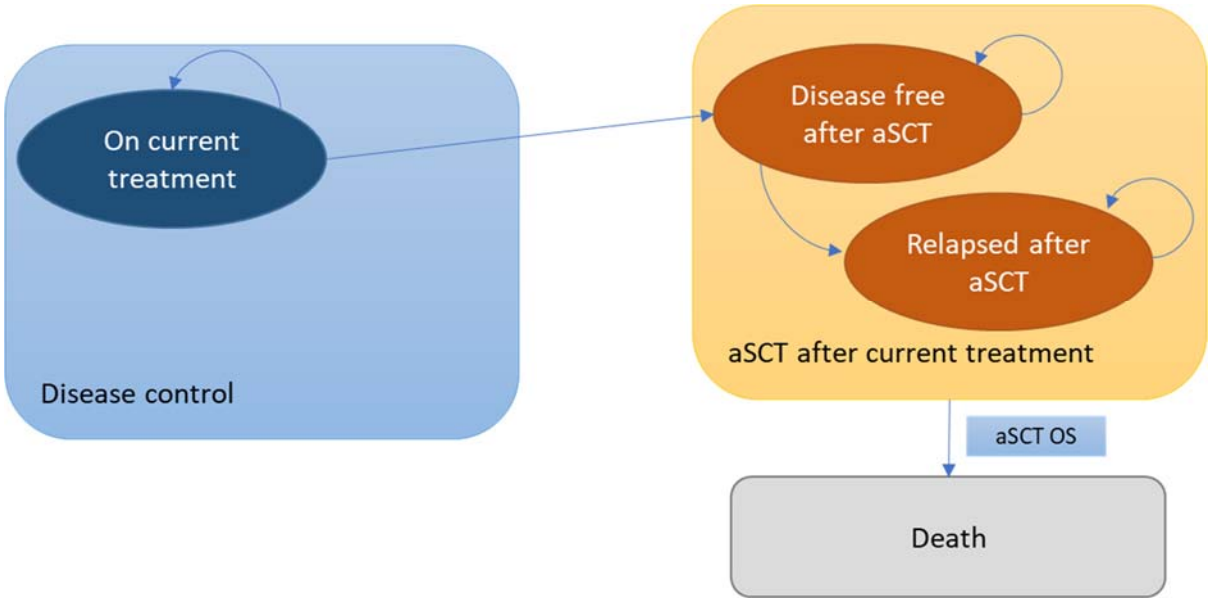
Figure 20: Model schematic for patients who do not have aSCT



Key: ToT, time on treatment; NTFS, next treatment-free survival; OS, overall survival.

Figure 21 describes the pathway for patients who undergo aSCT after their current treatment. These patients also start in the 'Disease control' health state receiving their current treatment (mogamulizumab or current UK practice (Established Clinical Management [ECM]) until a pre-specified time point when they are scheduled to receive aSCT. Patients in the mogamulizumab arm require a 50-day wash-out period,[13] therefore the aSCT was assumed to take place 7 weeks after the specified time point. No such wash-out period was required for patients in the ECM arm. After aSCT, same as in NICE TA577,[30] patients may experience a disease-free period or they may relapse. Patients may also die at any time point following their aSCT. Thus, after the decision-tree, these patients also follow the traditional PartSA with DFS and OS.

Figure 21: Model schematic for patients undergoing aSCT after their current treatment

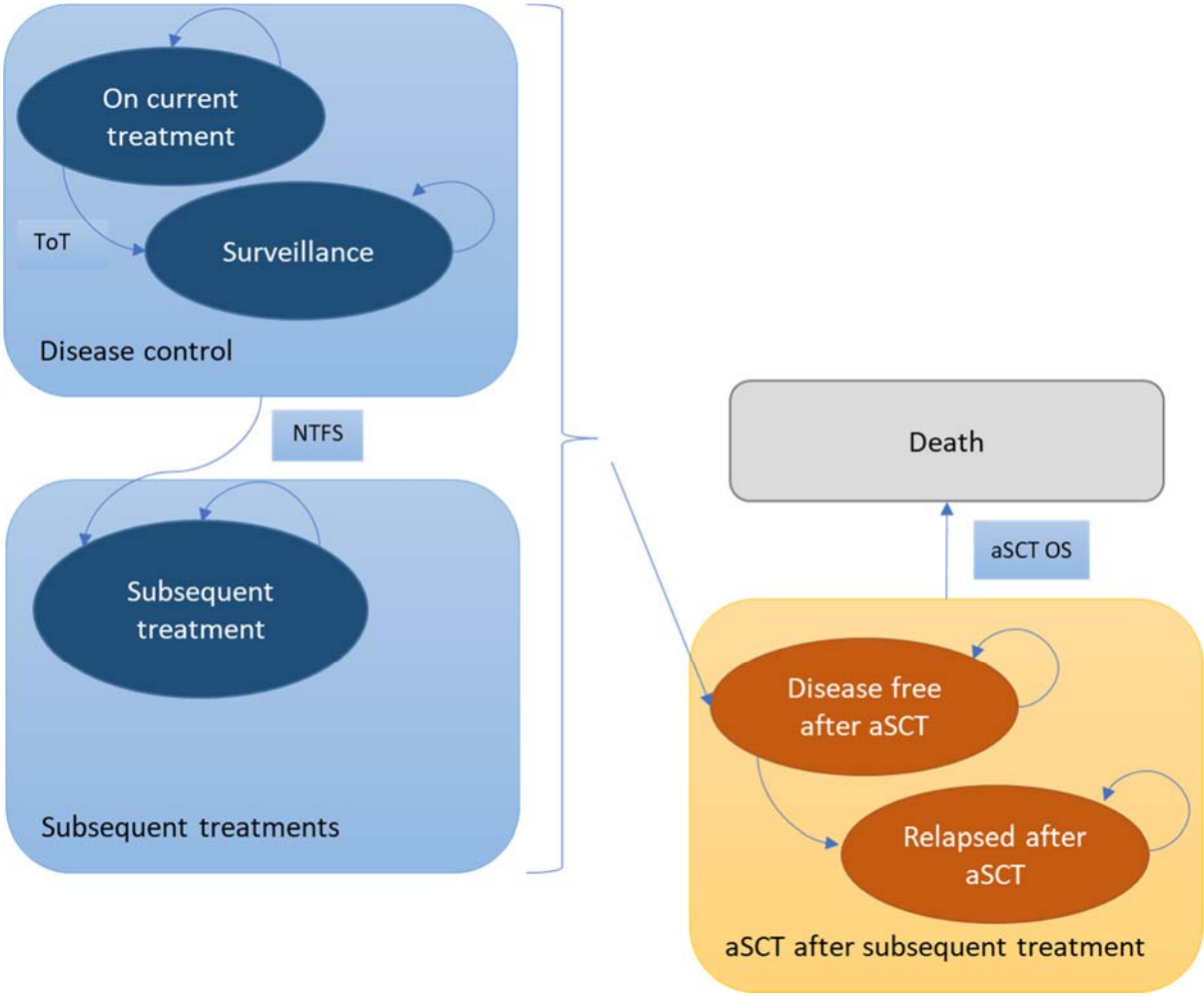


Key: aSCT, allogenic stem cell transplant; OS, overall survival.

Patients who undergo aSCT after a subsequent treatment follow a similar pathway to reach the 'Subsequent treatment' health state as those who do not undergo aSCT, i.e. they receive treatment ('On current treatment'), they may have a treatment-free period while their disease is still controlled ('Surveillance'), then receive a subsequent treatment ('Subsequent treatment') (see Figure 22). At a pre-specified time-point all patients in the model move to the aSCT health state. After aSCT, again

same as in the NICE TA577,[30] patients may experience a disease-free period, or they may relapse. Patients may also die at any time point following their aSCT.

Figure 22: Model schematic for patients undergoing aSCT after a subsequent treatment



Key: ToT – time on treatment, NTFS – next treatment-free survival, aSCT – allogenic stem cell transplant, OS – overall survival

The above described model structure differs from the one used in TA577 in two aspects: it assumes that loss of disease control drives changes in patients' quality of life, resource utilisation and the changes in treatments rather than progression, and, in line with clinical practice in the UK, it allows for patients to receive aSCT at two time-points (after current treatment as well as after a subsequent treatment).

The model uses weekly cycles to allow tracking the changes in mogamulizumab's administration schedule over a 30-year time horizon. A comparison with the assumptions used in TA577 is presented in Table 21.

The proportion of patients in each health state was determined by the appropriate survival curves and the proportion of patients receiving aSCT. Half-cycle correction was not included due to the short cycle length (one week). Both costs and health outcomes were discounted by 3.5% as described in the NICE Reference case.

Table 21: Features of the economic analysis

	Previous appraisals	Current appraisal	
Factor	**TA577**	**Chosen values**	**Justification**
Time horizon	45 years	30 years	Maximum life expectancy of patients based on the clinical expert interviews[49]
Treatment waning effect?	Not included explicitly	Included implicitly in the independently fitted survival curves	The independently fitted survival curves take waning effect into account. In line with previous TAs
Source of utilities	Pre- and post-progression: ALCANZA trial End of life: Swinburn et al., 2015 After SCT: Van Agthoven et al. 2001	Disease control and On subsequent treatment: MAVORIC trial End of life: Swinburn et al., 2015 After SCT: Van Agthoven et al. 2001	Utilities were available from the MAVORIC trial, thus, to be consistent with the efficacy and safety results, they were incorporated Utilities from the ALCANZA trial were included in scenario analyses
Source of costs	Expert opinion	Inpatient and outpatient costs: UK HES database Community care: Resource use from NICE TA577 (values accepted by the Committee) updated with current unit costs	As previous costs were based on expert opinion, Kyowa Kirin sought to reduce uncertainty by determining actual inpatient and outpatient costs in the NHS

B.3.2.3. Intervention technology and comparators

The economic evaluation compares mogamulizumab to current clinical practice in the UK (Established Clinical Management [ECM]) which comprises a number of treatments currently in use in England and Wales for patients with advanced MF and SS.

Mogamulizumab is implemented in the model as per its marketing authorisation. The recommended dose is 1 mg/kg mogamulizumab administered as an intravenous infusion. 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. A 24-month stopping rule has been implemented based on clinical input and benefits determined from MAVORIC trial.

The MAVORIC trial was a head-to-head RCT versus an active comparator, vorinostat; however, vorinostat is not licensed for use in Europe and is not used as standard of care in the UK. Section B.2.9 above had provided evidence that vorinostat is a reasonable proxy for ECM without mogamulizumab with outcomes similar to those observed in the ALCANZA trial's physician's choice arm[75] and the bexarotene phase II pivotal trial.[55] The composition of the ECM arm was determined based on clinical expert opinion through a short survey and in-depth interviews (see Appendix U),[49] while treatment schedules and dosing were determined based on the respective marketing authorisations supplemented by expert opinion. Table 22 details the composition and treatment schedules for treatments included in the ECM arm of the evaluation.

Table 22: Composition of ECM arm

Treatment	Proportion	Treatment schedule and dosing
Methotrexate	[redacted]	25mg, one day per week
Bexarotene	[redacted]	300 mg/m^2 daily
Interferon alfa-2a* (peginterferon)	[redacted]	180 mcg once a week
Gemcitabine	[redacted]	1,000 mg/m^2 on day 1 and 8 of 21-day cycle
CHOP	[redacted]	Cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 on day 1, prednisolone 40 mg/m^2 on days 1-5 of 21-day cycle
Liposomal doxorubicin	[redacted]	20 mg/m^2 twice monthly
Etoposide	[redacted]	120-240 mg/m^2 for five days every month
Prednisolone	[redacted]	40 mg/m^2 on days 1-5 of 21-day cycle
PUVA	[redacted]	2 per week for 14 weeks
ECP	[redacted]	On 2 consecutive days every 28 days
TSEBT	[redacted]	4 per week for 4 weeks (may be repeated once)
Key: CHOP, combination of cyclophosphamide, doxorubicin, vincristine and prednisolone; PUVA, phototherapy UV-A; ECP, extracorporeal phototherapy; TSEBT, total skin electron beam therapy **Note:** *As interferon alfa-2a has been withdrawn from the market and the stores are being used up, it is substituted with pegylated derivatives of interferon alfa (peginterferon).		

BV has not been included among the comparators as it is given to a different patient population (see Section B.3.2.1)

B.3.3. Clinical parameters and variables

The cost-effectiveness model is based on the following clinical parameters and variables (Table 23):

- OS for patients not receiving aSCT: based on patient level data from the MAVORIC trial data for patients with advanced disease, excluding patients who have received aSCT
- Next-treatment-free survival (NTFS): based on patient level data from the MAVORIC trial data for patients with advanced disease
- Time on (randomised) treatment (ToT): based on patient level data from the MAVORIC trial data for patients with advanced disease
- Disease-free survival (DFS) and OS for patients undergoing SCT from the NICE TA577

- Dose intensity including delays and interruptions: based on patient level data from the MAVORIC trial data for patients with advanced disease
- Adverse events (AEs): based on the MAVORIC trial result from the safety population
- PFS: investigator assessed PFS, the primary endpoint in the MAVORIC trial was used in scenario analysis based on patient level data from the MAVORIC trial data for patients with advanced disease
- Proportion of patients receiving aSCT (Described in Section B.3.5.4)

Table 23. Summary of clinical parameters applied in the economic model in the base case

Variable	Treatment	Data source
Overall survival (OS)	Mogamulizumab	MAVORIC trial post-hoc analyses excluding patients with aSCT
	ECM	MAVORIC trial post-hoc analyses for vorinostat adjusted for crossover, excluding patients with aSCT
	aSCT	NICE TA577 using real-world data from the London supra-regional centre
Next-treatment-free survival (NTFS)	Mogamulizumab	MAVORIC trial post-hoc analyses
	ECM	MAVORIC trial post-hoc analyses for vorinostat
Time on treatment (ToT)	Mogamulizumab	MAVORIC trial post-hoc analyses
	ECM	MAVORIC trial post-hoc analyses for vorinostat
Disease-free survival (DFS)	aSCT	NICE TA577 using real-world data from the London supra-regional centre
Dose intensity	Mogamulizumab	MAVORIC trial CSR
	ECM	Assumed same as for mogamulizumab
Adverse events (AEs)	Mogamulizumab	MAVORIC trial CSR
	ECM	MAVORIC trial CSR, assumed same as for vorinostat

Parametric survival analyses of the MAVORIC time-to-event (TTE) NTFS, OS and ToT data are pivotal in informing the proportions of patients in each model health state in each cycle of the base case economic model, as described in Section B.3.2.2.

In line with guidance from NICE DSU 14, six alternative parametric model structures were used to capture and extrapolate data for each TTE outcome of interest: exponential, generalised gamma, Gompertz, Weibull, log-logistic, log-normal.[94] TTE analyses were conducted in R: KM plots were produced using 'survminer' package.[95] The package "flexsurv" was used for parametric survival analysis.[96]

For each TTE outcome, it was assessed whether treatment effect was best captured using a treatment arm covariate in a single parametric model (a "joint" model), or by separate ("independent") models fitted to each treatment arm. Visual inspection of KM data, and diagnostic plots were used, with consideration of the different implicit assumptions of modelling treatment effect as a covariate across different parametric models, as described throughout Section B 3.3.1-3.3.4, and in Appendix V.

Selection of the base case parametric model for each TTE outcome was based on standard criteria, following Technical Support Document (TSD) 14:

- Objective statistical measures of goodness of fit to observed KM data: Akaike information criterion (AIC)[97] and Bayesian information criterion (BIC) statistics[98]
- Visual inspection of goodness of fit to observed KM data
- Visual inspection of diagnostic plots, including log cumulative hazard plots, Schoenfeld residuals plot and quantile- quantile plot

Additionally, the clinical plausibility of extrapolations beyond observed KM data was explored, comparing predictions with the different models to three alternative sources of data:

- Published observational data (described in Section B.3.3.1),
- UK Hospital Episode Statistics data (Appendix Q) and
- The experience of leading NHS consultants experienced with the treatment and care of MF and SS patients in an NHS England setting (described further in Section 3.10 and in Appendix U)

The current section summarises result for the target population. Details of the intention-to-treat population from the MAVORIC trial are reported in Appendix V, and its effect on results assessed scenario analyses.

B.3.3.1. Overall survival excluding patients with aSCT

For OS, all analyses below have excluded patients receiving aSCT, as the OS of the MAVORIC trial could not take into account the survival of these patients due to their longer survival. OS after aSCT was modelled using external data (see Section B.3.3.3).

The MAVORIC study was not powered to detect OS differences between treatment arms. Furthermore, treatment switching, or crossover, from vorinostat to mogamulizumab was allowed for patients if they had received at least two cycles of treatment and showed confirmed disease progression or had intolerable toxicity (grade ≥3 adverse events, excluding inadequately treated nausea, vomiting, diarrhoea, and alopecia), despite dose reduction and appropriate management of side-effects. Therefore, the unadjusted OS data are heavily confounded by consequence of the one-way crossover design: 135 patients (72.6%) of patients switched to mogamulizumab from the vorinostat arm.[67]

In current NHS practice, this patient group cannot switch to mogamulizumab when established clinical management (ECM) fails, thus crossover adjustment is required. According to the NICE DSU TSD 16 both simple and complex methods are available.[99] Simple methods such as censoring or excluding patients who crossover would remove prognostically worse patients from the comparator arm, and as such likely artificially inflate the treatment effect. Therefore, two complex methods were considered: the inverse probability of censoring weights (IPCW) and the two-stage method.

Whilst the rank-preserving structural failure time (RPSFT) approach was also considered as a mean to adjust for treatment switching it was not pursued in detail as it produced a counter-intuitive point estimate (due to the assumption of a time-invariant treatment effect on the HR scale) with considerable uncertainty, and the implausibility of the “common treatment effect” assumption in this setting (see Appendix R for further details).

Inverse probability of censoring weights (IPCW)

The IPCW method weights patients in the control arm according to their probability of switching treatment. This method artificially increases weights for patients with low

probability of treatment switch and decreases weights for patients with high probability of treatment switch. Patients who switch are censored at time of cross-over. Patients in the treatment arm (no switch by design) have weight equivalent to 1.

A key assumption of this method is no unmeasured confounders. If there are any baseline or time-dependent prognostic factor data for mortality that independently predict informative censoring (switching) which were not collected, then the results could be biased. The analysis considered the following characteristics: Progression status, ECOG, Histology (MF/SS), Disease Stage, age > 65 years, adverse events, and region. Detailed information about this method and the assumptions made are detailed in Appendix V.

Figure 23 presents the crossover adjusted KM curves by randomised treatment arm, while Table 24 presents summary statistics for OS in the advanced population using IPCW, with patients receiving aSCT excluded.

Figure 23: MAVORIC OS Kaplan-Meier data, advanced population with IPCW adjustment

Key: KW-0761, mogamulizumab; OS, overall survival; IPCW, Inverse probability of censoring weights.
Note: Patients were censored upon receiving aSCT.

Table 24: MAVORIC OS summary statistics, with IPCW adjustment

Treatment	N	Median (months; 95% CI)	HR (95% CI)
Vorinostat	[redacted]	[redacted]	[redacted]
Mogamulizumab	[redacted]	[redacted]	

Diagnostic plots for these data are included in Appendix V. They suggest that the proportional hazards (PH) assumption does not hold, thus the separate fits were used. Combined AIC and BIC statistics suggest that log-normal and generalised gamma models provide the best fits (Table 25). When considering the separate AIC and BICs, generalised gamma and log-normal provide the best fit for vorinostat and all AIC/BIC were very close for mogamulizumab.

Table 25: AIC and BIC statistics for independently fitted parametric survival models - Advanced disease OS with IPCW adjustment

Model	AIC V	AIC M	cAIC	BIC V	BIC M	cBIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; cAIC, combined AIC; cBIC, combined BIC; IPCW, Inverse probability of censoring weights; M, Mogamulizumab; V, vorinostat.
Note: Patients were censored upon receiving aSCT.

Parametric survival models shown alongside observed data are provided in Figure 24 (within trial fit) and Figure 25 (extrapolated fit) for independent fits. (Results for joint fits are available in Appendix V.)

Figure 24: MAVORIC OS excluding aSCT with IPCW adjustment, advanced population, independent within-trial fits

Key: aSCT: allogeneic stem cell transplant; IPCW, inverse probability of censoring weights; KW-0761, mogamulizumab; OS, overall survival.

Figure 25 MAVORIC OS excluding SCT with IPCW adjustment, advanced population, independent extrapolated fits

Key: aSCT, allogeneic stem cell transplant; IPCW, inverse probability of censoring weights; KW-0761, mogamulizumab; OS, overall survival.

[redacted].

To assess the clinical plausibility of these estimates, the vorinostat/ECM predictions were compared to published observational data, data from the HES database and clinical expert opinion (see Appendix U). Three publications were identified from the literature. Agar 2010 uses the ICARSIS database, which contains data on 1,502 patients with MF/SS collected from 1980 – 2009.[8] Kim 2003 assessed data on 525 patients collected from 1958 to 1999 with MF/SS.[32] Talpur 2012 is a study of 1,263 patients with MF/SS, seen between 1982-2009.[31] In the HES database survival was only available for 82 MF and 14 SS patients after one prior systemic treatment. (For more information on the HES database study, please see Appendix Q).

The published data and the HES database however included populations with better expected survival, as they had significantly lower proportion of patients with SS (47% vs. 7-15% for MAVORIC trial and published and HES data respectively) and significantly lower proportion of patients with stage IV disease (52% vs. 6-7% for MAVORIC trial and published data respectively). The MAVORIC patients were also heavily pre-treated, which is unlikely to be the case for observation data, where it was not part of the inclusion criteria. Additionally, the published observational data are historical, thus changes in treatment practice could have changed. As a result, survival estimates from the available observation data is expected to be a high upper limit of the expected survival for the MAVORIC advanced population.

Table 26: Comparison of the MAVORIC population and populations from available observational data

	MAVORIC trial (ITT, vorinostat arm)[60]	Kim 2003[32]	Agar 2010[8]	Talpur 2012[31]	HES data
% MF	53%	93%	93%	85%	92%
% SS	47%	7%	7%	15%	8%
IA	0%	30%	29%	NR	NR
IB	15%	37%	39%	NR	NR
IIA	12%		3%	NR	NR
IIB	12%	27	11%	NR	NR
IIIA	5%		7%	NR	NR
IIIB	4%		4%	NR	NR
IVA1	44%	6%	4%	NR	NR
IVA2	6%		2%	NR	NR
IVB	2%		1%	NR	NR

Key: ITT: intention-to-treat, HES: Hospital Episode Statistics, NR: not reported, MF: mycosis fungoides, SS: Sezary syndrome

Survival estimates compared from crossover adjusted extrapolations for the ECM arm and from the external data are presented in Table 27. The distributions (with IPCW crossover adjustment) that in most cases do not exceed the observed survival seen in the published and the HES data are the exponential and the log-normal distributions. In the ITT population, which is somewhat closer to the observational study populations, exponential distribution was the most clinically plausible. More information of these comparisons is contained in Appendix V.

Table 27: Survival rates for MF-SS from literature (advanced disease)

Crossover adjustment	Source (comparison to MAVORIC patients)	1-year	3-years	5-years	10-years	20-years
-	HES database (MF patients, not advanced, 2nd line)	57%	31%	25%		
-	Talpur 2012: Stage IIb-IV (n=349) (lower proportion of SS patients, potentially lower proportion of stage IV and heavily pre-treated patients)	91%	68%	51%	34%	18%
-	Kim 2003‡ (lower proportion of SS patients, potentially lower proportion of heavily pre-treated patients)	67%	40%	32%	15%	3%
-	Agar 2010‡ (lower proportion of SS patients, potentially lower proportion of heavily pre-treated patients)	-	-	37%	22%	14%
	Expert opinion (ITT population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	ECM exponential	67%	30%	14%	2%	0%
IPCW	ECM generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	ECM Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	ECM log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	ECM log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	ECM Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSE	ECM exponential	83%	57%	39%	15%	2%
TSE	ECM generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSE	ECM Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSE	ECM log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSE	ECM log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSE	ECM Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ECM: established clinical management/vorinostat arm from MAVORIC
Note: ‡ Weighted average using the proportion of patients in different disease stage from the MAVORIC trial

After consideration of the goodness-of fit-statistics, visual inspection of the curves and diagnostic plots, and validation with external data, independently fitted models were chosen for the base case: exponential model for vorinostat/ECM and log-normal for mogamulizumab.

Additionally, in the model the weekly probability of death has been limited to be no greater than the latest available age- and gender-equivalent general population values from Office for National Statistics (ONS) data for England.[100] The mean baseline age of 63.04 and the proportion of female patient of 41.9% was used from the MAVORIC trial. This affects the base case OS projections after nearly 20 years in the mogamulizumab arm; later in the ECM arm.

Two-stage estimation (TSE)

The TSE method models the potentially different treatment effects at the beginning versus in the later course of a trial, then estimates the treatment effect using the counterfactual survival time as if no treatment switch had occurred after the pre-specified secondary baseline. Detailed information about this method and the assumptions made are available in Appendix V.

Figure 26 presents KM curves by randomised treatment arm, while Table 28 presents summary statistics for OS in the advanced population adjusted using the TSE method, with patients receiving stem cell transplant excluded.

Figure 26 MAVORIC OS KM, with two-stage adjustment, advanced population

Key: KW-0761, mogamulizumab; OS, overall survival.
Note: Patients were censored upon receiving aSCT.

Table 28: MAVORIC OS summary statistics, with two-stage adjustment

Treatment	N	Median (months; 95% CI)	HR (95% CI)
Vorinostat	[redacted]	[redacted]	[redacted]
Mogamulizumab	[redacted]	[redacted]	

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NA, not applicable; OS, overall survival.
Notes: Hazard ratio is adjusted for disease stage, disease type and region. Patients were censored upon receiving aSCT.

Diagnostic plots for these data are included in Appendix V. In brief, they suggest that the proportional hazards (PH) assumption does not hold, suggesting the use of separate fits.

Table 29 shows AIC and BIC statistics for the model fits. The combined AIC and BIC suggest log-normal and exponential models provide the best fits. When considering the separate AIC and BICs, exponential and log-normal provide the best fit for vorinostat, and exponential and log-logistic provide the best fit for mogamulizumab. However, all models are very close to each other.

Table 29 AIC and BIC statistics for PSM fits to advanced disease OS with two-stage adjustment KM data

Model	AIC V	AIC M	cAIC	BIC V	BIC M	cBIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: cAIC combined AIC; cBIC: combined BIC; M, Mogamulizumab; V, vorinostat.						

Parametric survival models shown alongside observed KM curves are provided in Figure 27 (within trial fit) and Figure 28 (extrapolated fit) for independent fits. The fits are again very similar. Based on the clinical plausibility seen in Table 27, none of the TSE models look plausible. Additionally, both post-hoc analyses of the second TTNT data (see Section B.2.6.4) and clinical expert opinion suggests,49 that mogamulizumab has a spill-over effect, that is it provides benefit on next treatment also, which is not seen in the TSE models. Thus, TSE models do not provide clinical or biological plausibility and thus are not considered in the base case, only in the scenario analyses.

Figure 27: MAVORIC OS excluding SCT with two-stage adjustment, advanced population, independent within-trial fits

Figure 28: MAVORIC OS excluding SCT with two-stage adjustment, advanced population, independent extrapolated fits

B.3.3.2. Next-treatment-free survival

NTFS is defined as time from randomisation to the start of next treatment or death. The inclusion of death as an event as opposed to a censor in NTFS distinguishes it from TTNT and makes it suitable for the partitioned survival structure of the CE model as described in Section B.3.2.2.

Figure 29 presents the KM curve of NTFS by randomised treatment arm and Table 30 presents summary statistics. NTFS KM curves overlap in both treatment arms for approximately the first two months. This is likely explained by patients being assessed for progression at 28-day intervals, so would not start their next treatment until after this time. After approximately 2 months the curves start to separate, with the vorinostat arm experiencing a higher rate of NTFS events compared to the mogamulizumab arm.

Figure 29: MAVORIC NTFS KM data, advanced population

Table 30: MAVORIC NTFS summary statistics, advanced population

Treatment	Median (months; 95% CI)	HR (95% CI)
Vorinostat ([redacted])	[redacted]	[redacted]
Mogamulizumab ([redacted])	[redacted]	
Key: CI, confidence interval, HR, hazard ratio; NTFS, next-treatment-free survival. **Notes:** Hazard ratio is adjusted for disease stage, disease type and region.		

Diagnostic plots for these data are included in Appendix V. The NTFS data are nearly complete. Given the patterns observed in in the KM curve and diagnostic plots, there is uncertainty surrounding whether the PH assumption holds. As such, independent parametric survival models for each treatment arm may be considered more appropriate than a joint model. Table 31 shows AIC and BIC statistics for the model fits. For vorinostat generalised gamma models provide the best statistical fit according to AIC/BIC statistics, while for the mogamulizumab arm, generalised gamma and log-normal models provide the best fit.

Table 31: AIC and BIC statistics for PSM fits to advanced disease NTFS KM data

Model	AIC V	AIC M	cAIC	BIC V	BIC M	cBIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: CI, confidence interval, HR, hazard ratio; NTFS, next-treatment-free survival.						

Parametric survival models shown alongside KM data are provided in Figure 30 (within trial fit) and Figure 31 (extrapolated fit).

Figure 30: MAVORIC NTFS, advanced population, independent within-trial fits

Figure 31: MAVORIC NTFS, advanced population, independent extrapolated fits

Based on visual inspection and goodness-of-fit statistics, independently fitted generalised-gamma was selected for NTFS in the base case.

B.3.3.3. Life after allogenic stem-cell transplant

As described in Section B.3.2.2, the proposed introduction of mogamulizumab to the NHS England treatment pathway has implications for subsequent treatment choice and outcomes; most notably aSCT. Patients can receive aSCT if they have achieved good PR or CR and are eligible for the treatment at two timepoints:

- After current treatment (mogamulizumab or ECM) or
- After subsequent treatment.

The MAVORIC trial was designed to test difference in PFS, therefore its design did not allow patients to be bridged to aSCT prior to progression. Nevertheless, it is anticipated based on the clinician survey and the in-depth interviews,[49] that mogamulizumab, similarly to ECM, will lead to patients bridging to aSCT after achieving a good PR or CR and the required 50-day wash-out period.[13] As a result, to estimate the proportion of patients bridged to aSCT after current treatment (mogamulizumab and ECM) a short clinician survey was conducted. For the mean time to receive aSCT, the same assumption of 18 weeks after the initiation of treatment was used as in the BV NICE appraisal.[30]

The MAVORIC trial allowed patients to receive aSCT after subsequent treatment. [redacted]. Additionally, the short survey has also elicited data for this which was included in a scenario analyses. Mean time from randomisation to aSCT was [redacted] weeks in the mogamulizumab and the comparator arm respectively in the MAVORIC trial.

The base case values and those for scenario analyses are presented in Table 32.

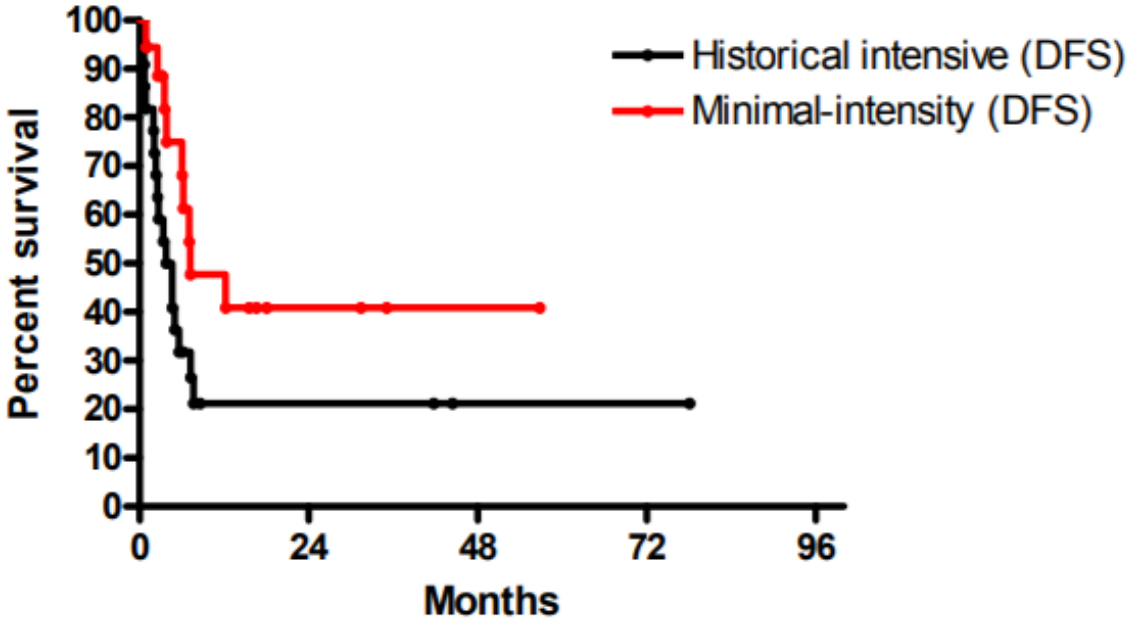
Table 32: Timing and proportion of patients receiving allogeneic stem cell transplant

Timing and comparator	Base case values	Source	Scenario analyses
After current treatment			
% immediately after mogamulizumab	[redacted]	Clinician survey*	0%
% Immediately after ECM	[redacted]	Clinician survey*	0%
Timing of aSCT after mogamulizumab	18 weeks	NICE TA577	-
Timing of aSCT after ECM	18 weeks	NICE TA577	-
After subsequent treatment			
After subsequent treatment to mogamulizumab	[redacted]	MAVORIC trial	[redacted]
After subsequent treatment to current clinical practice	[redacted]	MAVORIC trial	[redacted]
Timing of aSCT after mogamulizumab	[redacted]	MAVORIC trial	-
Timing of aSCT after ECM	[redacted]	MAVORIC trial	-

Key: aSCT, allogeneic stem cell transplant; ECM, established clinical management.
*MAVORIC trial design did not allow patients to receive aSCT prior to progression.

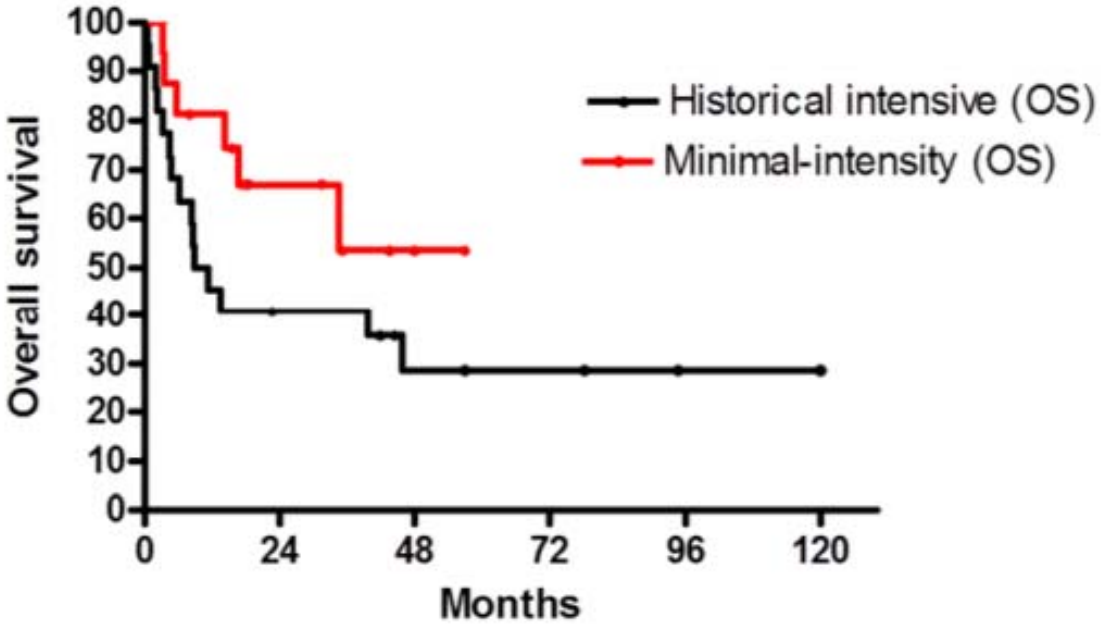
The OS outcomes described in Section B.3.3.1 do not include patients who have received aSCT. Thus, disease-free survival (DFS) and OS, presented as KM curves based on real-world data from the London supra-regional centre using the minimal intensity Stanford Protocol in the NICE TA577 was replicated in Figure 32 and Figure 33[30].

Figure 32: DFS following aSCT KM data, London supra-regional centre[30]



Key: alloSCT, allogenic stem cell transplant; DFS, disease free survival; KM, Kaplan–Meier.

Figure 33: OS following aSCT KM data, London supra-regional centre[30]

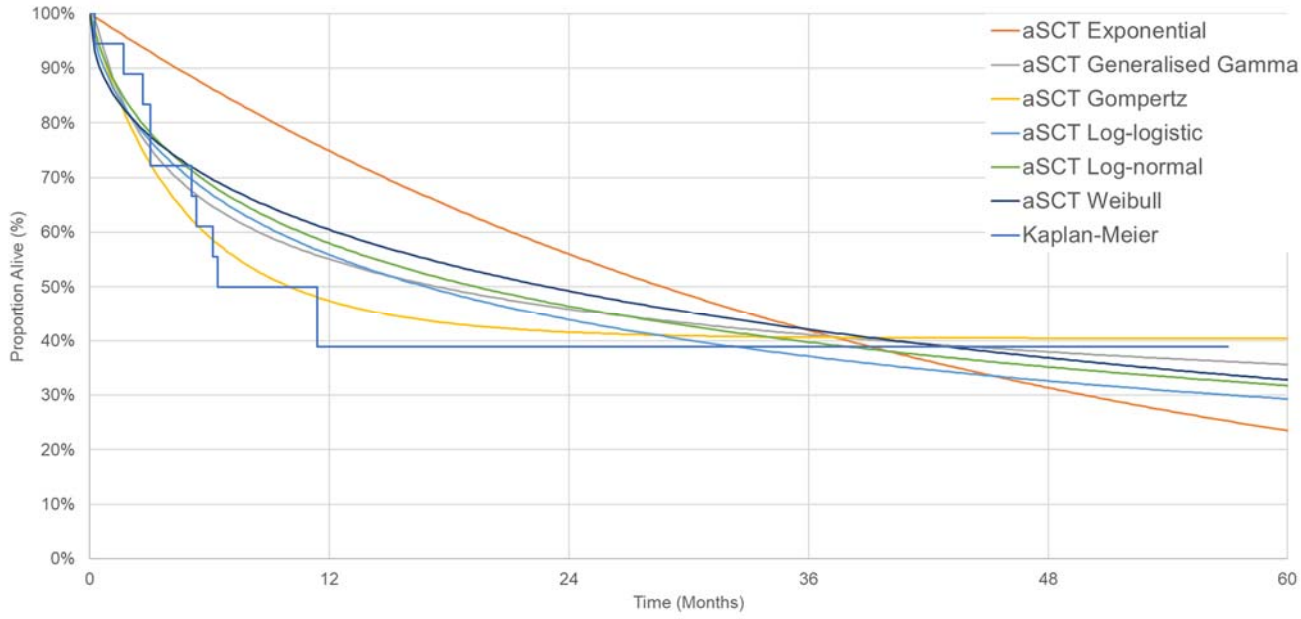


Key: alloSCT, allogenic stem cell transplant; KM, Kaplan–Meier OS, overall survival.

The ‘minimal intensity’ aSCT data used in NICE TA577 was determined by the Committee as appropriate to reflect contemporary NHS England practice across the UK; this is assumed to hold for this appraisal also. The DFS and OS KM curves were digitalised (using GetData software)[101] and standard parametric survival models were fitted to the derived pseudo-patient-level data[30] (Figure 34 and Figure 35).

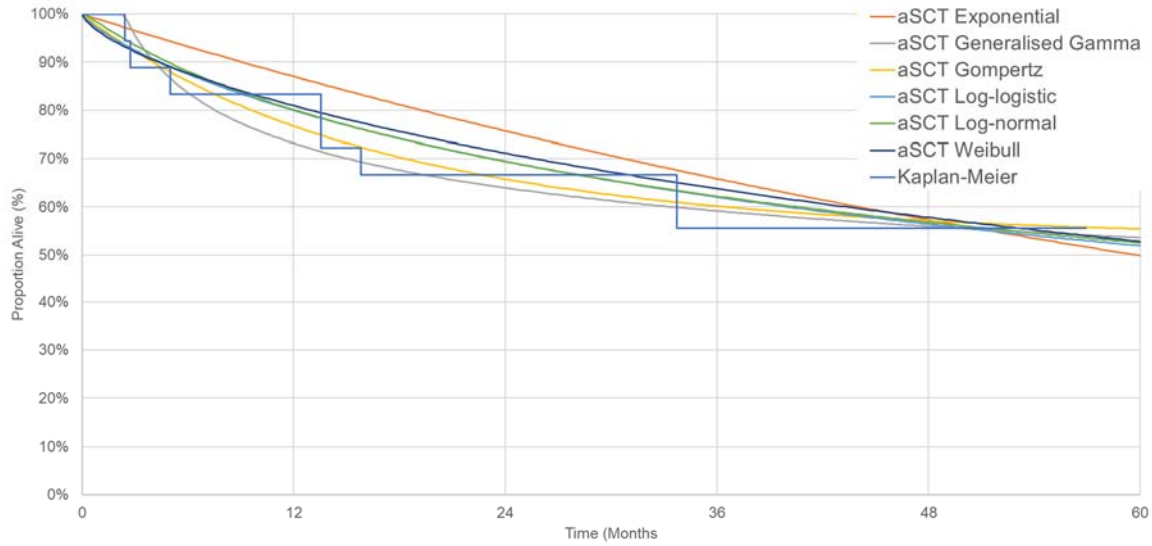
Based on the statistical fit criteria (Table 33) and the visual fit, for DFS Gompertz distribution was the best fit, while for OS the lognormal model fitted the best. This is in line to the reported results from the TA577 company submission.[30]

Figure 34: DFS after aSCT – Digitised KM data and PSMs



Key: alloSCT, allogenic stem cell transplant; DFS, disease-free survival; Gen, generalised; KM, Kaplan–Meier; PSM, parametric survival model.

Figure 35: OS after aSCT – Digitised KM data and PSMs



Key: alloSCT, allogenic stem cell transplant; KM, Kaplan–Meier, OS, overall survival; PSM, parametric survival model.

Table 33: AIC and BIC statistics for PSMs fitted to digitised DFS and OS for aSCT

Model	DFS		OS	
	AIC	BIC	AIC	BIC
Exponential	105.9	106.8	89.3	90.2
Weibull	97.9	99.7	89.8	91.6
Gompertz	87.0	88.8	87.8	89.6
Log-logistic	95.4	97.2	89.1	90.9
Log-normal	94.8	96.6	88.4	90.2
Generalised gamma[a]	94.6	97.3	NA	NA

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; DFS, disease free survival; NA, not applicable; OS, overall survival; PSM, parametric survival model.
Note: [a] In NICE TA577 the generalised gamma function did not converge when fitting it to DFS and OS data. However, it did converge when fitted to the pseudo-patient DFS data in this application.

In TA577, clinical input was used to support the base case choice of curves to model outcomes after alloSCT.[30] The Gompertz model was preferred to model DFS as it was the only model that reflected the expectation of a decreasing probability of relapse reducing over time to zero (a plateau).[30] This behaviour was validated by clinical experts who considered that after 12 months of receiving an aSCT, patients would enter a long-term remission where it would be unlikely to observe new relapse

events.[30] In the TA577 appraisal, the manufacturer also presented a second data cut for the data with results for PFS, but these data were redacted.[30] After clinical validation PFS (redacted) was considered more suitable than DFS as the latter is a more stringent endpoint (requiring complete response at or prior to transplant) and would omit patients who would otherwise be considered in remission under a PFS definition.[30] By using DFS data in this submission, it is likely that the proportion of patients *in remission* post-aSCT is underestimated, leading to conservative estimates as higher proportion of patients in the mogamulizumab arm are expected to benefit from aSCT.

For the post-aSCT OS in NICE TA577, the log-normal model fit was selected, based on the timepoint were the DFS curve converged with the OS curve (i.e. the timepoint at which all relapsed patients were implied to have died.[30] Although the (redacted) updated London supra-regional centre data-cut used in TA577 also included an update for OS, the final TA577 analysis was based on the first OS data-cut as the OS data were consistent across both datasets.[30] Following TA577, the log-normal model was used in the base case.

B.3.3.4. Dose intensity

The mean dose intensity reported during the randomised treatment period of MAVORIC was 97.5% for mogamulizumab.[67] Since the median dose intensities were similar between the treatment arms (97.49% for mogamulizumab and 95.12% for vorinostat), and no dose intensity was available for the treatments for the ECM arm, the same dose intensity was assumed for drug treatments in the ECM arm.

B.3.3.5. Time-on-treatment

To accurately capture treatment costs, MAVORIC ToT KM data were considered. Figure 36 presents the MAVORIC KM data by randomised treatment arm for the ToT data. The vorinostat ToT KM curve from the MAVORIC trial is assumed to represent the maximum treatment duration for the ECM ToT. Treatments that are given for shorter, limited duration, e.g. total skin electron beam therapy (TSEBT) or phototherapy UV-A (PUVA), the mean shorter, limited duration was included. The ToT for vorinostat is however shorter than what is seen in clinical practice with some of the components of ECM. For example, in the MAVORIC trial the mean ToT is 4.47

months for vorinostat, while methotrexate and bexarotene is usually given for 6-18 months, interferon alfa-2a for 4-18 months.[49] In these cases the shorter duration observed for vorinostat was used to remain conservative. Thus, the analyses underestimate the cost of ECM, resulting in conservative cost-effectiveness.

Figure 36: MAVORIC time on treatment Kaplan-Meier curves, advanced population

Key: tx, treatment; KW-0761, mogamulizumab.

Given the complete nature of the data for this endpoint, KM data are used directly to capture mogamulizumab and vorinostat ToT. Parametric distributions are available in the model for scenario analyses.

B.3.3.6. Adverse events

Adverse events (AEs) were taken from the safety population of the MAVORIC trial assuming the same rate of events for ECM as for the vorinostat arm. Only grade 3 and 4 AEs were assumed to have important impact on the costs and quality of life. Table 34 presents the occurrence of grade 3/4 AEs in the MAVORIC trial. Incidence

rates over the entire treatment period were used and costs applied as a lump sum at the start of treatment.

Table 34: Number of adverse events in the MAVORIC trial

AE	Mogamulizumab	Vorinostat
Thrombocytopenia	0	13
Constipation	1	2
Diarrhoea	1	9
Nausea	1	3
Vomiting	0	1
Asthenia	0	4
Fatigue	3	11
Peripheral oedema	0	1
Pyrexia	1	0
Cellulitis	4	4
Pneumonia	7	1
Sepsis	2	4
Upper respiratory tract infection	0	2
Infusion-related reaction	3	0
Aspartate aminotransferase increased	2	1
Weight decreased	1	2
Decreased appetite	2	2
Muscle spasms	0	2
Dysgeusia	0	1
Headache	0	1
Pulmonary embolism	0	5
Drug eruption	8	0
Hypertension	8	12

B.3.4. Measurement and valuation of health effects

Quality of life consequences for the patients were taken into account using EQ-5D-3L data from the pivotal trial in the main health states as per NICE reference case. MF and SS, especially in the advanced stages have a large impact not only on the patients' quality of life, but also on the carers'. Studies show, that in advanced CTCL, there is a significantly high demand on carers' and family resources.[11, 41] In Selman et al. (2015) carers "described an overwhelming burden of care; the disease's detrimental effect on social life; financial burdens; stigma; and problems with sleep and sex life". The intense schedule of dressings, the visible nature of the disease

places a longer and higher burden on the carers. As a result, it is important to incorporate carers' burden in the cost-effectiveness analyses to be able to accurately account for the costs and health benefits of mogamulizumab. Quality of life consequences for the carers were measured in a vignette study conducted by Kyowa Kirin.

B.3.4.1. Health-related quality-of-life data from clinical trials

As described in Section B.2.6.2, patient-reported HRQL data were collected using several instruments in MAVORIC trial, including EQ-5D-3L questionnaire. Patients in MAVORIC trial completed these surveys on Day 1 of the first 28-day study treatment cycle, and again during the last 3 days of each odd-numbered treatment cycle (odd and even cycles in the case of pruritus evaluation) until treatment discontinuation, at which point each patient completed these questionnaires one final time during an end-of-treatment visit. As reported in Section B.2.6.2, completion rates were high, at over 90% throughout the study. However, the number remaining on treatment was low by Cycle 13 (beyond Year 1), as illustrated in Section B.3.3.4.

The HRQL data collected in MAVORIC up to the primary endpoint analysis DBL (31st December 2016) represent a valuable addition to the scarce published evidence for quality of life in Stage IIb+ MF and SS patients, as Section B.3.4.3 will highlight. The data across instruments, as presented in Section B.2.6.2, indicate that mogamulizumab led to improved well-being compared with vorinostat and that HRQL improvements were sustained for longer with mogamulizumab treatment compared with vorinostat. However, as is the case with HRQL data collected in other pivotal regulatory trials, good-quality data on HRQL in patients after discontinuation – and, by association, beyond disease progression – is limited.

The NICE reference case specifies a preference for patient-reported EQ-5D data for decision making, with the utility of EQ-5D HRQL changes valued by the general public.[102] To analyse MAVORIC HRQL data in line with this preference, what has become known as 'the UK tariff' was applied to MAVORIC EQ-5D-3L questionnaire data, to generate patient-specific EQ-5D-3L utility data associated with each completed questionnaire.[103]

To analyse these data in a manner that can inform health state utility values and associated uncertainty distributions for the cost-effectiveness model structure described in Section B.3.2.2, post hoc analyses were conducted.[74]

The MAVORIC data was analysed using longitudinal mixed models; post-baseline EQ-5D utility scores were regressed on fixed effects of (i) baseline EQ-5D utility score, (ii) randomised treatment (KW-0761 versus vorinostat), (iii) current treatment (KW-0761 versus vorinostat), and (iv) progression status (yes versus no), as well as all possible interaction terms.[74] Table 35 shows results from the final model of a stepwise backwards selection process using these variables. This final model is free of interaction terms, and neither current nor randomised treatment status were found to be independent predictors of patient utility.

Table 35: Best fitting model parameter estimates from post-hoc mixed model analysis of predictors of post-baseline MAVORIC UK-tariff EQ-5D utility

Parameters	Parameter estimate[2] (SE), p-value[3]
Intercept	[redacted]
Baseline EQ-5D-3L Utility	[redacted]
Disease Progression	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; EQ-5D-3L, 3-level EQ-5D.
Notes: [1] Model fit was assessed by AIC/BIC in a backwards-selection process, with the lowest (most negative) judged to be the best fit; [2] Parameter estimates are beta estimates from longitudinal linear mixed models of EQ-5D utility, adjusted for all variables in the list of model predictors included in the table above; [3] P-value for beta=0.

Mean adjusted cycle-specific utilities as well as mean utilities for the on-treatment period and the last observation as observed in the MAVORIC trial are presented in Table 36.

Table 36: Adjusted mean utilities from the MAVORIC trial

	Mogamulizumab Group (N=184)			Vorinostat Group (N=186)		
Cycle	**N**	**Mean**	**95% CI**	**N**	**Mean**	**95% CI**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On treatment period (used after cycle 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last observation post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*This value includes the utilities for patients who have crossed over to mogamulizumab also.

Obtaining utilities for the post-treatment period or for the time patients received subsequent therapies is difficult as according to protocol patients were administered the EQ-5D-3L instrument during each treatment cycle, and at the end of treatment visit, i.e., there is limited information available following the stopping of current treatment.

As a result, the last observation values for mogamulizumab if post-progression was assumed to be a good proxy the period on subsequent treatment. The value was similar to what seen in the ALCANZA trial for the progressed patients (0.61 and 0.64 in the advanced population for predicted and observed values respectively, and 0.66 and 0.68 it the ITT population for predicted and observed values respectively). Given the substantial proportion of patients crossing over to mogamulizumab in the vorinostat arm, utility values calculated from the trial for the post-vorinostat period are biased by the impact of mogamulizumab received as a subsequent treatment and were not used.

Beyond these issues, there are the limitations of the EQ-5D instrument in CTCL generally. In TA577 (FAD 3.13), the clinical experts explained that neither the EQ-5D-3L nor the Skindex-29 fully capture all skin-related and physiological symptoms

of CTCL.[104] The committee 'concluded that BV appears to improve health-related quality of life', despite the company's analysis failing to estimate a significant association.[104] The committee 'agreed that this was at least partly because of the health-related quality of life tools available, such that the benefit of BV may not be fully captured in the trial data. It concluded that this should be factored into its considerations of the cost-effectiveness evidence'.[104]

Data in Table 35 was used to inform base case analyses, as summarised in Sections B.3.4.4 and B.3.6.1. Alternative scenario analysis options were provided in the cost-effectiveness model.

B.3.4.2. Mapping

As NICE reference case HRQL data were collected in MAVORIC, mapping data from the clinical trial was unnecessary.

B.3.4.3. Health-related quality-of-life studies

Studies assessing patients' quality of life

A search for published studies reporting HRQL or utility data for relapsed or refractory CTCL patients was conducted alongside the search for cost-effectiveness studies, cited in Section B.3.1 and reported in Appendix G. The study selection methods and results of the HRQL review are shown in Appendix H.

The search yielded only three unique studies for inclusion: the 2018 Lancet publication for MAVORIC;[60] the TA577 committee papers, which report EQ-5D data from the ALCANZA study;[30] and an application to the Australian Government's Medical Services Advisory Committee for extracorporeal photopheresis for CTCL.[105] The visible utility data from the latter is limited to a disutility estimate for adverse effects as a result of treatment with interferon alfa 2 beta, methotrexate or alemtuzumab; thus, the MAVORIC data and TA577-reported ALCANZA patient utility data appear to be the only published or directly available evidence for health state utility estimates in CTCL. This finding is consistent with the TA577 company search for HRQL evidence, which found no CTCL EQ-5D data other than that collected in their own ALCANZA study.[30]

The TA577 ERG's preferred utility value for PFS was calculated using an average of the EQ-5D-3L values from the BV and comparator groups, reported as 0.689. [30] This was considered appropriate for decision making by the committee[30], with the caveats noted in Section B.3.4.1. The company estimate for post-progression survival utility was 0.61 (95% CI: 0.52, 0.70) for the advanced population, based on their submitted utility regression analysis.[30] This is similar to that seen at the end of treatment visit in the MAVORIC trial described in Section B.3.4.1.

Other utility data used in TA577 decision making were not specific to CTCL patients. For utility values associated with subsequent allogeneic STC, the company used data from a study of patients undergoing transplantation for refractory or relapsed non-Hodgkin or Hodgkin lymphoma in which quality-of-life data were collected.[106] The utility values sourced and used in TA577 – 0.42 for days 0–14 post-SCT, 0.60 from then to 3 months, and 0.77 beyond 3 months[106] – reflect both the burden of such treatment and the long-term quality of life potential for those whose grafts are successful.

The company also sourced a utility estimate for end-stage care from the wider literature: specifically, a health state valuation study eliciting information on public valuations of vignettes characterising various relapsed or refractory Hodgkin's lymphoma and systemic anaplastic large cell lymphoma health states.[107] The value sourced, 0.38, was applied to capture the high-intensity period of care at the end of life, when the burden of care is high and effective treatments are no longer an option. There was debate between the ERG and the company over the appropriate length of this period for cost-effectiveness modelling in TA577; the ERG preference based on independent clinical opinion was 6 months.[108]

Studies assessing carers' quality of life

The TA577 company submission did not include evidence on the direct HRQL effect of BV upon carers, yet the quality of life of those who love and care for MF and SS patients is, of course, also affected by the disease. As well as experiencing empathetic distress, loved ones often play the role of informal carer, a role that is heightened in late-stage, poorly controlled disease. Although evidence on the HRQL effects of disease and treatment on carers of patients with this disease is limited, and quantitative evidence is absent, the research cited in Section B.1.3 is valuable in

providing qualitative evidence of the HRQL burden of CTCL upon both carers and patients.[11, 41] In the more recent of these studies, the authors report thematic results from semi-structured qualitative interviews with 15 bereaved family caregivers of 11 patients with CTCL recruited via a supra-regional CTCL clinic.[11] The authors report: 'Caregivers often had vivid recollections of the challenges of caring for their relative with advanced CTCL and some took on quasi-professional roles as a result'.[11]

Given the caregiver burden associated with CTCL, there is a strong argument for considering caregiver burden in the assessment of any new treatment. This is particularly important if such a treatment can delay or prevent patients reaching the most advanced stages of the disease, when the caregiver burden is greatest. Following recent DSU guidance on the inclusion of caregiver burden in economic evaluations, a study to evaluate carer utilities has been undertaken.[42] Three health state vignettes were developed to describe the experience of caring for an individual with advanced CTCL. Corresponding to the economic model structure, one health state described the experience of caring for an individual who was receiving second line treatment, one described caring for an individual on third line treatment, and one describing an end of life state. As the burden for a caregiver may continue when the patient dies due to a period of mourning and adjustment, a fourth state described the year immediately after a patient's death. The content of the vignettes was informed by a targeted review of qualitative studies with individuals with CTCL and/or their caregivers and interviews with CTCL specialists. Only factors that are important to caregivers of individuals with CTCL were included, rather than any impact specific to patients, such as disfigurement or pain. The vignettes are included in Appendix M. The EQ-5D-5L rating for each state was scored using a mapping function for the EQ-5D-5L and scores reflected UK preference weights. The sample was broadly representative of the UK in terms of age, sex, and ethnicity.

Table 37 shows the EQ-5D weights for each health state vignette. The weights are very low, demonstrating the substantial burden caring and being a partner of an individual with CTCL. The utility scores from the EQ-5D values range from 0.56 (second line treatment) to 0.31 (end of life care). There is a recovery in utility scores after the patient has died, but the utility score remained low (0.59).

Table 37: EQ-5D weights for each health state vignette (N=100)

Caregiver health state	Mean (SD)	Standard error	95% Confidence intervals
2nd line treatment	0.559 (0.244)	0.024	0.511 – 0.607
3rd line treatment	0.366 (0.225)	0.023	0.322 – 0.411
End-of-life care	0.313 (0.241)	0.024	0.265 – 0.361
Post-patient death	0.589 (0.251)	0.025	0.539 – 0.639

B.3.4.4. Health-related quality-of-life data used in the cost-effectiveness analysis

Table 38 summarises base case utility assumptions, with reference to previous elements of Section B.3.4. The main patient health state utility values are those observed in MAVORIC trial. The treatment- and cycle-specific utility values were used until cycle 12, thereafter the mean values across the whole treatment period were applied. For the subsequent treatment health state mean values measured at the last observation post-progression in the mogamulizumab arm of the MAVORIC trial were applied, as values in the comparator arm also include the impact of cross-over to mogamulizumab. This value is in line with what was seen in the ALZANCA trial in TA577 (Section B.3.4.3).[30] Other patient health state utility assumptions are TA577 decision-making values, as described in Section B.3.4.3.

Table 38: Summary of utility values for cost-effectiveness analysis

State	Utility value	95% CI	Reference in submission	Justification
On Tx, cycle 1-2, mogamulizumab	[redacted]	[redacted]	B.3.4.1	Patient-reported EQ-5D data from the pivotal RCT
On Tx, cycle 3-4, mogamulizumab	[redacted]	[redacted]		
On Tx, cycle 5-6, mogamulizumab	[redacted]	[redacted]		
On Tx, cycle 7-8, mogamulizumab	[redacted]	[redacted]		
On Tx, cycle 9-10, mogamulizumab	[redacted]	[redacted]		
On Tx, cycle 11-12, mogamulizumab	[redacted]	[redacted]		
On Tx, cycle 12+, and Surveillance, mogamulizumab	[redacted]	[redacted]		
On Tx, cycle 1-2, ECM	[redacted]	[redacted]		
On Tx, cycle 3-4, ECM	[redacted]	[redacted]		
On Tx, cycle 5-6, ECM	[redacted]	[redacted]		
On Tx, cycle 7-8, ECM	[redacted]	[redacted]		
On Tx, cycle 9-10, ECM	[redacted]	[redacted]		
On Tx, cycle 11-12, ECM	[redacted]	[redacted]		
On Tx, cycle 12+, and Surveillance, ECM	[redacted]	[redacted]		
Subsequent treatments, mogamulizumab and ECM	[redacted]	[redacted]		Patient-reported EQ-5D data from the pivotal RCT for mogamulizumab due to cross-over
End-stage care	0.38	(0.307, 0.456)	B.3.4.3	Best available values from systematic review of the literature; also used for decision making in TA577
Post-SCT (first two weeks)	0.42	(0.339, 0.503)		
Post-SCT (week 3 to month 4)	0.60	(0.480, 0.714)		
Post-SCT (3 months onwards)	0.77	(0.603, 0.901)		

There are no gold standard ways to apply carer utilities. If carer utilities are only accounted for while the patient is alive, it would confer a survival benefit on to carers too, which would be methodologically incorrect. If carer utilities were to be accounted for even after the patient's death, due to the rebound in utility values shown in the

vignette study as described in section B.3.4.3 above , then treatments were patients die earlier would be deemed more beneficial, which opens up ethical questions. Therefore, in the evaluation a carer utility gain was included in the value of the incremental difference between caring for a patient in second line of treatment versus caring for a patient in third line of treatment (utility value of 0.559-0.366=0.193) only for carers for mogamulizumab patients and only for the incremental time-period spent by patients in the mogamulizumab arm versus the ECM arm in the disease control health state.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

Resource use for patients with advanced CTCL depends on the individual collection of symptoms and therefore varies greatly between individuals. Much of the care, especially in the later stages is received in the community and often administered by informal carers, making it harder to identify. Therefore, although resource use related to secondary care was based on the HES database, resource use related to community care and treatments was based on published literature including information identified by a systematic literature review, and data from previous NICE TAs and expert opinion.

Unit costs for non-drug resources were obtained from the National Schedule of Reference Costs 2017-2018[109] and the Personal Social Services Research Unit (PSSRU) report[110] and unit costs of drugs were obtained from the British National Formulary (BNF 2019[111]) and the Drugs and pharmaceutical electronic market information tool (eMIT 2019) for generic products.[112] Costs, where applicable were inflated to 2018/19 using the Health Services Index presented in the PSSRU report.

B.3.5.1. Intervention and comparators' costs and resource use

The recommended dose for mogamulizumab based on the MAVORIC trial is 1 mg/kg. The MAVORIC trial also reported a mean relative dose intensity of 94.41%, which was applied throughout the treatment time period. The cost of a single vial containing 20 mg of mogamulizumab is £1,329. [redacted] The mean weight for European patients in the MAVORIC trial was 76.77kg, therefore the mean dose

required for a single administration would have been 94.41%*1 mg/kg*76.77 kg=72.48 mg, requiring the use of four 20mg vials. Wastage with dose banding used by NHS England for monoclonal antibodies allows a 10% discrepancy in the administered dose, therefore patients whose required dose is less than 10% higher than the dose available in a given number of vials, can still receive only those vials without the need to open a new vial. For patients above the 10% limit, a new vial would be opened, leaving some of the contents unused and discarded. Table 39 presents the weight bands (taking into account the mean relative dose intensity) and the distribution of European patients according to the number of vials required for each treatment administration in the MAVORIC trial. The average cost per administration was calculated to be [redacted].

Table 39: Distribution of patients in MAVORIC according to number of vials needed for each administration with dose banding

Vials	Weight band upper limit (kg)	Distribution	Dose (mg)	Cost (£)
1	23.30	0%	20	[redacted]
2	46.61	1.44%	40	[redacted]
3	69.91	33.09%	60	[redacted]
4	93.21	50.36%	80	[redacted]
5	116.51	12.95%	100	[redacted]
6	139.82	2.16%	120	[redacted]
7	163.12	0.00%	140	[redacted]

Assuming no wastage with dose banding (i.e., if vials could be shared between patients and no unused contents), the mean cost per administration would be [redacted]. This cost was tested in a scenario analysis.

The composition of and the proportion of patients receiving each treatment in the established clinical management arm has been reported in Table 22. The cost of comparators is provided in Table 40: comparator treatment dosing was taken from TA577, the KOL survey and the London Cancer Alliance 2019.[30, 49, 113] The formulation of each treatment for the costing was chosen to be the closest to the average required dose per administration. For the body surface area, the mean value from the European patients in the MAVORIC trial (1.91m^2) was used.

Table 40: Comparator drug costs

Treatment	Drug form	Dose required	Frequency	Unit cost	Unit size	Dose Size	Unit	Source of costs	Source of dose
Methotrexate (oral)	Tablet	23.44 mg	Once a week	£4.37	100	2.5	mg	eMIT 2019[112]	Brentuximab NICE TA577[30], BNF 2019
Bexarotene (oral)	Capsule	300 mg/m^2	Once daily	£937.50	100	75.0	mg	BNF 2019[111]	Brentuximab NICE TA577[30], BNF 2019
Interferon alfa-2a (peginterferon)	Pre-filled syringes	180 mcg	Once a week	£76.51	1	180.0	mcg	BNF 2019[111]	EMA EPAR [114]
Gemcitabine	Solution for infusion	1000 /m^2	Day 1 and 21 of the cycle	£42.86	1	2000.0	mg	eMIT 2019[112]	KOL survey[49]
Cyclophosphamide (CHOP)	Powder for solution for injection vials	750 mg/m^2 IV	Day 1 of 21-day cycle	£13.47	1	1000	mg	eMIT 2019[112]	London Cancer Alliance 2019[113]
Doxorubicin (CHOP)	Solution for injection vials	50 mg/m^2 IV	Day 1 of 21-day cycle	£17.78	1	50	mg	eMIT 2019[112]	London Cancer Alliance 2019[113]
Vincristine (CHOP)	Solution for injection vials	1.4 mg/m^2 IV	Day 1 of 21-day cycle	£17.82	5	2	mg	eMIT 2019[112]	London Cancer Alliance 2019[113]
Prednisolone (also in CHOP)	Tablet	40 mg/m^2 (max 100mg)	Day1,2,3,4,5 of 21-day cycle	£20.25	56	25	mg	eMIT 2019[112]	London Cancer Alliance 2019[113]
Liposomal doxorubicin	Vial	20 mg/m^2	Twice monthly	£712.49	1	50	mg	BNF 2019[111]	KOL survey[49]
Etoposide (oral)	Capsule	120-240 mg/m^2	Daily for 5 days monthly	£87.23	10	100	mg	BNF 2019[111]	BNF 2019[111], KOL survey[49]
Phototherapy UV-A (PUVA)	NA	NA	2 per week for 14 weeks	£100.67	NA	NA	NA	NHS RC 2019, JC47Z	NA

Treatment	Drug form	Dose required	Frequency	Unit cost	Unit size	Dose Size	Unit	Source of costs	Source of dose
Extracorporeal photopheresis (ECP)	NA	NA	On 2 consecutive days every 28 days	£498.67	NA	NA	NA	NHS RC 2019, JC47Z	NA
Total skin electron beam therapy (TSEBT)	NA	NA	4/week for 4 weeks, assumed to be repeated once	£537.55	NA	NA	NA	NHS RC 2019, SC56Z	NA

The cost of treatment administration was taken from the 2017-8 NHS reference costs (Table 41). The first administration of peginterferon, and each administration of mogamulizumab, gemcitabine and liposomal doxorubicin was assumed to cost the same as the administration of simple parenteral chemotherapies, while CHOP was assumed to require the complex parenteral administration. The first administration of all other drug therapies was assumed to cost the same as the delivery of oral chemotherapies.

Table 41. Administration costs

Currency	Currency Description	Unit cost
SB11Z	Deliver Exclusively Oral Chemotherapy	£141
SB12Z	Deliver Simple Parenteral Chemotherapy at First Attendance	£229
SB13Z	Deliver more Complex Parenteral Chemotherapy at First Attendance	£286
Source: National Schedule of Reference Costs Year: 2017-18 - All NHS trusts and NHS foundation trusts - HRG Data		

B.3.5.2. Health-state unit costs and resource use

In NICE TA577, health state costs were based on expert opinion and were heavily criticised by the ERG and the Committee. To reduce the uncertainty of these estimates, a retrospective study has been conducted using the HES database containing details of all inpatient admissions, Accident and Emergency (A&E) attendances and outpatient appointments at NHS hospitals in England. Each patient in the HES dataset is given a unique identification code (with patient and clinician identifiers removed) allowing for robust retrospective longitudinal pathway analysis, through any diagnosis or treatment, within the inpatient, outpatient or A&E setting where treatment is given in any location in the English NHS.

For the purpose of this model patients were included if meeting the following eligibility criteria:

- Diagnosis: Patient has one of the following ICD-10 (International Classification of Disease version 10) codes in HES record:
  - C84.0: Mycosis fungoides
  - C84.1: Sézary disease

- The ICD-10 code (C84.0, C84.1 or C84.8) can be in any position (1-20) in the patient's record.
- Date of activity: Diagnostic code occurs at least once between 1st October 2010 and 31st March 2019

Patients were excluded if they had ICD-10 diagnosis codes for both MF (C84.0) and SS (C84.1) within their record, had diagnosis of C84.0, C84.1 or C84.8 within the 18 months prior to the start of the study observation period (i.e. diagnosis occurring between 1st April 2009 to 30th September 2010 for MF [C84.0] or SS [C84.1].

Each patient was tracked from their first diagnosis/first occurrence in the available dataset up to the study end point (31 March 2019). All patient activity was aggregated at specific time points (e.g. diagnosis, first and each treatment switch event, death) through to the study end point. Analyses were presented for two main cohorts:

- Cohort A: All patients with a first diagnosis of CTCL between 1 October 2010 and 31 March 2019, with the date of the first diagnosis as the index date. This was used to determine costs for second- and third-line patients.
- Cohort B: Patients who died during the study period with patients tracked back from their date of death. Patient activity was aggregated for the 6-month periods prior to death. This was used to estimate end of life costs.

Costs have been adjusted for inflation and are calculated based on individual person-weeks within time window for Cohort A, and as 6-monthly costs for Cohort B. Further information is available in Appendix Q.

The cost estimates for the different time periods for inpatient/outpatient care is presented in Table 42 and Table 43. For the model weighted average costs for MF/SS patients using the distribution from the MAVORIC trial was estimated.

Table 42: Costs per patient-week from the HES database from diagnosis

	Mycosis fungoides				Sézary syndrome			
	C84.0				C84.1			
	Diagnosis to first progression	First progression to second progression	Second progression to third progression	Third progression onwards	Diagnosis to first progression	First progression to second progression	Second progression to third progression	Third progression onwards
Inpatient + Outpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 43. Costs per patient-week from the HES database from death

Mycosis fungoides				Sézary syndrome			
C84.0				C84.1			
Up to 6 months prior to death	From 6 to 12 months prior to death	From 12 to 18 months prior to death	From 18 to 24 months prior to death	Up to 6 months prior to death	From 6 to 12 months prior to death	From 12 to 18 months prior to death	From 18 to 24 months prior to death
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For community-based costs, resource use from the NICE TA577 using ERG's preferred scenario was multiplied with current unit costs, resulting in the health state costs presented in Table 44.

Table 44: Health state costs used in the model

	Disease control	Subsequent treatments	End-stage care	Source
Home visit	£9.00	£9.00	£75.75	NICE TA577
Skin and wound care	£ -	£ -	£99.42	NICE TA577
Dressings	£114.84	£114.84	£536.66	NICE TA577
Other drug treatment	£ -	£1.61	£5.37	NICE TA577
Total without inpatient-outpatient	***£123.84***	***£125.45***	***£717.20***	**-**
Inpatient/outpatient costs from HES	[redacted]	[redacted]	[redacted]	***HES database***
Total costs per week using HES database	[redacted]	[redacted]	[redacted]	**-**

B.3.5.3. Adverse reaction unit costs and resource use

AE costs were calculated based on the reported incidence of relevant grade 3-4 AEs reported in MAVORIC (Section B.3.3.6). Costs for each of the AEs were taken from previous TAs (TA306, TA567, TA584, TA600) and inflated to 2017/2018 cost year. The cost for sepsis was a weighted average of related codes in NHS reference costs (WJ06A-J). Expert opinion was required for aspartate aminotransferase increase, constipation, dysgeusia, headache, infusion related reactions, muscle spasm and peripheral oedema. Details are provided in Table 45.

Table 45: Cost of grade 3-4 adverse events

Costs	Mean (Inflated)	Mean	Year	Source	Comments
Aspartate aminotransferase increased	£0.00	£0.00		Expert opinion	Assumed no cost implicated
Asthenia	£93.80	£91.77	2016/ 2017	Assumption	Assumed same as Fatigue
Cellulitis	£974.07	£953.00	2016/ 2017	NICE TA306 (ERG Report)	Resource use survey

Costs	Mean (Inflated)	Mean	Year	Source	Comments
Constipation	£0.00	£0.00		Expert opinion	Over the counter laxatives
Decreased appetite	£389.75	£381.32	2016/ 2017	NICE TA567 (ERG Report Table 23)	Assumed same as anorexia; Weighted average of FD04C, FD04D, FD04A; Day case
Diarrhoea	£400.93	£392.26	2016/ 2017	NICE TA567 (ERG Report Table 23)	Weighted average of FD10J, FD10K-M; Day case
Drug eruption	£130.02	£127.21	2016/ 2017	NICE TA600, originally from Brown et al, 2013 (Table 83 of MS)	
Dysgeusia	£0.00	£0.00		Expert opinion	Assumed no cost implicated
Fatigue	£93.80	£91.77	2016/ 2017	NICE TA567 (ERG Report Table 23)	As per TA306 pixantrone; inflated to 2017
Headache	£0.00	£0.00		Expert opinion	Over the counter paracetamol
Hypertension	£180.14	£176.24	2016/ 2017	NICE TA584 (ERG Report Table 44)	Consultant led follow up visit - Medical oncology. Service code 370
Infusion-related reaction	£0.00	£0.00		Expert opinion	Assumed no cost implicated
Muscle spasms	£0.00	£0.00		Expert opinion	Assumed no cost implicated
Nausea	£623.11	£609.63	2016/ 2017	NICE TA567 (ERG Report Table 23)	As per TA306 pixantrone;

Costs	Mean (Inflated)	Mean	Year	Source	Comments
					inflated to 2017
Peripheral oedema	£0.00	£0.00		Expert opinion	Assumed no cost implicated
Pneumonia	£908.66	£889.00	2016/ 2017	NICE TA306 (ERG Report)	Resource use survey
Pulmonary embolism	£1,463.94	£1,432.27	2016/ 2017	NICE TA584 (ERG Report Table 44)	Weighted average of pulmonary embolus HRG codes (DZ09J-DZ09Q).
Pyrexia	£454.22	£444.39	2016/ 2017	NICE TA567 (ERG Report Table 23)	Weighted average of WJ07A-D; Day case. Non-elective short stay.
Sepsis	£2,166.66	£2,166.66	2017/ 2018	Weighted average of NHS Reference costs	WJ06A-J
Thrombocytopenia	£314.33	£307.53	2016/ 2017	NICE TA567 (ERG Report Table 23)	Weighted average of SA12G-SA12K; Day case
Upper respiratory tract infection	£431.61	£422.27	2016/ 2017	NICE TA567 (ERG Report Table 23)	Assumed same as infection; Weighted average of WH07B-G; Day case
Vomiting	£623.11	£609.63	2016/ 2017	NICE TA567 (ERG Report Table 23)	As per TA306 pixantrone; inflated to 2017
Weight decreased	£389.75	£381.32	2016/ 2017	NICE TA567 (ERG Report Table 23)	Assumed same as anorexia; Weighted average of FD04C, FD04D,

Costs	Mean (Inflated)	Mean	Year	Source	Comments
					FD04A; Day case

B.3.5.4. Miscellaneous unit costs and resource use

The cost of aSCT was based on the methodology used in NICE TA567, which was using UK data. The transplant cost, £35,472.26, is the weighted average of three NHS Reference Costs 2017/18 Total HRGs (SA38A, SA39A and SA40Z), while the follow-up costs, £42,239.35, for two years was based on the UK Stem Cell Strategy Oversight Committee (2004) inflated to 2017/2018. The costs of treatments after aSCT were estimated based on NICE TA577.[30] NICE TA577 assumed that a proportion of the time spent in the aSCT relapse health state (57.10%) is spent receiving active therapy (company submission pg. 149). The cost of subsequent treatment for patients without and with aSCT was £5,891 and £2,415, respectively (Company submission pg. 149).[115] The value used in this model is assumed to keep the same proportion compared to the total costs of subsequent treatment for patients without aSCT (i.e. 2415/5891 = 41%). The model applies a weekly cost based on the mean OS for patients in the mogamulizumab arm relapsing after aSCT. Monitoring costs after relapse are assumed the same as in the Subsequent treatment health state.

Subsequent treatments after mogamulizumab and ECM were assumed the same and were from the clinician survey and interviews (Table 46). Length of subsequent treatments were based on expert opinion and literature and are presented in Table 47. The cost of subsequent treatments were added as lump sum, at the time of moving to the Subsequent treatment health state.

Table 46: Distribution of subsequent treatments

Subsequent therapy	Mogamulizumab: % patients receiving treatment	ECM: % patients receiving treatment
Bexarotene	[redacted]	[redacted]
Bexarotene + ECP	[redacted]	[redacted]
Interferon alfa-2a	[redacted]	[redacted]
Interferon alfa-2a + ECP	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
CHOP	[redacted]	[redacted]
Liposomal doxorubicin	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]
PUVA	[redacted]	[redacted]
TSEBT	[redacted]	[redacted]

Table 47: Length of treatment for subsequent therapies

	Time on treatment (days)	Reference
Bexarotene	176.7	Duvic et al 2001
Bexarotene + ECP (columns C-F refer to ECP)	317.6	Duvic et al 2001 (Bexarotene); Expert opinion (ECP)
Interferon alfa-2a	332.8	Expert opinion
Interferon alfa-2a + ECP	317.6	Expert opinion
Gemcitabine	112.0	Expert opinion
CHOP	112.0	Expert opinion
Liposomal doxorubicin	112.0	Expert opinion
Prednisolone	112.0	Expert opinion
PUVA	98.0	Expert opinion
TSEBT	28.0	Expert opinion

B.3.6. Summary of base-case analysis inputs and assumptions

B.3.6.1. Summary of base-case analysis inputs

The base case inputs are summarised in Table 48. Further details are available in Appendix S.

Table 48: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Discount rates			
Discount rate for costs	3.5%	0% and 5% tested in scenario analyses	B.3.2.2
Discount rate for health benefits	3.5%	0% and 5% tested in scenario analyses	B.3.2.2
Patient characteristics			
Mean age	63.04 years	SE, normal distribution	B.3.3.1
Mean body surface area	1.91m^2	SE, normal distribution	B.3.5.1
Mean body weight	76.77kg	SE, log-normal distribution	B.3.5.1
Female proportion of patients	41.9%	Not included directly, only through general population mortality	B.3.8.1
Use of aSCT			
% receiving aSCT immediately after mogamulizumab	[redacted] (Table 32)	SE, beta distribution	B.3.3.3
% receiving aSCT immediately after ECM	[redacted] (Table 32)	SE, beta distribution	B.3.3.3
Timing of aSCT after mogamulizumab	18 weeks (Table 32)	SE, normal distribution	B.3.3.3
Timing of aSCT after ECM	18 weeks (Table 32)	SE, normal distribution	B.3.3.3
% receiving aSCT after subsequent treatment to mogamulizumab	[redacted] (Table 32)	SE, beta distribution	B.3.3.3
% receiving aSCT after subsequent treatment to ECM	[redacted] (Table 32)	SE, beta distribution	B.3.3.3
Timing of aSCT after subsequent	[redacted] (Table 32)	SE, normal distribution	B.3.3.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
treatment to mogamulizumab			
Timing of aSCT after subsequent treatment to ECM	[redacted] (Table 32)	SE, normal distribution	B.3.3.3
Survival curves			
DFS after aSCT	Gompertz distribution (Figure 34)	Cholesky decomposition using variance-covariance matrices	B.3.3.3
OS after aSCT	Log-normal distribution (Figure 35)		B.3.3.3
ToT for mogamulizumab	Kaplan-Meier curve from MAVORIC trial (Figure 36)		B.3.3.5
ToT for ECM			B.3.3.5
OS for mogamulizumab excluding aSCT patients	Log-normal distribution (Figure 24,Figure 25)		B.3.3.1
OS for ECM excluding aSCT patients	IPCW crossover adjusted exponential distribution (Figure 24, Figure 25)		B.3.3.1
NTFS for mogamulizumab	Generalised gamma distributions (Figure 29, Figure 30, Figure 31)		0
NTF for ECM			0
Utilities			
Utilities for Disease control – Mogamulizumab arm	Per cycle utilities until cycle 12, then [redacted] (Table 38)	95% CIs, beta distribution	B.3.4.4
Utilities for Disease control – ECM arm	Per cycle utilities until cycle 12, then [redacted] (Table 38)	95% CIs, beta distribution	B.3.4.4
Utilities for subsequent treatment	[redacted] (Table 38)	95% CIs, beta distribution	B.3.4.4
Utilities for End stage care	0.38 (Table 38)	95% CIs, beta distribution	B.3.4.4
Post-SCT utilities	0-2 weeks: 0.42 3 weeks-month 4: 0.60 3 months onwards: 0.77	95% CIs, beta distribution	B.3.4.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	(Table 38)		
Carers' utilities	Disease control: 0.559 Subsequent treatment: 0.366 (Table 37)	95% CIs, beta distribution	B.3.4.3
Costs			
Mogamulizumab cost per cycle	[redacted] (Table 39)	SE, normal distribution	B.3.5.1
Comparator drug costs (per cycle)	£0.39 for methotrexate to £537.55 for TSEBT (Table 40)	SE, normal distribution	B.3.5.1
Administration costs (per administration)	£141, £229 and £286 (Table 41)	SE, normal distribution	B.3.5.1
Health state costs (per cycle)	Disease control: [redacted] Subsequent treatment: [redacted] End stage care: [redacted] (Table 44) Monitoring post aSCT relapse: [redacted]	SE, normal distribution	B.3.5.2 B.3.5.4
Grade 3 and 4 adverse event costs (per cycle)	Mogamulizumab: £4.81 ECM: £15.88 (based on Table 34 and Table 45)	SE, normal distribution	B.3.5.3 B.3.3.6
Subsequent treatment costs (total)	£13,184.79 (estimated from Table 40, Table 41, Table 46, Table 47)	SE, normal distribution	B.3.5.4
Subsequent treatment costs after aSCT (total)	£5,405.07	SE, normal distribution	B.3.5.4
Other			
Composition of the ECM arm	Table 22	Dirichlet distribution	B.1.1.1

Key: CI, confidence interval.

B.3.6.2. Assumptions

The main assumptions used in the base case are described in Table 49.

Table 49: Summary of assumptions of the economic analysis

#	Assumption	Likely direction of bias	Justification
1	The model health states capture the elements of the disease and care pathway that are important for patient health outcomes and NHS/PSS costs.	No bias expected	Sections A.10, B.3.2.2
2	Patients are assumed to have the potential to receive aSCT after current treatment and after subsequent treatment if eligible and have achieved a good PR or CR.	Direction of bias in uncertain, effect on ICER is minor	Section B3.2.2
3	Time to next treatment is a better proxy for changes in quality of life, resource use and treatment pattern than progression	The use of progression slightly increases ICER, but ignores treatment-free period seen in the MAVORIC trial and clinical expert opinion	Section B3.2.2
4	Efficacy data from the MAVORIC trial for vorinostat is applicable for the current clinical management in the UK	Direction of bias in uncertain	Section B3.2.3
5	Overall survival for patients not receiving aSCT can be extrapolated: • using log-normal distribution for mogamulizumab • using IPCW crossover adjustment with all parameters included and extrapolated with exponential distribution for ECM • based on statistical fit and clinical/biological plausibility	While external validation supported these choices, the use of IPCW and these distributions potentially overestimate the benefit of mogamulizumab The use of the IPCW model with all parameters included slightly underestimates the treatment benefit	Section B 3.3.1

#	Assumption	Likely direction of bias	Justification
6	Next treatment-free survival can be extrapolated with separately fitted generalised gamma distributions	The effect on the ICER is minor, other distributions estimate slightly better or slightly worse benefit	Section B3.3.2
7	Time on treatment with vorinostat can be assumed to be the maximum time on treatment for the components of ECM	As the vorinostat time on treatment is shorter than the treatment duration with some of the treatments used in ECM (e.g. bexarotene, methotrexate, interferon), it underestimates treatment duration with ECM, and overestimates the ICER	Section B3.3.5
8	The only benefit to carer's quality of life is increased time in the Disease control state. Increasing life expectancy in itself is assumed not to affect carers' quality of life.	It is likely to underestimates the benefit to carers' quality of life and overestimate the ICER	Section B3.4.4
9	For community-based health care costs the data based on expert opinion accepted by the ERG and Committee in NICE TA577 represents the actual costs	Due to lack of data the direction of bias in uncertain	Section B3.5.2
10	A half-cycle correction was not applied to outcomes	Due to the short cycle length (1 week), no bias is expected	Section B.3.2.2

B.3.7. Base-case results

B.3.7.1. Base-case incremental cost-effectiveness analysis results

In the base case, mogamulizumab results in a discounted incremental LYs of 3.69, [redacted] (Table 50). This led to a discounted QALY gain of 2.83 (Table 51).

Table 50: Discounted disaggregated life -years (LYs)

	Mogamulizumab	Established clinical management	Increment	% increment
Disease control - Current treatment	[redacted]	[redacted]	[redacted]	[redacted]
Disease control - Surveillance	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments/ESC	[redacted]	[redacted]	[redacted]	[redacted]
aSCT DF	[redacted]	[redacted]	[redacted]	[redacted]
aSCT Relapsed	[redacted]	[redacted]	[redacted]	[redacted]
Total	**6.40**	**2.71**	**3.69**	**100%**
Key: aSCT, allogeneic stem cell transplant; DF, disease free; ESC, end stage care.				

Table 51. Discounted disaggregated quality-adjusted life-years (QALYs)

	Mogamulizumab	Established clinical management	Increment	% increment
Disease control - Current treatment	[redacted]	[redacted]	[redacted]	[redacted]
Disease control - Surveillance	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments/ESC	[redacted]	[redacted]	[redacted]	[redacted]
aSCT DF	[redacted]	[redacted]	[redacted]	[redacted]
aSCT Relapsed	[redacted]	[redacted]	[redacted]	[redacted]
Total	**4.60**	**1.78**	**2.83**	**100%**
Key: aSCT, allogeneic stem cell transplant; DF, disease free; ESC, end stage care.				

Including the [redacted], the discounted incremental costs were £95,576.88[redacted]

[redacted] (Table 52). [redacted] due to the fact that the comparator treatments are mostly cheaper generic versions or short-term interventions, leading to almost all of the mogamulizumab drug costs being additional cost [redacted] due to the high cost of MF/SS in the community setting due to the intense schedule of dressings and other wound care.

Table 52. Discounted disaggregated costs [redacted]

	Mogamulizumab	Established clinical management	Increment	% increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs - current treatment	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs - Surveillance	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs - Subsequent treatments	[redacted]	[redacted]	[redacted]	[redacted]
ESC costs – Progressed	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs - non aSCT	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]
aSCT costs and monitoring DF	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs - aSCT	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring aSCT – Relapsed	[redacted]	[redacted]	[redacted]	[redacted]
ESC costs – aSCT	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	£95,577	100%
Key: aSCT, allogeneic stem cell transplant; DF, disease free; ESC, end stage care.				

This, with the [redacted], resulted in an incremental cost-effectiveness ratio (ICER) of £33,819/QALY (Table 53).

Table 53: Base-case results (discounted) [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Established clinical management	[redacted]	2.71	1.78					
Mogamulizumab	[redacted]	6.40	4.60	£95,577	3.69	2.83	£33,819	£33,819
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

B.3.8. Sensitivity analyses

Various sensitivity analyses were conducted to explore the main areas of uncertainty within the model, including parameter uncertainty and structural uncertainty. Parameter uncertainty was assessed in the univariate (one-way) sensitivity analysis and probabilistic sensitivity analysis (PSA). Structural uncertainty was explored using the alternative simple partitioned survival analysis using PFS and in a series of scenario analyses, including assumptions around the structural form of OS and NTFS, the sources used to inform parameters and assumptions regarding the underlying calculations.

B.3.8.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to account for variability in outcomes due to parameter uncertainty. The probabilistic analyses were run for 1,000 replications where parameter estimates were repeatedly sampled from probability distributions to determine an empirical distribution for costs, LYs and QALYs. NTFS, OS, ToT, DFS, probabilities, costs and utilities were varied simultaneously and independently of each other. Time horizon and discount rates were excluded from the PSA, since they are not subject to parameter uncertainty.

Parametric distributions were varied using the means and variance-covariance matrices of the parameters in Cholesky decomposition.[92] This helped to account for the correlation between parameters.

For utilities a beta distribution was used due to the bounds of the distribution (i.e., 0 to 1), using the standard error as the source of variation to calculate alpha and beta parameters of the distribution.[92, 93] Similarly beta distribution was used for percentages, such as dose intensity or proportion of patients receiving aSCT. Composition of ECM was varied with Dirichlet distribution. Log-normal distribution was used for body weight and normal distribution or all other parameters. For more details please see Appendix T.

The probabilistic results are presented in Table 54 and are similar to the deterministic results. The results are presented on the cost-effectiveness plane in

Figure 37. The probability of mogamulizumab being cost-effective at the £30,000/QALY threshold is 21.8%, while at the £50,000/QALY threshold 97.80%.

Table 54: Comparison of the probabilistic and deterministic results

	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALYs)	ICER (£/LYs)
Deterministic results	95,576.88	2.83	3.69	33,819.17	25,914.05
Probabilistic results	95,135.76	2.83	3.69	33,610.88	25,788.68
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.					

Figure 37: Cost-effectiveness plane

Figure 38: Cost-effectiveness acceptability curves (CEACs)

B.3.8.2. Deterministic sensitivity analysis

Univariate deterministic sensitivity analysis was performed where each parameter was varied according to its 95% CI or standard error, while holding all other parameters constant. Where the published study or source for parameter values did not report standard errors or CIs, 20% variation of the mean was assumed. All parameters with uncertainty were included in the sensitivity analyses. Time-horizon and discount rates were not varied as these where not subject to parameter uncertainty, however, the impact of alternative discount rates and time horizon were examined in scenario analyses, as described below. Unit costs and resource use for non-drug resources were not independently varied, but as health state costs. For a detailed list of parameters varied and range of variation tested in the one-way univariate sensitivity analysis see Appendix T.

As all scenarios were in the upper right-hand quadrant of the cost-effectiveness plane (mogamulizumab is more effective and more costly), the estimation of incremental net benefit (INB) was not needed. The tornado diagram showed that the results are most sensitive to the utility for the 'Subsequent treatment' health state, survival extrapolations, mogamulizumab costs and the disease management / monitoring costs for the 'Subsequent treatment' health state (Figure 39).

Figure 39: Tornado diagram [redacted]

B.3.8.3. Scenario analysis

Scenario analyses were conducted to test the robustness of the model considering the structural and methodological uncertainties. These included assumptions around:

- Time horizon;
- Discount rate;
- Population;
- Model structure;
- Extrapolation;
- Utilities; and
- Costs.

The results are presented in Table 55. The results were relatively stable with most scenarios resulting in ICERs between £30,000-£40,000/QALY. One scenario resulted in ICER below £30,000/QALY. Only three scenarios resulted in ICERs between £40,000-£50,000:

- Using TSE for the crossover adjustment, that did not seem clinically plausible
- Extrapolating OS in both arms with Weibull distribution, which had the worse AIC/BIC out of all the distributions in both treatment arms
- Extrapolating OS in both arms with generalised gamma distribution, which suggested very optimistic survival predictions for ECM, that lacked clinical validity and suggested a potential plateau that is not seen in clinical practice or the literature for ECM.

Table 55: Deterministic scenario analysis

Parameter	Base case	Scenario analysis	Justification	Technology	Total costs	Total QALYs	ICER
Base case				**ECM**	[redacted]	**1.78**	**£33,819**
				Mogamulizumab	[redacted]	**4.60**	
Annual discount rate (costs and health outputs)	3.5%	6%	Testing model result sensitivity to time-preference discount rate assumptions	ECM	[redacted]	1.64	
				Mogamulizumab	[redacted]	3.95	£37,665
Discount rate (costs and health outputs)	3.5%	0%		ECM	[redacted]	2.05	
				Mogamulizumab	[redacted]	6.01	£28,661
Model time horizon reduced	30	20	Less than 10% of patients are expected to be alive at 20 years with ECM	ECM	[redacted]	1.74	
				Mogamulizumab	[redacted]	4.30	£35,779
Population: ITT	Advanced	ITT	MAVORIC trial population	ECM	[redacted]	2.34	
				Mogamulizumab	[redacted]	4.72	£35,643
Per mg costing (vial sharing) for mogamulizumab	Dose banding: [redacted] per administration	[redacted] per administration	Centres seeing more patients may be able to share vials	ECM	[redacted]	1.78	
				Mogamulizumab	[redacted]	4.60	£32,837
No aSCT after current treatment	Clinician survey ECM: 4.6% Moga 8.0%	0% for both arms	Corresponds to MAVORIC trial protocol	ECM	[redacted]	1.58	
				Mogamulizumab	[redacted]	4.49	£34,433
KOL survey values for probability of aSCT after subsequent treatments	MAVORIC trial ECM: [redacted] Moga: [redacted]	Clinician survey ECM: 6.3% Moga: 8.0%	Consistency in data source between the two time points for aSCT	ECM	[redacted]	1.97	
				Mogamulizumab	[redacted]	4.60	£34,623
Use of exponential for NTFS	Generalised gamma	[redacted]	Testing alternative functional forms for extrapolation	ECM	[redacted]	1.78	
				Mogamulizumab	[redacted]	4.55	£34,642
Use of Weibull for NTFS		[redacted]		ECM	[redacted]	1.77	£34,794

Parameter	Base case	Scenario analysis	Justification	Technology	Total costs	Total QALYs	ICER
				Mogamulizumab	[redacted]	4.54	
Use of lognormal for NTFS		[redacted]		ECM	[redacted]	1.77	
				Mogamulizumab	[redacted]	4.60	£33,818
Use of loglogistic for NTFS		[redacted]		ECM	[redacted]	1.77	
				Mogamulizumab	[redacted]	4.62	£33,492
Use of Gompertz for NTFS		[redacted]		ECM	[redacted]	1.78	
				Mogamulizumab	[redacted]	4.57	£34,215
Use of exponential for OS for both arms	EMC: exponential Moga: lognormal	[redacted]		ECM	[redacted]	1.78	
				Mogamulizumab	[redacted]	3.99	£39,189
Use of Weibull for OS for both arms		[redacted]		ECM	[redacted]	1.83	
				Mogamulizumab	[redacted]	3.76	£42,900
Use of lognormal for OS for both arms		[redacted]		ECM	[redacted]	1.81	
				Mogamulizumab	[redacted]	4.60	£33,955
Use of loglogistic for OS for both arms		[redacted]		ECM	[redacted]	1.75	
				Mogamulizumab	[redacted]	4.40	£35,224
Use of generalised gamma for OS for both arms		[redacted]		ECM	[redacted]	2.65	
				Mogamulizumab	[redacted]	4.21	£49,553
Use of Gompertz for OS for both arms		[redacted]	Not applicable, Gompertz predictions clinically not valid (>30% survival at 30 years for ECM)				
Use of restricted set of variables for IPCW adjustment	IPCW - Full variable set	IPCW - Restricted variable set	Use of full set may lead to over-fitting, restricted variable set reduces uncertainty	ECM	[redacted]	1.77	
				Mogamulizumab	[redacted]	4.60	£33,745

Parameter	Base case	Scenario analysis	Justification	Technology	Total costs	Total QALYs	ICER
Use of two-stage adjustment to correct for cross-over with full variable set		Two-stage estimation – Full variable set	Testing alternative method to correct for cross-over	ECM	[redacted]	2.91	
				Mogamulizumab	[redacted]	4.60	£45,872
Use of two-stage adjustment to correct for cross-over with restricted variable set		Two-stage estimation – Restricted variable set		ECM	[redacted]	2.81	
				Mogamulizumab	[redacted]	4.60	£44,123
Use of average treatment-specific utility throughout the disease control health state (no cycle-specific utilities)	Cycle-specific utilities for first 12 cycles	Average utility throughout disease control health state	Reducing variability of treatment impact over time	ECM	[redacted]	1.80	
				Mogamulizumab	[redacted]	4.62	£33,833
Use of ALCANZA trial post-progression utility value for subsequent treatment health state	MAVORIC trial: 0.682	ALCANZA trial: 0.61	Used in TA577	ECM	[redacted]	1.68	
				Mogamulizumab	[redacted]	4.36	£ 35,767
Use of TTO values for carer utilities	EQ-5D values	TTO values	Testing alternative method to evaluate carer utilities	ECM	[redacted]	1.78	
				Mogamulizumab	[redacted]	4.55	£34,509
Exclusion of carer utilities	Included	Excluded	Implementation of carer utilities is uncertain	ECM	[redacted]	1.78	
				Mogamulizumab	[redacted]	4.43	£36,065
Model structure based on progression	Disease control-based	Progression-based	Aligns with TA577 model structure	ECM	[redacted]	1.70	
				Mogamulizumab	[redacted]	4.44	£34,834

B.3.8.4. Summary of sensitivity analyses results

While there are important uncertainties in the cost-effectiveness analyses, the results are stable with the ICERs of almost all of the scenarios and one-way sensitivity analyses falling between £28,000-£40,000 per QALY. The only scenarios that have ICERs outside this range result in ICERs between £40,000-£50,000 per QALY and are clinically implausible. The probabilistic analyses show the CEAC steeply increasing between the thresholds of £30,000 and £50,000, with the probability of mogamulizumab being cost-effective at the £30,000/QALY threshold is 21.8%, while at the £50,000/QALY threshold 97.8%.

B.3.9. Subgroup analysis

The base case population was a subgroup of the MAVORIC trial, while the ITT population was presented as a scenario analysis in section B.3.8.3.

B.3.10. Validation

B.3.10.1. Validation of cost-effectiveness analysis

The cost-effectiveness analyses have undergone both conceptual and technical validation. Conceptual validation was provided by five in depth face-to-face interviews with three clinical experts with experience in treating MF/SS patients and with the use of mogamulizumab.[49] Additionally, an advisory board meeting was conducted including a clinical expert.[50] On these meetings, the model concept, the inputs and methods used, and the results were discussed. For more information please see Appendix U.

In addition to conceptual validation, a comprehensive and rigorous quality check was performed once programming was finished. A model validator not involved in the original programming checked the calculation and reference formulas, and an additional team member checked the values of numbers supplied as model inputs.

B.3.11. Interpretation and conclusions of economic evidence

MF and SS are orphan population, with a high disease burden and high unmet need. Mogamulizumab is a new immune oncology treatment for MF and SS patients with at least one prior treatment.

A flexible, transparent cost-utility model was developed based on the pivotal, MAVORIC trial using the standard partitioned survival analysis approach, and incorporating the possibility of patients receiving aSCT, the only potentially curative treatment, as seen in the MAVORIC trial and in previous NICE appraisal in MF/SS (TA577). Due to its unique mechanism of action, disease control or time to next treatment was used in place of progression determining the health states, i.e. next-treatment-free survival (NTFS) was incorporated instead of PFS. The model compared mogamulizumab to the Established Clinical Management in a subpopulation, that is in line with clinical practice and the NICE TA577 and has the highest unmet need, advanced MF/SS patients (stage ≥IIB MF and all SS) with at least one prior treatment who are ineligible or refractory to BV

Using the submitted [redacted] for mogamulizumab, mogamulizumab led to a QALY gain of 2.83 and a discounted incremental cost of £95,577. [redacted] of the incremental costs were [redacted] due to ECM including mostly cheaper generic treatments or short-term interventions and [redacted] the intense schedule of dressings and other wound care in the community care setting. This resulted in an incremental cost-effectiveness ratio (ICER) of £33,819/QALY [redacted] mogamulizumab.

As with all models, especially those for orphan populations, there are important uncertainties. However multiple additional steps were taken by Kyowa Kirin to reduce these uncertainties where possible including:

- Conducting multiple addition studies, e.g.
    - retrospective cost study in the UK Hospital Episode Statistics database to reduce uncertainties around the health state costs emphasized in NICE TA577,
    - a vignette study to assess carers' burden highlighted similarly in the NICE TA577

    - short clinician survey to fill in data gaps, such as the probability of aSCT after current treatment and long-term survival
- Considering and assessing multiple methodological approaches, e.g.
    - using all three complex crossover adjustment methods recommended by the NICE Technical Support Document and exploring their applicability
    - assessing the use of the MAVORIC vorinostat arm as a proxy for ECM by comparing it to published data (ALCANZA trial physician choice arm, bexarotene phase II study) and eliciting expert input
- Thoroughly exploring clinical plausibility of the survival extrapolations using:
    - published observation data,
    - the UK Hospital Episode Statistics database and
    - expert input
- Conducting extensive validation of model structure, assumptions, inputs and generalisability to the UK patient population using multiple in-depth interviews with leading NHS consultants experienced with the treatment and care of MF and SS patients in an NHS England setting
- Conducting extensive sensitivity analyses, including parameter and structural sensitivity analyses with a flexible and transparent model

These efforts resulted in a model, where, despite the uncertainties, the results were stable with the ICERs of almost all scenarios and one-way sensitivity analyses falling between £28,000-£40,000 per QALY. The only scenarios that have ICERs outside this range (£40,000-£50,000 per QALY) were clinically implausible.

In an orphan disease with a high unmet need and high disease burden, with a [redacted] offered, the ICER for mogamulizumab is around the NICE threshold in all plausible scenarios.

B.4. References

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Baseline characteristics of ALCANZA and MAVORIC patients

Appendix M: Caregiver burden study

Appendix N: HRQL tools

Appendix O: Additional results and post-hoc analyses from the MAVORIC trial

Appendix P: Baseline characteristics of the PROCLIPI population

Appendix Q: Analysis of Hospital Episode Statistics (HES) data for patients with CTCL in England

Appendix R: Results from RPSFTM cross-over analysis

Appendix S: Base case inputs

Appendix T: Sensitivity analyses

Appendix U: Clinical validation

Appendix V: Survival analyses

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mogamulizumab for treated mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma [ID1405]

Clarification questions

January 2020

File name	Version	Contains confidential information	Date
ID1405 mogamulizumab Clarification letter to PM_MASTER_updated marking 24022020	2	No	24th February 2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Literature searches

A1. Please provide full details for the searches of conference proceedings referred to in Appendix D.1, including the specific resources searched, the search strategies, search terms used, and results.

The details of the conferences searched, and the search terms used are as below:

Conference name	Access date	URL	Search terms	Number of included studies
American Society of Clinical Oncology (ASCO: 2018–19)	8th July 2019	https://meetinglibrary.asco.org/	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis Sézary, Primary cutaneous, Pagetoid reticulosis, Lymphomatoid Papulosis	3
European Society for Medical Oncology (ESMO: 2017–18) [a]	8th July 2019	ESMO abstract-book 2017: https://www.esmo.org/content/download/117241/2057634/file/ESMO-2017-Abstract-Book.pdf ESMO abstract-book 2018: https://www.esmo.org/content/download/149891/2691140/file/ESMO-2018-Abstract-Book-partial-version.pdf		0
International Conference on Malignant Lymphoma (ICML:2017–19)	8th July 2019	ICML abstract-book 2017: http://www.lymphcon.ch/icml/website/doc/ICML_AbstractBooks_vecchi/14-ICMLJune14-172017/14-ICMLAbstractBook.pdf		5

Conference name	Access date	URL	Search terms	Number of included studies
		ICML abstract-book 2019: http://www.lymphcon.ch/icml/website/doc/15-ICML_Abstract_Book.pdf		
International Society of Cutaneous Lymphomas (ISCL: 2018–19)	8th July 2019	https://www.jidonline.org/content/abstracts		1
World Congress of Cutaneous Lymphomas (WCCL: 2016)	9th July 2019	http://www.cutaneouslymphoma.org/Portals/0/meeting_support/3WCCL_Final_Program.pdf		1
International Society for Pharmacoeconomics and Outcomes Research (ISPOR 2017–18): European [a]	9th July 2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp		1
International Society for Pharmacoeconomics and Outcomes Research (ISPOR: 2018-19): Annual	9th July 2019	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp		0
American Society of Haematology (ASH: 2017–18)	9th July 2019	ASH 2017: http://www.bloodjournal.org/content/130/suppl_1 ASH 2018: http://www.bloodjournal.org/content/132/suppl_1		0
EORTC Cutaneous Lymphoma Meeting 2018	9th July 2019	https://www.sciencedirect.com/journal/european-journal-of-cancer/vol/101/suppl/S1		1
European Medicines Agency (EMA)	11th July 2019	https://www.ema.europa.eu/en		2
Notes: a, conference was not published for 2019 at the time of conferences hand searching.				

A2. No search strategy is provided for the Cochrane Database of Systematic Reviews (CDSR) in Appendix D; the CENTRAL search strategy reported in Table D4 is a duplicate of the MEDLINE In-process (PubMed) strategy reported in Table D3.

Please provide full search strategies for CDSR and CENTRAL.

Please find below the Cochrane CENTRAL and CDSR search strategies employed in the clinical SLR:

Cochrane (CENTRAL): searched on 2 July 2019

S. No	Search terms	Results
1	MeSH descriptor: [Lymphoma, T-Cell, Cutaneous] explode all trees	82
2	MeSH descriptor: [Sezary Syndrome] explode all trees	15
3	MeSH descriptor: [Mycosis Fungoides] explode all trees	51
4	MeSH descriptor: [Pagetoid Reticulosis] explode all trees	0
5	MeSH descriptor: [Lymphomatoid Granulomatosis] explode all trees	4
6	MeSH descriptor: [Lymphomatoid Papulosis] explode all trees	2
7	"cutaneous t cell lymphoma":ab,ti,kw OR "sezary syndrome":ab,ti,kw OR "mycosis fungoides":ab,ti,kw OR "alibert bazin":ab,ti,kw OR "granuloma fungoides":ab,ti,kw OR "skin t-cell lymphoma":ab,ti,kw OR "granuloma sarcomatodes":ab,ti,kw OR wucherflechte:ab,ti,kw OR ctcl:ab,ti,kw OR "lymphomatoid papulosis":ab,ti,kw OR "pagetoid reticulosis":ab,ti,kw OR "woringer-kolopp disease":ab,ti,kw OR "woringer kolopp*":ab,ti,kw OR "granulomatous slack skin":ab,ti,kw	447
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	448
9	#8 in Cochrane Reviews, Trials	446

Decision problem

A3. Priority question. The final scope issued by the National Institute for Health and Care Excellence (NICE) defined the population of interest to be *"adults with mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma following at least one prior systemic therapy"*. The population addressed in the decision problem presented in the company submission (CS) is narrower, namely *"adults with advanced mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma (i.e. stage ≥IIB MF* [mycosis fungoides] *and all SS* [Sézary syndrome]*) following at least one prior systemic therapy who are clinically ineligible for or refractory to treatment with brentuximab vedotin (BV)"*.

Please confirm that the population in the CS is narrower than that defined in the NICE scope.

The population in the CS is narrower than that defined in the NICE scope (and thus narrower than the marketing authorisation). As reported in the CS (Section B.1.1), this population reflects patients with the greatest unmet need in current clinical practice and thus where mogamulizumab provides the most clinical benefit and where, based on UK clinical opinion, mogamulizumab is anticipated to be used within the current treatment pathway.

A4. Priority question. The final scope issued by NICE defined the comparator of interest to be *"established clinical management without mogamulizumab"*. However, MAVORIC, the main trial supporting the CS, compared mogamulizumab to vorinostat which the company *"…considered a reasonable proxy for standard of care in England, as supported by naïve comparisons of PFS* [progression-free survival] *data for physician's choice in ALCANZA (bexarotene and methotrexate), comparisons of ORR* [overall response rate] *seen with vorinostat in the MAVORIC trial to bexarotene in a Phase II study and the experience of clinical experts…"*. The CS further stated that *"within NHS England, methotrexate, bexarotene and IFN* [interferon] *comprise the most commonly used treatments for advanced MF or SS patients who have received at least one prior systemic therapy and who are clinically ineligible for, or refractory to, treatment with BV; thus, these treatments make up the key comparators for this submission"*.

Regarding the comparison to ALCANZA:

a. **Please provide evidence to show that vorinostat is a reasonable proxy for established clinical management as defined in the scope, including methotrexate, bexarotene and IFN (interferon), in regards to both efficacy and safety outcomes.**

In order to enable a robust sample size for the MAVORIC study, alternatives to current NHS standard of care had to be available, as the majority of European patients were likely to have already received most currently available treatments. Vorinostat, which is not currently licensed in Europe, was chosen as the comparator of choice to enable high recruitment of patients during MAVORIC, as treating patients with an unlicensed comparator and/or re-challenging with agents used previously used in clinical practice may have presented ethical challenges. Furthermore, vorinostat is the only available comparator with data in SS patients.

As discussed in the CS (see Section B.2.9), vorinostat is considered a reasonable proxy for established clinical management as defined in the scope, based on a review of the key clinical evidence (RCT and regulatory evidence in the CTCL population) and UK clinical expert opinion. A summary of the evidence presented in Section B.2.9 is summarized in Table 1.

Table 1: Summary of clinical evidence presented in the CS in support of vorinostat as a reasonable proxy for established clinical management as defined in the scope

Vorinostat as a proxy for established clinical management	• The physician's choice arm of the ALCANZA study was considered to represent established clinical management by NICE during TA577[1] • PFS curves from the vorinostat arm of the MAVORIC study and the physician's choice arm of the ALCANZA study overlap (see Figure 17 of the CS) • A leading expert stated "the efficacy of vorinostat can be assumed the same as for established clinical management in the UK" during clinical consultation [2] • Across 193 CTCL patients, of which 93 had advanced stage disease refractory to prior systemic therapy, bexarotene resulted in an ORR in the skin of 31% [3] – This is similar to the ORR based on skin assessment only of 30%, as observed in the vorinostat arm of the MAVORIC study [4]
Key: CS, company submission; CTCL, Cutaneous T-cell lymphoma; ORR, objective response rate; PFS, progression-free survival.	

Further to this previously summarized evidence, Table 2 provides an overview of the study characteristics and efficacy outcomes for all bexarotene, methotrexate and interferon (IFN) non-RCTs identified through clinical SLR (the MAVORIC and ALCANZA studies were the only RCTs identified). Considerable heterogeneity is observed across trial designs, patient populations and outcomes that limits the usefulness of these data in addition to the key clinical evidence previously described.

Table 3 presents a summary of adverse events from all identified studies investigating bexarotene, IFN or vorinostat. Of note, the SLR identified no studies reporting AEs relating to methotrexate. Overall, the safety profile of vorinostat appears to be a conservative estimate of the combined safety profile of established clinical management with higher rates of adverse events (AE) observed compared to AE rates for bexarotene and IFN.

Table 2: Summary of bexarotene, IFN and methotrexate-based studies (non-RCTs)

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment /comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
Sokolowska-Wojdylo 2016[5]	• NR • Observational non-comparative • NR • Multicentre • Poland	RR, TTR, DoR	Bexarotene	21	• 19 (90.47) • 2 (9.52)	58.6 (19–84)	IA: 1 IB: 1 IIA: 1 IIB: 4 III: 4 IIIA: 5 IVA1: 3 IVB: 2	ORR of 81% in patients treated with bexarotene therapy at a mean duration of therapy 14.5 months. An ORR was defined as the sum of clinical CR or PR
Breneman 2002[6]	• Phase I/II • nRCT non-comparative • Open label • Multicentre • US	RR	Bexarotene gel	19	NR	NR	All patients with Stage IA through to IIA (one patient with IIB, protocol deviation)	ORR of 47% for bexarotene therapy in MF patients at a treatment duration of 59 months
Duvic 2017[7]	• Phase I/II • nRCT non-comparative • Open label • Multi-centre • US, Italy	RR	Bexarotene + pralatrexate	34	• 30 (88) • 3 (9)	66 (39–85)	NR	• ORR of 60.6% for bexarotene + pralatrexate combination therapy • Median PFS - 12.8 (range: 0.5-29.9)

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment /comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
Papadavid 2008[8]	• NR • Observational comparative • NR • Single centre • Greece	RR, safety and tolerability	Bexarotene 300 mg/day oral + PUVA	9	• 9 (100) • 0 (0)	NR	IA: 1 (11.1) IB: 6 (66.1) IIA: 1 (11.1) III: 1 (11.1)	The 150 mg bexarotene treatment group had a higher global ORR (100%) compared with the 300 mg group (57%) at the study end. An ORR was defined as the sum of clinical CR or PR. However, the superiority of 150 mg group could not be advocated due to very small sample size (N=2)
			Bexarotene 150 mg/day oral + PUVA	5	• 5 (100) • 0 (0)	NR	IB: 3 (60) IIB: 1 (20) III: 1 (20)	
Hughes 2015[9]	• NR • Observational comparative • NR • Multicentre • Australia	TTNT	Low dose methotrexate	84	NR	NR	NR	• Median TTNT = 5 months • Median TTNT from 1L MTX = 4.4 months • Median TTNT from mid-line MTX = 7.5 months • Median TTNT from late-line MTX = 1.6 months

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment /comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
			Interferon-alpha	68	NR	60.3	NR	• Median TTNT = 8.7 months
			Bexarotene	20	NR	66.6	NR	• Median TTNT = 4.1 months
Talpur 2014[10]	• Phase II • Observational comparative • NR	RR, safety and tolerability	Bexarotene 300 mg + pralatrexate	3	• 3 (100) • 0 (0)	Mean: 57.6 (range: 41-77)	NR	Of three patients treated with bexarotene 300 mg plus pralatrexate, only one had shown global ORR (i.e. 33.33%). Of 11 patients treated with bexarotene 150 mg + pralatrexate, six had shown a global ORR (i.e. 54.54%)
			Bexarotene 150 mg + pralatrexate	11	• 11 (100) • 0 (0)	Mean: 62.27 (range: 42-82)	NR	
Talpur 2002[11]	• NR • Observational non-comparative • NA[&] • Single centre	RR, safety and tolerability	Bexarotene based regimen	16	• 14 (87.5) • 2 (12.5)	65 (43–79)	IIB: 1 (6.25) III: 9 (56.25) IVA: 4 (25) IVB: 2 (12.5)	Global ORR of 68.75% in patients treated with bexarotene based regimen

Study name	• **Study phase** • **Study design** • **Blinding** • **Study centre** • **Study country**	List of endpoints	Treatment /comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
	• USA							
Rupoli 2016[12]	• Phase II • nRCT non-comparative • Multicentre • Italy	RR, EFS and safety	Bexarotene + PUVA	15	NR	NR	IB–IVA	Bexarotene plus PUVA combination therapy was associated with a global ORR in 60% of patients at a median follow up of 53 months
Illidge 2013[13]	• Phase II • nRCT non-comparative • NR • Multicentre • UK	ORR at 24 weeks, RR, PFS, OS, safety, change in mSWAT and QoL	Gemcitabine + bexarotene	36	NR	65 (38–83)	IB: 5 (13.9) IIA: 2 (5.6) IIB: 8 (22.2) III: 8 (22.2) IVA: 13 (36.1)	• Higher global ORR at Week 12 (31.4%) compared with global ORR at Week 24 (14.3%) in the patients treated with gemcitabine plus bexarotene combination therapy • Median PFS – 5.3 • Median OS – 21.2 months (median follow-up 16.4 months)
Bunn Jr 1987[14]	• NR	RR, safety	Recombinant interferon -alfa	20	NR	NR	II: 5 (25) III: 2 (10)	• At 6 months, a global ORR of 50%

Study name	• **Study phase** • **Study design** • **Blinding** • **Study centre** • **Study country**	List of endpoints	Treatment /comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
	• nRCT non-comparative • NR • NR • NR •						IV: 13 (65)	was associated with recombinant interferon alfa 50 mIU three times a week
Aviles 2015[15]	• NR • nRCT comparative • Open label • NR • NR	OS, safety RR, DOR, PFS	Interferon + methotrexate	201	• 201 (100) • 0 (0)	64.5 (36–71)	II B: 73 (36) IIIB: 57 (28) IV A: 40 (20) IV B: 29 (14)	• Global CR was observed in 80% of patients treated with Interferon + retinoids combination • OS - Significantly higher survival rate in patients treated with interferon plus methotrexate compared with interferon plus retinoids (i.e. 70% versus 67%; p=0.03) • PFS - at five years of follow-up, no significant difference in PFS
			Interferon + retinoids	176	• 176 (100) • 0 (0)	62.9 (43–75)	II B: 76 (42) IIIB: 36 (20) IV A: 35 (19) IV B: 31 (17)	

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment /comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
								rate was observed between patients treated with interferon plus methotrexate (60%) versus interferon plus retinoids (62%; p=0.8)
Roenigk Jr 1990[16]	• Phase I • nRCT non-comparative • NR • Multicentre • NR • NR	RR, DoR, TTR, safety	Interferon alpha-2a + PUVA	15	NR	NR	IB: 7 (63.6) IIB: 2 (18.2) III: 1 (9.1) IVB: 1 (9.1)	• Interferon alpha-2a (6-30 mIU three times weekly) combination therapy with PUVA resulted in a global ORR of 90.9%
Foss 1992[17]	• Phase II • nRCT non-comparative • NR • NR • NR	RR, OS	Pentostatin + interferon alfa-2a	29	NR	NR	IV A: 8 (80) IVB: 2 (20)	• Interferon alpha-2a (10–50 mIU three times a week) combination therapy with pentostatin (Nipent®) was associated with a global ORR of 30% • Median OS - 15

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment /comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
Kuzel 1995[18]	• Phase I/II • nRCT non-comparative • NR • NR • USA	RR, DoR, safety	Interferon alfa-2a + phototherapy	8	NR	NR	NR	• Global ORR of 75% was observed in interferon alpha-2a (3–12 mIU three times a week) combination therapy with phototherapy treated population
Foss 1994[19]	• Phase II • nRCT non-comparative • NR • NR • NR	RR, TTP	Fludarabine + interferon Alfa-2a	21	NR	NR	NR	• Interferon alpha-2a (5 mIU three times a week) combination therapy with fludarabine resulted in a global ORR of 50%
Kohn 1990[20]	• Phase II • nRCT non-comparative • NR • NR • NR	RR, RR (blood, skin, lymph node, viscera), DoR, TTR, safety	Recombinant interferon -alfa	24	NR	60 (25–70)	NR	• Recombinant interferon alfa (10–50 mIU/m2) therapy was associated with a global ORR of 29% at the study end (Cut-off: 1 December 1988). The study reported a superior ORR in

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment /comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
								skin disease (25%) compared with blood (4.16%) and lymph nodes (12.5%) • Median OS of patients receiving recombinant interferon alfa therapy was 13 months (range <1–>54)
McDonald 1978 [21]	• NR • nRCT non-comparative • NR • Multicentre • USA	RR, DOR, safety	Methotrexate + Citrovorum factor	11	• 6 (100) 0 (0)	Mean: 58.5 (range: 41–78)	NR	• All 11 patients experienced a good to excellent response • Complete remissions were induced in 7/11 patients

Key: DoR, duration of response; EFS, event-free survival; EQ-5D, EuroQol 5-Dimension; EPOCH, etoposide, prednisone, vincristine (Oncovin®), cyclophosphamide and doxorubicin hydrochloride (hydroxydaunorubicin hydrochloride); FACT-G, Functional Assessment of Cancer Therapy - General; ORR: overall response rate; PFS: progression-free survival; PUVA, psoralen plus ultraviolet A therapy, TTNT, time to next treatment; TTR, time to response.

Table 3: Summary of vorinostat, bexarotene and interferon adverse events from non-RCTs

Study name	Treatment/comparator	N	Any adverse event, n (%) Any grade Grade ≥3	Rash, n (%) Any grade Grade ≥3	Diarrhoea, n (%) Any grade Grade ≥3	Fatigue, n (%) Any grade Grade ≥3	Pyrexia, n (%) Any grade Grade ≥3	Peripheral neuropathy, n (%) Any grade Grade ≥3	Anaemia, n (%) Any grade Grade ≥3	Nausea, n (%) Any grade Grade ≥3	Pruritus, n (%) Any grade Grade ≥3	Thrombocytopenia, n (%) Any grade Grade ≥3	Vomiting, n (%) Any grade Grade ≥3
Vorinostat based study													
Duvic 2007[22]	Vorinostat	37	NR NR	NR NR	18 (49)[$] NR	27 (73)[$] NR	NR 3 (8)	NR NR	4 (11)[$] 3 (8)	18 (49) NR	NR NR	20 (54)[$] 7 (19)	9 (24)[$] NR
Olsen 2007[23]	Vorinostat	74	NR 21 (28)[$]	NR NR	36 (48.6)[$] 0 (0)	34 (45.9) 4 (5.4)[$]	NR NR	NR NR	9 (12.2)[$] 1 (1.4)[$]	32 (43) 3 (4.1)[$]	10 (14) 1 (1)	16 (21.6)[$] 4 (5.4)[$]	11 (15) 1 (1)
Geskin 2010[24]	Vorinostat 200–400 mg-based regimens	14	NR NR	NR NR	2 (14.2) NR	2 (14.2) NR	NR NR	NR NR	6 (42.8) 2 (14.2)	2 (14.2) NR	NR NR	4 (28.5) 2 (14.2)	NR NR
Wada 2012[25]	Vorinostat	6	NR NR	NR NR	2 (33.3)[$] NR	NR NR	2 (33.3)[$] 0	NR NR	NR NR	4 (66.7)[$] 0 (0)	NR NR	4 (66.7)[$] 1 (16.7)[$]	3 (50)[$] NR
Kogge 2015[26]	Vorinostat	NR	NR NR	1 (7)[$] NR	2 (13)[$] NR	NR NR	1 (7)[$] NR	NR NR	7 (47)[$] 1 (7)[$]	3 (20)[$] NR	NR NR	3 (20)[$] NR	3 (20)[$] NR
Bexarotene based studies													
Duvic 2017[27]	Bexarotene + pralatrexate	34	NR NR	NR NR	8 (24) 2 (6)	19 (56) 0 (0)	NR NR	NR NR	10 (29) 1 (3)	16 (47) 0 (0)	NR NR	NR NR	NR NR
Papadavid 2008[8]	PUVA* + bexarotene 300 mg/day oral	9	6 (66.6) NR	NR NR	NR NR	NR NR	NR NR	NR NR	1 (11.1) NR	NR NR	NR NR	NR NR	NR NR
	PUVA* + bexarotene 150 mg/day oral	5	5 (100) NR	NR NR	NR NR	NR NR	NR NR	NR NR	0 (0) NR	NR NR	NR NR	NR NR	NR NR

Study name	Treatment/comparator	N	Any adverse event, n (%) Any grade Grade ≥3	Rash, n (%) Any grade Grade ≥3	Diarrhoea, n (%) Any grade Grade ≥3	Fatigue, n (%) Any grade Grade ≥3	Pyrexia, n (%) Any grade Grade ≥3	Peripheral neuropathy, n (%) Any grade Grade ≥3	Anaemia, n (%) Any grade Grade ≥3	Nausea, n (%) Any grade Grade ≥3	Pruritus, n (%) Any grade Grade ≥3	Thrombocytopenia, n (%) Any grade Grade ≥3	Vomiting, n (%) Any grade Grade ≥3
Talpur 2002[11]	Bexarotene based regimen	16	NR NR	NR NR	1 (6) NR	NR NR	NR NR	NR NR	11 (69) NR	0 (0) NR	NR NR	NR NR	NR NR
Illidge 2013[28]	Gemcitabine + bexarotene	35	NR 25 (71.4)	NR 2 (5.7)	NR NR	NR 2 (5.7)	NR 1 (2.9)	NR NR	NR 1 (2.9)	NR NR	NR NR	NR 2 (5.7)	NR NR
Interferon based studies													
Bunn Jr 1987[29]	Recombinant interferon alfa	20	NR NR	NR NR	NR NR	NR NR	20 (20) $ NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR
Aviles 2015[30]	Interferon + methotrexate	201	NR NR	NR NR	NR NR	NR NR	6 (3) NR	NR NR	NR NR	NR NR	NR NR	1 (0.5) NR	NR NR
	Interferon + retinoids	176	NR NR	NR NR	NR NR	NR NR	11 (6.3) NR	NR NR	NR NR	NR NR	NR NR	3 (1.7) NR	NR NR
Kohn 1990[20]	Recombinant interferon alfa	24	NR NR	NR NR	NR NR	NR NR	24 (24)$ NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR

Key: NR, not reported.

Note: $, related to the drug.

b. Please provide a comparison of the population, intervention, comparator and outcomes (PICO) used in MAVORIC and ALCANZA and discuss any differences.

Population

Table 4 presents a comparison of the baseline characteristics between patients in the MAVORIC and ALCANZA studies.[31;4;32]

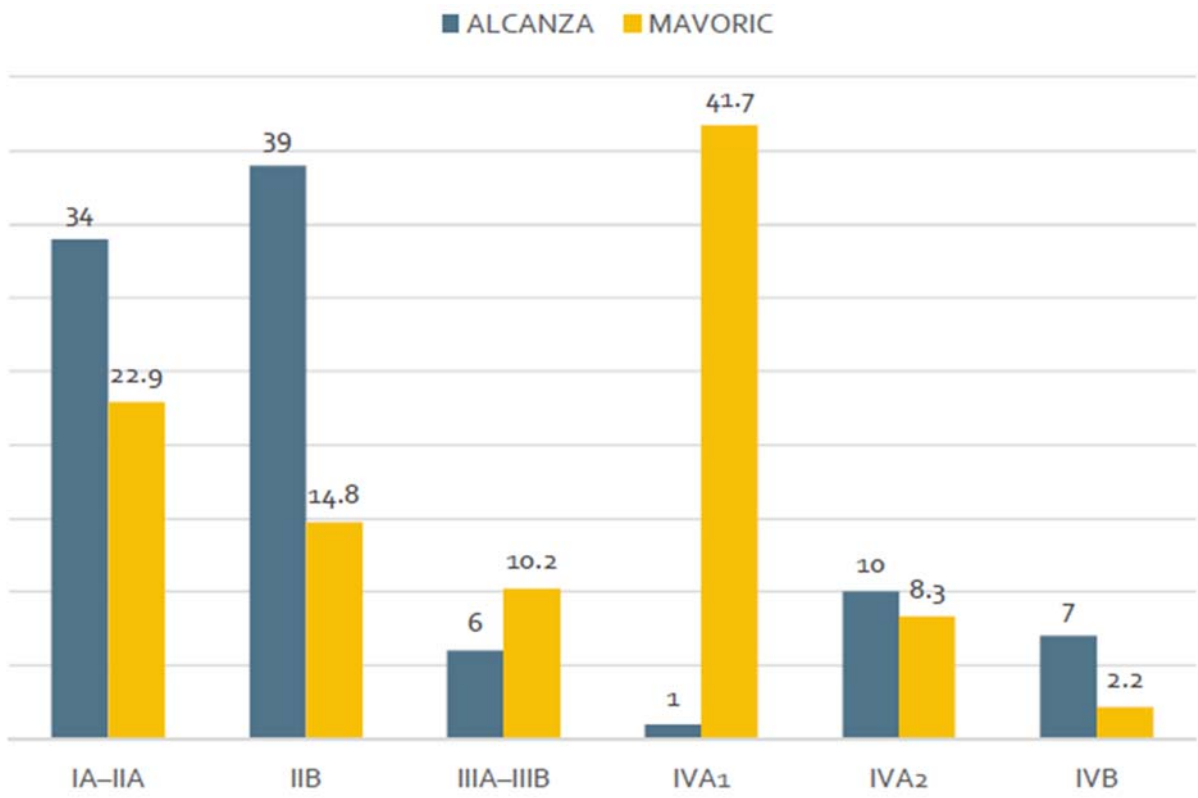
Table 4: Baseline demographic and disease characteristics of patients in the ALCANZA and MAVORIC studies

	ALCANZA		MAVORIC	
	Brentuximab vedotin (n=64)	**Physician's choice of methotrexate or bexarotene (n=64)**	**Mogamulizumab (n=186)**	**Vorinostat (n=186)**
Age, median years (range)	62 (51–70)	59 (48-67)	63 ([redacted])	65 (56-72)
Male, n (%)	33 (52)	37 (58)	109 (59)	107 (58)
Race, n (%)				
White	56 (88)	53 (83)	125 (67.2)	135 (73)
Other	5 (8)	10 (16)	[redacted]	[redacted]
ECOG PS, n (%)				
0	43 (67)	46 (72)	106 (57.0)	104 (56)
1	18 (28)	16 (25)	78 (41.9)	82 (44)
2	3 (5)	2 (3)	2 (1.1)	0
Time from initial diagnosis, median months (range)	42.2 (12.8–87.4)	37.0 (12.3-102.7)	41.0 (17.4–78.8)	35.4 (16.2-68.2)
Disease type, n (%)				
MF	48 (75)	49 (77)	105 (56.5)	99 (53)
SS	N/A	N/A	81 (43.5)	87 (47)
Disease stage, n (%)				
IB-IIA	15 (31)	18 (37)	36 (19.4)	49 (26)
IIB	19 (40)	19 (39)	32 (17.2)	23 (12)
IIIA-IIIB	4 (8)	2 (4)	22 (11.8)	16 (9)
IVA_1	0	1 (2)	73 (39.2)	82 (44)
IVA_2	2 (4)	8 (16)	19 (10.2)	12 (6)
IVB	7 (15)	0	4 (2.2)	4 (2)

Lines of prior systemic therapy, median (range)	2 (1-4)	2 (1-3)	3 (2–5)	3 (2-5)
Key: ECOG, Eastern Cooperative Oncology Group; MF, mycosis fungoides; PS, performance status; SS, Sezary syndrome. **Source:** Kim et al. 2018 [31]; MAVORIC CSR, 2017 [4]; Prince et al. 2017 [32]				

Overall, patients in MAVORIC were more heavily pre-treated than those in ALCANZA (median lines of prior therapy: 3 versus 2, respectively) and the number of patients with advanced disease (IIB-IVB) was greater in MAVORIC compared with ALCANZA (Figure 1). Patients in MAVORIC had a higher disease burden compared to those in ALCANZA (ECOG 0: 56% versus 70%; ECOG 1: 43% versus 27%, respectively), and the proportion of patients with advanced disease (IIB-IVB) was also greater in MAVORIC compared with ALCANZA (Figure 1). Within the advanced disease group, the proportion of patients with Stage IVA–IVB disease was greater in MAVORIC compared with ALCANZA (52% versus 18%, respectively). It should also be noted that all patients in MAVORIC had MF (55%) or SS (45%) disease classification with pcALCL patients being excluded, whereas in ALCANZA, there were no SS patients - all patients had MF or pcALCL disease classification. Furthermore, ALCANZA excluded patients with high blood tumour burden, and all patients enrolled were CD30-positive.

Figure 1: ALCANZA and MAVORIC populations by percentage of patients at given clinical stage



Intervention

- MAVORIC – Mogamulizumab
- ALCANZA – Brentuximab Vedotin

Comparators

- MAVORIC – Vorinostat
- ALCANZA – Physician's Choice (Methotrexate or Bexarotene)

The comparator treatment in ALCANZA (physician's choice) was considered to represent established clinical management by NICE during TA577.[1] The comparator treatment in MAVORIC (vorinostat) is considered a reasonable proxy to established clinical management, and was a necessary choice to enable a robust trial population and avoid potential ethical challenges with retreatment in this advanced patient population (see response to A4a).

Outcomes

PFS

- MAVORIC – The primary endpoint was investigator-assessed PFS in the randomized population using the Global Composite Response Score (based on skin, blood, nodes and viscera) according to the International society for Cutaneous Lymphomas (ISCL)/ European Organization for Research and Treatment of Cancer (EORTC) consensus guidelines (2011)[33]

- ALCANZA – Disease progression was a secondary outcome determined via an independent review of Global Composite Response Score using ISCL/EORTC consensus guidelines (2011).[33] An independent biopsy for confirmation of lymph node progression was conducted where appropriate.[34]

ORR

- MAVORIC – ORR was defined as the proportion of patients who were responders based on the investigator's assessment of overall responses using the Global Composite Response Score as per ISCL/EORTC consensus guidelines that was subsequently confirmed by two or more consecutive observations for a minimum of 4 weeks.

- ALCANZA – ORR4 was defined as the proportion of patients who were responders based on an independent review facilities assessment of overall responses using the Global Composite Response Score as per ISCL/EORTC consensus guidelines that was subsequently confirmed by sustained skin response per mSWAT assessment at the subsequent cycle for a minimum of 4 months.

In both MAVORIC and ALCANZA, disease progression and response were assessed using the global composite response (based on skin, blood, nodes and viscera) according to the ISCL/EORTC consensus guidelines.[33] However, there were differences in the schedules of assessment. During MAVORIC, responses in skin (mSWAT) and blood were evaluated every 4 weeks (28-day cycles) during treatment. In the ALCANZA trial, although the response in skin (mSWAT) was evaluated every 4 weeks (28-day cycles), blood assessments were only conducted at the end of Cycles 3, 6, 9, 12, and 15 during treatment. Similarly, in the MAVORIC

study, computerized tomography (CT) scans to determine nodal and visceral responses were performed every 8 weeks in Year 1 and every 16 weeks in Year 2.

However, in the ALCANZA trial, the frequency of CT scan assessments was dependent on nodal or visceral involvement at baseline: patients without nodal or visceral involvement were scanned at screening, during the cycle following the first skin response and six cycles (or ≥4 months) thereafter, or in the event of suspected new/progressive disease in the lymph nodes/viscera; patients with baseline nodal/visceral disease received CT scans at screening and at the end of Cycles 3, 6, 9, 12, and 15 during treatment. In addition, lymph node progression was confirmed by biopsy where appropriate in ALCANZA, but this was not conducted in MAVORIC.

In ALCANZA, progression was determined via independent review; whereas for MAVORIC, progression analyses were carried out by the investigator to avoid confusing progression with the rash that is commonly associated with mogamulizumab treatment. As such, investigator-assessed results were chosen as the primary endpoint over blinded independent review for MAVORIC because the investigator was able to physically examine the patient, and thus distinguish between disease progression and drug-induced skin rash. Differences are also observed in the duration of response assigned to ORR endpoints with ALCANZA measuring response lasting for at least four months, compared to MAVORIC which measured response lasting for at least four weeks.

The consequences of these differences are unknown, It might be anticipated that the reduced frequency of full GRS assessment and the need for lymph node progression confirmation through biopsy in the ALCANZA trial may delay the detection of progression and decrease the number of lymph node progression observations compared to the MAVORIC trial. It could also be anticipated that the confirmation of response based on skin assessment alone in ALCANZA could overestimate response compared to confirmation based on full Global Composite Response Score assessment. However, the 4-week sustained response need in MAVORIC could overestimate response compared to the 4-month sustained response need in ALCANZA.

OS

- MAVORIC – 73% of patients randomized to the vorinostat arm who had received two full treatment cycles and demonstrated progression of disease at the 8-week (Cycle 2, Day 26-28) assessment, or anytime thereafter, crossed over to treatment with mogamulizumab

- ALCANZA – 63% of patients randomized to the physician's choice arm of ALCANZA crossed over to brentuximab vedotin

Given OS for both ALCANZA and MAVORIC are confounded by crossover, the unadjusted OS outcomes within these studies is not representative of the survival which would be expected in UK clinical practice. Crossover adjusted results have been presented within the submission for MAVORIC, similarly crossover adjusted results were presented for ALCANZA in the brentuximab submission (for the advanced stage population) using the rank preserving structural failure time (RPSFT) method, however the company stated the results were not clinically plausible. [35] Therefore, a comparison of the OS data between the two studies is not feasible as the observed data is not representative of clinical practice and robust analyses to adjust for crossover are not available for both studies.

c. In addition to the comparison of PFS curves for vorinostat (MAVORIC, intention-to-treat [ITT)] and physician's choice (ALCANZA, ITT), please provide comparisons of all other outcomes, including overall survival (OS) and ORR. This should include all survival curves and summary statistics, including median survival.

As discussed in the response to A4b there are numerous differences between the ALCANZA and MAVORIC studies in terms of the patient characteristics, the number of treatments patients received prior to the study (patients in MAVORIC more heavily pre-treated compared to ALCANZA), the treatments patients received subsequently after their randomised treatment (MAVORIC had a high proportion of patients who switched from the comparator arm to the intervention compared to ALCANZA), and the endpoint definitions. The differences in patient characteristics show that the MAVORIC population included more severe patients in the ITT population than ALCANZA; MAVORIC also included a greater proportion of advanced stage patients

than ALCANZA – advance stage patients are associated with substantial reductions in OS compared to patients with earlier stage disease. [36, 37]. Note, of the advanced stage patients; 40% of physician's choice patients in ALCANZA were stage IIB compared with 17.2% in the vorinostat arm of MAVORIC, conversely, 39.2% of patients in the vorinostat arm of MAVORIC patients were stage IVA1 with there being no stage IVA1 patients in the physician's choice arm of ALCANZA patients, the advanced stage population of MAVORIC could therefore be considered more severe than that of ALCANZA. The ALCANZA study did not include any SS patients, whereas in MAVORIC 45% of patients were SS, which is associated with worse survival higher risk of disease progression.[36] In addition, the ALCANZA study excluded patients with a high tumour burden which is also associated with reduced OS,[38] and all patients in ALCANZA were CD30+; although the prognostic value of CD30 is unclear.[39]

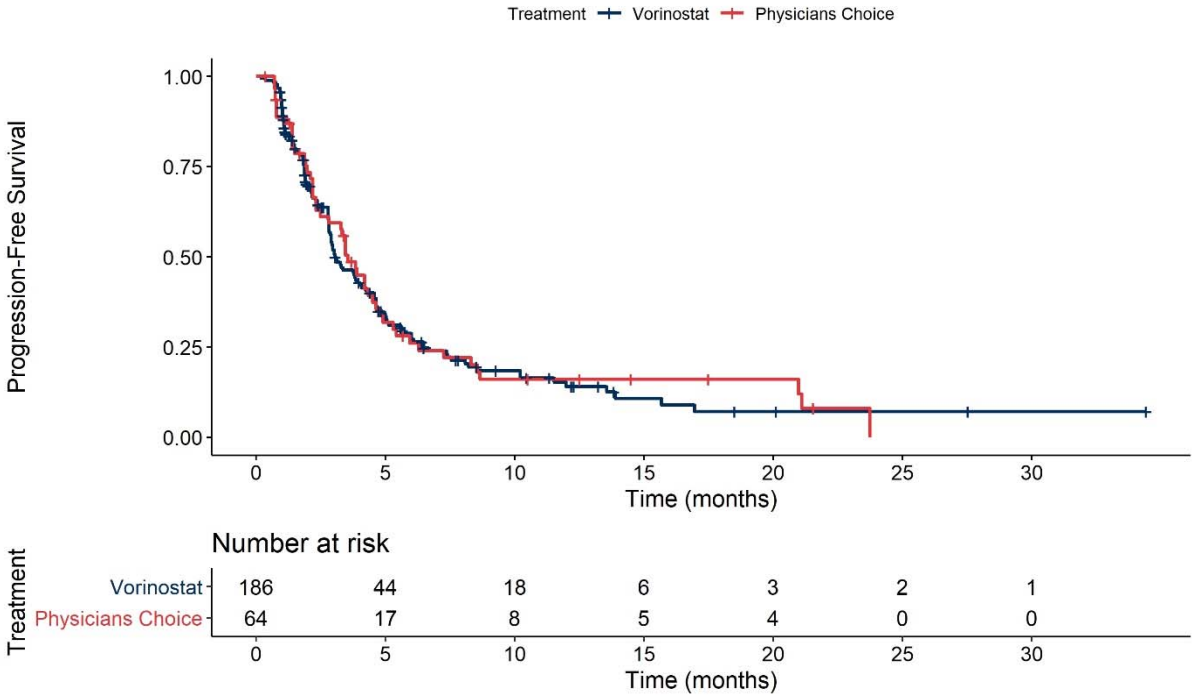
Given these differences, notably the difference in disease stage, a naïve comparison between vorinostat and physician's choice should be considered as informative when considering the evidence between vorinostat and treatments used in clinical practice, however it is also likely to underestimate the efficacy of vorinostat due to these differences. When overlaying the KM curves from the two studies for PFS (Figure 2) it is observed that the two treatments are very similar throughout and the curves cross multiple times (HR: 1.05 [95% CI: 0.76, 1.46]). This would suggest that given the differences in patient characteristics described above, for PFS vorinostat would provide a conservative estimate as proxy for standard of care relative to mogamulizumab.

Whereas, for OS (Figure 3) vorinostat performs marginally better than physician's choice (HR: 0.85 [95% CI: 0.47, 1.54]) however, this analysis is not representative of clinical practice for either treatment as both treatments are heavily confounded by treatment crossover and PLD is not openly available from ALCANZA to allows this adjustment to be performed. This OS analysis has been presented as requested, but due to the reasons discussed above the results may be biased and should therefore be interpreted with caution.

Note, due to the differences in assessment schedules in MAVORIC and ALCANZA in blood assessments, an analysis of ORR was conducted using response derived

using skin assessments only. and this outcome (Table 7) favours physician's choice; however, this comparison is not significantly different to vorinostat (RR 0.72 [95% CI: 0.35, 1.49]). The results of these naïve analyses for PFS and ORR in skin therefore provide further supporting evidence to suggest that vorinostat in MAVORIC is similar to physician's choice in ALCANZA and is therefore a reasonable proxy for UK clinical practice.

Figure 2: Kaplan–Meier investigator-assessed progression-free survival curves for observed vorinostat (MAVORIC - ITT) versus physician's choice (ALCANZA - ITT) – 2016 data cut

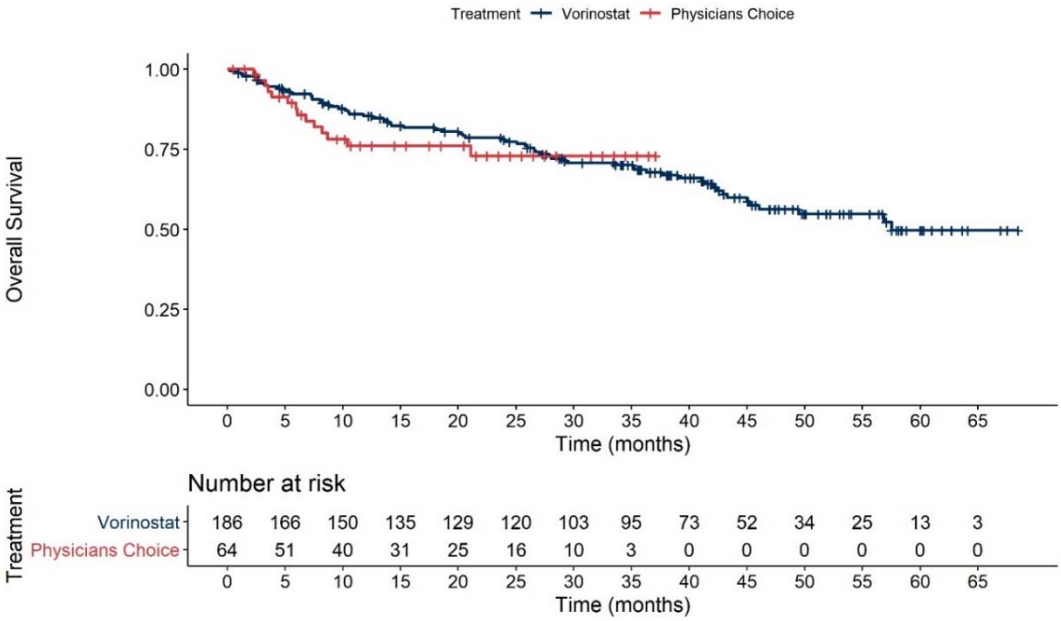


Key: ITT, intention-to-treat.

Table 5: Summary statistics investigator-assessed progression-free survival for observed vorinostat (MAVORIC - ITT) versus physician's choice (ALCANZA - ITT) – 2016 data cut

Treatment	N	Events	Median Progression-Free Survival (95% CI)	HR (95% CI)
Vorinostat	186	131	3.06 (2.83, 4.24)	1.05 (0.76, 1.46)*
Physician's choice	64	50*	3.54 (2.49, 4.81)*	
Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; N, number of patients. **Notes:** *, estimated from digitised data Hazard ratio less than 1 favours vorinostat. Hazard ratio greater than 1 favours physician's choice.				

Figure 3: Kaplan–Meier overall survival curves for observed vorinostat (MAVORIC - ITT) versus physician's choice (ALCANZA - ITT) – 2019 data cut*



Key: ITT, intention-to-treat.

*Note: an updated data cut (2 March 2019) which focused on safety outcomes and collected only limited efficacy data (OS and time to discontinuation [TTD]) has been used for this analysis (this is consistent with the data used in the submission)

Table 6: Summary statistics overall survival for observed vorinostat (MAVORIC - ITT) versus physician's choice (ALCANZA - ITT) – 2019 data cut

Treatment	N	Events	Median Survival (CI)	HR (CI)
Vorinostat	186	67	57.5 (45.2, NR)	0.85 (0.47, 1.54)*
Physician's choice	64	14*	NR (NR, NR)*	
Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; N, number of patients. **Notes:** * estimated from digitised data; Hazard ratio less than 1 favours vorinostat. Hazard ratio greater than 1 favours physician's choice.				

Table 7: Skin responses for the treatments of interest

Treatment (Population)	Sample size	N responders	N evaluable	Proportion of ORR in skin (CR+PR)	Rate ratio (95% CI)
Vorinostat (ITT population)	186	29	186	0.16	0.72 (0.35, 1.49)
Physician's choice (ITT population)	64	13	64	0.20	

Key: CI, confidence interval; CR, complete response; N; number of patients; ORR, overall response rate; PR, partial response.
Notes: Rate ratio greater than 1 favours vorinostat. Rate ratio less than 1 favours physician's choice.

The MAIC analysis gives an indication of vorinostat and physician's choice in a similar population however there are clear limitations in the overlap of patients between the patient populations which violates the assumption of no unmeasured prognostic factors or treatment effect modifiers needed for the unanchored MAIC analysis. However, as highlighted above, patients in MAVORIC are likely to have a worse prognosis than those in ALCANZA. Given this and the comparable results between vorinostat and physicians choice both before and after matching, vorinostat would provide a conservative estimate as proxy for standard of care relative to mogamulizumab.

Regarding the comparison to the phase II study:

According to the CS, MAVORIC used *"the updated international global composite response scoring system that accounted for all four potential disease compartments: skin, blood, lymph nodes, and viscera"* while in the cited phase II study (reference 55 of the CS) responses were *"determined by a composite score of five clinical signs (surface area, erythema, plaque elevation, scaling and hypo/hyperpigmentation) which also considered all extracutaneous CTCL* [cutaneous T-cell lymphoma] *manifestations"*.

d. Please discuss differences in the definitions of ORR in MAVORIC and the phase II study (reference 55 of the CS).

The bexarotene study data captured all associated extracutaneous CTCL manifestations; the response to bexarotene in other disease compartments,

specifically blood, lymph nodes, and viscera were not captured. Conversely, in the MAVORIC study, response was measured using the updated international global composite response scoring system that accounts for all four potential disease compartments: skin, blood, lymph nodes, and viscera.[33] As such, the ORR results from MAVORIC can be considered more robust than those reported across clinical trials for bexarotene, and therefore the comparison between vorinostat and bexarotene should be considered a conservative estimate

Overall response data for bexarotene are taken from regulatory evidence across clinical trials of 193 patients with CTCL, as reported in the Summary of Product Characteristics (SmPC).[3] Of these patients, 93 had advanced stage disease refractory to prior systemic therapy, and of these, 61 were treated at an initial dose of 300 mg/m^2/day.[3] The overall response rate according to a composite assessment of five clinical signs (surface area, erythema, plaque elevation, scaling and hypo/hyperpigmentation) was 31% (19/61).

e. Please provide a table comparing outcomes other than ORR between the phase II study and MAVORIC.

The only other efficacy outcome commonly assessed in both MAVORIC and the Phase II/III study reported by Duvic et al. was time to response (TTR). Table 8 presents a summary of TTR for the MAVORIC and Phase II/III study.

Table 8: Time to response results from the MAVORIC and Phase II/III study

	MAVORIC		**Duvic et al. 2001**
	Mogamulizumab (n=186)	**Vorinostat (n=186)**	**Bexarotene 300 mg/m^2/d (n=56)**
TTR, median (IQR)	3.3 months (2.0–6.4)	5.1 months (2.9–8.5)	180 days (14–197)
Key: IQR, interquartile range; TTR, time to response. Source: Duvic et al, 2001[40];			

The safety profile of mogamulizumab and vorinostat during MAVORIC was different to that reported for bexarotene during the Phase II/III, Duvic et al. 2001 study. The only commonly reported adverse events were diarrhoea, asthenia and headache. Of particular note, cases of mild–severe pruritus were reported with bexarotene that has

been noted as a severely debilitating symptom that greatly reduces the quality of life of both MF and SS patients.[41]

Table 9: Overview of adverse events: Safety population

	MAVORIC		Duvic et al. 2001
	Mogamulizumab (n=184)	**Vorinostat (n=186)**	**Bexarotene 300 mg/m^2/d (n=56)**
Adverse Events (AEs), n (%)			
Any AEs	[redacted]	[redacted]	93 (99)
Serious Adverse Events, n (%)			
Drug-related Treatment-emergent SAEs	36 (19.6)	30 (16.1)	2 (4)
Discontinuation due to AEs, n (%)			
Drug-related TEAEs	[redacted]	[redacted]	4 (7)
Key: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.			

Regarding the experience of clinical experts:

f. Please provide the report on the survey of clinical expert opinion, mentioned above.

All supporting evidence of clinical expert opinion conducted to support the submission, were provided in reference "49. Kyowa Kirin-2019" of the Document B reference pack and are provide in this reference pack for completeness.[2]

Systematic literature review

A5. Priority question. According to Table D6 of the CS, *"all pharmacological interventions and phototherapies for the treatment of R/R* [relapsed/refractory] *CTCL"* were eligible. However, the same cell then lists eight interventions under a heading *"Extractions for studies of interventions based on UK* [United Kingdom] *clinical practice"*. This list does not include all treatments listed in the NICE scope.

Please clarify if any studies of any treatments listed in the NICE scope were excluded.

Please note that the clinical SLR was developed from a global perspective and the initial screening process considered all pharmacological treatments used in the CTCL. The more focused list of treatments specific to the UK (IFN; Brentuximab vedotin; Bexarotene; Methotrexate; Gemcitabine; Vorinostat; mogamulizumab and CHOP regimen) which was applied to these studies to identify those studies which would provide information specific to the UK case. The treatments were based on treatment pathway and algorithm used in the UK for treatment of R/R MF and SS, as presented in the BAD guidelines,[42] and also confirmed via UK clinical opinion and represent the key systemic treatments used within the UK,[2] as can be seen by proportion of use presented in Table 22 of the CS.

A6. Priority question. Literature search results.

a. Were all the identified studies considered for inclusion in indirect comparisons, including network meta-analyses?

The SLR was conducted from a global perspective and, to be fully inclusive, did not exclude based on pharmacological therapy. Therefore, the studies identified from the original review included outcomes for treatments which were not of relevance for the decision problem. The SLR for the submission was refocused at data extraction stage for studies of treatments which reflected the key treatments (regardless of the dosages used) with the UK setting. Of these 34 unique studies identified, there were only 2 RCT were identified, MAVORIC and ALCANZA. As set out with the decision problem, the active treatment for ALCANZA is not relevant for the proposed population so it was not possible to form a network for comparison of mogamulizumab to treatments of interest to the submission.

Furthermore, the 34 studies were further filtered to identify those which are fully representative of the UK treatment setting. This included identifying the appropriate patient population, studies were re-reviewed to identify only those treatment regimens applicable to the UK, including combination therapies and dosages reflective of NHS clinical practice, based on clinical consultation.[2] Finally, studies were restricted by relevant outcomes, namely OS, PFS and ORR. These single-arm studies were fully reviewed for appropriateness for inclusion in a matched adjusted indirect comparison and results are set out within Table 17 of the CS (Section B.2.9., Upon review it was deemed that, due to issues of sample size and also limited

information on disease stage and outcomes reported in these studies, it was not appropriate to pursue this population adjustment analysis as results of any analysis would be highly confounded. Therefore, the Phase III active controlled RCT, MAVORIC; the largest trial in CTCL and the most robust study resulting in the least uncertainty, provides the best evidence on the clinical benefits of mogamulizumab compared vorinostat - a reasonable proxy for to UK comparators.

b. **Please provide the list of the 142 full text articles excluded after full text screening (Figure D1).**

Please find embedded below the full details of the 142 studies which were excluded from the SLR following review of the full-text publication

List of the 142 full text articles exclude

A7. Priority question. Only English language studies were eligible for inclusion (Table D6). According to Figure D1 of the CS, a total of 191 references have been excluded based on language.

a. **Please re-screen these references to ensure no relevant publication has been missed.**

b. **Please provide a list of these references.**

No relevant Non-English study has been found after re-screening the abstracts which were excluded based on language criteria. The full list is attached embedded below as requested.

ID1405_Non-English.xlsx

Included studies

A8. Priority question. The population addressed in the CS (see question A3) was defined as *"adults with advanced mycosis fungoides or Sézary syndrome*

cutaneous T-cell lymphoma (i.e. stage ≥IIB MF **[mycosis fungoides]** ***and all SS*** **[Sézary syndrome]*) following at least one prior systemic therapy who are clinically ineligible for or refractory to treatment with brentuximab vedotin (BV)"*. According to the CS, 80% of participants in MAVORIC represented that subgroup.**

a. **Please provide evidence that the trial population matches this definition, especially in regards to *"one prior systemic therapy who are clinically ineligible for or refractory to treatment with brentuximab vedotin (BV)"***

There is no single criterion or set of criteria that can be applied to determine eligibility for brentuximab vedotin (BV) treatment, or to predict patients that may be refractory to such treatment, prior to administration. Nonetheless, this is a patient group identified through individual patient assessment and informing treatment decisions in clinical practice, and clinical opinion is that the results of the MAVORIC trial are generalisable to this group.[2]

Although CD30 status could be considered a potential marker for BV eligibility (as BV is only licensed for use in CD30+ patients), CD30 is not a predictive factor for treatment response to mogamulizumab (or vorinostat)[2], and therefore CD30 status was not a pre-specific subgroup of interest to the MAVORIC trial. Moreover, as noted above, several criteria are taking into consideration when determining eligibility for BV treatment in clinical practice; this decision would not be based on CD30 status alone.[2]

b. **Please provide baseline characteristics and results for the company's proposed subgroup in MAVORIC (i.e. 80% in line with the company's proposed positioning) and clarify what proportion are ineligible for or refractory to BV.**

Baseline characteristics for the group of patients in MAVORIC with advanced (Stage ≥IIB) disease who represent approximately 80% of the total trial population are provided in Table 10. Results for this group were provided in Section B.2.7 of the CS.

In line with the response to A8a, this group is considered representative of the target population for mogamulizumab. However, a definite proportion of patients within this

group that would be considered clinically ineligible for or refractory to treatment with BV in clinical practice cannot be provided, given the lack of single criterion or set of criteria for this group. There were twenty patients who had failed previous treatment with BV enrolled to MAVORIC, for whom baseline demographic and disease characteristics are available (Table 10). Response outcomes for this group are provided in Table 11.

As summarised in Table 10, baseline characteristics of the ITT and advanced populations are very similar. Results across these groups were also consistent, discussed in the CS (see Section B.2.7). Differences are observed in the baseline characteristics of the prior BV population e.g. in the time from initial diagnosis and median prior therapies as we might expect a priori. Response results for this group appear to be consistent (with regard to relative treatment effect) to those observed in the ITT and advanced populations (see Section B.2.6.2 and B.2.7), although the small sample size in this group and imbalance in patient numbers across treatment arms warrant significant caution to be applied to the interpretation of these data.

Table 10: Baseline demographic and disease characteristics of patients in MAVORIC

	ITT population (n=372) [4]	**Advanced population (n=287) [43]**	**Prior BV population (n=20) [44]**
Median age, years (range)	[redacted]	65-67 (26-101)	[redacted]
<65 years, n (%)	[redacted]	NR	[redacted]
Male, n (%)	[redacted]	173 (60.3)	[redacted]
Race, n (%)			
White	[redacted]	NR	[redacted]
Black or African American	[redacted]	NR	[redacted]
Other	[redacted]	NR	[redacted]
Not reported	[redacted]	NR	[redacted]
ECOG performance status[a], n (%)			
0	[redacted]	155 (54.0)	[redacted]
1	[redacted]	130 (45.3)	[redacted]
Time from initial diagnosis (months), median (range)	[redacted]	29.63-39.97 (1.0-362.1)	[redacted]
Current clinical stage, n (%)			
IB–IIA	[redacted]	0	[redacted]
IIB	[redacted]	55 (19.2)	[redacted]

	ITT population (n=372) [4]	Advanced population (n=287) [43]	Prior BV population (n=20) [44]
IIIA-IIIB	[redacted]	38 (13.2)	[redacted]
IVA_1	[redacted]	155 (54.0)	[redacted]
IVA_2	[redacted]	31 (10.8)	[redacted]
IVB[b]	[redacted]	8 (2.8)	[redacted]
Current sites of disease, n (%)			
Skin	[redacted]	NR	[redacted]
Nodes	[redacted]	NR	[redacted]
Viscera	[redacted]	NR	[redacted]
Blood	[redacted]	NR	[redacted]
Other (including bone marrow)	[redacted]	NR	[redacted]
Previous CTCL therapies[c], n (%)			
Skin-directed therapies			
PUVA	[redacted]	NR	[redacted]
Topical steroid	[redacted]	NR	[redacted]
Bexarotene-topical	[redacted]	NR	[redacted]
Systemic therapies			
Bexarotene-oral	[redacted]	NR	[redacted]
Interferon-alpha	[redacted]	NR	[redacted]
Methotrexate	[redacted]	NR	[redacted]
ECP	[redacted]	NR	[redacted]
Romidepsin	[redacted]	NR	[redacted]
Nitrogen mustard	[redacted]	NR	[redacted]
Doxorubicin HCL liposome	[redacted]	NR	[redacted]
Pralatrexate	[redacted]	NR	[redacted]
Carmustine	[redacted]	NR	[redacted]
Brentuximab vedotin	[redacted]	NR	[redacted]
Denileukin diftitox	[redacted]	NR	[redacted]
Chlorambucil	[redacted]	NR	[redacted]
Etoposide	[redacted]	NR	[redacted]
IL-12	[redacted]	NR	[redacted]
Other (skin-directed and systemic)	[redacted]	NR	[redacted]
Median prior systemic therapies (range)	[redacted]	[redacted]	[redacted]
CR or PR to last prior CTCL therapy	[redacted]	98 (34.1)	[redacted]

Key: BV, brentuximab vedotin; CCR4, C-C chemokine receptor type 4; CR, complete response; CTCL, cutaneous T cell lymphoma; ECOG, Eastern Cooperative Oncology Group; ECP, extracorporeal photopheresis; HCL, hydrochloride; IQR, interquartile range; NR, not reported; PR, partial response; PUVA, psoralen plus ultraviolet light therapy

	ITT population (n=372) [4]	Advanced population (n=287) [43]	Prior BV population (n=20) [44]
Notes: [a], two patients in the ITT and advanced population had ECOG=1 at pre-treatment but ECOG=2 on Cycle 1, Day 1; [b], two patients in the ITT population (one in each treatment group) were noted to have stage IVB disease at baseline but did not have measurable visceral disease at baseline; [c], all patients had received at least one prior CTCL therapy. **Source**: Kyowa Kirin, 2019 [44]; Leoni et al, 2019 [43]; MAVORIC CSR, 2017.[4]			

Table 11: Summary of response rate (by investigator assessment): Prior BV population

	Mogamulizumab (n=16)	Vorinostat (n=4)
ORR (confirmed CR + PR), n (% [95% CI])	[redacted]	[redacted]
Risk ratio (95% CI)	25.0 (-33.8, 53.1)	
p-value	0.2568	
Key: BV, brentuximab vedotin; CI, confidence interval; CR, confirmed response; PR, partial response; ORR, overall response rate. **Source:** Kyowa Kirin, 2019 [44];		

c. Please provide results for the subgroup of participants that fulfil the criterion outlined in the NICE final scope (see question A3).

The ITT analyses from MAVORIC (as provided in the CS) fulfil the criterion outlined in the NICE final scope.

A9. Priority question. Please provide a Table with definitions of all outcomes used in the MAVORIC trial as well as all supporting references.

Table 12 provides definitions of all outcomes used in the MAVORIC trial as described in the associated clinical study report,[4] with supporting references, where applicable.

Table 12: Outcomes used in the MAVORIC trial

Outcome	Definition
Progression-free survival (PFS	The primary efficacy variable was PFS based upon the assessment by the Investigator, defined as the time from the day of randomization to a treatment arm until documented PD or death due to any cause. Documented disease progression included disease progression in any compartment based on the Investigator's assessment per CTCL response criteria or documented disease progression reported during

	the follow-up period. The date of progression was the earliest date at which documented disease progression could be declared. As per the response criteria used (Olsen, 2011)[33], for subjects who exhibited conditions of PD but continued on study treatment due to a questionable clinical impression, the subject was not considered to have progressed unless PD was confirmed at least 4 weeks after the date of the initial questionable PD. In this case, the initial date was used as the date of PD. If the questionable clinical impression of PD was not confirmed, the subject was not deemed to have documented PD at the time of initial questionable PD.
Overall response rate (ORR)	ORR was defined as the proportion of subjects who were responders (confirmed CR or PR) based on the Investigator's assessment. Confirmed CR or PR was defined as documented CR or PR based on the Investigator's assessment of overall response per Global Composite Response Score that was subsequently confirmed by two or more consecutive observations for a minimum of 4 weeks. In the case where a subject had successive visit responses of CR, N/A, CR, then, as long as the time between the two visits of CR was greater than 4 weeks, the subject was defined as a responder. Subjects lacking valid data to assign a response status were included in the denominator for response rate calculation based on the ITT Set and, hence, were considered non-responders.
Best overall response	Best overall response was defined as the best response recorded across all time points from the start of treatment until disease progression/recurrence or end of treatment. The subject's best response assignment was dependent on the achievement of both measurement and confirmation criteria.
Duration of response (DOR)	For subjects with confirmed response (CR or PR), DOR was defined as the time from the date that criteria for CR/PR (whichever was first recorded) were met until the first date that PD or death was objectively documented. Subjects who did not relapse were censored at the day of their last tumour assessment (from any compartment).
Time to response (TTR)	For subjects who achieved a best overall response of CR or PR during the randomized treatment period, the TTR was summarized descriptively. TTR was defined as the time from the date of randomization to the date that criteria for CR/PR (whichever was first recorded) were first met. Subjects who did not respond over the course of the study had a missing value for TTR.
Overall survival (OS)	OS was defined as the time from the date of randomization until the date of death of the subject due to any cause. Subjects who were still alive at the end of the survival follow-up period or were lost to follow-up at the time of analysis were censored on the last date the subject was known to be alive.
Time-to-treatment failure (TTF)	TTF was defined as the time from the day of randomization to a treatment arm until discontinuation of randomized treatment due to any reason except for those subjects who discontinued randomized treatment due to one year on treatment with a CR. Subjects who experienced an overall CR and discontinued randomized treatment after one year of treatment were censored at the last dose date of the randomized treatment. Subjects who were randomized but did not take any study drug were censored at the last documented visit date.

Time-to-next treatment (TTNT)	TTNT was defined as time from the start date of first subsequent treatment to the start date of second subsequent therapy.
Skindex-29 Score	The Skindex-29 instrument measures the effect of skin disease on health-related quality of life (Chren, 1996).[45] It is composed of 29 items assessing three domains: emotions, symptoms, and functioning. The items are scored on a 5-point Likert-type scale (never, rarely, sometimes, often, all the time). Responses to each item are transformed to a linear scale of 100 (never=0, rarely=25, sometimes=50, often=75, all the time=100) for the purpose of scale score calculation. A scale score is the mean of a subject's responses to the items in a given scale and the composite Skindex-29 score is calculated as the average of the 3 scale scores to measure the overall impact on quality of life. Higher scores indicate a higher impact of skin disease.
FACT-G total score	The FACT-G is a validated instrument for assessing health-related quality of life in subjects with cancer (Webster, 2003). The FACT-G consists of 27 items in the following 4 domains: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). The total FACT-G score is obtained by summing individual subscale scores. Response scores on negatively-phrased questions are reversed before summing. Higher scores for the scales and subscales indicate better quality of life.
EQ-5D-3L index score	The EuroQol/EQ-5D is a standardized, reliable and validated instrument to measure health-related quality of life. The EQ-5D self-reported questionnaire includes the EQ-5D descriptive system and a visual analogue scale (VAS). The EQ-5D 3 level version (EQ-5D-3L) descriptive system comprises the following dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The EQ-5D index score is calculated based on the descriptive system using a set of item weights (value sets) to derive a single score ranging from -0.109 to 1, with 1 representing full health. The value sets for the US were used for the calculation of the EQ-5D index score (Shaw, 2005). The EQ-5D self-reported questionnaire also includes a visual analogue scale (VAS), which records the respondent's self-rated health status on a graduated (0-100) scale, with 100 = best imaginable health state and 0 = worst imaginable health state.

A10. Priority question. According to the CS, time to next treatment (TTNT) *"was defined as time from the start date of first subsequent treatment to the start date of second subsequent therapy"*. However, according to a recent conference abstract presenting a post-hoc analysis of MAVORIC (Kim YH et al. Hematological Oncology 37(S2):285-286, June 2019) *"TTNT was defined as time to any significant therapy (systemic treatment, total skin radiation, or psoralen-UVA therapy)"*.

Two clinical experts (cited in the checkpoint form) suggested that *"TTNT is a better proxy not only for treatment changes, but also for quality of life and resource utilisation than PFS"* (progression-free survival).

a. **Please provide the criteria used to decide on next treatment.**

Apologies for the confusion. The post-hoc analyses presented in the CS is two-fold and better defined as:

- The ICML poster by Kim et al. (see Section B.2.6.4; page 62) presented TTNT as the time from the start date of randomised treatment (end date of mogamulizumab treatment for crossover patients) to the start date of next systemic treatment (excluding topical steroids or focal radiation)

- Time to next next treatment, defined as the time from the start date of next systemic treatment to the start date of second next treatment, taken from the data on file post-hoc analyses conducted by Kyowa Kirin (see Section B.2.6.4; page 63).

b. **Please explain the discrepancy between the definitions given in the CS and by Kim et al. 2019.**

Please see the response to A10a.

c. **Please confirm that topical steroids or focal radiation are excluded from the definition of this endpoint and provide sensitivity analysis data for these participants.**

Systemic treatment, did not include topical steroids of focal radiation as such treatments target a limited area of disease (i.e., are not systemic). Based on this definition, no sensitivity analyses including non-systemic treatment in the definition of time to next treatment are possible; these are not considered relevant to the decision problem.

d. **Please provide supporting evidence of the in-depth interview with the two clinical experts.**

All supporting evidence of clinical validation conducted to support the submission, including the in-depth interview with three clinical experts referred to here are

provided in reference “49. Kyowa Kirin-2019” of the Document B reference pack, and provided within this reference pack for completeness.[2]

A11. Priority question. In the MAVORIC trial, the median number of treatments prior to mogamulizumab was 3 (see table 8 in CS).

a. **Please provide a breakdown of treatment types prior to mogamulizumab, i.e. radiation therapy, chemotherapy, photodynamic therapy etc.**

Previous skin-directed or systemic CTCL therapies received by patients enrolled to the MAVORIC study are summarized in the baseline characteristics table in the CS (Table 8; pages 37-38) but are reproduced here for ease of reference (Table 13). In addition, 28.8% of patients (52 in the mogamulizumab arm and 55 in the vorinostat arm) had received prior radiotherapy.[4]

Table 13: Prior CTCL therapy in MAVORIC: ITT population

	Mogamulizumab (n=186)	**Vorinostat (n=186)**
Skin-directed therapies		
PUVA	[redacted]	[redacted]
Topical steroid	[redacted]	[redacted]
Bexarotene-topical	[redacted]	[redacted]
Systemic therapies		
Bexarotene-oral	107 (57.5)	110 (59.1)
Interferon-alpha	81 (43.5)	94 (50.5)
Methotrexate	[redacted]	[redacted]
ECP	[redacted]	[redacted]
Romidepsin	45 (24.2)	32 (17.2)
Nitrogen mustard	[redacted]	[redacted]
Doxorubicin HCL liposome	[redacted]	[redacted]
Pralatrexate	14 (7.5)	13 (7.0)
Carmustine	[redacted]	[redacted]
Brentuximab vedotin	16 (8.6)	4 (2.2)
Denileukin diftitox	[redacted]	[redacted]
Chlorambucil	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]
IL-12	[redacted]	[redacted]
Other (skin-directed and systemic)	[redacted]	[redacted]

Key: ECP, extracorporeal photopheresis; HCL, hydrochloride; IL, interleukin; PUVA, psoralen plus ultraviolet light therapy.**Source:** Kim et al. 2018[31]; MAVORIC CSR, 2017.[4]

b. Was prior treatment in MAVORIC generalisable to the UK setting? Please provide evidence.

Therapies received by UK patients enrolled to the MAVORIC study are summarized in Table 14. Comparison across the ITT and UK populations show that prior treatment data are generally aligned with a median of three prior treatments to mogamulizumab and the most common prior skin-directed therapies being PUVA and topical steroids, and the most common prior systemic therapies being oral bexarotene, interferon-alpha, methotrexate, and ECP. This generalisability is supported by a key UK clinical expert.[46]

Table 14: Prior CTCL therapy in MAVORIC: UK population

	Mogamulizumab (n=16)	**Vorinostat (n=12)**
Skin-directed therapies		
PUVA	[redacted]	[redacted]
Topical steroid	[redacted]	[redacted]
Systemic therapies		
Bexarotene-oral	[redacted]	[redacted]
Interferon-alpha	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]
ECP	[redacted]	[redacted]
Doxorubicin HCL liposome	[redacted]	[redacted]
Chlorambucil	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]
Other	[redacted]	[redacted]
Prior radiotherapy		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Number of prior systemic CTCL regimens		
Median (range)	[redacted]	[redacted]

Key: ECP, extracorporeal photopheresis; HCL, hydrochloride; IL, interleukin; PUVA, psoralen plus ultraviolet light therapy.
Source: Data on file.

A12. According to the CS, *"a blinded independent review of PFS (secondary endpoint) was also performed to assess response and validate the date of progression"*.

Please provide the results of this independent assessment.

The results of the PFS analysis conducted by independent review is presented in Appendix O.2 of the CS; in summary, the results were similar to those of the investigator assessment.

A13. The CS stated that *"the OS* [overall survival] *outcomes described in Section B.3.3.1 do not include patients who have received aSCT"* [allogenic stem cell transplant]

Please provide OS sensitivity analysis results that include patients who received aSCT.

The aSCT patients have been excluded and their survival was estimated based on external data, as an analysis of MAVORIC OS treating censoring as uninformative may be biased due to the longer survival of patients receiving aSCT (out of 25 patients receiving aSCT only 4 deaths were observed). For this question however the crossover adjustment and the survival analysis including patients who have received aSCT have been conducted. Please see results in Appendix 3. Please note this analysis assumed non-informative censoring, and as a result it was likely to underestimate overall survival with mogamulizumab as the censoring in these patients was likely to be informative.

A14. The CS highlighted that *"in the MAVORIC study, the skin only response rate for vorinostat was 12.4%, around half that reported in the registrational trial. Potential reasons include advances in, and increasing familiarity with, skin assessment techniques, changes in assessment criteria, and very large differences in size and number of sites and design of the Phase III versus Phase II studies"*.

In addition to the previously mentioned results on vorinostat, were there any differences between the Phase III and Phase II studies regarding the participants treated with mogamulizumab? If so, please provide and discuss these results.

Table 15 presents the baseline characteristics of patients treated with mogamulizumab in the MAVORIC study compared to the Phase I/II study reported by Duvic et al.[47] Overall, baseline demographic and disease characteristics between patients in the MAVORIC study and the Phase I/II study were similar, although some differences were observed in performance status and clinical staging, with patients treated with mogamulizumab in the Phase I/II study being of better general fitness and less advanced clinical staging on average.

Table 15: Baseline demographic and disease characteristics of patients treated with mogamulizumab in MAVORIC study and the registrational trial

	MAVORIC (n=186)	Phase I/II study (n=41)
Median age, years (range)	63.5 ([redacted])	66 (35–85)
Male, n (%)	109 (58.6)	24 (58.5)
Race, n (%)		
White	125 (67.2)	36 (87.8)
Black or African American	[redacted]	3 (7.3)
Other	[redacted]	1 (2.4)
Not reported	24 (12.9)	1 (2.4)
ECOG performance status[a], n (%)		
0	106 (57.0)	31 (75.6)
1	78 (41.9)	9 (21.9)
Current clinical stage, n (%)		
IB–IIA	36 (19.4)	4 (9.8)
IIB	32 (17.2)	9 (22.0)
IIIA-IIIB	22 (11.8)	2 (4.9)
IVA_1	73 (39.2)	22 (53.7)
IVA_2	19 (10.2)	
IVB[b]	4 (2.2)	4 (9.8)
Primary diagnosis, n (%)		
MF	105 (56.5)	22 (53.7)
SS	81 (43.5)	19 (46.3)

Key: ECOG, Eastern Cooperative Oncology Group; MF, mycosis fungoides; SS, Sézary Syndrome.
Source: Duvic et al. 2015[47]; Kim et al. 2018[31]; MAVORIC CSR, 2017.[4]

Table 16 presents a summary of ORR by disease compartment for the MAVORIC study and the Phase I/II study. Overall, response rates between both patient populations were similar within each disease compartment. The slightly higher response rates in the blood and lymph node compartments in the Phase I/II study may be due to a better prognosis of patients in the Phase I/II study at baseline but the low patient numbers mean any such interpretation should be made with caution.

Table 16: Summary of response rate by disease compartment for mogamulizumab-treated patients

Response by compartment for patients treated with mogamulizumab	MAVORIC (n=186)	Phase I/II study (n=41)
Skin	**(n=186)**	**(n=38)**
ORR (confirmed CR + PR), n (%)	78 (41.9)	16 (42.1)
Blood	**(n=122)**	**(n=19)**
ORR (confirmed CR + PR), n (%)	83 (68.0)	18 (94.7)
Lymph nodes	**(n=124)**	**(n=28)**
ORR (confirmed CR + PR), n (%)	21 (16.9)	7 (25.0)
Viscera	**(n=3)**	**(n=N/A)**
ORR (confirmed CR + PR), n (%)	0 (0)	NR
Key: CI, confidence interval; CR, complete response; N/A, not applicable; NR, not reported; ORR, overall response rate; PR, partial response. **Source:** Duvic et al. 2015[47]; Kim et al. 2018[31]; MAVORIC CSR, 2017.[4]		

A15. Please discuss any potential limitations due to the differences in administration between the intervention (mogamulizumab, administered as an intravenous infusion) and the comparator (vorinostat, administered orally) in the MAVORIC trial, e.g. (but not limited to) blinding of participants, time of onset of potential side effects etc.

The different routes of administration between mogamulizumab and vorinostat (intravenous vs oral) impacted decisions on blinding as it would not be ethical to provide placebo IV infusion to patients in order to fully blind the investigators during this study. Taken together with the decision to measure PFS through investigator-assessment for primary endpoint analysis, this could pose a risk of detection bias. However, assessment of progressive disease (PD) was considered according to a pre-defined set of criteria (the global composite response criteria) provided to all investigators and investigator-assessed outcomes were validated through blinded independent review of PFS.

The different side effect profile, rather than the potential differences in time of onset of side effects also influenced the decision to have an open-label design. All adverse events were collected up to 90 days after the last study drug dose or initiation of other therapy in MAVORIC, to capture any differences in the side effect profiles of mogamulizumab and vorinostat, as reported in Section B.2.10.

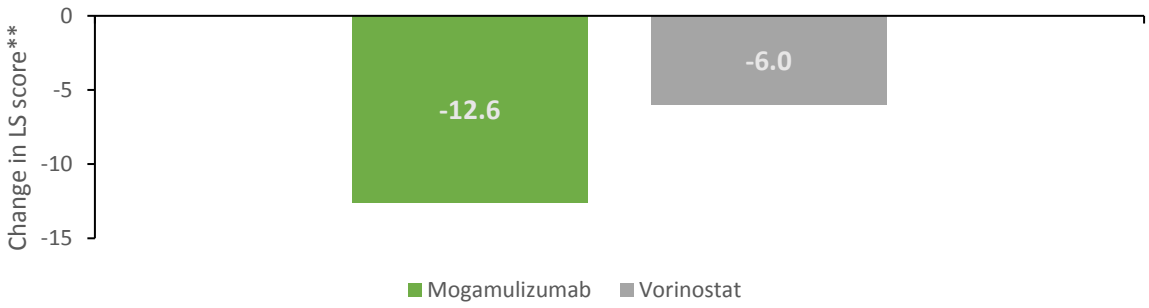
A16. The secondary endpoints of MAVORIC included the change from baseline through the 6 month assessment in Skindex-20 score, Functional Assessment of Cancer Therapy – General (FACT-G) total score and EuroQol 5 dimensions 3 level questionnaire (EQ-5D-3L) index score. However, these are not reported in section B.2.6.2 of the CS. Please provide summary statistics for the change from baseline to 6 months for each of these outcome measures for each treatment group as well as the corresponding treatment effect (mean and 95% CI) and the results of any statistical analysis.

Summary statistics and treatment effects for the outcomes listed are provided below.

Skindex-29

Skindex-29 results indicated significant improvements at 6 months following treatment with mogamulizumab compared with vorinostat (changes in least square [LS] score from baseline -12.6 (95% CI: -15.94, -9.29) versus 6.0 (95% CI: -9.39, -2.52); p=0.0002; Figure 5).[48]

Figure 5: Change in Skindex-29 LS score from baseline through six months during MAVORIC

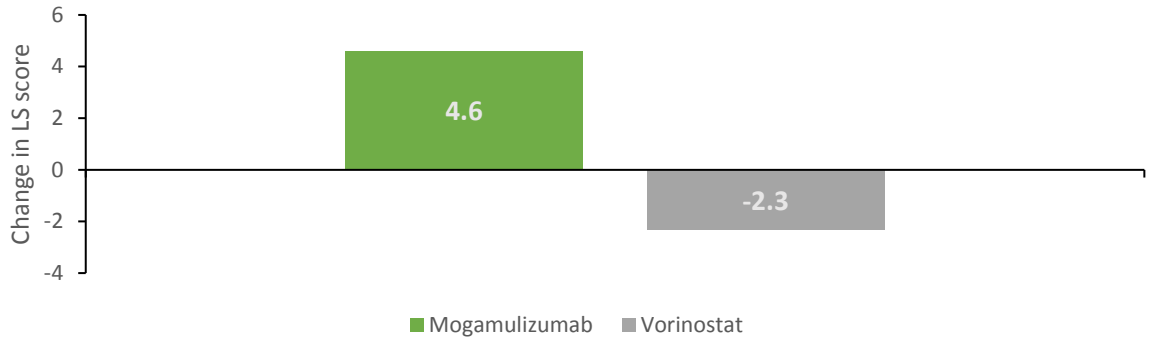


Key: LS, least square.
Notes: *p=0.0002; **Lower scores indicate better health-related quality of life.
Source: Kim et al., 2018.[48]

FACT-G

Treatment with mogamulizumab resulted in higher changes from baseline at six months in LS scores (4.6 [95%CI: 2.14, 7.04] versus -2.3 [95%CI: -4.84, 0.21]; Figure 6) demonstrating a significant improvement in quality of life of 6.9 (95% CI: 4.33, 9.47; p<0.0001) versus vorinostat.[48]

Figure 6: Change in FACT-G LS score from baseline through six months during MAVORIC

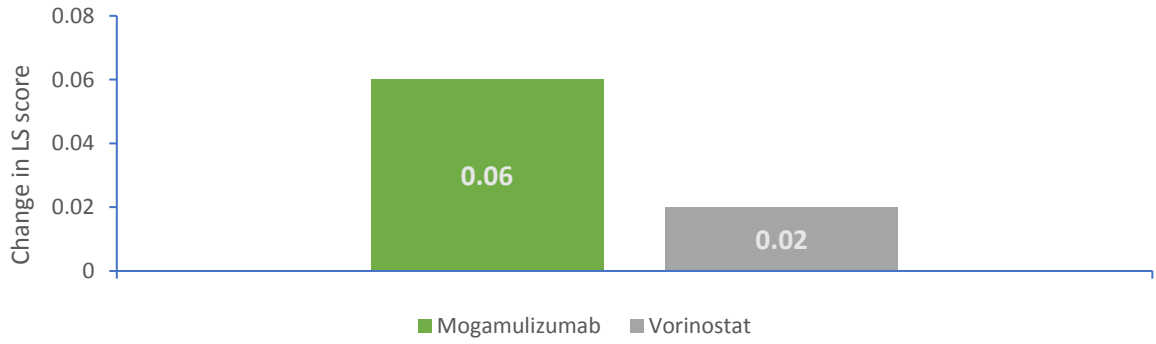


Key: FACT-G, Functional Assessment of Cancer Therapy – General; LS, least square.
Notes: *p<0.0001 versus vorinostat.
Source: Kim et al., 2018.[48]

EQ-5D-3L

Numerically higher changes in LS score from baseline to six months following treatment with mogamulizumab versus vorinostat (0.06 [95% CI: 0.028, 0.085] versus 0.02 [95% CI: -0.008, 0.052]; p=0.021; Figure 7).[48]

Figure 7: Change in EQ-5D LS score from baseline through six months during MAVORIC



Key: EQ-5D, EuroQoL 5 dimensions questionnaires; LS, least square.
Source: Kim et al., 2018.[48]

A17. In Section B.3.3.1 there is conflicting information on OS for patients not receiving aSCT as Table 24 stated that *"patients receiving aSCT excluded"* while the footnote for Figure 23 stated that *"patients were censored upon receiving aSCT"*. Please clarify whether these patients were excluded or censored. How many patients in each group received aSCT? Why were they excluded from the

OS analysis instead of being included and censored at the point they received aSCT?

Patients receiving aSCT were excluded. The footnote for figure 23 is in error. These patients were excluded as the survival of patients receiving aSCT was modelled independently based on external data and then “summed" in the model. This model was developed in this way to allow the proportion of patients receiving aSCT to be varied based on external information and also to account for the fact that simple censoring was likely to be informative for these patients (their post censoring survival is likely to be different from patients not receiving an aSCT).

The overall population survival is essentially estimated as a "weighted average" of the survival curves from the trial for patients who did not receiving aSCT and survival curves for patients receiving aSCT based on external data. The weights represent the estimated proportion of patients receiving aSCT.

A18. Please provide more details on safety outcomes, e.g. by recreating / expanding on Table 26 (*“AEs Reported in ≥ 5% of Safety Population and ≥ 2% More with Mogamulizumab”*) of the multi-discipline review of the United States Food and Drug Administration (FDA).

Table 26 of the multi-discipline review of the United States Food and Drug Administration (FDA) was created by the FDA group directly therefore this cannot be recreated directly. However, the FDA analyses was based on data taken from Table 14.3.1.2 of the MAVORIC clinical study report. This table is provided in the supplementary safety tables files reference,[49] alongside this response document.

As summarised in the CS (see Section B.2.10.2), the most common treatment-emergent adverse events (TEAEs) were infusion-related reactions (34%), drug eruption (24%), diarrhoea (24%), and fatigue (24%) while in the vorinostat arm the most common TEAEs were diarrhoea (62%), nausea (43%), thrombocytopenia (40%) and fatigue (38%).

While infusion-related reactions and drug eruption were more frequent in the mogamulizumab arm than in the vorinostat arm, most of these events were mild or moderate in severity with only three Grade ≥3 infusion-related reactions and eight Grade ≥3 drug eruption events recorded. It should also be noted that both of these

events are known to occur with mogamulizumab therapy due to its mode of action and were therefore expected (discussed further in Section B.2.13).

Section B: Clarification on cost-effectiveness data

Model structure

B1. Priority question: In the CS, within disease control two different health states were defined, namely *"disease control on treatment"* and *"disease control surveillance"*. In addition to these disease control health states, another health state, *"disease control surveillance continued"*, was incorporated into the economic model: In line with the *"disease control surveillance"* health state, patients in the *"disease control surveillance continued"* health state are off treatment and did not receive subsequent treatment yet. However, in contrast to patients in the *"disease control surveillance"* health state, patients in the *"disease control surveillance continued"* health state experienced disease progression.

a. **Considering that there appears to be a utility decrement associated with progression, as shown in Table 35 of the CS, please justify why the same quality-adjusted life years (QALYs) and costs were applied to patients in the *"disease control surveillance"* and the *"disease control surveillance continued"* health states, despite their differences in progression status.**

b. **Please provide a scenario in which differential QALYs and resource use / costs for patients in the *"disease control surveillance continued"* health state are applied.**

The model has been built to allow for structural sensitivity analyses regarding the model health states, thus two models have been included in the same structure in the submitted Excel file:

1. Model based on NTFS, OS and aSCT
2. Model based on PFS, OS and aSCT

To switch between models, please use the drop-down menu on the Controls sheet in cell I9.

1. Model based on NTFS, OS and aSCT

This model is the base case. In the Excel file, it uses the following columns to define these health states without aSCT:

- Disease control
    - Disease control - On treatment: Column V determined by the ToT curve with a maximum set by the PFS curve
    - Disease control - Surveillance: Columns W,X: It is determined by the area between NTFS and ToT. To be able to include both models in the same structure, this heath state is divided into two, the area between ToT-PFS (Disease control – Surveillance, column W) and the area between PFS-NTFS (Disease control – Surveillance cont'd, column X).
- Subsequent treatments and end stage care: Column Y: It is determined by the area between NTFS and OS
- Death non-aSCT: Column Z: Determined by OS

This model assumes, that utilities are dependent on having disease control in line with clinical expert opinion, thus only utility decrement associated with the loss of disease control are included at the time of the loss of disease control. The same is assumed for health state costs. Thus, the column labelled Disease control – Surveillance cont'd has the same health state costs and utilities assigned as the column Disease control – Surveillance, since they belong to the same health state.

2. Model based on PFS, OS and aSCT

This model is structural scenario analysis. In the Excel file, it uses the following columns to define these health states without aSCT:

- Pre-progression

    - On treatment: Column V determined by the ToT curve with a maximum set by the PFS curve
    - Off treatment: Columns W: It is determined by the area between ToT and PFS
- Post-progression
    - Off treatment: Column X: Determined by the area between PFS-NTFS
    - On next treatment and end stage care: Column Y: It is determined by the area between NTFS and OS
- Death non-aSCT: Column Z: Determined by OS

This model assumes, that utilities are dependent on having progression in contrast with clinical expert opinion, thus only utility decrement associated with progression are included at the time of the progression. The same is assumed for health state costs. Thus, for columns V and W, the same health state costs and utilities are assigned since they belong to the same health state. The two models are compared in Table 17.

In the scenario labelled 'Model structure based on progression' in Table 55 of the CS the column labelled 'disease control surveillance continued' (column X) in the NTFS-based model (labelled Post-progression – Off treatment in the PFS-based model) receives the post-progression utility and health cost values. Please see the scenario replicated below in Table 18. This scenario results in 3% increase in the ICER.

Table 17. Comparison of the two models included in the same structure

Variable	NTFS based model	PFS based model
Health states without aSCT		
First health state	Disease control – On treatment (column V in model) Disease control – Surveillance (column W+X in model)	Pre-progression – On treatment (column V in model) Pre-progression – Off treatment (column W in model)
Subsequent health state	Subsequent treatment (column Y in model)	Post-progression

Variable	NTFS based model	PFS based model
Death	Death (column Z in model)	Death (column Z in model)
Survival curves		
Survival curves used	NTFS, OS, DFS, ToT	PFS, OS, DFS, ToT
Utilities		
Utilities for first health state –Mogamulizumab arm	Disease control: Per cycle utilities until cycle 12, then [redacted]	Pre-progression: Per cycle utilities until cycle 12, then [redacted](same as in NTFS based model)
Utilities for first health state – ECM arm	Disease control: Per cycle utilities until cycle 12, then [redacted]	Pre-progression: Per cycle utilities until cycle 12, then [redacted](same as in NTFS based model)
Utilities for subsequent health state	Subsequent treatment [redacted]	Post-progression on treatment: 0.64 Post-progression off treatment: 0.495 (from TA577 ERG preferred scenario)
Carers' utilities	Disease control: 0.559 Subsequent treatment: 0.366	Pre-progression: 0.559 Post-progression: 0.366 (same as in NTFS based model)
Costs		
Health state costs (per cycle)	Disease control: [redacted] Subsequent treatment: [redacted] End stage care: [redacted] Monitoring post aSCT relapse: [redacted]	Disease control: [redacted] Subsequent treatment: [redacted] End stage care: [redacted] Monitoring post aSCT relapse: [redacted] (same as in NTFS based model)
Key:		

Table 18. Scenario analyses [redacted]

Question(s)	Parameter	Technology	Total costs	Total QALYs	ICER
-	**Base case in MS**	**ECM**	[redacted]	**1.78**	**£33,819**
		Mogamulizumab	[redacted]	**4.60**	
B1		ECM	[redacted]	1.70	£34,834

Question(s)	Parameter	Technology	Total costs	Total QALYs	ICER
	Utilities, health states costs dependent on progression (PFS-based model)	Mogamulizumab	[redacted]	4.44	
B2	45-year time horizon	ECM	[redacted]	1.78	£33,740
		Mogamulizumab	[redacted]	4.63	
B3	ALCANZA physician's choice scenario	ECM	[redacted]	1.76	£32,636
		Mogamulizumab	[redacted]	4.64	

B2. In contrast to technology appraisal (TA) 577 in which a model time horizon of 45 years was used, a time horizon of 30 years was used in the current appraisal. This was assumed to be the maximum life expectancy of patients based on clinical expert interviews. Nevertheless, in the company's base-case analysis, 8% of the patients in the mogamulizumab arm are still alive after 30 years.

Please extend the time horizon, in line with TA455, to 45 years and provide updated cost-effectiveness results.

We have extended the time horizon to 45 years keeping the age specific mortality from the general population as the maximum limit.[50] Please see the results in Table 18.

Intervention & comparators

B3. Priority question. Please provide a scenario analysis in which the comparator (standard care) effectiveness, adverse events and costs (OS, PFS, time on treatment (ToT), dose intensity, health-related quality of life (HRQoL), adverse events) are all informed using data from physician's choice (i.e. methotrexate or bexarotene) from the ALCANZA (ITT) study. This may be performed using OS and PFS data from ALCANZA and those from the mogamulizumab arm of MAVORIC, either adjusted or unadjusted for differences in baseline characteristics between the two trials.

The ALCANZA trial population differs from the MAVORIC population, and most importantly from the target population of this appraisal (See question A4.b). Additionally, the physician's choice arm of the ALCANZA trial included 46% of patients crossing over to the BV arm,[35] that is it includes 46% of patients receiving BV subsequent to methotrexate or bexarotene. As a result, the unadjusted OS survival curve of the physician's choice arm is not representative of the clinical practice for this target population and its inclusion would be misleading.

The inclusion of an adjusted BV arm, while there are major differences between the two trial – with the MAVORIC trial including patients with worse prognosis – could potentially act as a useful maximum limit for effectiveness of the Established clinical management (ECM) arm of the cost-effectiveness model. However unfortunately, this is not available. In the NICE TA577, the manufacturer included adjusted curve using RPSFT model, however according to the FAD: "The company attempted to adjust for this treatment switching but considered the results to be clinically implausible. The committee acknowledged the company's concerns, such as the limited number of events in each arm, but considered that the adjustment may have been conducted incorrectly."[1] No corrected adjustment with RPSFT model, or any alternative models have been presented, and Kyowa Kirin does not have access to the patient level data of the ALCANZA trial to conduct such adjustment. As a result, the effectiveness of the physician's choice arm could not be incorporated.

In a scenario analysis, Kyowa Kirin however included adverse events, health state costs, ToT, dose intensity and utilities informed using data from physician's choice (i.e. methotrexate or bexarotene) arm from the ALCANZA (ITT) study. The inputs are presented in Table 19. Kaplan-Meier curves for ToT were not available for the ITT population, only for the advanced population, thus the reported median numbers were fitted with an exponential distribution.[32] As the ALCANZA-based model only considered those AEs that occurred ≥5% of patients in either arms of the ALCANZA trial, the same approach was used for the MAVORIC trial. In the base case all AEs were taken into account. AE cost per cycle from TA577 were inflated to 2018/19 using the Health Services Index presented in the PSSRU report.[51]

The results of this scenario are presented in Table 18. The ICER in this scenario decreased by 3.5%.

Table 19. Inputs for the ECM arm taken from the physician's arm of the ALCANZA (ITT) study

	MS base case with 45-year time horizon	**ALCANZA scenario**	**Comments**
time horizon (years)	45	45	As requested in question B2
ToT for ECM			
Methotrexate	Vorinostat ToT	median 77 days	MAVORIC trial vs. ALCANZA trial
Bexarotene	Vorinostat ToT	median 114 days	MAVORIC trial vs. ALCANZA trial
distribution for ECM			
Methotrexate	[redacted]	41%	Clinical expert opinion vs. ALCANZA trial
Bexarotene	[redacted]	59%	
Interferon alfa-2a	[redacted]	0%	
Gemcitabine	[redacted]	0%	
CHOP	[redacted]	0%	
Liposomal doxorubicin	[redacted]	0%	
Etoposide	[redacted]	0%	
Prednisolone	[redacted]	0%	
Vorinostat	[redacted]	0%	
PUVA	[redacted]	0%	
ECP	[redacted]	0%	
TSEBT	[redacted]	0%	
dose intensity for ECM	[redacted]	90%	MAVORIC trial vs. ALCANZA trial

	MS base case with 45-year time horizon	ALCANZA scenario	Comments
Disease control - health state utility for ECM	Cycle specific utilities until cycle 12, then [redacted]	0.69	MAVORIC trial vs. ALCANZA trial
Disease control - health state costs for ECM arm	[redacted]	£205.89	MS base case used HES database study for inpatient/outpatient costs ALCANZA scenario used TA577 ERG preferred resource use based on expert opinion with current unit costs
AEs for mogamulizumab			
Aspartate aminotransferase increased	2	0	The ALCANZA scenario only took into account grade 3+ AEs if they occurred in ≥5% in either arm of pivotal trial
Asthenia	0	0	
Cellulitis	4	0	
Constipation	1	0	
Decreased appetite	2	0	
Diarrhoea	1	0	
Drug eruption	8	0	
Dysgeusia	0	0	
Fatigue	3	3	
Headache	0	0	
Hypertension	8	8	
Infusion-related reaction	3	0	
Muscle spasms	0	0	

	MS base case with 45-year time horizon	ALCANZA scenario	Comments
Nausea	1	0	
Peripheral oedema	0	0	
Pneumonia	7	0	
Pulmonary embolism	0	0	
Pyrexia	1	0	
Sepsis	2	0	
Thrombocytopenia	0	0	
Upper respiratory tract infection	0	0	
Vomiting	0	0	
Weight decreased	1	0	
AE cost per cycle for ECM	£15.88	£6.17	Inflated from 2015/16 using the Health Services Index presented in the PSSRU report[51] The CS base case took into account all grade 3+ AEs, while the ALCANZA scenario only those that occurred in ≥5% in either arm of pivotal trial

Treatment effectiveness

B4. Priority question. Given that the primary endpoint in MAVORIC was PFS, not next treatment-free survival (NTFS), please provide a scenario analysis using PFS and OS instead of NTFS and OS. Please also comment on whether patients in the vorinostat arm switched sooner after disease progression compared with patients experiencing disease progression in the mogamulizumab arm.

Please see the scenario using PFS and OS instead of NTFS and OS in Table 18 in Question B1. It was also presented in the MS among the scenario analyses as 'Model structure based on progression' in Table 55. Please see further details in the answer for Question B1.

In the advanced population, the median NTFS was [redacted] for mogamulizumab and vorinostat respectively. The median PFS was [redacted] for mogamulizumab and vorinostat respectively. [redacted].

According to clinical experts, the next treatment-free period after progression can be longer with mogamulizumab due to the higher response rates with mogamulizumab and better response (longer and better quality of response), so you can 'watch and wait'.[2] With mogamulizumab, even if the patient has progressed, the disease becomes indolent. That is, even if the disease has crossed the threshold for the progression criterion, the disease was slower after mogamulizumab. [2]

This is supported by the analyses of the time-to-next-next-treatment (TTNNT) (see CS Section B.2.6.4), which suggests that mogamulizumab can potentially result in longer TTNT even for the subsequent treatment. This supports the clinical expert opinion, that mogamulizumab changes the natural progression of the disease even after treatment is stopped.

B5. Priority question. OS estimates for the comparator in the ITT population are likely to be biased by crossover. The company states that it follows decision support unit (DSU) guidance for adjusting for crossover, however, results of a scenario using one of the DSU recommended methods (rank-preserving structural failure time (RPSFT) method) are not provided. The two different

adjustment methods that were provided resulted in significant differences in OS estimates for the comparator.

a. **Considering this uncertainty and potential bias in the two provided methods (unmeasured confounders, inverse probability of censoring weights (IPCW) method more appropriate for observational datasets with large sample sizes), please include a scenario analysis with results from the RPSFT method.**

b. **Please provide justification for why the IPCW method was chosen in the base-case instead of the TSE method, especially considering that the two-stage estimation (TSE) method appears to produce estimates more in line with external data (Table 27 of the CS).**

c. **Given that crossover adjustment methods produce vastly different results and are likely to be biased (due to unmeasured confounders), and given that the DSU recommends the use of external data where possible, please discuss the possibility of using an alternative data source, such as physician's choice (i.e. methotrexate or bexarotene) from the ALCANZA study to estimate OS for the comparator (established clinical management (ECM), vorinostat). Please provide a scenario analysis with comparator OS estimated using these alternative data.**

a. Scenario analysis with RPSFT model for crossover adjustment

Whilst the RPSFT approach was also considered in the CS as a means to adjust for treatment switching it was not pursued in detail as it produced a counter-intuitive point estimate (due to the assumption of a time-invariant treatment effect on the HR scale) with considerable uncertainty, and the implausibility of the "common treatment effect" assumption in this setting. Details of the RPSFT analyses were submitted in Appendix R of the CS. For this question, to include it as a scenario, survival analyses were conducted similarly to the IPCW and the two-stage estimation. For further details, please see Appendix 2.

The results are clinically implausible, showing approximately 1-year survival advantage in the Disease control health state, however an approximately one year disadvantage on subsequent treatments (Table 20). This contradicts the post-hoc analyses showing longer time on subsequent treatment after mogamulizumab compared to vorinostat. It also contradicts the experience of all clinical experts interviewed,[2] who suggested, that mogamulizumab also effects the efficacy after discontinuation of treatment by slowing down disease progression. The cost-effectiveness results with this scenario presented in Table 21 therefore are based on clinically implausible results and should not form the basis of decision-making.

Table 20. Scenario analysis with RPSFT model for crossover adjustment: QALY and LYG results

	Mogamulizumab	**Established clinical management**	**Increment**
Life-years (LYs) gained (undiscounted)			
Disease control - Current treatment	[redacted]	[redacted]	[redacted]
Disease control - Surveillance	[redacted]	[redacted]	[redacted]
Subsequent treatments/ESC	[redacted]	[redacted]	[redacted]
aSCT DF	[redacted]	[redacted]	[redacted]
aSCT Relapsed	[redacted]	[redacted]	[redacted]
Total	**8.43**	**7.45**	**0.97**
Quality-adjusted life-years (QALYs) gained (undiscounted)			
Disease control - Current treatment	[redacted]	[redacted]	[redacted]
Disease control - Surveillance	[redacted]	[redacted]	[redacted]
Subsequent treatments/ESC	[redacted]	[redacted]	[redacted]
aSCT DF	[redacted]	[redacted]	[redacted]
aSCT Relapsed	[redacted]	[redacted]	[redacted]
Total	**6.03**	**5.01**	**1.02**

Table 21. Scenario analysis with RPSFT model for crossover adjustment [redacted]

Treatment	**Total costs**	**Toal LYs**	**Total QALYs**	**ICER (£/QALY)**
Established clinical management	[redacted]	5.96	4.01	
Mogamulizumab	[redacted]	6.40	4.60	£103,423

b. External validation of the IPCW method vs. TSE

To assess the clinical plausibility of these estimates, the vorinostat/ECM predictions were compared to published observational data, data from the HES database and clinical expert opinion. For the comparison with the predicted survival estimates, please note that survival estimates from the available observation data is expected to be a high upper limit of the expected survival for the MAVORIC advanced population. This is due to the external data including:

- Populations with lower proportion of patients with SS (7-15% vs. 47% in the MAVORIC trial)
- Lower proportion of patients with stage IV disease (6-7% vs. 52% in the MAVORIC trial)
- Less heavily pre-treated patients.

Similarly, clinical expert opinion was elicited not for the advanced population, but for the ITT population of the MAVORIC trial. For more information, please see Section B.3.3.1 of the MS.

Keeping this in mind, the predicted survival with the TSE is:

- In year 1: above this upper limit from the HES database, Kim et al 2003 and the expert opinion with all distributions[2, 52, 53]
- In year 3: above this upper limit from the HES database, Kim et al 2003 and the expert opinion with all distributions[2, 52, 53]
- In year 5: above this upper limit from the HES database, Kim et al 2003 and the expert opinion with all distributions, and at or above the upper limit from Agar et al. 2010 with all distributions[2, 36, 52, 53]
- In year 10: at or above the upper limit from Kim et al. 2003 with all distributions except Gompertz and Weibull distributions[53]

- In year 20: above the upper limit from Kim et al. 2003 with all distributions except exponential, Gompertz and Weibull distributions[53]

The IPCW method with exponential distribution is only above the upper limit from the HES database in year 1 (Table 22). As a result, the IPCW crossover adjustment was selected as providing more clinically plausible survival predictions.

Table 22 (Table 27 in MS): Survival rates for MF-SS from literature (advanced disease)

Crossover adjustment	Source (comparison to MAVORIC patients)	1-year	3-years	5-years	10-years	20-years
-	HES database (MF patients, not advanced, 2nd line)	57%	31%	25%		
-	Talpur 2012: Stage IIb-IV (n=349) (lower proportion of SS patients, potentially lower proportion of stage IV and heavily pre-treated patients)	91%	68%	51%	34%	18%
-	Kim 2003‡ (lower proportion of SS patients, potentially lower proportion of heavily pre-treated patients)	67%	40%	32%	15%	3%
-	Agar 2010‡ (lower proportion of SS patients, potentially lower proportion of heavily pre-treated patients)	-	-	37%	22%	14%
	Expert opinion (ITT population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	ECM exponential	67%	30%	14%	2%	0%
IPCW	ECM generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	ECM Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	ECM log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	ECM log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	ECM Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSE	ECM exponential	83%	57%	39%	15%	2%

Crossover adjustment	Source (comparison to MAVORIC patients)	1-year	3-years	5-years	10-years	20-years
TSE	ECM generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSE	ECM Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSE	ECM log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSE	ECM log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSE	ECM Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ECM: established clinical management/vorinostat arm from MAVORIC
Note: ‡ Weighted average using the proportion of patients in different disease stage from the MAVORIC trial

c. Use of physician's choice arm (i.e. methotrexate or bexarotene) from the ALCANZA study

While the use of the above external data (Table 22) to estimate OS for the ECM arm is useful given the uncertainties inherent in crossover adjustment techniques, unfortunately none of the external data available match the population of interest. The physician's choice arm from the ALCANZA study includes not only a different population from the MAVORIC trial (please see Question A4.b for further details), but also has the same issue as the vorinostat arm, that is, 46% of patients crossed over to the BV arm. As no appropriate crossover adjusted data are available and Kyowa Kirin has no access to the patient level data from the ALCANZA trial to conduct crossover adjustment, it cannot be used as a comparator arm to mogamulizumab. Similarly, the physician's choice arm from the ALCANZA study cannot be used for external validation, as it does not represent clinical practice due to the 46% of patients crossing over to BV.

B6. Priority question. The choice of parametric distributions for estimating survival is unclear in some instances. For OS, for example, the choice of distribution (exponential) for the comparator under-estimates expert opinion and external data (Table 27 of CS), and does not provide the best statistical fit. Please provide more information / justification for choices of parametric distributions:

a. OS (IPCW adjusted analysis): the generalised gamma has the best statistical fit for vorinostat and the exponential for mogamulizumab, yet

these distributions are not chosen. Please justify this and also use the ALCANZA study to externally validate OS estimates.

The best fitting distribution was selected based on the following:

- Objective statistical measures of goodness of fit to *observed* KM data: Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics[54, 55]
- Visual inspection of goodness of fit to observed KM data
- Visual inspection of diagnostic plots, including log cumulative hazard plots, Schoenfeld residuals plot and quantile- quantile plot
- External validation to published observational data, UK Hospital Episode Statistics data and the experience of leading NHS consultants experienced with the treatment and care of MF and SS patients in an NHS England setting. Please note the external data provide only an upper limit to the estimates, as they are for populations with better survival than the population used for the MAVORIC trial and this submission. (Please see answer to Question B.5. for further information.) As the AIC/BIC just give an assessment to how well the distributions fit the observed data and this may not give an indication as to how appropriate a distribution is for extrapolation beyond the observed data, external validation is crucial as described in the relevant NICE Technical Support Document.[56]

a. OS (IPCW adjusted analysis) extrapolation

While for the ECM (vorinostat) arm, generalised gamma provides the lowest AIC/BIC, it results in a survival curve with a high long-term survival, that is clinically implausible. The 20-year prediction with the generalised gamma is 10%, which contrasts with the 3% observed survival for a population with better survival due to lower proportion of SS patients and potentially lower proportion of heavily pre-treated patients[53]. It also contrasts with the 1% prediction based on clinical experience for the ITT population of the MAVORIC trial. Additionally, the generalised gamma suggests flattening of the survival curve, which would suggest cure for a proportion of patients with ECM, that is not seen in clinical practice with this heavily pre-treated, advanced population after ECM.

In the mogamulizumab arm, AIC/BIC for all distributions are very close (477-479 for AIC and 482-498 for BIC). However, using visual inspection, lognormal distribution

(which with log-logistic distribution has the second lowest AIC/BIC) fits better than the exponential curve (with slightly lower AIC (477 vs. 478) and BIC (483 vs. 490)) at the first half of the curve, where more data are available.

Additionally, the evidence shows a potentially disease modifying effect for mogamulizumab, which would result in a longer tail, as opposed to ECM (vorinostat) arm (see Question B.4). However, the use of exponential distribution for the mogamulizumab arm and generalised gamma for the ECM arm would result in a longer tail for the ECM arm compared to the mogamulizumab arm, which is contrary to the evidence and has no clinical plausibility (Figure 8). The effect of the different distributions for OS has been explored in scenario analyses in the MS and has limited effect on the ICER.

The ALCANZA trial, as described in Questions A4, B.3 and B.5 is not appropriate for validation of survival estimates due to the differences in patient populations and the high proportion of patients crossing over from the physician's choice arm to the BV arm.

Figure 8. OS scenario assuming exponential distribution for the mogamulizumab arm and generalized gamma for the ECM arm with IPCW crossover adjustment

b. NTFS: the generalised gamma was chosen for both vorinostat and mogamulizumab, despite the lognormal making the better fit for the latter.

b. NTFS extrapolation

For the NTFS, in the ECM arm, generalised gamma provides lower AIC (550 vs. 565 for generalised gamma and lognormal respectively) and lower BIC (559 vs. 570 for generalised gamma and lognormal respectively). Additionally, the generalised gamma distribution fits the observed Kaplan-Meier curve well throughout the curve with the exception of the last time-point, which has very limited data. The lognormal curve however runs below the observed curve from 8 months onwards (Figure 30 of the CS), and above the curve prior to that.

In the mogamulizumab arm, both the AIC (618 vs. 616 for generalised gamma and lognormal respectively) and BIC (626 vs. 622) are very similar and fit the observed curve well. Given the similar fit, and that there is also no strong evidence that the two treatment arms should have different distributions, generalised gamma was selected for both treatment arms. Using the generalised gamma distribution for the ECM arm and lognormal for the mogamulizumab arm changes the ICER only by 0.9% due to the similar fits (Table 23).

Table 23. Results with extrapolating NTFS using generalised gamma distribution for the ECM arm and lognormal for the mogamulizumab arm

Treatment	Total costs	Total LYs	Total QALYs	ICER (£/QALY)
Established clinical management	[redacted]	2.71	1.78	
Mogamulizumab	[redacted]	6.40	4.58	£34,137

c. Please discuss whether alternative methods for extrapolating both OS and NTFS were considered, such as hybrid models or piecewise models (in line with NICE DSU TSD 14). Please report cost effectiveness results using these methods in scenarios and ensure these options are added to the model.

Hybrid or piecewise models were not considered. In the case of NTFS and the OS in the mogamulizumab arm, the single distributions fitted well, and there was no need to consider alternative methods, that would increase uncertainty. For the OS ECM arm (using IPCW), there is a large drop at the beginning of the adjusted survival curve, that

suggests the use of piecewise fitting. However, this drop is due to the MAVORIC trial design allowing patients to crossover only after two full cycle of treatment and an additional minimum 2 weeks waiting period. The survival curve can be assumed to be smoother in clinical practice without this artificial drop. The single distributions correct for this drop.

However, in response to this suggestion, piecewise distribution was fitted to the OS on the ECM arm. The switch point was after the sharp drop at 12 months. Up to this point the Kaplan-Meier curve was used and after this point an exponential distribution fits the data well. However, due to this artificial drop the results are clinically implausible as seen in Figure 9. Thus, it was not implemented in the cost-effectiveness analysis.

Figure 9. Piecewise fit for the ECM (vorinostat) arm and single distribution for the mogamulizumab arm

B7. Priority question. A 24-month treatment stopping rule for mogamulizumab was assumed in the model, which is neither in line with the licence nor with the evidence from MAVORIC. If such a stopping rule was to be enforced, effectiveness is likely over-estimated in the trial compared to what it would be in practice.

a. **Please provide a table that includes the proportion of people on mogamulizumab treatment at different timepoints (6, 12, 18, 24 and 30 months).**

b. **Please provide any supporting evidence for mogamulizumab maintaining the same effectiveness (as observed in MAVORIC), despite being administered for a maximum of 24 months only.**

c. **Please explain how treatment waning is implicitly included in the independently fitted survival curves, as stated in Table 21 of the CS.**

d. **Please provide a scenario in which treatment waning is applied to mogamulizumab OS, NTFS and PFS, such that stopping treatment early is reflected. For example, after stopping mogamulizumab treatment, the effectiveness of the comparator arm or external data could be used in the modelling**

e. **Please provide a scenario in which there is no stopping rule.**

a. Table including the proportion of people on mogamulizumab treatment at different time points

Please see below the results in Table 24.

Table 24. Proportion of people on mogamulizumab over time

Time in model (months)	Proportion receiving mogamulizumab in advanced population	Proportion receiving mogamulizumab in ITT
6	[redacted]	[redacted]
12	[redacted]	[redacted]
18	[redacted]	[redacted]
24	[redacted]	[redacted]
30	[redacted]	[redacted]

b. The effect of the 24-month cut-off

The MAVORIC trial did not implement the 24-month cut-off, thus it provides no evidence of its effect, similar to the cut-offs implemented for reimbursement purposes for other treatments in various indications. However, since at 24 months only

approximately 14% of patients would be still receiving mogamulizumab in the advanced population and 10% in the ITT population of the MAVORIC trial, it would not affect the effectiveness of the population to a large extent. This was supported by expert opinion, emphasising that the vast majority of patients would have had the mogamulizumab benefit by this time point.[46] Additionally, as seen in the post-hoc analyses, the effect of mogamulizumab continues after treatment discontinuation (please see Question B.4), its consequences would be even smaller.

c. Inclusion of the waning effect

The independently fitted curves do not assume a constant hazard ratio, thus any waning effects that are seen in the observed data could transfer into the extrapolated survival curves. However, no assumption of waning effect was included.

d. Assumption of waning effect

The scenario requested was implemented by applying the hazard ratio for PFS, NTFS and OS for ECM versus mogamulizumab calculated from the MAVORIC trial (i.e. assuming survival reflect experience of patients in the ECM arm) for the proportion of patients who were still predicted to be on treatment at 24 months. The original curves were kept for those who have already stopped treatment before 24 months, as their experience would not be altered by the introduction of the stopping rule. Implementing this assumption increased the ICER by 8% (Table 25). However, as seen in Question B.4, the effect of mogamulizumab continues after treatment discontinuation, thus this scenario uses a very conservative assumption of the mogamulizumab effect stopping immediately after the 24-month stopping rule.

Table 25. Scenario analyses with treatment waning effect implemented at 24 months [redacted]

Treatment	Total costs	Total LYs	Total QALYs	ICER (£/QALY)
Established clinical management	[redacted]	2.71	1.78	
Mogamulizumab	[redacted]	5.94	4.28	£36,448

e. The effect of no stopping rule

Please see the effect of no stopping rule below in Table 26.

Table 26. Scenario results with no stopping rule

Treatment	Total costs	Total LYs	Total QALYs	ICER (£/QALY)
Established clinical management		2.71	1.78	
Mogamulizumab		6.40	4.60	£38,349

B8. In line with question A13, please provide a scenario analysis, in which patients undergoing aSCT are not excluded for the estimation of OS.

The aSCT is a potentially curative treatment, therefore prognosis of patients undergoing aSCT differs significantly from those not receiving aSCT. Therefore, the assumption of non-informative censoring in the case of survival curve estimation for OS does not hold, as those undergoing aSCT have a higher probability of being alive and therefore being censored at the end of the trial duration (out of 25 patients receiving aSCT only 4 deaths were observed). For these reasons, we do not think that patients undergoing aSCT should be included in this way in the estimation of OS. Nonetheless, the survival curve calculations have been undertaken and Figure 10 and Figure 11 below presents the estimated OS curves for all patients, including for those who received an aSCT.

Figure 1. OS curves for mogamulizumab for all patients

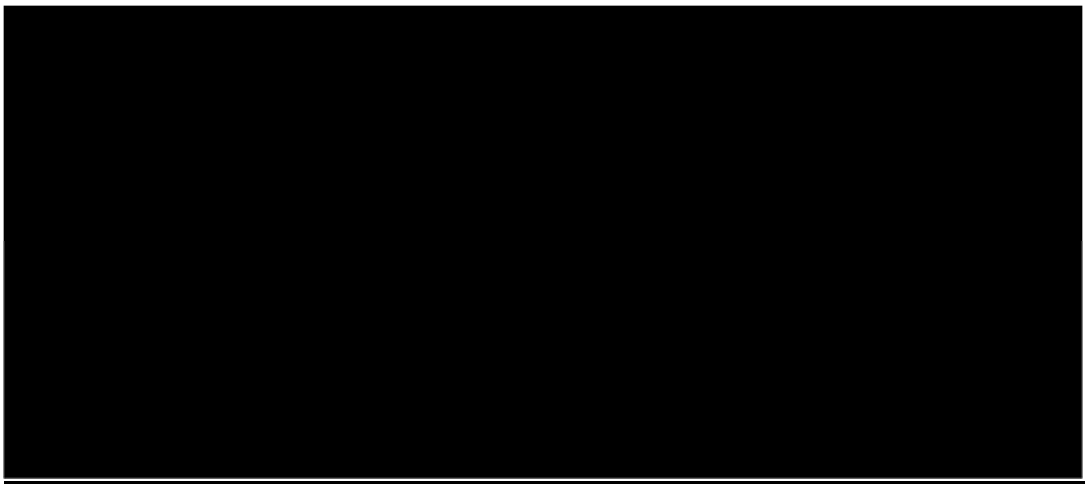
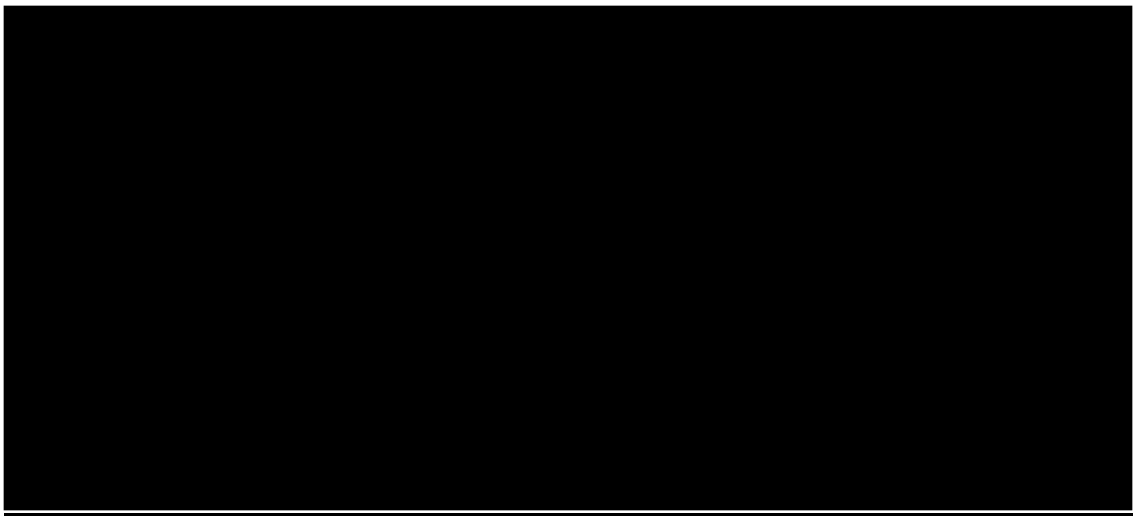


Figure 11. OS curves for ECM for all patients



Since the cost-effectiveness model includes separate survival partition models for those patients never receiving aSCT and for those undergoing aSCT at different time points, the scenario including the OS curves calculated for all patients including those who received aSCT was implemented in two ways. In the first instance the above OS curves for all patients were used only in the patients never undergoing aSCT survival partition model, and patients were only allowed to receive aSCT after subsequent treatments to correspond with the MAVORIC trial protocol. This method is biased, as it double counts the benefit of aSCT, as the OS curves for all patients lead to a better prognosis than the OS curves for those not undergoing aSCT, and therefore this overestimates the benefit of mogamulizumab due to the higher proportion of patients receiving aSCT. The results of this are presented in Table 27.

Table 27. Scenario results using all patient OS for PartSA model of patients never undergoing aSCT only

Treatment	**Total costs**	**Total LYs**	**Total QALYs**	**ICER (£/QALY)**
Established clinical management		2.49	1.60	
Mogamulizumab		6.66	4.77	£32,576

If the same OS curves for all patients are used in all three survival partition models, then the scenario is biased against mogamulizumab as the all patient OS curves

significantly underestimate the survival times for those undergoing aSCT. The results of this second scenario are presented in Table 28.

Table 28. Scenario results using OS for all patients in all three PartSA models [redacted]

Treatment	Total costs	Total LYs		Total QALYs	ICER (£/QALY)
Established clinical management	[redacted]	2.39		1.53	
Mogamulizumab	[redacted]	6.58		4.70	£32,836

Both of these scenarios have only minor effect on the ICER.

B9. Please provide a reference and / or more detail on how the proportions of patients receiving aSCT after current treatment (Table 32 of the CS) were derived.

The proportion of patients receiving aSCT after current treatment was not available in the MAVORIC trial. The MAVORIC trial was designed to test difference in PFS, therefore its design did not allow patients to be bridged to aSCT prior to progression. Nevertheless, it is anticipated based on the clinician survey and the in-depth interviews,[2] that mogamulizumab, similarly to ECM, will lead to patients bridging to aSCT after achieving a good PR or CR and the required 50-day wash-out period.[57] As a result, to estimate the proportion of patients bridged to aSCT after current treatment (mogamulizumab and ECM) a short clinician survey was conducted. The short survey is included in CS in Appendix U. The individual answers are presented below in Table 29.

Table 29. Proportion of patients receiving aSCT after current treatment

aSCT immediately after:	Average	KOL 1	KOL 2	KOL 3
Mogamulizumab	[redacted]	[redacted]	[redacted]	[redacted]
Current clinical practice	[redacted]	[redacted]	[redacted]	[redacted]

B10. Disease-free survival (DFS) and OS after aSCT are likely biased by a long plateau at the end of the KM data. In this plateau, it is likely that a significant proportion of patients were censored and lost to follow-up, and its inclusion is

therefore not informative and will lead to biased curve-fitting. Please produce an analysis of DFS and OS after aSCT, that includes censoring and in which only the KM data approximately up to 24 months are used (Figure 34 of the CS) for curve-fitting. Please include results from this analysis in a scenario.

The DFS and the OS curves were taken from NICE TA577, and unfortunately censoring was not available. Kyowa Kirin has no access to the data to perform additional analyses. As a result, we cannot provide this scenario. However, as mentioned in section 3.2 and 3.6 of TA577 FAD: “clinical experts noted that allogeneic stem cell transplants may consolidate treatment response to achieve durable remission, or possibly cure”.[1] Additionally, it mentions in Section 3.17 that “clinical experts advised that patients whose disease does not relapse within 15 months after transplant are expected to have sustained remission thereafter”, which suggests a plateau for these patients.

The manufacturer in TA577 submitted additional, longer follow-up and PFS data, which not only supported the original assumption, but provided even better outcomes. However, these are academic in confidence and Kyowa Kirin does not have access to this evidence. It does however suggest that the assumptions used in the current model, are conservative.

Adverse events

B11. Relating to question A4 and B3, please justify the assumption that vorinostat adverse event rates are expected to be the same as UK standard care adverse event rates.

The influence of AEs on the ICER is minimal. For example, deleting all the effect of AEs on costs, results in an ICER of £33,890/QALY vs. the base case £33,819/QALY. Please see the comparison of AEs between vorinostat and physician’s choice arm of the ALCANZA trial, which is a good approximation for UK standard care in Question A4.

Health related quality of life

B12. Priority question. The pattern of utility values over time is sometimes counter-intuitive or appears random (for example for mogamulizumab, there is an

increase in cycle 5, decrease in cycle 7, increase in cycle 9, etc. See Tables 36 and 38).

a. Please provide an explanation / rationale for this pattern.

There is a trend of the utilities increasing over time while patients are on mogamulizumab, as seen in the tables mentioned and in Table 30, Table 31 and Figure 12 below. This may be due to the response to treatment, and the subsequent potential reduction or disappearance of symptoms. It could also be due to differential survival/death rates as a least square model will not account for this. However, the differences between individual cycles are small and are not statistically significant, and as a result could be by chance. For example, the mentioned increase in cycle 5 in the mogamulizumab arm is 0.025 and the values have strongly overlapping confidence intervals. Similarly, the decrease in cycle 7 is 0.027 and the increase in cycle 9 is 0.049.

Table 30. Adjusted Mean EQ-5D HUI Scores by Randomized Treatment in the Pre-progression Phase (used in CS Table 36, 38)

	Mogamulizumab Group (N=184)			Vorinostat Group (N=186)		
Cycle[1]	**N**	**Mean**	**95% CI**	**N**	**Mean**	**95% CI**
Baseline	182	[redacted]	[redacted]	184	[redacted]	[redacted]
Cycle 1	168	[redacted]	[redacted]	155	[redacted]	[redacted]
Cycle 3	123	[redacted]	[redacted]	78	[redacted]	[redacted]
Cycle 5	101	[redacted]	[redacted]	52	[redacted]	[redacted]
Cycle 7	85	[redacted]	[redacted]	35	[redacted]	[redacted]
Cycle 9	70	[redacted]	[redacted]	26	[redacted]	[redacted]
Cycle 11	50	[redacted]	[redacted]	20	[redacted]	[redacted]

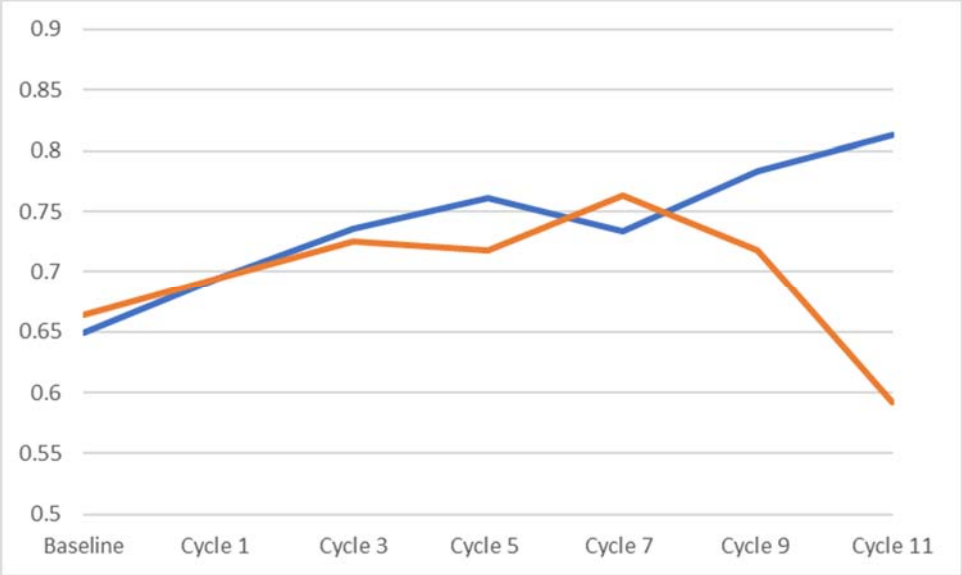
Abbreviations: EQ-5D HUI = EuroQol 5-Dimention Health Utility Index; CI = Confidence Interval.
[1] Only pre-progression cycles where at least 10% of subjects from each treatment group remain in the study are displayed and estimates were adjusted for histological subtype (SS/MF).

Table 31. Analysis of Change in EQ-5D Scores from Baseline During Randomized Treatment Period (Six Month Average) ITT

	LS Mean*				LS Mean* Difference			
Treatment	**Estimate**	**SE**	**95% CI**		**Estimate**	**SE**	**95% CI**	**p-value**
Mogamulizumab	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Vorinostat	[redacted]	[redacted]	[redacted]					

Abbreviations: ITT = Intent-to-treat, LS Mean = Least Squares Mean Estimate, SE = Standard Error, 95% CI = 95% Confidence Interval, EQ-5D = EuroQoL Five Dimensions Questionnaire, VAS = Visual Analog Scale.
* P-value for the 6-month average is from a mixed model including visits through cycle 5 (odd cycles only) with treatment, disease type, disease stage, and region as fixed effects and baseline score as a covariate.

Figure 12. Adjusted Mean EQ-5D HUI Scores by Randomized Treatment in the Pre-progression Phase



b. In a deterministic scenario analysis, the use of an average treatment-specific utility value throughout the disease control health state was applied. Please explain how this utility value was estimated.

Utilities were only collected while patients were on treatment (including patients crossing over to mogamulizumab) and during one additional visit after stopping treatment. The single health state utilities for the disease control health state was estimated as the average of all observations if at those visits the subject did not progress. The visit was defined as pre-progression (and by definition in disease control and on treatment) if it was prior to the date of investigator defined initial

progression free survival. This did not include patients who have crossed over from vorinostat to mogamulizumab, as the crossover was allowed only after progression.

The values were adjusted using the exhaustive model described in the MS. In summary, longitudinal mixed models of post-baseline EQ-5D HUI scores were regressed on fixed effects of randomized treatment (mogamulizumab vs vorinostat), treatment with mogamulizumab (on vs off), CTCL subtype (mycosis fungoides vs Sezary Syndrome), progression period (pre-progression period, post-progression period, pre-progression and post-progression KW mogamulizumab vs vorinostat, time-varying), and all 2-way interaction terms. An R-side random subject effect was included was included to account for repeated measures for assessment visits with the best fit variance/covariance matrix according to AIC/BIC of (1) unstructured, (2) first-order heterogeneous autoregressive, (3) first order autoregressive, and (4) compound symmetry. Backward selection of fixed effects was then performed to select the final model with the best fit according to AIC/BIC. Parameter estimates, standard errors, and p-values were reported for the full model and each step along the backward selection process. The variance/covariance matrix of fixed effects for the final model was also reported along with model results. (Please see more details in CS section B.3.4.1.)

c. **Please explain the rationale for having different utilities for the different time points in the base-case instead of having one "on treatment" health state utility (as in that scenario).**

The use of the utilities for the different time points takes into account the trend of increasing utilities seen in the mogamulizumab arm and reflects the experience of the patients in the MAVORIC trial more closely. The time specific utilities were used until cycle 12, and thereafter the single health state utilities were included. The use of time specific utilities vs. single health state has a negligible effect of the results, changing the ICER by 0.04%. (Please see Table 55 of the CS for more details.)

B13. Priority question. Carer disutilities were based on a vignette study, in which vignettes were informed by a targeted review of qualitative studies with individuals with CTCL and/or their caregivers and interviews with CTCL specialists. Further, the EuroQol five-dimensional questionnaire (five-level

version) (EQ-5D-5L) rating for each state was scored using a mapping function for the EQ-5D-5L and scores reflected UK preference weights.

a. **Please provide an analysis mapping to EQ-5D-3L, to be in line with the utility values collected in MAVORIC, and as recommended by the NICE position statement (updated October 2019).**

The development of the EQ-5D-5L meant that the EuroQol Group had a new measure but without preference-based scores.[58] Two solutions were developed to meet this need. Prof Ben van Hout led the development of a mapping function to predict EQ-5D-3L utilities from EQ-5D-5L responses.[59] This work was meant as an initial solution until new value sets could be collected. However, the value set work that was conducted and led by Prof Nancy Devlin in the UK has not been widely adopted because of criticisms received from the NICE DSU. Therefore, for submissions to NICE it is recommended that all EQ-5D-5L data are scored using the van Hout function for now (the so-called "Position Statement"). No value set for the EQ-5D-5L exists for Scotland. All EQ-5D-5L data collected in the current study has been scored using the van Hout function.

b. **Please provide further information on recruitment for the vignette study, as it is only stated that members of the UK general public were recruited using convenience sampling.**

The TTO interviews were conducted by field interviewers in Edinburgh (N=40), Somerset/Bristol (N=20) and Sheffield (N=40). They recruited members of the general population using convenience sampling. This included approaching potential participants and snowball recruiting.

c. **It is unclear why the carer utility gain was assumed for carers of mogamulizumab patients and applied to the incremental time period patients spent in the disease control state when treated with mogamulizumab versus ECM. Please provide justification for why this specific method was chosen (in that particular health state, for the applied duration, and as a utility gain as opposed to a disutility).**

There are no gold standard ways to apply carer utilities. One possibility is to include the carer utilities in all health states in which the patient is alive. However, if carer utilities

are only accounted for while the patient is alive, it would mean, that the survival benefit of the patients is transferred on to carers too, that is, carers would also have an additional survival benefit in the given quality of life. That would be methodologically incorrect.

Another option would be to account for carer utilities even after the patient's death, due to the rebound in utility values shown in the vignette study as described in the MS section B.3.4.3. This would mean modelling carers life expectancy also, where for the duration of the survival benefit of the patient, instead of the values measured for after the patient's death, the carer utilities relevant for the given health states are used. However, since the post-death carer utilities are higher than the utilities for the later health states, then treatments with which patients die earlier would be deemed more beneficial, since the treatment with worse efficacy would avoid the low health state utilities in favour of the higher post-death utilities. This opens up ethical questions.

Therefore, in the evaluation a carer utility gain was included in the value of the incremental difference between caring for a patient in second line of treatment versus caring for a patient in third line of treatment (utility value of 0.559-0.366=0.193) only for carers for mogamulizumab patients and only for the incremental time-period spent by patients in the mogamulizumab arm versus the ECM arm in the disease control health state. This means, that the benefit for carers comes from being able to keep the patients in the better, "Disease control" health state longer with mogamulizumab. While this might underestimate the advantage of the treatment to carers, it avoids the methodological and ethical issues discussed above.

B14. It is unclear how utility values in Table 36 were derived.

Please provide an explanation on how utility values in Table 36 were derived, how it relates to Table 35 and how data from Tables 35 and 36 are used in the model.

Utilities in the MAVORIC trial were only collected while patients were on treatment (including patients crossing over to mogamulizumab) and during one additional visit after stopping treatment.

The values in Table 36 of the CS show the health state utilities. These were derived the following way:

- Cycle specific utilities: These included pre-progression visits (and by definition in disease control and on treatment). The visit was defined as pre-progression if it was prior to the date of investigator defined initial progression-free survival. This did not include patients who had crossed over from vorinostat to mogamulizumab, as the crossover was allowed only after progression.

- On treatment utilities: The mean of observations for visits where the subject was assigned to mogamulizumab or vorinostat i.e. for subjects randomized to mogamulizumab this is all on-treatment visits, or for subjects randomized to vorinostat it is the crossover visits only (if the subject crossed over)

- Last observation post-progression: This is only for subjects that progressed and as a result stopped treatment and potentially started another one. All visits that occur on or post progression, as defined above, are classed as post progression visits determined by the date of investigator defined first progression. The latest of these observed visits is the last observation post progression.

The values were adjusted using the exhaustive model described in the CS. Please see Question B12 for more details.

B15. The CS reported that (grade 3 and 4) adverse events were assumed to have an important impact on the costs and quality of life and that incidence rates over the entire treatment period were used and costs applied as a lump sum at the start of treatment.

Please include the impact of adverse events on HRQoL.

The utility values for the Disease control – On treatment health state were estimated from the MAVORIC trial separately for the two treatment arms. As a result, the impact of all adverse events on quality of life for both treatment arms are included in the utility values used in the model and no additional disutility was required to be included for adverse events.

Resource use & costs

B16. Priority question. Health state unit costs were informed by a retrospective Hospital Episode Statistics (HES) database study and NICE TA577 for community-based costs.

a. **Please explain what calculations were made to inform costs used in the model (those that are listed in Table 44 of the CS), including details of how estimates in Tables 42 and 43 were used to inform Table 44.**

b. **Please explain how the end-stage care cost (shown in Table 43) was implemented in the model, specifically how the different durations before death were incorporated.**

The HES database study (please see CS section B.3.5.2 and Appendix Q for more details) assessed costs for two cohorts:

- Cohort A: All patients with a first diagnosis of CTCL between 1 October 2010 and 31 March 2019, with the date of the first diagnosis as the index date. This was used to determine costs for second- and third-line patients.
- Cohort B: Patients who died during the study period with patients tracked back from their date of death. Patient activity was aggregated for the 6-month periods prior to death. This was used to estimate end of life costs.

In cohort A (Table 42 of the MS), the total costs per patient-week estimates were estimated for four separate health states. The costs from the health states 'Diagnosis to first progression' and 'Third progression onwards' were not used, as the former was not relevant for the population assessed, which had prior systemic treatment, while the later health state was based on limited number of patients. The costs for 'First progression to second progression' was used for the model health state 'Disease control' and the costs for 'Second progression to third progression' for the model health state 'Subsequent treatment'. As the distribution of MF and SS patients in the HES database differed from that of the MAVORIC trial, the results for MF and SS were weighted using the distribution of MF-SS from the MAVORIC trial (55% MF and 45% SS).[31] This resulted in [redacted] for the Disease control and the Subsequent treatment' health states respectively.

In cohort B (Table 43 in MS), based on expert opinion and the previous NICE TA in MF/SS, 6-monthly intervals were determined prior to death. Similarly to the health states costs, MF and SS costs were weighted using the distribution of MF-SS from the MAVORIC trial. The results are presented in Table 32. As the main cost increase is seen in the last six months of life, the end of life costs have been implemented only for this time period. This is in line with NICE TA577 and the clinical expert opinion, which is the source of community-based costs.[2, 35] As the end of life costs are assigned to only those not receiving aSCT in line with the NICE TA577,[35] and a higher proportion of patients receive aSCT after mogamulizumab, this was a conservative assumption. The end of life costs are added as lump sum costs to the incident deaths.

Table 32. Costs per patient-week from the HES database from death (weighted using the distribution of MF-SS from the MAVORIC trial)

Time period	Up to 6 months prior to death	From 6 to 12 months prior to death	From 12 to 18 months prior to death	From 18 to 24 months prior to death
Cost/week	[redacted]	[redacted]	[redacted]	[redacted]

As the HES database only includes inpatient and outpatient costs, community-based resource use (home visits, skin and wound care, dressing and other drug treatment) from the NICE TA577 using ERG's preferred scenario was multiplied with current unit costs.[35] Adding the outpatient/inpatient costs from the HES database to the community-based costs from the updated NICE TA577 costs resulted in the total heath state costs presented in Table 44 of the CS. (For more details, please see Appendix 1.)

B17. The drug cost of mogamulizumab assumes dose banding. The CS reports a *"mean relative dose intensity"*.

a. **Please provide an explanation of *"mean relative dose intensity"*, for both mogamulizumab and vorinostat.**

b. **Please explain whether dose banding was also used in MAVORIC and use dose banding for the comparator, where appropriate.**

a. The % dose intensity is estimated as (total actual dose/total duration of treatment/7) / (total planned dose/total planned weeks). The planned dose is the average of the planned dose per subject, the actual dose is the average of the actual dose received per subject.

b. Dose banding, as recommended by NHS England for monoclonal antibodies, is used for the estimation of costs with wastage (see MS section B.3.5.1 for more details).[60] It is not used for determining the dose, only for the costing of the dose. The dose is determined in the MAVORIC trial as per trial protocol: "The dose of mogamulizumab chosen for this study was 1 mg/kg administered as an iv infusion over at least 60 minutes once weekly for the first 28-day cycle, followed by infusions on Days 1 and 15 of each subsequent 28-day cycle (once every 2 weeks) until disease progression or unacceptable toxicity."

B18. Please provide more information on how comparator proportions and treatment duration were informed for all the comparators listed in Table 40 of the CS.

The proportion of patients using each comparator was based on expert opinion elicited using the short survey either by mail or face-to-face interview. Please see MS Appendix U for the short survey and participants, and the KOL interview notes among references submitted. Replies for each clinician were reweighted to add up 100% without clinical trials. The distribution of comparators were asked separately for MF and SS and replies were weighted using the distribution of MF-SS from the MAVORIC trial (55% MF and 45% SS).[31] Results for MF and SS separately are presented in Table 33 and Table 34. The weighted average is presented in Table 22 of the MS.

Table 33. Comparator proportions for MF

	Average	KOL 1	KOL 2	KOL 3
Methotrexate (oral)	[redacted]	[redacted]	[redacted]	[redacted]
Bexarotene (oral)	[redacted]	[redacted]	[redacted]	[redacted]
Interferon alpha-2a	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapies			[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
CHOP	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Total skin electron beam therapy (TSEBT)	[redacted]	[redacted]	[redacted]	[redacted]

Etoposide (oral)	[redacted]	[redacted]	[redacted]	[redacted]
Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care: steroid, such as prednisolone	[redacted]	[redacted]	[redacted]	[redacted]

Table 34. Comparator proportions for SS

	Average	KOL 1	KOL 2	KOL 3
Methotrexate (oral)	[redacted]	[redacted]	[redacted]	[redacted]
Extracorporeal photopheresis (ECP)	[redacted]	[redacted]	[redacted]	[redacted]
Bexarotene (oral)	[redacted]	[redacted]	[redacted]	[redacted]
Interferon alpha-2a	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
CHOP	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Total skin electron beam therapy (TSEBT)	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide (oral)	[redacted]	[redacted]	[redacted]	[redacted]
Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care: steroid, such as prednisolone	[redacted]	[redacted]	[redacted]	[redacted]

For treatment duration the vorinostat ToT KM curve from the MAVORIC trial is assumed to represent the maximum treatment duration for the ECM ToT. Treatments that are given for shorter, limited duration, e.g. total skin electron beam therapy (TSEBT) or phototherapy UV-A (PUVA), the mean shorter, limited duration was included. The ToT for vorinostat is however shorter than what is seen in clinical practice with some of the components of ECM. For example, in the MAVORIC trial the mean ToT is 4.47 months for vorinostat, while methotrexate and bexarotene is usually given for 6-18 months, interferon alfa-2a for 4-18 months.[2] In these cases, the shorter duration observed for vorinostat was used to remain conservative. Thus, the analyses underestimate the cost of ECM, resulting in conservative cost-effectiveness estimates.

The effect of using the treatment duration of each comparator, and the use of bexarotene as the main comparator as per the NHS England budget impact analysis calculations is presented in Table 36. Both scenarios reduced the ICER.

Treatment durations were based on the NHS England budget impact analysis for bexarotene, methotrexate and interferon and on expert opinion through the short survey and face-to-face clinician interviews. For treatments where no treatment

duration is provided by NHS England or the clinical experts the vorinostat ToT is used as proxy (Table 35).

Table 35. Treatment durations for individual comparators

	Treatment duration	Source
Methotrexate (oral)	48 weeks	NHS England budget impact analysis
Bexarotene (oral)	48 weeks	NHS England budget impact analysis
Interferon alpha-2a	1 year	NHS England budget impact analysis
Gemcitabine	Vorinostat ToT	MAVORIC trial
CHOP	Vorinostat ToT	MAVORIC trial
Doxorubicin	Vorinostat ToT	MAVORIC trial
Total skin electron beam therapy (TSEBT)	4/week for 4 weeks, sometimes repeated again	Expert survey
Etoposide (oral)	6 months	Expert survey
Phototherapy	13 weeks	Expert survey
Best supportive care: steroid, such as prednisolone	Vorinostat ToT	MAVORIC trial

Table 36. Scenario analyses for comparator treatment duration and comparator selection with [redacted]

Parameter	Technology	Total costs	Total QALYs	ICER
Base case in MS	**ECM**	[redacted]	**1.78**	£33,819
	Mogamulizumab	[redacted]	**4.60**	
Treatment duration of comparators based on expert opinion (with 45-year time horizon)	ECM	[redacted]	1.78	£31,922
	Mogamulizumab	[redacted]	4.63	
Bexarotene as main comparator and treatment duration as per NHS England budget impact analysis (with 45-year time horizon)	ECM	[redacted]	1.78	£27,222
	Mogamulizumab	[redacted]	4.63	

B19. The length of treatment for subsequent therapies and subsequent treatment costs were modelled based on expert opinion and interviews. It is, however, not clear, how the numbers provided in Tables 46 and 47 of the CS were derived (as these do not seem to be based on reference 49 of the CS).

Please provide detail on how these estimates were informed.

Similarly to comparator treatments, distribution of subsequent treatments are based on expert opinion, i.e. reference 49 in the MS. Subsequent treatments were elicited from clinical expert through the short survey and face-to-face interviews separately for MF and SS (Table 37 and Table 38), then a weighted average was estimated using the distribution of MF and SS in the MAVORIC trial. For more detail, please see Question B18.

Table 37. Distribution of subsequent treatments for MF

	Average	KOL 1	KOL 2	KOL 3
Bexarotene	[redacted]	[redacted]	[redacted]	[redacted]
Phototherapy UV-A (PUVA)	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Interferon alpha	[redacted]	[redacted]	[redacted]	[redacted]
CHOP	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Total skin electron beam therapy (TSEBT)	[redacted]	[redacted]	[redacted]	[redacted]
No active treatment (BSC): steroid, such as prednisolone	[redacted]	[redacted]	[redacted]	[redacted]

Table 38. Distribution of subsequent treatments for SS

	Average	KOL 1	KOL 2	KOL 3
Bexarotene	[redacted]	[redacted]	[redacted]	[redacted]
Phototherapy UV-A (PUVA)	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Interferon alpha	[redacted]	[redacted]	[redacted]	[redacted]
Interferon+ECP	[redacted]	[redacted]	[redacted]	[redacted]
Bexarotene + ECP	[redacted]	[redacted]	[redacted]	[redacted]
CHOP	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Total skin electron beam therapy (TSEBT)	[redacted]	[redacted]	[redacted]	[redacted]
No active treatment (BSC): steroid, such as prednisolone	[redacted]	[redacted]	[redacted]	[redacted]

B20. Please provide a reference for and detail on what was included in the 2-year follow-up costs after aSCT based on UK Stem Cell Strategy Oversight Committee 2004, especially considering the possibility of overlap / double-counting with costs of treatment after aSCT as estimated based on TA577.

Please find both the original UK Stem Cell Strategy Oversight Committee report,[61] and the NICE TA567 that updated and used the results of the report attached. The report calculated the total cost of SCT including procedure and long-term care post-transplant (up till 2 years after procedure). NICE TA567 estimates the follow-up cost of aSCT separately "as a proportion of allogeneic SCT costs based on the relative cost of allogeneic SCT compared to autologous SCT, as reported in Blommestein et al. (2012)". The results are presented in NICE TA567 Committee paper Table 21 and issue 18 in erratum).[62]

To avoid double counting, in the first 2 years after aSCT, no additional follow-up costs were added in the model.

Cost effectiveness results and sensitivity analyses

B21. All cost and resource use parameters were included in the probabilistic sensitivity analysis (PSA) using a normal distribution. However, the standard recommendation in the handbook of Briggs et al. is to use a gamma distribution for cost and resource use parameters.

Please include a scenario using a gamma distribution for all cost parameters.

The above mentioned handbook and related publications state that "If there is much information available to inform a parameter's estimate, then by the central limit theorem—the sampling distribution of the arithmetic mean will follow a normal distribution (with sufficient sample size), whatever the data's underlying distribution—then the normal distribution can be used in a PSA and a standard confidence interval in a DSA". [63]Individual cost estimates may be skewed, but across the whole population the mean cost can be assumed to follow a normal distribution. Nonetheless, a scenario analysis was undertaken using a gamma distribution to represent uncertainty in the cost parameters. The results are available below in Table 39 and Figure 13 and Figure 14 and have no or very minor effect on the results.

Table 39. Scenario results with gamma distributions for cost parameters [redacted]

	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALYs)
Deterministic results	[redacted]	2.83	3.69	33,819
Probabilistic results	[redacted]	2.79	3.63	33,971

Figure 2. Scatter plot results with gamma distributions for cost parameters [redacted]

Figure 3. CEAC results with gamma distributions for cost parameters

B22. Please include the ToT estimates in the PSA.

Since the curves were complete, ToT was included in the model based on the actual observed KM curves from the MAVORIC trial. Inclusion of KM curves in the PSA is difficult, as individual drops in the curves should be varied at time-points where events occurred. Instead a scenario is presented in Table 40, Figure 15 and Figure 16 where ToT is fitted with the generalised gamma distribution. The effect on the results are minor.

Table 40. Scenario PSA results with generalised gamma distribution for ToT

	Incremental costs	Incremental QALYs	Incremental LYs	ICER (£/QALYs)
Deterministic results		2.83	3.69	34,159
Probabilistic results		2.78	3.63	34,461

Figure 4. Scatter plot for scenario results with generalised gamma distribution for ToT [redacted]

Figure 5. CEACs for scenario results with generalised gamma distribution for ToT [redacted]

Validation and transparency

B23. Priority question. Please provide a cross-validation of the submitted cost effectiveness analysis compared with NICE TA577, including a summary table that considers:

- **Model structure and major assumptions**
- **Intervention and comparators**
- **Estimates such as proportions receiving aSCT after current treatment, proportions of comparators and subsequent treatments, and other influential transition probabilities**
- **HRQoL data used**
- **Health state unit costs**

- **Results, and if applicable, possible explanations for different results especially in the comparator group (regarding OS and PFS, life-years (LYs) and QALYs gained, and health state and comparator costs) compared with NICE TA577.**

Please see the comparison requested in Table 41 below.

Table 41. Comparison of the current CEM and the NICE TA577 CEM

	Current CEM	NICE TA577 CEM	Reasons for the differences
Model structure	Based on PartSA with the inclusion of aSCT Based on OS, NTFS, DFS	Based on PartSA with the inclusion of aSCT Based on OS, PFS, DFS (Manufacturer 1st version, 2nd version uses confidential PFS for aSCT instead of DFS)	NTFS is more closely aligned with symptoms and disease control, and as a result a better proxy for treatment changes, quality of life and resource utilisation, thereby, for determining health states
Major assumptions: comparators	Vorinostat is a good proxy for established clinical practice	Physician's choice of bexarotene and methotrexate is a good proxy for established clinical practice	MAVORIC trial included a more severe and more heavily pre-treated population which resulted in challenges in recruitment and limited treatment options. As a result vorinostat was selected as comparator.
Major assumptions: aSCT	Patients can receive aSCT after current and subsequent treatment	Patients can receive aSCT after treatment (after current and subsequent treatments are not separated)	NICE TA577 didn't separate the two timepoints patients can receive aSCT, however the FAD mentioned, that "not all patients who had a transplant in ALCANZA did so directly after having brentuximab vedotin". The current CEM tried

	Current CEM	NICE TA577 CEM	Reasons for the differences
			to explicitly model these two time points.
Major assumption: crossover adjustment	Overall survival for patients not receiving aSCT can be adjusted for crossover using IPCW method for ECM based on statistical fit and clinical/biological plausibility	Crossover adjustment was problematic	The Manufacturer attempted crossover adjustment in TA577 using only RPSFT method, however according to the FAD: "The company attempted to adjust for this treatment switching, but considered the results to be clinically implausible. […] considered that the adjustment may have been conducted incorrectly."
Intervention	Mogamulizumab	Brentuximab vedotin	-
Comparator	Established clinical practice from clinical expert survey	Assumed bexarotene and methotrexate represents established clinical practice	ALCANZA trial included bexarotene and methotrexate in the comparator arm
% receiving aSCT after current treatment	[redacted]	16.7%-40% vs. 7.1%	There were differences in the populations for the ALCANZA and the MAVORIC trials
% receiving aSCT after subsequent treatment	[redacted]		
Utilities for patients	Disease control: Per cycle utilities until cycle 12, then [redacted] for mogamulizumab and [redacted] Subsequent treatment: [redacted] End stage care: 0.38 Post-aSCT: 0-2 weeks: 0.42	Progression-free: 0.69 (ERG scenario) Post-progression – On next treatment: 0.64 (ERG scenario) Post-progression – Off treatment: 0.495 (assumption by ERG) End stage care: 0.38	The health states were different, however the utilities for Subsequent treatments and Post-progression – On next treatment were very similar. Similarly, utilities at baseline for MAVORIC ([redacted]) were

	Current CEM	NICE TA577 CEM	Reasons for the differences
	3 weeks-month 4: 0.60 3 months onwards: 0.77	Post-aSCT: 0-2 weeks: 0.42 3 weeks-month 4: 0.60 3 months onwards: 0.77	similar to the utilities pre-progression in the ALCANZA trial, however utilities for mogamulizumab increased over time, which was not shown for BV, potentially due to the different treatment modalities.
Carers' utilities	Included	Not included	While TA577 emphasized the importance of carers' burden in these indications, no data was elicited, while Kyowa Kirin conducted a vignette study to assess the quantitative effect of carers' burden
Health state costs	Disease control: [redacted] Subsequent treatment: [redacted] End stage care: [redacted]	Pre-progression: £205.89 Post-progression: £376.03 End stage care: £797.89 (ERG preferred scenario updated with current unit costs, for more information see [redacted]1)	TA577 based costs on expert opinion. Results were heavily criticized by the ERG and the Committee for not being representative. Kyowa Kirin has conducted a database study to estimate the inpatient/outpatient costs for the NHS to reduce this uncertainty. The results of the study supported the Committee's criticism of the TA577 costs, that they were overestimated.

	Current CEM	NICE TA577 CEM	Reasons for the differences
QALYs	4.6 vs. 1.8 for mogamulizumab and ECM respectively	CiC	-
Total costs	[redacted] vs. £59,538 for mogamulizumab and ECM respectively	CiC	-
ICER	[redacted]	£29,613 per QALY	ICER are similar

Section C: Textual clarification and additional points

C1. Priority question. After receiving the CS, the Evidence Review Group (ERG) requested the full clinical study report (CSR) for the MAVORIC trial. In response, the company provided a number of PDF documents with selected Tables and Figures.

Please provide the full CSR for the MAVORIC trial, i.e. including the main text and all supporting appendices.

Response with provision of all sections of the CSR (zipped file called 0761-010 CSR): the naming convention in the CSR matches the ID's/labelling of the respective files

There are two folders within: '0761-010' and 'listings,' as well additional files

In '0761-010' there are sub-folders labelled with numerals. These refer to the investigational site numbers and in each folder are the individual subject CRFs for those subjects that experienced a SAE, died or were withdrawn due to an AE

In '0761-010' there is a sub-folder labelled 'study report body' which contains the report itself, appendix 14 files, the subject narratives, and additional reports related to the study (e.g., biomarker).

In '0761-010' there are also additional files (e.g., all versions of the protocol, investigator CVs, etc), all of which are referenced within the CSR body.

In 'listings' there are all the appendices from Section 16 of the CSR; note that '16.3 Case Report Forms' is the file '0761-010-sample-crf-en' found as a loose file in the '0761-010' sub-folder

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Appendix 1: Estimation of Health state costs

Resource use for the health states were taken from NICE TA577 using the ERG preferred scenarios from NICE TA577 FAD - Committee Papers Table 7: Resource use assumptions, ERG scenario 3 or, in case of end-stage care, NICE TA 577, ERG Erratum in Appraisal consultation documents, Table 33. Unit costs were updated using current unit costs according to the NICE reference case. Since values were based on expert opinion, inpatient and outpatient costs were substituted with the results of the HES database study by Kyowa Kirin.

Table 42. Resource use and unit costs based on the NICE TA577

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	Resource use reference for End-stage
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
Hospital outpatient									
Clinical nurse specialist	100%	0.19	100%	0.38	100%	0.25	90.00	PSSRU 2018 - Band 5 hospital nurse cost per hour of patient contact	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Dermatologist visit	0%	0.00	100%	0.50	50%	0.17	114.00	NHS reference costs 2018 - Dermatology consultant-led	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Oncologist outpatient visit	100%	0.19	100%	0.38	0%	0.00	104.00	NHS reference costs 2018 - Medical oncology non-consultant-led	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Consultant oncologist visit	100%	0.19	100%	0.54	100%	0.17	173.00	NHS reference costs 2018 - Medical oncology consultant-led	NICE TA 577, Company submission, Table 49
Psychologist	0%	0.00	0%	0.00	5%	0.25	109.00	PSSRU 2018 - Consultant: psychiatric - cost per	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	Resource use reference for End-stage
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
								working hour	
Hospital inpatient									
Dermatology day centre or oncology ward	0%	0.00	0%	0.00	20%	0.11	806.00	NHS reference costs 2018 - JC41Z Major skin procedures day case	NICE TA 577, Company submission, Table 49
Home visit									
District nurse visit	100%	0.25	100%	0.25	100%	0.25	36.00	PSSRU 2018 - Nurse (GP practice) per hour	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Macmillan nurse/social services	0%	0.00	0%	0.00	100%	0.25	224.00	7 * PSSRU 2018 - Social work assistant cost per hour of client-related work	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Palliative care support team	0%	0.00	0%	0.00	100%	0.25	43.00	PSSRU 2018 - Occupational therapist per hour (community occupational therapist)	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Investigations and tests									
Complete blood count	100%	0.25	100%	0.67	0%	0.00	2.51	NHS reference costs 2018 -	

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	Resource use reference for End-stage
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
								DAPS05: Haematology	
Liver function test	100%	0.25	100%	0.33	0%	0.00	1.11	NHS reference costs 2018 - DAPS04: Clinical Biochemistry	
Urea and electrolytes test	100%	0.25	100%	0.33	0%	0.00	1.11	NHS reference costs 2018 - DAPS04: Clinical Biochemistry	
LDH (lactate dehydrogenase)	0%	0.00	100%	0.33	0%	0.00	1.11	NHS reference costs 2018 - DAPS04: Clinical Biochemistry	
CT scan	50%	0.08	50%	0.17	0%	0.00	139.15	NHS reference costs 2018: RD27Z - Computerised Tomography Scan of more than Three Areas (outpatient)	
PET scan	50%	0.08	50%	0.17	0%	0.00	139.15	NHS reference costs 2018:	

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	Resource use reference for End-stage
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
								RD27Z - Computerised Tomography Scan of more than Three Areas (outpatient)	
Skin and wound care									
Radiotherapy	0%	0.00	0%	0.00	90%	0.11	992.92	2*NHS reference costs 2018-SC25Z: Deliver a Fraction of Total Body Irradiation	NICE TA 577, Company submission, Table 49
Betnovate	0%	0.00	0%	0.00	80%	0.34	4.12	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 49	NICE TA 577, Company submission, Table 49
Dressings									
Localised coverage	37.5%	49.00	37.5%	49.00	37.5%	7.00	6.25	Unit based on NICE TA577 ACD document: Committee Papers Company Submission	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	Resource use reference for End-stage
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
								Document B Table 45	
Mepitel dressings	0%	0.00	0%	0.00	12.5%	21.00	14.25	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 49	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Mepilex large sheet dressings	0%	0.00	0%	0.00	12.5%	14.00	63.64	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 49	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Mepilex small dressings	0%	0.00	0%	0.00	12.5%	21.00	10.17	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 49	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Mepilex heels	0%	0.00	0%	0.00	12.5%	14.00	12.87	Unit based on NICE TA577 ACD document: Committee Papers	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	Resource use reference for End-stage
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
								Company Submission Document B Table 49	
Elasticated garments	0%	0.00	0%	0.00	12.5%	1.00	26.12	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 49	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Medium Allevyn	0%	0.00	0%	0.00	37.5%	49.00	17.36	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 49	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Other drug treatment (pain relief)									
Oramorph	0%	0.00	0%	14.00	100%	14.00	0.27	BNF 2019	
Oromorph (breakthrough pain / iv)	0%	0.00	80%	1.00	80%	0.25	0.09	BNF 2019	
Other drug treatment (antihistamines)									
Hydroxyzine	0%	0.00	50%	4.67	100%	4.67	0.02	BNF 2019	
Gabapentin	0%	0.00	33%	14.00	50%	14.00	0.03	BNF 2019	
Other drug treatment (antidepressants)									
Mirtazapine	0%	0.00	50%	7.00	50%	7.00	0.04	BNF 2019	

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	Resource use reference for End-stage
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
Pregabalin	0%	0.00	50%	7.00	50%	7.00	0.10	BNF 2019	
Other drug treatment (antibiotics)									
Flucloxacillin	0%	0.00	100%	4.83	100%	3.22	0.10	BNF 2019	
Aciclovir	0%	0.00	25%	28.00	25%	28.00	0.05	BNF 2019	
Other drug treatment (antibiotics)									
Fusidic acid	0%	0.00	0%	0.00	80%	0.02	4.16	BNF 2019	
Total Cost (per week) (£)	205.89		376.03		797.89				

Table 43. Other drug costs

Treatment	Drug form	Dose required	Unit cost	Unit size	Dose Size	Unit	Source of costs	Source of dose	Comment
Oramorph	capsule	60	£ 16.20	60	60.0	mg	BNF 2019	Brentuximab NICE TA	Drug tariff price
Oromorph (breakthrough pain / iv)	IV	10	£ 1.89	2	100.0	ml	BNF 2019	Brentuximab NICE TA	Drug tariff price
Hydroxyzine	tablet	25	£ 0.62	25	28.0	mg	BNF 2019	Brentuximab NICE TA	Drug tariff price
Gabapentin	capsule	300	£ 3.48	300	100.0	mg	BNF 2019	Brentuximab NICE TA	Drug tariff price
Mirtazapine	tablet	30	£ 1.24	30	28.0	mg	BNF 2019	Brentuximab NICE TA	Drug tariff price
Pregabalin	capsule	300	£ 5.55	300	56.0	mg	BNF 2019	Brentuximab NICE TA	Drug tariff price
Flucloxacillin	capsule	500	£ 2.80	500	28.0	mg	BNF 2019	Brentuximab NICE TA	Drug tariff price
Aciclovir	tablet	200	£ 1.20	200	25.0	mg	BNF 2019	Brentuximab NICE TA	Drug tariff price
Fusidic acid	cream	30	£ 4.16	30	1.0	g	BNF 2019	Brentuximab NICE TA	Drug tariff price

Table 44. Health state cost calculation used for the Mogamulizumab cost-effectiveness model

	Disease control	Subsequent treatments	Pre-progression	Post-progression	End-stage Care
Hospital outpatient	£ 69.73	£ 224.14	£ 69.73	£ 224.14	£ 325.45
Hospital inpatient	£ -	£ -	£ -	£ -	£ 17.73
Home visit	£ 9.00	£ 9.00	£ 9.00	£ 9.00	£ 75.75
Investigations and tests	£ 12.31	£ 26.43	£ 12.31	£ 26.43	£ -
Skin and wound care	£ -	£ -	£ -	£ -	£ 99.42
Dressings	£ 114.84	£ 114.84	£ 114.84	£ 114.84	£ 536.66
Other drug treatment	£ -	£ 1.61	£ -	£ 1.61	£ 5.37
Total	***£ 205.89***	***£ 376.03***	***£ 205.89***	***£ 376.03***	***£ 1,060.38***
Total without inpatient-outpatient	***£ 123.84***	***£ 125.45***	***£ 123.84***	***£ 125.45***	***£ 717.20***
Inpatient/outpatient costs from HES	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs per week using HES database	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Patient organisation submission

Mogamulizumab for treated mycosis fungoides or Sézary syndrome T-cell lymphoma [ID1405]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Our work is made possible by the generosity, commitment, passion and enthusiasm of all those who support us. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. This includes that no more than 20% of our income can come from these companies and there is a cap of £50k per company. Acceptance of donations does not mean that we endorse their products and under no circumstances can these companies influence our strategic direction, activities or the content of the information and support we provide to people affected by lymphoma.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12	Kyowa Kirin - £15,500 (sponsorship of education and training/survivorship events; publications; core services) Accord Healthcare – NA ADVANZ Pharma - NA Cipla EU - NA

months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	Eisai - NA Hospira UK - NA Medac - NA Nordic Pharma - NA Orion Pharma - NA Pfizer - NA Roche Products - £12,000 (sponsorship of education and training/survivorship events; publications; core services) Rosemont Pharmaceuticals - NA Sandoz - NA Takeda - £27,500 (sponsorship of education and training/survivorship events; publications; core services)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We asked patient contacts who we support to comment. We also had a call-out on our social media channels for patients with a relevant diagnosis to come forward who would like us to consider their views. We sent questionnaires to people who responded, asking about their experience of current treatment and what they think might be the advantages or disadvantages of new treatments, with particular emphasis on quality of life. We have used their responses as the basis of this submission. We have also included information based on our prior experience with patients with this condition.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	People with cutaneous T-cell lymphoma (CTCL) usually live with their condition for many years, and experience symptoms flaring up from time to time. Being accurately diagnosed can take a long time – sometimes years – which patients find frustrating and isolating. Many people experience itching both as a symptom and as a side effect of treatment. Itching all the time can have a significant impact on quality of life, making people irritable and miserable. It can be difficult to sleep, so people with CTCL may frequently be very tired. If inflammation is widespread, some people find it difficult to control their body temperature, and develop fevers, chills and shakes, even hypothermia. Skin may be painful, particularly if people have tumours or if areas of skin weep or become infected. There is a risk of infections when skin is broken and irritated. Psychological and social wellbeing are significantly affected, particularly at more advanced stages. Patients can suffer severe discomfort, itching, pain and fatigue with subsequent effects on employment, leisure activities, relationships and day-to-day living. In addition, the psychological impact of the condition is significant: patients report feelings of uncertainty, frustration, embarrassment, helplessness, confusion, worry, anxiety and depression. CTCL can also affect employment due to time off work for hospital appointments and treatments and the effects of the condition itself. Some people are unable to carry on their occupation, which also has a financial impact. Carers can also be significantly affected by CTCL. They are often the main source of emotional and psychological support for a loved one with CTCL. Although this is invaluable, it can also be draining. Carers also play a practical role that can affect their day-to-day life, from taking time off work to accompany their loved one to appointments and treatment sessions, to helping them apply topical treatments and helping with the extra laundry that some topical treatments lead to.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are many possible treatments for CTCL, but the effects are often short-lived. Topical treatments and phototherapy can work for some people, but don't work for others. Many treatments are not tried and tested for skin lymphomas, but are used for other conditions. Coupled with most doctors' lack of knowledge about the disease, this increases patients' fears that the treatment won't work. One of the major drawbacks of current treatment options is the lack of a durable response. Many patients respond briefly to treatment and have only a short period treatment-free before symptoms recur and they require more treatment. This can be very onerous, involving many cycles of treatment at centres that may be some distance from home. People who don't respond to topical treatments or phototherapy may need systemic treatments, including chemotherapy or radiotherapy. Patients with advanced CTCL who have not responded to previous therapy might even need an allogeneic stem cell transplant. Stem cell transplants have a massive impact on quality of life, typically requiring an extended hospital stay, time off work and a prolonged recovery period. Existing treatments can have side effects that significantly affect patients' quality of life. These might include, for example, itching or painful skin reactions that disrupt sleep, as well as fatigue caused by treatments themselves. Systemic chemotherapy and stem cell transplants can have serious side effects and late effects. Specialist treatments can involve travelling significant distances for repeated hospital appointments. As well as affecting quality of life, this can have a financial impact in terms of time off work to travel to appointments (for both patients and carers) and costs of travel and hospital parking charges. It can also very stressful. In addition, skin care regimes and wound dressing in later stages are time-consuming, inconvenient and messy for both the patient and their family or carer.

8. Is there an unmet need for patients with this condition?	Yes, there is an unmet need for an effective, well tolerated and durable therapy that reduces the burden of symptoms and treatment.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	None of the patients we surveyed have been treated with mogamulizumab, but they reported that existing treatments did not keep the disease under control for long. A treatment with a longer duration of response would be a big advantage and could lead to improvements in quality of life due to a lower impact of both symptoms and side effects from repeated rounds of treatment. Symptoms have a considerable impact on the day-to-day lives of patients and even small improvements can be beneficial. The fact that mogamulizumab can be administered in the standard outpatient setting is an advantage over some specialised treatments that are not available in local centres.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with all new treatments, patients are concerned about potential side effects. Patients feel it would be important that clinicians explained the likely effects so they could weigh up the potential risks and benefits in order to make an informed decision. Patients who do not live close to a hospital might find it difficult to travel for outpatient treatment at least every 3 weeks, particularly as the treatment may be continued for a prolonged period (licensed until disease progression or unacceptable toxicity).

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Cutaneous T-cell lymphoma has a significant negative impact on the quality of life of patients and their carers.
- The duration of response to current treatments for cutaneous T-cell lymphoma is limited. Many patients respond only briefly to treatment and have only a short period treatment-free before symptoms recur.
- Existing treatments can have side effects that significantly affect patients' quality of life. Specialist treatments can also involve travelling considerable distances for repeated hospital appointments.
- There is a clear unmet need for an effective, well tolerated and durable therapy that reduces the burden of symptoms and treatment.
- Patients feel that a treatment with a longer duration of response would be a big advantage over current treatment options and could lead to improvements in quality of life due to a lower impact of both symptoms and side effects from repeated rounds of treatment.

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Professional organisation submission

Mogamulizumab for treated mycosis fungoides or Sézary syndrome T-cell lymphoma [ID1405]

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Association of Dermatologists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify): Just to add that I now have experience prescribing mogamulizumab outside of a clinical trial and have treated 5 patients (since august 2019) on the compassionate use program and out of clinical trial it appears safe and effective
5a. Brief description of the organisation (including who funds it).	**Professional body for UK dermatologists.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Mogamulizumab is targeted against the malignant T-cells and reduces tumour burden and improves quality of life (symptom, function and emotions). It reduces tumour burden in all compartments (responses: blood 68%, skin 42% and lymph nodes 17%) and dramatically in blood. It is well tolerated and may be continued to be given until loss of clinical benefit and within the MAVORIC trial median treatment time was 170 days with mogamulizumab with lasting responses of median of 13.1months in MF and 17.3months in Sezary syndrome.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	We consider responses in MF/SS as an improvement of 50% but many patients derive clinical benefit from skin symptoms, emotions and functions below 50%.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a huge unmet need for patients with cutaneous lymphoma, there are few drugs and most have limited responses (30-40%) and short duration 9-12 months. More drugs are desperately needed and immunotherapies are preferred over chemotherapy as reducing patients own innate immunity with chemotherapy appears to promote progression in some patients and is therefore recommended after failure of immunotherapies or in high grade transformed disease.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	The BAD guidelines referenced below were published 2019, treatments are listed as first, second or third line and for each line there are a list of therapies in no particular order of preference. Most treatments are given till loss of clinical benefit and consecutive therapies are given. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Gilson D, Whittaker SJ, Child FJ, Scarisbrick JJ, Illidge TM, Parry EJ, Mohd Mustapa MF, Exton LS, Kanfer E, Rezvani K, Dearden CE, Morris SL. Br J Dermatol. 2019 Mar;180(3):496-52
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Please see above

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Our guidelines are national. As therapies are listed no order of preference there may be local preferences to therapies and patient individualised treatment approaches
• What impact would the technology have on the current pathway of care?	Mogamulizumab would be a much needed addition to the choic of first line systemic therapies in cutaneous lymphoma
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Would add another much-needed treatment as patients live several years with disease and treatment options run out
• In what clinical setting should the technology be used? (For example,	Specialist clinic only

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None, can be given on iv day suite
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes currently we have patients who have exhausted all available treatment options and would benefit from mogamulizumab
• Do you expect the technology to increase length of life more than current care?	This is not known yet
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, MAVORIC showed this compared with vorinostat and start of trial I think we must add something on QoL in CTCL. Patients with CTCL have painful, itchy and often unsightly skin lesions and as a result suffer a reduced HRQoL [ref]. This is compounded by living with an incurable cancer with a lack of effective treatments. Most treatments result in only partial responses of short duration (<1 year) so patients consequently have active lesions throughout [ref Gilson Br J Derm Guidelines]. Those with earlier

	stages often exhaust the small repertoire of anti-CTCL treatments and have to be managed with supportive therapy alone. 8. Molloy K, Jonak C, Woei-A-Ji S, Guenova E, Busschots A, Bervoets A, Hauben E, Knobler R; Stefanie Porkert; ard Cowan, Evangelina Papadavid, Marie Beylot-Barry, Peng C, Howles A, Yoo J, Evison F, Scarisbrick J. Characteristics associated with significantly worse quality of life in mycosis fungoides/Sézary syndrome from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study. Br J Dermatol epub 2019 9. Constanze Jonak, Stefanie Porkert, Simone Oerlemans, Evangelia Papadavid, Kevin Molloy, Eva Lehner-Baumgartner, Antonio Cozzio, Fabio Efficace, Julia Scarisbrick. Health-related quality of life in cutaneous lymphomas: past, present and prospective. Acta Derm 2019;99(7):640-646
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Mogamulizumab is effective in MF and SS
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	No it is straightforward, have been using on compassionate use given on a day facility and no problems encountered

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, reduced tumour burden, improved progression free survival (mogamulizumab therapy resulted in superior investigator-assessed progression-free survival compared with vorinostat therapy (median 7·7 months [95% CI 5·7–10·3] in the mogamulizumab group vs 3·1 months [2·9–4·1] in the vorinostat group; hazard ratio 0·53, 95% CI 0·41–0·69; stratified log-rank p<0·0001) MAVORIC). There was also improved quality of life compared to vorinostat and before trial. The pre-planned analyses of Skindex-29, FACT-G, 3-level EQ-5D, and ItchyQoL found mogamulizumab-treated patients had a

	greater improvement in patient-reported outcomes at the 6-month assessment than did vorinostat treated patients; these findings were statistically significant (appendix p 20).
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes it provides a safe and effective therapy for MF/SS and will provide a new treatment option for patients who have no further lines of therapy available and are suffering painful itchy and disfiguring skin lesions
• Is the technology a 'step-change' in the management of the condition?	It will add another treatment for these patients where there is a dearth of available therapies
• Does the use of the technology address any particular unmet need of the patient population?	This is will be a better treatment option for our patients with efficacy, improved QOL and safety in MF/SS, and provide a therapy for those with no other options
17. How do any side effects or adverse effects of the technology affect the	Safety profile is good, infusion reaction is common and may be safely managed with hydrocortisone / piriton and tends to settle with subsequent cycles

management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes Compartmental responses, qol, progression free survival, TTNT
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
• Are there any adverse effects that were not apparent in clinical trials	no

but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. Are you aware of any new evidence for the comparator treatment since the publication of NICE technology appraisal guidance [TA577]?	
21. How do data on real-world experience compare with the trial data?	Mogamulizumab is available on compassionate use in UK I have personnel experience of treating 5 patients with good efficacy and tolerability similar or better than MAVORIC. I have personnel communications with US where mogamulizumab is available who report similar experiences.
Equality	
22a. Are there any potential equality issues that should be	N/A

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- There is an umnet need for more treatments in MF/SS may patients run out of treatment options and suffer from skin symptoms and reduced QOL
- Compared to available therapies mogamulizumab provides a safe and effective therapy with prolonged response rates > 1 year
-
-
-

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI-ACP-RCP-RCR**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and	**None**

purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	CTCL is generally considered incurable, ideally treatment induces remission and improves progression-free and overall survival. An important aim is to improve symptoms.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in mSWAT score (a skin assessment tool based on percentage of body surface area affected) or reduction in malignant lymphocyte count in blood. For patients, improvement in symptoms including pain, itching and general quality of life is very important.
8. In your view, is there an	CTCL is a rare disease and patients may live with their condition for many years, although some have a

unmet need for patients and healthcare professionals in this condition?	more fulminating course, including patients with Sezary syndrome. Patients with advanced stage CTCL have a median overall survival of around 5 years. Living with CTCL not only severely impacts on patients' physical and psychological wellbeing, there is also a huge emotional, physical and financial burden on their families and carers, who may have to change dressings, help with the application of topical steroids and emollients and deal with increased laundry needs for exfoliating skin. There is an urgent need for effective treatment which improves symptoms, quality of life and survival.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	In early stages, CTCL can respond well to skin directed therapies including PUVA, UVB and topical emollients and steroids. Total skin electron beam therapy (TSEBT) is a highly effective treatment with high response rates, though efforts remain focussed on finding effective maintenance therapies to sustain responses. Palliative radiotherapy to lesions is also very effective. Systemic anti-cancer agents are most commonly used to treat advanced subtypes of CTCL and Sezary syndrome including bexarotene, interferon-alpha and methotrexate. Response rates are generally low, though a small proportion of patients may have sustained responses to one or another of these agents. However, they all have particular toxicities so that even a patient is responding, treatment may have to be stopped due to intolerability. An additional option for erythrodermic MF and Sezary includes the use of extracorporeal photophoresis (ECP). Multi-agent chemotherapy regimens such as CHOP or CHOEP are generally not used as standard care as although there can be an initial response, this is rarely sustained and they confer significant toxicities including the risk of infection which is a particular concern for patients with CTCL who might have fungating skin tumours. NICE have recently approved the use of brentuximab vedotin after at least one systemic therapy so this may also be included as a comparator as can gemcitabine or liposomal doxorubicin (Caelyx) but again, these chemotherapies have short responses and standard toxicities including myelosuppression. HDAC inhibitors are not available in the UK.
• Are any clinical guidelines used in the	British Association of Dermatology and UK Cutaneous Lymphoma Group guidelines for the management of

treatment of the condition, and if so, which?	primary cutaneous lymphomas 2018
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Reasonably well defined, there are a limited range of options available for different disease stages, in reality patients progress through most of them sequentially. Particular toxicity profiles may make some treatments less suitable for some patients with comorbidities eg hyperlipidaemia with bexarotene, peripheral neuropathy with brentuximab etc. Some treatments are only delivered in a small number of specialist centres eg TSEBT, ECP and stem cell transplantation.
• What impact would the technology have on the current pathway of care?	Provides an additional treatment option, in particular for patients with advanced stage disease and blood involvement who have a worse prognosis and more symptomatic disease.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	This agent does require administration as an iv infusion on a regular basis, similar to conventional chemotherapy or brentuximab, and less convenient than oral systemic agents like methotrexate, or bexarotene.
• In what clinical setting	Secondary care, specialist CTCL clinics.

should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This expertise already exists in dermatology/oncology practices.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	No evidence that it would do that.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, the evidence suggests that it can for a proportion of patients

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Potentially more effective for advanced stage mycosis fungoides patients, particularly where there is blood involvement and patients with Sezary syndrome. Less additional benefit in early stage patients.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Straightforward treatment to deliver and monitor on day units.
14. Will any rules (informal or	Standard monitoring of response assessment using skin scoring (mSWAT), blood counts and clinical

formal) be used to start or stop treatment with the technology? Do these include any additional testing?	examination or CT scans. All standard of care.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Symptomatic improvement.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	

• Is the technology a 'step-change' in the management of the condition?	Yes in that it provides evidence of benefit for the group of patients who have a particularly aggressive disease course and poor outcomes. For some patients, it may treat and stabilise their lymphoma and allow a stem cell transplant.
• Does the use of the technology address any particular unmet need of the patient population?	Yes in that more effective therapies are required, in particular therapies without significant toxicities that can be continued until progression.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	None that are unusual or unexpected or unmanageable.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	The comparator, vorinostat (or any other HDAC inhibitor) is not available for use in the UK but is probably a reasonable single agent comparator for the clinical trial in this setting.

• What, in your view, are the most important outcomes, and were they measured in the trials?	Global skin responses (mSWAT) and quality of life measures as listed.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	In reality we would not expect this to have a huge impact on long term survival, but even improvement of symptoms can have a significant impact on how patients manage on a day to day basis.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None
20. Are you aware of any new evidence for the comparator treatment since the publication of NICE technology appraisal	No

guidance [TA577]?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Rare cancer, unmet need
- Cancer causes huge burden on physical, emotional, psychosocial and financial health
- Mogamuzulimab shows good response rates particularly in advanced MF, blood involvement and patients with Sezary syndrome.
- Straightforward to deliver treatment and assess response
- Well tolerated

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists (RCPath) / British Society for Haematology (BSH)**

3. Job title or position	
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Membership organisation representing pathologists.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
M5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	I think we must add something on QoL in CTCL. Patients with CTCL have painful, itchy and often unsightly skin lesions and as a result suffer a reduced HRQoL [ref]. This is compounded by living with an incurable cancer with a lack of effective treatments. Most treatments result in only partial responses of short duration (<1 year) so patients consequently have active lesions throughout [ref Gilson Br J Derm Guidelines]. Those with earlier stages often exhaust the small repertoire of anti-CTCL treatments and have to be managed with supportive therapy alone. 8. Molloy K, Jonak C, Woei-A-Ji S, Guenova E, Busschots A, Bervoets A, Hauben E, Knobler R; Stefanie Porkert; ard Cowan, Evangelina Papadavid, Marie Beylot-Barry, Peng C, Howles A, Yoo J, Evison F, Scarisbrick J. Characteristics associated with significantly worse quality of life in mycosis fungoides/Sézary syndrome from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study. Br J Dermatol epub 2019 9. Constanze Jonak, Stefanie Porkert, Simone Oerlemans, Evangelia Papadavid, Kevin Molloy, Eva Lehner-Baumgartner, Antonio Cozzio, Fabio Efficace, Julia Scarisbrick. Health-related quality of life in cutaneous lymphomas: past, present and prospective. Acta Derm 2019;99(7):640-646

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator	

treatment since the publication of NICE technology appraisal guidance [TA577]?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Mogamulizumab for treated mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma ID1405

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Julia Scarisbrick**
2. Name of organisation	**British Association Dermatology (BAD) & ROYAL COLLEGE OF PATHOLOGISTS**

3. Job title or position	**Consultant Dermatologist and Lead Cutaneous Lymphoma Service Birmingham**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? **x**☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**x**☐ yes Just to add that I now have experience prescribing mogamulizumab outside of a clinical trial and have treated 5 patients (since august 2019) on the compassionate use program and out of clinical trial it appears safe and effective

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Mogamulizumab is targeted against the malignant T-cells and reduces tumour burden and improves quality of life (symptom, function and emotions). It reduces tumour burden in all compartments (responses: blood 68%, skin 42% and lymph nodes 17%) and dramatically in blood. It is well tolerated and may be continued to be given until loss of clinical benefit and within the MAVORIC trial median treatment time was 170 days with mogamulizumab with lasting responses of median of 13.1months in MF and 17.3months in Sezary syndrome.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	We consider responses in MF/SS as an improvement of 50% but many patients derive clinical benefit from skin symptoms, emotions and functions below 50%.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a huge unmet need for patients with cutaneous lymphoma, there are few drugs and most have limited responses (30-40%) and short duration 9-12 months. More drugs are desperately needed and immunotherapies are preferred over chemotherapy as reducing patients own innate immunity with chemotherapy appears to promote progression in some patients and is therefore recommended after failure of immunotherapies or in high grade transformed disease.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	The BAD guidelines referenced below were published 2019, treatments are listed as first, second or third line and for each line there are a list of therapies in no particular order of preference. Most treatments are given till loss of clinical benefit and consecutive therapies are given. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Gilson D, Whittaker SJ, Child FJ, Scarisbrick JJ, Illidge TM, Parry EJ, Mohd Mustapa MF, Exton LS, Kanfer E, Rezvani K, Dearden CE, Morris SL. Br J Dermatol. 2019 Mar;180(3):496-52
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Please see above
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Our guidelines are national. As therapies are listed no order of preference there may be local preferences to therapies and patient individualised treatment approaches
• What impact would the technology have on the current pathway of care?	Mogamulizumab would be a much needed addition to the choic of first line systemic therapies in cutaneous lymphoma

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Would add another much needed treatment as patients live several years with disease and treatment options run out
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinic only
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None, can be given on iv day suite
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes currently we have patients who have exhausted all available treatment options and would benefit from mogamulizumab

• Do you expect the technology to increase length of life more than current care?	This is not known yet
• Do you expect the technology to increase health-related quality of life more than current care?	Yes , MAVORIC showed this compared with vorinostat and start of trial
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Mogamulizumab is effective in MF and SS
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	No it is straight forward, have been using on compassionate use given on a day facility and no problems encountered

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	no
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, reduced tumour burden, improved progression free survival (mogamulizumab therapy resulted in superior investigator-assessed progression-free survival compared with vorinostat therapy (median 7·7 months [95% CI 5·7–10·3] in the mogamulizumab group vs 3·1 months [2·9–4·1] in the vorinostat group; hazard ratio 0·53, 95% CI 0·41–0·69; stratified log-rank p<0·0001) MAVORIC). There was also improved quality of life compared to vorinostat and before trial. The preplanned analyses of Skindex-29, FACT-G, 3-level EQ-5D, and ItchyQoL found mogamulizumab-treated patients had a greater improvement in patient-reported outcomes at the 6-month assessment than did vorinostat treated

	patients; these findings were statistically significant (appendix p 20).
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes it provides a safe and effective therapy for MF/SS and will provide a new treatment option for patients who have no further lines of therapy available and are suffering painful itchy and disfiguring skin lesions
• Is the technology a 'step-change' in the management of the condition?	It will add another treatment for these patients where there is a dearth of available therapies
• Does the use of the technology address any particular unmet need of the patient population?	This is will be a better treatment option for our patients with efficacy, improved QOL and safety in MF/SS , and provide a therapy for those with no other options
18. How do any side effects or adverse effects of the technology affect the	Safety profile is good, infusion reaction is common and may be safely managed with hydrocortisone / piriton and tends to settle with subsequent cycles

management of the condition and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes Compartmental responses, qol, progression free survival, TTNT
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
• Are there any adverse effects that were not apparent in clinical trials	no

but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
21. How do data on real-world experience compare with the trial data?	Mogamulizumab is available on compassionate use in UK I have personnel experience of treating 5 patients with good efficacy and tolerability similar or better than MAVORIC. I have personnel communications with US where mogamulizumab is available who report similar experiences.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	N/A
22b. Consider whether these issues are different from issues with current care and why.	

Key messages
23. In up to 5 bullet points, please summarise the key messages of your statement. • There is an umnet need for more treatments in MF/SS may patients run out of treatment options and suffer from skin symptoms and reduced QOL • Compared to available therapies mogamulizumab provides a safe and effective therapy with prolonged response rates > 1 year • • •

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NICE National Institute for Health and Care Excellence

Patient expert statement

Mogamulizumab for treated mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma [ID1405]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**George Fletcher**

2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with the condition is quite demanding as treatment to moisturise the skin is time consuming and skin is socially difficult to manage and causes embarrassing. Lack of sleep at night is quite wearisome.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I understand that there are no dedicated treatments for Sezary's Syndrome and all the drug and Chemotherapies so far have not improved my condition until the Mogamulizamab Infusion.
10. Is there an unmet need for patients with this condition?	Yes as I understand it is a rare condition with very little treatment research of the condition and .
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Since being put on Mogambulizamab my condition has much improved especially my skin condition..
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The lengthy fortnightly visits to the hospital for the infusion treatment.
Patient population	
13. Are there any groups of patients who might benefit	As a Sezary's Syndrome sufferer, then this group of patients would likely to have their skin condition much improved, as with me, if the Mogamulizamab treatment I have experienced can be shown to work well for all sufferers

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	I cannot think that the treatment has any equality issues.
Other issues	
15. Are there any other issues that you would like the committee to consider?	Early intervention of the treatment would have greatly saved me many years of the Sezary's Syndrome condition and all the side effects being some 14 years
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • 7 • 8	

- 9
- 11
- 15

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NICE National Institute for Health and Care Excellence

Patient expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Stan Martin Cummins**

2. Are you (please tick all that apply):	**x** a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Lymphoma Action
4. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	x yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

5. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
6. How did you gather the information included in your statement? (please tick all that apply)	**x** I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
7. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**1.Itching.** The itching controls every aspect of my life. Very poor sleep patterns due to applying emollients 24 hours a day and I am exhausted due to this. I am unable to get a decent night's sleep as the itching causes pain in all my joints. I am constantly shaking and have involuntary movements and twitches and am unable to control my body temperature to such a degree I sometimes sleep inside a sleeping bag under a duvet cover and cannot get warm. Minor household chores and exercise are impossible. I am not functioning as a human being

	2.Hands and feet Open wounds all over my body but in particular my hands and feet. Open painful fissures and plaques on feet that require regular podiatry care to prevent infection. Brittle nails with very unusual growth with inward turning nails that are extremely painful. Admission to The Christie due to cellulitis and unable to walk properly due to open painful fissures. Pain in legs and feet when walking as my gait is affected by the wounds. Open wounds on hands with large portions of skin peeling off that is an infection risk. unable to hold pen or crockery and have to wear gloves filled with creams 24 hours a day **3.Pain** Pain all over body in particular joints. Muscle aches and sore sticky eyes. **4.Hearing loss.** Due to large amounts of excess skin dropping into my ears I loose my hearing on a regular basis. Ear syringing worked at first but no longer does and I have been advised to stop this process as I risk permanent damage to my hearing. As such I am now in the care of ENT for specialist treatments and hearing loss causes further issues with my sleep and balance and has recently been the cause of a recent abandonment of MRI scan. **5.Family life/support/other factors** A number of things are impacted with my SS diagnosis. Embarrassment- shedding skin/choice of clothing. Cancer for a second time/depression/exhaustion/restrictions on family life. The number of hospital and GP visits/financial burdens as am I am no longer able to work. Missing the routine of work and colleague causes some anxiety but I am now in a different world. My wife Angela has taken this second diagnoses as well as she can. She has been superb and is managing her own health and employment well. She is looking after her elderly mother as well as our daughter and also assists with my emollients which can become tiresome.

	As I am up most of the night because of the itching and application of creams I have decided to move into our back bedroom to allow my wife to get some decent sleep as she still has to work. Being classed as extremely clinically vulnerable due to Coronavirus this has added to my wife's workload. I have been self-isolating meaning that my wife's now does all the house hold shopping and all other outdoor activities.
Current treatment of the condition in the NHS	
8. What do patients or carers think of current treatments and care available on the NHS?	I have received excellent specialist treatment from Professor Richard Cowan and all his staff at The Christie Hospital in Manchester. The current treatment I am receiving is superb and has transformed my life. Mogamulizumab has transformed my life in recent months. Previous treatments like ECP and Interferon never really had any beneficial results in improving my condition whereas now mogamulizumab has. My skin/itch/energy levels/depression and appearance have all dramatically improved.

9. Is there an unmet need for patients with this condition?	Yes
Advantages of the technology	
10. What do patients or carers think are the advantages of the technology?	N/a
Disadvantages of the technology	
11. What do patients or carers think are the disadvantages of the technology?	N/a
Patient population	
12. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	N/a

Equality	
13. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/a
Other issues	
14. Are there any other issues that you would like the committee to consider?	None
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your statement:

- Sezary syndrome is an awful devastating disease that effects all aspect of your life including home/family/work/life/sleep/itch/fear
- Sezary syndrome controls all aspects of family life from cooking/cleaning/shopping/family days out/going to restaurant etc.
- Mogamulizumab treatments have transformed my life and I can now function as a human being
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Mogamulizumab for treated mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma [ID1405]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Stephen Scowcroft**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Lymphoma Action
4. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

5. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes
6. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
7. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	

Current treatment of the condition in the NHS	
8. What do patients or carers think of current treatments and care available on the NHS?	
9. Is there an unmet need for patients with this condition?	
Advantages of the technology	
10. What do patients or carers think are the advantages of the technology?	
Disadvantages of the technology	
11. What do patients or carers think are the disadvantages of the technology?	
Patient population	
12. Are there any groups of patients who might benefit	

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
13. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
14. Are there any other issues that you would like the committee to consider?	
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your statement: • •	

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Questions for clinical expert

Mogamulizumab for treated mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma [ID1405]

1. Current treatment and comparator

1.1 In current clinical practice, do patients experience treatment-free periods (treatment is stopped but symptom control is maintained)? If so, approximately how long would symptom control last before a new treatment is needed or disease progresses?

Clinical expert: Currently we use mogamulizumab in clinical practice and it's continued unless there are intolerable side-effects or if there is a loss of response. We have limited experience but we don't intend to stop treatment while there is a clinical benefit and the same approach is also used for other treatments. There are very limited treatment options for these patients, immunotherapy treatments are typically continued if there is clinical benefit (measured by responses such as a reduction in disease burden and improvement in health-related quality of life

1.2 The company have positioned mogamulizumab for severe disease (stage ≥IIB for MF and all SS) after at least 1 prior therapy and who are not eligible for or are refractory to brentuximab vedotin.

a) In your clinical opinion, does the company's positioning cover third-line treatment only?

b) How do you define severe disease in clinical practice?

c) In people with severe disease, approximately what proportion would you expect to be ineligible for or refractory to brentuximab vedotin? And how easily would you be able to identify these patients in clinical practice?

Clinical expert: Yes, this will cover third-line treatment for those eligible for brentuximab but it is only licensed for people with CD-30 positive disease only (around 15 to 20%) so those with CD-30 negative disease would not be eligible for brentuximab and in this case mogamulizumab would be a second-line treatment option. Third-line treatment with mogamulizumab may be appropriate for patients with IB to IIIA disease but it may be used a second-line option for patients with IIIB to IVA disease because mogamulizumab has shown excellent responses in blood tumour burden.

There are some patients with stage IB disease that is refractory to skin-directed therapy and bexarotene who may also potentially benefit from mogamulizumab.

In clinical practice, severe disease is defined as refractory disease with worsening disease, high symptom burden and poor health-related quality of life.

1.3 What treatments are currently used if brentuximab vedotin is not appropriate?

a) For third-line treatment, are methotrexate, bexarotene and peginterferon used in clinical practice and in what proportions? Are any other treatments used (e.g. extracorporeal photopheresis [ECP], prednisolone)?

b) Is vorinostat ever used in England to treat MF or SS? Have you had any clinical experience with vorinostat? In your clinical opinion, is it likely to have a similar treatment effect as treatments currently used in the NHS in England?

Clinical expert: For third-line treatment in people with severe disease, treatment is generally in line with the guideline from the British Association of Dermatologists and UK Cutaneous Lymphoma Group. Brentuximab is not used for people who have CD-30 negative disease so treatment for this group may include interferon, methotrexate or bexarotene. The most common third-line treatments for stage Ib and IIb disease is bexarotene and brentuximab if possible, followed by chemotherapy. For stage IV disease we are less concerned about using chemotherapy because patients will have systemic disease. Chemotherapy is used after immunotherapies and is generally for palliative care or as a bridge to stem cell transplant. Recently interferon

has become unavailable because both companies (Merck and Roche) have stopped its production which is very challenging because there is a lack of treatment options, so mogamulizumab is very important for refractory disease. Vorinostat is only used in clinical trial settings but this treatment is not considered very effective (response rates <10% in MAVORIC) and it's not available in the UK.

2. Allogenic stem cell transplant (aSCT)

2.1 Approximately what proportion of people would have aSCT and of these how many would be cured?

Clinical expert: Stem cell transplant is a disease-modifying treatment but we don't know whether it's curative. A study has shown that around 50% will have a complete response and half will have early stage relapse after transplant. Life threatening disease may be improved but long term survival data is not yet known (from a recent paper published by clinical expert in British Journal of Dermatology[1]).

2.2 When is aSCT most commonly used in the treatment pathway; after brentuximab vedotin or later in the treatment pathway? Would this be based on fixed time points or depend on a patient's response to treatment?

Clinical expert: Patients would be eligible for aSCT if they have advanced, refractory disease and it's commonly used after the first remission because you don't often get a second remission. There are additional criteria that patients must meet to be considered eligible, for example they should be young, fit enough for transplant and have no co-morbidities.

2.3 In your clinical opinion, is treatment with mogamulizumab likely to impact on a patient's eligibility for aSCT?

Clinical expert: No, we have experience using mogamulizumab as a bridge to stem cell transplant in a few patients and it doesn't impact eligibility although need to wait 8 weeks before all HSCT to reduce impact on GvHD.

3. Stopping rule for mogamulizumab

3.1 Do you have any clinical experience with mogamulizumab? Please describe.

Clinical expert: Yes, I currently use mogamulizumab in clinical practice.

3.2 **PRIORITY**: In your clinical opinion, would a 2-year stopping rule for mogamulizumab be easy to implement in NHS clinical practice?

Clinical expert: A 2 year stopping rule would be inappropriate if patients were still having a clinical benefit. This would likely only impact a very small proportion of people because the trial showed a mean treatment of around 170 days for mogamulizumab and median disease free progression was 7.7 months (~231 days) but there are so few available treatment options that a stopping rule would not be considered acceptable.

3.3 If mogamulizumab was stopped after 2 years, is it clinically plausible that its treatment benefit would continue after it was stopped? If so, approximately how long would this last?

Clinical expert: Treatment with mogamulizumab should continue while patients have a clinical benefit. Patients could have a life expectancy of 3 to 5 years from diagnosis and so if there was a clinical benefit, this treatment should not be stopped.

4. Overall survival

4.1 **PRIORITY**: In your clinical experience, what is the current average expected survival time for people with MF and SS after at least 1 prior therapy?

a) What is the current average survival time for people with severe disease for whom brentuximab is not appropriate?

Clinical expert: For people eligible for second-line treatment this would be around 1 year to 18 months and for people eligible for third-line treatment, this would be around 6 months or less. The survival time from diagnosis is around 3 to 5 years.[2]

4.2 **PRIORITY**: On average, for third-line treatment for severe disease how many people would you expect to be alive after 1 year, 5 years and 10 years? Would you expect anyone to be alive after 20 years? Would you expect these to differ based on whether people had aSCT?

Clinical expert: For people eligible for third-line treatment survival may be around 50% at 1 year and drop to 10% at 5 years. Stem cell transplant changes the survival rate but very few people eligible for third-line treatment would be eligible for a transplant.

5. Health-related quality of life

5.1 In your clinical opinion, is a patient's health-related quality of life generally consistent over the treatment period (before disease progression)?

Clinical expert: Quality of life is unlikely to decline and when disease is stable and patients are having a clinical benefit, there would be an improved quality of life. We wouldn't continue treatment if quality of life was declining.[3,4]

5.2 Compared with other cancers, do you think MF and SS has a similar impact on carers?

Clinical expert: This disease is very disabling for patients and their carers because it is disfiguring and symptoms include open wounds (which may smell), social isolation, pain, depression and it is a terminal disease.

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Mogamulizumab for treating mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Willem Witlox, Mickaël Hiligsmann, Ben Wijnen, Charlotte Ahmadu, Steve Ryder and Manuela Joore acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker, Regina Leadley and Vanesa Huertas Carrera acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Isabel Syndikus provided clinical expertise. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

A&E	Accident and emergency
AE	Adverse event
AiC	Academic in confidence
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
aSCT	Allogenic stem cell transplant
ASH	American Society of Hematology
AST	Aspartate aminotransferase
BAD	British Association of Dermatologists
BC	Base-case
BIC	Bayesian information criterion
BNF	British National Formulary
BP	Blood pressure
BV	Brentuximab vedotin
CCR4	C-C chemokine receptor type 4
CD	Cluster of differentiation
CDSR	Cochrane Database Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHOP	Gemcitabine; cyclophosphamide plus doxorubicin, vincristine, prednisolone
CI	Confidence interval
CiC	Commercial in confidence
cm	Centimetre
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
CTIVRS	Clin Trak Interactive Voice/Web Response System
DARE	Database of Abstracts of Reviews of Effects DFS Disease-free survival
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EBRT	External beam radiotherapy
ECM	Established clinical management
ECOG	Eastern Cooperative Oncology Group
ECP	Extracorporeal photopheresis
EED	Economic Evaluations Database
EFS	Event-free survival
EMA	European Medicines Agency
eMIT	Electronic market information tool
EO	Expert opinion
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions 3 levels
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EU	European Union
EUR	Erasmus University Rotterdam
EWB	Emotional well-being

FACT-G	Functional Assessment of Cancer Therapy – General
FAO	For the attention of
FDA	Food and Drug Administration
FWB	Functional well-being
HCL	hydrochloride
HES	Hospital Episode Statistics
HIV	Human immunodeficiency virus
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HTA	Health technology assessment
HTLV-1	Human T-lymphotropic virus 1
HUI	Health utility index
ICER	Incremental cost effectiveness ratio
ICML	International Conference on Malignant Lymphomas
ICTRP	International Clinical Trials Registry Platform
IFN	Interferon
IL	Interleukin
IQR	Interquartile
IPCW	Inverse probability of censoring weighting
ISCL	International Society for Cutaneous Lymphomas
ISSG	Information Specialists' Sub-Group
ITT	Intention-to-treat
IU	International unit
IV	Intravenous
kg	Kilogram
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
KW	Mogamulizumab
KW-0761	Mogamulizumab
LCT	Large cell transformation
LDH	Lactate dehydrogenase
LN	Lymph node
LYs	Life years
LYG	Life years gained
M	Metastasis
mcg	Microgram
MDT	Multidisciplinary team
MeSH	Medical Subject Headings
MF	Mycosis fungoides
mg	Milligram
min	Minute
MJ	Matters of judgement
mm	Millimetre
mmHg	Millimetres of mercury
Moga	Mogamulizumab
MSAC	Medical Services Advisory Committee
mSWAT	Modified Severity Weighted Assessment Tool
MTX	Methotrexate
N	Node
N/A	Not applicable
NCI	National Cancer Institute
NE	Not estimable
NHL	Non-Hodgkin lymphoma

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
nRCT	Non-randomised controlled trial
NTFS	Next treatment-free survival NYHA New York Heart Association
ONS	Office of National Statistics
ORR	Overall response rate
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
pcALCL	Primary cutaneous anaplastic large cell lymphoma
PD[1]	Progressed disease
PFS	Progression-free survival
PH	Proportional hazards
PICO	Population, intervention, comparator and outcomes
PICOS	Population, intervention, comparator, outcomes and study design
PICOTP	Population, Intervention, Comparison, Outcomes, Time, Perspective
PLD	Pegylated liposomal doxorubicin
PR	Partial response
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROCLIPI	PROspective Cutaneous Lymphoma International Prognostic Index
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen plus ultraviolet light therapy
PWB	Physical well-being
Q	Quartile
QALY	Quality-adjusted life year
QoL	Quality of life
R/R	Relapsed/refractory
RCT	Randomised controlled trial
RIC	Reduced intensity
RPFST	Rank-preserving structural failure time
RR	Risk ratio
SAE	Serious adverse event
SCT	Stem cell transplant
SD	Standard deviation
SDT	Skin-directed therapy
SEM	Standard error of mean
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SS	Sézary syndrome
STA	Single technology appraisal
SWB	Social/family well-being
T	Tumour
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TNM	Tumour, node, metastasis

[1] In addition to "progressive disease", the CS also used "progressed disease" and "progression of disease" for PD. This report refers to "progressive disease" throughout.

TNMB	Tumour, node, metastasis, blood
ToT	Time on treatment
TRUST	The TRansparent Uncertainty ASsessmenT tool
TSD	Technical support document
TSE	Two-stage estimation
TSEBT	Total skin electron beam therapy
TTD	Time to discontinuation
TTF	Time to treatment failure
TTNT	Time to next treatment
TTP	Time to progression
TTR	Time to response
Tx	Treatment
UK	United Kingdom
UKCLG	UK Cutaneous Lymphoma Group
ULN	Upper limit of normal
UMC	University Medical Centre
USA	United States of America
USCLC	United States Cutaneous Lymphoma Consortium
VAS	Visual Analogue Scale
Vor	Vorinostat
WCD	World Congress of Dermatology
WHO	World Health Organization
WTP	Willingness-to-pay
X	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterise histologic subcategories

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1. Summary

1.1 Critique of the decision problem in the company's submission

1.1.1 Population

The population in the decision problem addressed in the company submission (CS) is defined as *"adults with advanced mycosis fungoides* [mycosis fungoides] *or Sézary syndrome* [SS] *cutaneous T-cell lymphoma* [CTCL] *(i.e. stage ≥IIB MF and all SS) following at least one prior systemic therapy who are clinically ineligible for or refractory to treatment with brentuximab vedotin (BV)"*. This population is narrower than the population defined in the scope issued by the National Institute for Health and Care Excellence (NICE; *"Adults with mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma following at least one prior systemic therapy"*) as

1. it only includes adults with advanced MF or SS, defined as *"stage ≥IIB MF and all SS"*,
2. it only includes patients *"who are clinically ineligible for or refractory to treatment with brentuximab vedotin (BV)"*.

Therefore, conclusions should only be made in the narrower population addressed in the CS.

1.1.2 Intervention

The intervention defined in the CS is in line with the NICE scope, i.e. mogamulizumab.

1.1.3 Comparator

The CS defines the comparator to be *"established clinical management with mogamulizumab"* (ECM) which is line with the NICE scope. However, MAVORIC, the only randomised controlled trial (RCT) evaluating the effectiveness and safety of mogamulizumab in CTCL (see section 1.2), compared mogamulizumab to vorinostat which is not currently licensed in Europe. According to the CS, *"vorinostat can be considered a reasonable proxy for current standard of care in the NHS* [National Health Service]*, based on a naïve comparison of results from the vorinostat arm of the MAVORIC study and the physician's choice arm (methotrexate or bexarotene i.e. UK* [United Kingdom] *standard treatments) of the ALCANZA study as well as comparison to Phase II bexarotene data (...). It is also supported by clinical expert opinion, and the EMA* [European Medicines Agency] *accepted this comparison when granting marketing authorisation for mogamulizumab. Thus, the results of the MAVORIC study should be considered to translate to English clinical practice. Furthermore, vorinostat is the only drug with data in the SS population"*.

Even after the response to request for clarification, the Evidence Review Group (ERG) is concerned by the use of vorinostat as a comparator in MAVORIC as there is some uncertainty regarding the use of vorinostat as a proxy for ECM, see section 3.3 for details.

1.1.4 Outcomes

The CS covered the outcomes defined in the NICE final scope, namely:

- Progression-free survival (PFS)
- Response rates
- Overall survival (OS)
- Time to next treatment (TTNT)
- Health-related quality of life (HRQoL)
- Adverse effects of treatment

1.1.5 Other relevant factors

Relevant results from subgroup analyses are reported in section 4.2.5.6.

1.2 Summary of the key issues in the clinical effectiveness evidence

The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted as part of the systematic review to identify clinical efficacy and safety studies. A good range of databases and resources, including conference proceedings, were searched and the searches were transparent and reproducible. One set of searches was conducted to identify both efficacy and safety evidence. The searches included RCTs and observational study design filters in order to identify both efficacy and safety evidence. Searches were conducted in July 2019. The ERG was concerned about the overall quality of the searches conducted, as truncation and proximity operators were used inconsistently; MEDLINE and Embase were searched simultaneously without including both MeSH and EMTREE subject heading indexing terms, which may have impaired how well the strategies performed; the date ranges of searches were not reported; and the Cochrane Library searches were not accurately reported. However, the searches were adequate, and given the range of resources searched, it was unlikely that any relevant studies were missed.

The main source of effectiveness evidence was the MAVORIC trial (section 4.2.2). It was an RCT which should be considered to be an appropriate design to estimate the effectiveness of mogamulizumab vs. a comparator. However, as mentioned in section 1.1, there are concerns regarding the appropriateness of the comparator, vorinostat, to the scope and UK clinical practice. Furthermore, when estimating the effectiveness vs. vorinostat, crossover (switching) from vorinostat to mogamulizumab was permitted, occurring in 73.1% of cases. Therefore, outcomes measured after progression such as OS could be biased. Other outcomes, including PFS, might also be biased given that the trial was also open-label (section 4.2.3).

"Approximately 80% of patients" represented the population defined in the decision problem. In addition to issues related to the narrower definition, there is some doubt as to the generalisability of MAVORIC trial to this population. Specifically, a criterion for the company decision problem population is those *"who are clinically ineligible for or refractory to treatment with brentuximab vedotin (BV)"*. However, even after request for clarification, the number of participants considered to be *"ineligible for BV"* as well as how this status was determined remains unclear.

PFS assessed by blinded independent review (BIR) results favoured mogamulizumab over vorinostat (hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.49 to 0.84). However, as attested by clinical expert opinion, there is some uncertainty regarding progression assessment and results were not statistically significant for MF patients and those with disease stage IIB/II.

A number of measures of response rates are reported which generally favour mogamulizumab over vorinostat (see section 4.2.5.2 for details).

The results for the OS (BIR assessed) also favoured mogamulizumab (risk difference 19.4%, 95% CI 9.0 to 29.4). Because the company stated that the skin only response for mogamulizumab in MAVORIC was lower than in the *"registrational study"*, the ERG sought clarification, which showed that skin only response in MAVORIC (41.9%) was very similar to that in the phase I/II study (42.1%). It should be noted that OS was an exploratory outcome of the MAVORIC trial. The results for this outcome varied depending on the approach used to type of adjustment for switching and the censoring of participants receiving allogenic stem cell transplant (aSCT). The result of the analysis without crossover adjustment, but censoring for aSCT favoured vorinostat, although it was not statistically

significant (HR [redacted]). These methods are summarised in section 1.3 and discussed in detail in section 5.2.6. Critically, the ERG highlights the risk of bias for all the outcomes measured after progression that have resulted from the specific study design and flow of participants where 73% of vorinostat patients switched to mogamulizumab.

The median TTNT for mogamulizumab was statistically significantly longer than for vorinostat at 11.0 months (95% CI 8.8 to 12.6 months) compared to 3.2 months (95% CI 3.1 to 4.3 months).

The analyses to evaluate the changes in quality of life were made using three instruments Skindex-29, FACT-G (Functional Assessment of Cancer Therapy – General) and EQ-5D-3L (European Quality of Life-5 Dimensions 3 levels). Results favoured mogamulizumab over vorinostat, although follow-up was only up to 11 cycles, i.e. less than 12 months.

An overview of adverse events (AEs) in the safety population is provided in Table 1.1. The CS noted the incidence of treatment-emergent AEs to be comparable between the two treatment groups. The listed adverse events were found to be consistently reported with the clinical study report (CSR), with the most commonly reported AEs in the mogamulizumab group was infusion-related reactions while in the vorinostat group this was diarrhoea and fatigue.

The ERG notes the warning issued by the Food and Drug Administration (FDA) for the potential complications of aSCT after mogamulizumab.

Table 1.1: Overview of adverse events, safety population

	Pre-treatment and randomised treatment period		**Cross-over patients**
	Mogamulizumab (n=184)	**Vorinostat (n=186)**	**Mogamulizumab (n=136)**
Adverse Events (AEs), n (%)			
Any AEs	[redacted]	[redacted]	[redacted]
Any TEAEs	[redacted]	[redacted]	[redacted]
Drug-related TEAEs	[redacted]	[redacted]	[redacted]
NCI/CTCAE grade 3, 4, 5 AEs, n (%)			
Any Grade 3, 4, 5 AEs	[redacted]	[redacted]	[redacted]
Any Grade 3, 4, 5 TEAEs	[redacted]	[redacted]	[redacted]
Drug-related Grade 3, 4, 5 TEAEs	[redacted]	[redacted]	[redacted]
AEs with Outcome of Death	[redacted]	[redacted]	[redacted]
Serious adverse events, n (%)			
Any SAEs	[redacted]	[redacted]	[redacted]
Treatment-emergent SAEs	69 (37.5)	46 (24.7)	[redacted]
Drug-related Treatment-emergent SAEs	36 (19.6)	30 (16.1)	[redacted]
Discontinuation due to AEs, n (%)			
Any AEs	[redacted]	[redacted]	[redacted]
Any TEAEs	35 (19.0)	43 (23.1)	[redacted]
Drug-related TEAEs	[redacted]	[redacted]	[redacted]
Based on CS Table 19			

	Pre-treatment and randomised treatment period		Cross-over patients
	Mogamulizumab (n=184)	Vorinostat (n=186)	Mogamulizumab (n=136)
[a] includes one patient with TEAE with outcome of death that occurred during crossover and >30 days after the last dose of vorinostat, but was related to vorinostat [b] includes two patients with non-TEAEs with outcome of death AE = adverse event; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; SAE = serious adverse event; TEAE = treatment-emergent adverse event			

1.3 Summary of the key issues in the cost effectiveness evidence

The CS provided sufficient details for the ERG to appraise the literature searches. A good range of resources were searched and the searches were transparent and reproducible. Separate searches were conducted to identify cost effectiveness studies, health-related quality of life studies, and healthcare resource use data. A targeted search was conducted for health state utilities describing caregiver burden. However, the ERG was concerned about the overall quality of the searches conducted, as truncation and proximity operators were used inconsistently; MEDLINE and Embase were searched simultaneously without including both MeSH and EMTREE subject heading indexing terms, which may have impaired how well the strategies performed; and the date ranges of searches were not reported. However, the searches were adequate, and given the range of resources searched, it was unlikely that any relevant studies were missed. The searches were limited by date range from 2009 to 2019.

The company identified no economic evaluations addressing the decision problem it aimed to target. In the absence of economic evaluations for this decision problem, the company developed a *de novo* economic evaluation. The company's economic evaluation met most of the NICE reference case criteria, except for the inclusion of caregivers' utilities, which were based on a vignette study. It is worth highlighting that the company's decision problem is narrower in focus than NICE's scope, focusing on patients with advanced disease (stage ≥IIB MF and all SS patients). This meant that clinical effectiveness was based on a subgroup of MAVORIC; the intention-to-treat (ITT) population was used in an exploratory analysis. Due to lack of evidence on the appropriate UK comparator, ECM, the company in their economic evaluation used evidence on relative treatment effectiveness comparing mogamulizumab to a proxy used in MAVORIC: vorinostat, which is not licensed in the European Union or the UK.

The ERG appreciated the difficulty in obtaining appropriate comparative evidence as well as the company's efforts to establish that evidence on vorinostat could be used to inform the ECM arm in the model, but considered that the lack of direct comparator data for the ECM arm remained a major concern in the appraisal of mogamulizumab. The partitioned survival analysis using different pathways to reflect the possibility of patients receiving aSCT was deemed an appropriate reflection of clinical practice in theory. However, the company's technical implementation likely introduced bias in the model population, which the ERG considered not reflective of clinical practice.

There were also safety concerns about aSCT after treatment with mogamulizumab, which the company attempted to address by including a wash-out period in their model. Other concerns about the modelling of aSCT included that the variability of timing of aSCT was not reflected and that proportions of patients receiving aSCT were uncertain and likely over-estimated in the model. The company used NTFS instead of PFS (the primary endpoint in MAVORIC), based on it being more closely aligned with symptoms and disease control, which was therefore considered a better proxy for treatment changes, HRQoL and resource utilisation. After consultation with a clinical expert, the ERG agreed on this, but explored the impact of using a PFS-based model instead.

OS was based on MAVORIC, but it was only an exploratory, not a primary, endpoint. As such, MAVORIC was not powered to estimate OS, and maturity was not achieved. All OS extrapolations were therefore highly uncertain. The choice of parametric survival model for extrapolation of OS had a high impact on model outcomes and was associated with substantial uncertainty. In addition, the comparator OS estimates derived from MAVORIC were confounded by crossover, which required adjustment in statistical analyses. Different adjustment methods had vastly different results. All methods relied on assumptions that may not be fulfilled. Based on critical appraisal of the methods and consultation with a clinical expert, the ERG considered the TSE method to best reflect comparator OS, but with the caveat of uncertainty. The alternative, the IPCW method, was used in an exploratory analysis.

There was a lack of clarity in the estimation of utility values based on MAVORIC, which was not completely resolved. Furthermore, the inclusion of caregivers' utilities, whilst not unprecedented, lacked guidance on whether their inclusion was appropriate and, if so, how this should be done. The implementation of a 24-months stopping rule was not in line with MAVORIC or the licence and the ERG therefore preferred not to use it.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

Based on these considerations, the ERG made multiple changes to the model, including fixing errors, fixing violations and matters of judgement (see below and Table 1.2). It is important to note that both the company's and ERG's ICERs suffered from large uncertainty and should be interpreted with caution.

Fixing errors

1. Error in cost calculations for monitoring and subsequent treatments after aSCT in both mogamulizumab and ECM traces (cell link error). The ERG corrected the error.
2. Wash-out period not fully considered in modelling of aSCT after current treatment in the mogamulizumab trace. The ERG corrected the error.
3. Error in utility of PFS in TA577 scenario. The ERG corrected the error.

Fixing violations

4. 24-months stopping rule does not match the evidence or licence (section 5.2.9). The ERG disabled the stopping rule.
5. Time horizon is not lifetime (section 5.2.5). The ERG used the company's alternative setting of the time horizon to 45 years.
6. Incorrect implementation of patients receiving aSCT after current treatment (section 5.2.2). The ERG disabled aSCT after current treatment.

Matters of judgement

7. OS estimates confounded by crossover: IPCW method used in CS (section 5.2.6). The ERG used the TSE method instead of IPCW for adjusting for crossover.
8. OS uncertain extrapolations: choice of lognormal in CS (section 5.2.6). The ERG used the exponential model for extrapolating mogamulizumab OS instead of lognormal.
9. Extrapolation of NTFS: choice of generalised gamma in CS (section 5.2.6). The ERG used the lognormal model instead of the generalised gamma for mogamulizumab NTFS.
10. Extrapolation of DFS after aSCT: choice of Gompertz: The ERG used the lognormal model instead of the Gompertz for DFS after aSCT.
11. Caregivers' utilities: The ERG disabled caregivers' utilities.

12. Utilities in first 12 weeks choice of cycle-specific: The ERG used a single health state-specific utility for 'on treatment' (and not cycle-specific)

Table 1.2: ICER resulting from ERG's preferred assumptions (probabilistic, 10,000 simulations)

	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER £/QALY
Mogamulizumab	[redacted]	3.66	[redacted]	0.86	£98,856
ECM	[redacted]	2.80			

ECM = established clinical management; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Additional sensitivity analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates (Table 1.3). Exploratory analyses conditional on the ERG base-case included:

1. Include caregiver utilities as per company's modelling
2. PFS model structure instead of NTFS
3. ITT population instead of advanced disease
4. Inverse probability of censoring weighting (IPCW) method used for crossover adjustment
5. Model averaging using 30% IPCW/70% two-stage estimation (TSE) method
6. Use of OS estimates without crossover adjustment

Table 1.3: Exploratory analyses undertaken by the ERG (deterministic except 5)

Scenario	Section in main ERG report	Mogamulizumab		ECM		ICER £/QALY
		QALYs	Costs	QALYs	Costs	
ERG base-case		3.63	[redacted]	2.78	[redacted]	£100,690
1. Caregivers' utilities	5.2.8	3.81	[redacted]	2.78	[redacted]	£83,382
2. PFS model	5.2.2	3.49	[redacted]	2.63	[redacted]	£99,046
3. ITT population	5.2.3	3.84	[redacted]	2.89	[redacted]	£82,837
4. IPCW method	5.2.6	3.63	[redacted]	1.60	[redacted]	£51,223
5. 30% IPCW / 70% TSE (probabilistic)	5.2.6	3.66	[redacted]	2.44	[redacted]	£74,229
6. No crossover adjustment	5.2.6	3.63	[redacted]	3.95	[redacted]	Dominated

ECM = established clinical management; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IPCW = Inverse probability of censoring weighting; ITT = intention-to-treat; PFS = progression-free survival; QALY = quality-adjusted life year; TSE = two-stage estimation

2. Background

2.1 Introduction

In this report, the Evidence Review Group (ERG) provides a review of the evidence submitted by Kyowa Kirin in support of mogamulizumab, trade name POTELIGEO®, for treatment of adult patients with advanced stage mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy. In this section, the ERG summarises and critiques the company's description of the underlying health problem as well as the company's overview of the current service provision. The information for this critique is taken from document B of the company submission (CS).[1]

2.2 Critique of company's description of the underlying health problem

MF and SS are both a type of cutaneous T-cell lymphoma (CTCL) which are a subset of non-Hodgkin lymphoma (NHL).[2] While many CTCLs present as skin manifestation at diagnosis,[3] MF and SS are different in that there are four potentially involved components: skin, blood, lymph nodes and viscera.[4] Typically, MF presents as slightly scaly, pruritic, erythematous patches, or thin plaques.[5] Approximately 30% of patients develop advanced disease, characterised by tumours, ulceration, systemic involvement and death.[4, 6] SS is a more aggressive, leukemic form of CTCL characterised by the presence of malignant lymphocytes namely *"Sézary cells"* in the peripheral blood.[6, 7]

Diagnosing CTCL is problematic and can take up to six years.[8] This is due to the non-specific nature of multiple clinical presentations, the similarity to other chronic skin conditions (such as eczema and psoriasis), and the absence of definitive diagnostic criteria.[5] However, accurate diagnosis of CTCLs has been improved the recent by the publication of guidelines by the National Comprehensive Cancer Network.[8] The CS states that *"observation and palpation of the skin by a physician are the mainstays in suspecting CTCLs with regular biopsies required to make definitive diagnoses using defined histopathological criteria"*.[1]

Staging of MF and SS was first captured in the tumour, node, metastasis (TNM) classification published for CTCL in 1979 and was initially dependent on the type and extent of skin lesions and extracutaneous disease. Suggested modifications published in 2007 for MF/SS revised the nodal classification, added blood involvement and removed the ambiguity surrounding variables critical to standardised staging and classification,[3] resulting in the adapted version of the TNM staging system presented in Table 2.1. This considers concurrent disease involvement of all four compartments: skin, lymph nodes, blood and viscera; each of these compartments has prognostic significance in MF and SS.[4] Advanced disease is defined as stage IIB or above; thus, all SS patients are considered advanced.[9]

Table 2.1: Modified ISCL/EORTC proposed clinical staging

Clinical stage	Skin	Node	Visceral	Blood
Mycosis fungoides				
IA	T1	N0	M0	B0,1
IB	T2	N0	M0	B0,1
IIA	T1–2	N1, 2, X	M0	B0,1
IIB	T3	N0–2, X	M0	B0,1
IIIA	T4	N0–2, X	M0	B0
IIIB	T4	N0–2, X	M0	B1

Clinical stage	Skin	Node	Visceral	Blood
Sézary syndrome				
IVA1	T1–4	N0–2, X	M0	B2
IVA2	T1-4	N3	M0	B0-2
IVB	T1-4	N-3, X	1	B0-2

Based on Olsen et al. 2011[3]
Note: Grey shading representing advanced stages; For details on TNMB stages, see Table 2.2
EORTC = European Organisation for the Research and Treatment of Cancer; ISCL = International Society for Cutaneous Lymphomas; TNMB = tumour, node, metastasis, blood; X = clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize histologic subcategories

Table 2.2: Modified ISCL/EORTC Revisions to the TNMB classification of MF/SS

TNMB stage	Description
Skin*	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) v T_{1b} (plaque patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) v T_{2b} (plaque patch)
T_3	One or more tumours (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node†	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1 N_{1a} N_{1b}	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2} Clone negative Clone positive
N_2 N_{2a} N_{2b}	Clinically abnormal lymph nodes; histopathology Dutch grade 2 or NCI LN_3 Clone negative Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0 B_{0a} B_{0b}	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells Clone negative Clone positive
B_1 B_{1a}	Low blood tumour burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2 Clone negative

TNMB stage	Description
B_{1b}	Clone positive
B_2	High blood tumour burden: ≥ 1,000/µl Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

Based on Olsen et al. 2011[3]
* Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present. Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present. Tumour = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.
† Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions to include central nodes.[9] Lymph nodes are qualified as abnormal if > 1.5 cm in diameter.
‡ The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined
CD = cluster of differentiation, cm = centimetre; EORTC = European Organisation for the Research and Treatment of Cancer; ISCL = International Society for Cutaneous Lymphomas; LN = lymph node; M = metastasis; MF = mycosis fungoides; N = node; NCI = National Cancer Institute; SS = Sézary syndrome; T = tumour; TNMB = tumour, node, metastasis, blood

The CS states that *"between 2009 to 2013, 1,659 cases of diagnosed CTCL were recorded in England, of which 920 (55%) were MF and 42 (3%) were SS, thus representing an orphan sized population"*. Patients with stage IB disease have a median survival of 21.5 years, this dramatically reduces to less than five years for patients with advanced disease (stage IIB onwards); for patients with stage IVB disease median survival is under two years.[10]

ERG comment: The ERG considers the underlying health problem to have been clearly and comprehensively defined in document B of the CS.[1] The significant burden of disease on the patient, caregiver and healthcare system is clearly demonstrated with multiple accounts of personal experience.[11, 12]

2.3 Critique of company's overview of current service provision

The CS presents a thorough overview of the current service provision.[1]

First-line treatment for patients with advanced disease (stage ≥IIB MF and all SS patients) consists of systemic treatments such as bexarotene, interferon (IFN), methotrexate, extracorporeal photopheresis (ECP) and external beam radiotherapy (EBRT).[1] In MF and SS, a key objective is to extend periods of remission allowing patients to remain free from treatment for longer.[13] Subsequent treatments are usually initiated following symptomatic progression.

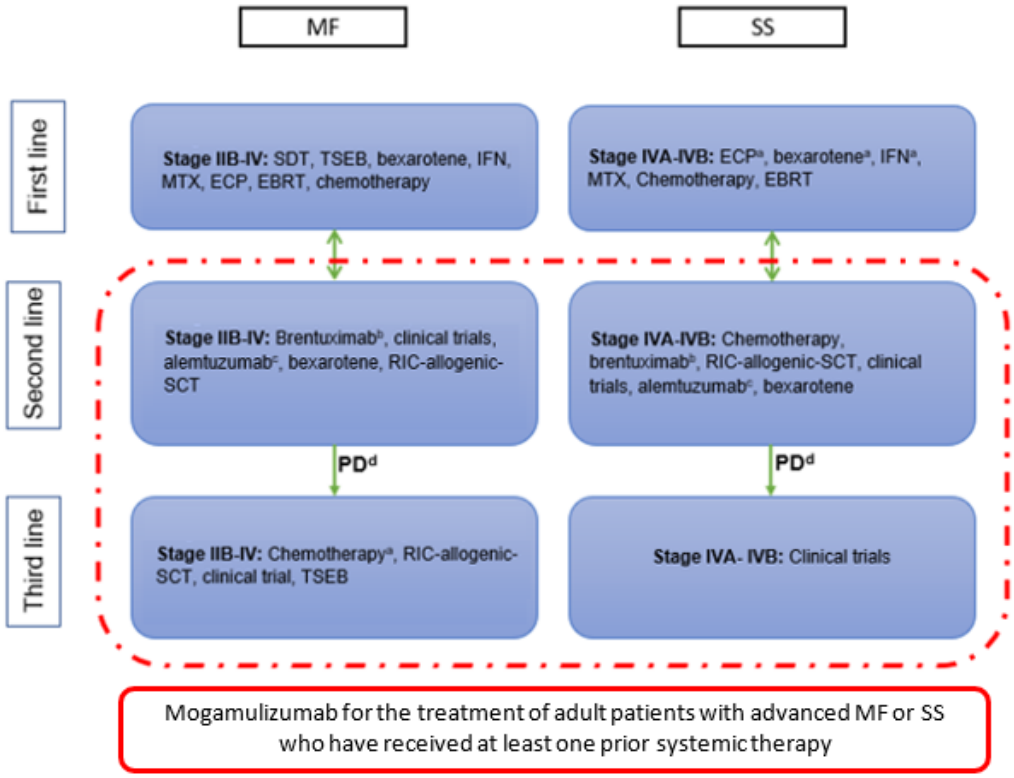
Second-line treatment options are similar, i.e. brentuximab vedotin (BV) is an option for advanced stage patients (stage ≥IIB MF and all SS) who are CD30-positive and clinically eligible; however, SS patients have minimal CD30 positivity and the efficacy of BV has not been studied in this population specifically. Alemtuzumab may be used off-label at second line although clinicians have confirmed its use in England is rare.[14] Systemic chemotherapy (e.g. gemcitabine; cyclophosphamide plus doxorubicin, vincristine, prednisolone [CHOP] regimens) may also be used at first- or later-lines of treatment for patients with advanced disease, or disease refractory to skin-directed therapy (SDT) or immunobiological agents but is used as a palliative treatment, rather than curative. Allogenic stem cell transplant (aSCT) is a treatment option for SS patients or advanced stage MF patients after first-line therapy. Although the treatment is potentially curative, this is limited to young, well-performing patients with a low tumour burden at the time of transplant.[4]

Third-line options are limited to entry into a clinical trial or a repeat of treatments previously received. With each relapse, response to treatment becomes reduced and shorter in duration. For the majority of patients, there is no cure for advanced MF or SS and patients often experience disease progression on therapy or become resistant to existing treatments.

The CS states that *"there is a clear unmet need for new treatment options for advanced MF and SS patients who are clinically ineligible for or refractory to treatment with BV and require systemic therapy that can target all disease compartments (skin, blood, lymph nodes and viscera) and extend periods of remission and disease control (i.e. where symptoms are controlled) allowing patients to remain free from subsequent treatment for longer"*, adding that *"there is also a clear unmet need for a therapy which provides a meaningful survival benefit and a tolerable safety profile"*. It is proposed that mogamulizumab will address this unmet need and its potential place in the treatment pathway is presented in Figure 2.1.

Mogamulizumab is a defucosylated, humanised IgG1 kappa immunoglobulin that selectively binds to CCR4, a G protein-coupled receptor for CC chemokines involved in trafficking of lymphocytes to various organs including the skin, resulting in depletion of the target cells.[15] 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.

Figure 2.1: Proposed placement of mogamulizumab in current treatment pathway for advanced stage patients (stage ≥IIB MF and all SS)



Based on section B 1.3 of the CS[1]. Figure adapted from the BAD and UKCLG guidelines[16]

[a] chemotherapy as recommended by the supranetwork MDT; [b] brentuximab is available only for CD30-positive patients; [c] alemtuzumab is not licensed for use in Europe; [d] PD and exhausted first- and second-line options.

BAD = British Association of Dermatologists; CD = cluster of differentiation; CS = company submission; EBRT = external beam radiotherapy; ECP = extracorporeal photopheresis; IFN = interferon; MDT = multidisciplinary team; MF = mycosis fungoides; MTX = methotrexate; PD = progressive disease; RIC = reduced

intensity; SCT = stem cell transplant; SDT = skin-directed therapy; SS = Sézary syndrome; TSEBT = total skin electron beam therapy; UK = United Kingdom; UKCLG = UK Cutaneous Lymphoma Group

ERG comment: The ERG notes that the comparator in the trial provided as evidence for the effectiveness of mogamulizumab is vorinostat. Vorinostat is not mentioned in the treatment pathway as a potential treatment option. The ERG questions why this comparator was used and suggests further justification should have been given (see section 3.3).

The MAVORIC trial comparing mogamulizumab to vorinostat in advanced MF and SS patients is a crossover trial where patients who fail on vorinostat crossover to mogamulizumab. However, the crossover does not involve patients crossing from mogamulizumab to vorinostat. The ERG discusses the methodology, including adjustments made to the results in section 4 of this report.

Figure 2.1 shows the proposed treatment pathway for advanced stage patients (stage ≥IIB MF and all SS). In the proposed pathway, the company submission (CS) specified mogamulizumab as second-line treatment.[1]

3. Critique of company's definition of decision problem

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma following at least one prior systemic therapy.	Adults with advanced mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma (i.e. stage ≥IIB MF and all SS) following at least one prior systemic therapy who are clinically ineligible for or refractory to treatment with brentuximab vedotin (BV).	In the pivotal MAVORIC study, approximately 80% of patients represented this subgroup. These patients have substantial reductions in OS and a greater burden of disease, hence represent a proportion of the total population with a great unmet need. Of these advanced patients, those who are ineligible for BV based on clinical judgement or who have previously received BV and have become refractory to this treatment represents patients with the greatest unmet need and the potential future clinical practice in the UK.	The population addressed in decision problem is narrower than the population defined in the NICE scope, see section 3.1.
Intervention	Mogamulizumab	Mogamulizumab	N/A	In line with NICE scope.
Comparator(s)	Established clinical management without mogamulizumab	Established clinical management without mogamulizumab	N/A	In line with NICE scope but concerns regarding comparator used in the included study, see section 3.3.
Outcomes	• Overall survival • Progression-free survival • Response rates • Time to next treatment • Adverse effects of treatment	• Overall survival • Progression-free survival • Response rates • Time to next treatment/ Next treatment-free survival • Adverse effects of treatment	Time to next treatment was also analysed as next treatment-free survival. Next treatment-free survival is defined as time from randomisation to the start of next treatment or death, similar to progression-free survival.	In line with NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• Health-related quality of life	• Health-related quality of life	Time to next treatment and treatment-free survival includes both time spent on treatment and the treatment-free period. This is driven by symptoms, that in turn drives the changes in quality of life and resource use that determine the health states according to clinical experts. As a result, it is more appropriate to base the health states on treatment changes, rather than changes in progression status. In the MAVORIC trial, mogamulizumab increased the treatment-free period compared to vorinostat, due to its unique mechanism of action.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	The cost effectiveness of mogamulizumab is expressed in terms of incremental cost per quality-adjusted life year.	N/A	Mostly in line with NICE scope, with concerns regarding population, comparator and caregivers' utilities, see above and section 5.2.8.
Subgroups to be considered	N/A	N/A		In line with NICE scope but some subgroup analyses reported, see section 3.5.

Based on Table 1 of the CS[1]

BV = brentuximab vedotin; CS = company submission; ERG = Evidence Review Group; MF = mycosis fungoides; N/A = not applicable; NICE = National Institute for Health and Care Excellence; OS = overall survival; SS = Sézary syndrome; UK = United Kingdom

3.1 Population

The population in the decision problem addressed in the CS is narrower than the population defined in the scope issued by the National Institute for Health and Care Excellence (NICE)[17] as

1. it only includes adults with advanced MF or SS, defined as *"stage ≥IIB MF and all SS"*,[1]
2. it only includes patients *"who are clinically ineligible for or refractory to treatment with brentuximab vedotin (BV)"*.[1]

As stated in Table 3.1, the company explained that in the MAVORIC trial, the only study evaluating the effectiveness and safety of mogamulizumab in CTCL, *"approximately 80% of patients represented this subgroup. These patients have substantial reductions in OS* [overall survival] *and a greater burden of disease, hence represent a proportion of the total population with a great unmet need"*.[1]

ERG comment: Overall, the evidence presented in the CS is on a narrower population than that defined in the NICE scope, i.e. conclusions should only be made in the narrower population addressed in the CS.[1, 17]

3.2 Intervention

The intervention defined in the decision problem addressed in the CS is in line with the NICE scope.[1, 17] As detailed in section 4.2.1, the intervention in the MAVORIC trial is mogamulizumab 1.0 mg/kg intravenously on days 1, 8, 15 and 22 of the first cycle, and days 1 and 15 on subsequent cycles.

ERG comment: The ERG has no comment regarding the definition of intervention in the decision problem addressed in the CS.

3.3 Comparators

The decision problem addressed in the CS defines the comparator to be *"established clinical management with mogamulizumab"* which is line with the NICE scope.[1, 17]

As noted in section 2.3, the MAVORIC trial compared mogamulizumab to vorinostat which is not mentioned in the treatment pathway proposed by the company (Figure 2.1).[1] According to the CS, *"although vorinostat is considered standard of care in the US, Canada, Australia and Japan, it is not currently licensed in Europe"*, i.e. is not standard of care in the UK.[1]

In section B.2.3. of the CS, the company argued that *"in order to enable a robust sample size for the MAVORIC study, alternatives to current NHS* [National Health Service] *standard of care had to be available, as the majority of European patients were likely to have received most currently available treatments (...) and re-challenge in a clinical trial setting would be inappropriate by introducing selection bias into the study. As such, the MAVORIC trial provided an attractive option to recruit patients by providing one new promising therapy option (mogamulizumab), and one previously unattainable therapy option (vorinostat), for which promising Phase II data are available (...). This allowed for high patient recruitment during MAVORIC, resulting in the largest randomised study investigating a systemic therapy in CTCL to date"*.[1]

The CS continued by stating that *"vorinostat can be considered a reasonable proxy for current standard of care in the NHS, based on a naïve comparison of results from the vorinostat arm of the MAVORIC study and the physician's choice arm (methotrexate or bexarotene i.e. UK* [United Kingdom] *standard treatments) of the ALCANZA study as well as comparison to Phase II bexarotene data (...).[18] It is also supported by clinical expert opinion,[13] and the EMA* [European Medicines Agency] *accepted this comparison when granting marketing authorisation for mogamulizumab. Thus, the results of the*

MAVORIC study should be considered to translate to English clinical practice. Furthermore, vorinostat is the only drug with data in the SS population".[1]

In the request for clarification, the ERG asked the company to provide further evidence supporting the use of vorinostat as comparator in the MAVORIC trial thus the CS.[19]

In response to the request for clarification, the company provided a summary of clinical evidence presented in the CS in support of vorinostat being a reasonable proxy for established clinical management as defined in the scope, see Table 3.2.[20]

Table 3.2: Summary of clinical evidence presented in the CS in support of vorinostat as a reasonable proxy for established clinical management as defined in the scope

• The physician's choice arm of the ALCANZA study was considered to represent established clinical management by NICE during TA577[21] • PFS curves from the vorinostat arm of the MAVORIC study and the physician's choice arm of the ALCANZA study overlap (see Figure 3.1) • A leading expert stated *"the efficacy of vorinostat can be assumed the same as for established clinical management in the UK"* during clinical consultation[13] • Across 193 CTCL patients, of which 93 had advanced stage disease refractory to prior systemic therapy, bexarotene resulted in an ORR in the skin of 31%.[18] This is similar to the ORR based on skin assessment only of 30%, as observed in the vorinostat arm of the MAVORIC study[22]
Based on Table 1 of the response to request for clarification[20] CS = company submission; CTCL = cutaneous T-cell lymphoma; NICE = National Institute for Health and Care Excellence; ORR = overall response rate; PFS = progression-free survival; TA = technology appraisal

The company also provided *"an overview of the study characteristics and efficacy outcomes for all bexarotene, methotrexate and interferon (IFN) non-RCTs* [randomised controlled trials] *identified through clinical SLR* [systematic literature review] *(the MAVORIC and ALCANZA studies were the only RCTs identified)"* (Table 3.3), stating that *"considerable heterogeneity is observed across trial designs, patient populations and outcomes that limits the usefulness of these data in addition to the key clinical evidence previously described"*.[20]

Furthermore, the company provided *"a summary of adverse events from all identified studies investigating bexarotene, IFN or vorinostat"* (Table 3.4) and highlighted that *"the SLR identified no studies reporting AEs relating to methotrexate. Overall, the safety profile of vorinostat appears to be a conservative estimate of the combined safety profile of established clinical management with higher rates of adverse events (AE) observed compared to AE rates for bexarotene and IFN"*.[20]

In response to the request to provide a comparison of the population, intervention, comparator and outcomes (PICO) used in MAVORIC and ALCANZA and to discuss any differences, the company provided Table 3.5.[19, 20] Comparing the baseline demographic and disease characteristics of patients in the ALCANZA and MAVORIC studies, the company noted that *"patients in MAVORIC were more heavily pre-treated than those in ALCANZA (median lines of prior therapy: 3 versus 2, respectively) and the number of patients with advanced disease (IIB-IVB) was greater in MAVORIC compared with ALCANZA (Figure 3.2). Patients in MAVORIC had a higher disease burden compared to those in ALCANZA (ECOG* [Eastern Cooperative Oncology Group] *0: 56% versus 70%; ECOG 1: 43% versus 27%, respectively), and the proportion of patients with advanced disease (IIB-IVB) was also greater in MAVORIC compared with ALCANZA (Figure 3.2). Within the advanced disease group, the proportion of patients with Stage IVA–IVB disease was greater in MAVORIC compared with ALCANZA (52% versus 18%, respectively). It should also be noted that all patients in MAVORIC had MF (55%) or*

SS (45%) disease classification with pcALCL [Primary cutaneous anaplastic large cell lymphoma] *patients being excluded, whereas in ALCANZA, there were no SS patients - all patients had MF or pcALCL disease classification. Furthermore, ALCANZA excluded patients with high blood tumour burden, and all patients enrolled were CD* [cluster of differentiation] *30-positive"*.[20]

The company acknowledged that *"there are numerous differences between the ALCANZA and MAVORIC studies in terms of the patient characteristics, the number of treatments patients received prior to the study (patients in MAVORIC more heavily pre-treated compared to ALCANZA), the treatments patients received subsequently after their randomised treatment (MAVORIC had a high proportion of patients who switched from the comparator arm to the intervention compared to ALCANZA), and the endpoint definitions. The differences in patient characteristics show that the MAVORIC population included more severe patients in the ITT population than ALCANZA; MAVORIC also included a greater proportion of advanced stage patients than ALCANZA – advance stage patients are associated with substantial reductions in OS compared to patients with earlier stage disease.[10, 23] Note, of the advanced stage patients; 40% of physician's choice patients in ALCANZA were stage IIB compared with 17.2% in the vorinostat arm of MAVORIC, conversely, 39.2% of patients in the vorinostat arm of MAVORIC patients were stage IVA1 with there being no stage IVA1 patients in the physician's choice arm of ALCANZA patients, the advanced stage population of MAVORIC could therefore be considered more severe than that of ALCANZA. The ALCANZA study did not include any SS patients, whereas in MAVORIC 45% of patients were SS, which is associated with worse survival higher risk of disease progression.[10] In addition, the ALCANZA study excluded patients with a high tumour burden which is also associated with reduced OS,[24] and all patients in ALCANZA were CD30+; although the prognostic value of CD30 is unclear.[25]"*.[20]

Discussing these differences, *"notably the difference in disease stage, a naïve comparison between vorinostat and physician's choice should be considered as informative when considering the evidence between vorinostat and treatments used in clinical practice, however it is also likely to underestimate the efficacy of vorinostat due to these differences. When overlaying the KM curves from the two studies for PFS (Figure 3.1) it is observed that the two treatments are very similar throughout and the curves cross multiple times (HR* [hazard ratio]*: 1.05 [95% CI* [confidence interval]*: 0.76, 1.46]). This would suggest that given the differences in patient characteristics described above, for PFS vorinostat would provide a conservative estimate as proxy for standard of care relative to mogamulizumab"*.[20] According to the response to request for clarification, *"for OS (Figure 3.4) vorinostat performs marginally better than physician's choice (HR: 0.85 [95% CI: 0.47, 1.54]) however, this analysis is not representative of clinical practice for either treatment as both treatments are heavily confounded by treatment crossover and PLD* [pegylated liposomal doxorubicin] *is not openly available from ALCANZA to allows this adjustment to be performed. This OS analysis has been presented as requested, but due to the reasons discussed above the results may be biased and should therefore be interpreted with caution"*.[20]

In addition, *"an analysis of ORR* [overall response rate] *was conducted using response derived using skin assessments only. and this outcome (Table 3.6) favours physician's choice; however, this comparison is not significantly different to vorinostat (RR* [risk ratio] *0.72 [95% CI: 0.35, 1.49]). The results of these naïve analyses for PFS and ORR in skin therefore provide further supporting evidence to suggest that vorinostat in MAVORIC is similar to physician's choice in ALCANZA and is therefore a reasonable proxy for UK clinical practice"*.[20]

Regarding the comparison to the phase II bexaretone study, the company was asked to *"discuss differences in the definition of ORR"* and to *"provide a table comparing outcomes other than ORR"*.[19] In response, the company stated that *"the bexarotene study data captured all associated extracutaneous*

CTCL manifestations; the response to bexarotene in other disease compartments, specifically blood, lymph nodes, and viscera were not captured. Conversely, in the MAVORIC study, response was measured using the updated international global composite response scoring system that accounts for all four potential disease compartments: skin, blood, lymph nodes, and viscera.[3] As such, the ORR results from MAVORIC can be considered more robust than those reported across clinical trials for bexarotene, and therefore the comparison between vorinostat and bexarotene should be considered a conservative estimate. Overall response data for bexarotene are taken from regulatory evidence across clinical trials of 193 patients with CTCL, as reported in the Summary of Product Characteristics (SmPC).[18] Of these patients, 93 had advanced stage disease refractory to prior systemic therapy, and of these, 61 were treated at an initial dose of 300 mg/m^2/day.[18] The overall response rate according to a composite assessment of five clinical signs (surface area, erythema, plaque elevation, scaling and hypo/hyperpigmentation) was 31% (19/61)".[20] Table 3.7 presents a comparison of time to response (TTR) for both MAVORIC and Duvic et al.[20]

Table 3.3: Summary of bexarotene, IFN and methotrexate-based studies (non-RCTs)

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment/ comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
Sokolowska-Wojdylo 2016[26]	• NR • Observational non-comparative • NR • Multicentre • Poland	Response rate, TTR, DOR	Bexarotene	21	• 19 (90.47) • 2 (9.52)	58.6 (19–84)	IA: 1 IB: 1 IIA: 1 IIB: 4 III: 4 IIIA: 5 IVA1: 3 IVB: 2	ORR of 81% in patients treated with bexarotene therapy at a mean duration of therapy 14.5 months. An ORR was defined as the sum of clinical CR or PR
Breneman 2002[27]	• Phase I/II • nRCT non-comparative • Open label • Multicentre • USA	Response rate	Bexarotene gel	19	NR	NR	All patients with Stage IA through to IIA (one patient with IIB, protocol deviation)	ORR of 47% for bexarotene therapy in MF patients at a treatment duration of 59 months
Duvic 2017[28]	• Phase I/II • nRCT non-comparative • Open label • Multi-centre • USA, Italy	Response rate	Bexarotene + pralatrexate	34	• 30 (88) • 3 (9)	66 (39–85)	NR	ORR of 60.6% for bexarotene + pralatrexate combination therapy Median PFS - 12.8 (range: 0.5-29.9)
Papadavid 2008[29]	• NR • Observational comparative	Response rate, safety and tolerability	Bexarotene 300 mg/day oral + PUVA	9	• 9 (100) • 0 (0)	NR	IA: 1 (11.1) IB: 6 (66.1) IIA: 1 (11.1)	The 150 mg bexarotene treatment group had a higher global ORR

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment/ comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
	• NR • Single centre • Greece						III: 1 (11.1)	(100%) compared with the 300 mg group (57%) at the study end. An ORR was defined as the sum of clinical CR or PR. However, the superiority of 150 mg group could not be advocated due to very small sample size (N=2)
			Bexarotene 150 mg/day oral + PUVA	5	• 5 (100) • 0 (0)	NR	IB: 3 (60) IIB: 1 (20) III: 1 (20)	
Hughes 2015[30]	• NR • Observational comparative • NR • Multicentre • Australia	TTNT	Low dose methotrexate	84	NR	NR	NR	Median TTNT = 5 months Median TTNT from 1L MTX = 4.4 months Median TTNT from mid-line MTX = 7.5 months Median TTNT from late-line MTX = 1.6 months
			Interferon-alpha	68	NR	60.3	NR	Median TTNT = 8.7 months

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment/ comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
			Bexarotene	20	NR	66.6	NR	Median TTNT = 4.1 months
Talpur 2014[31]	• Phase II • Observational comparative • NR • NR • NR	Response rate, safety and tolerability	Bexarotene 300 mg + pralatrexate	3	• 3 (100) • 0 (0)	Mean: 57.6 (range: 41-77)	NR	Of three patients treated with bexarotene 300 mg plus pralatrexate, only one had shown global ORR (i.e. 33.33%). Of 11 patients treated with bexarotene 150 mg + pralatrexate, six had shown a global ORR (i.e. 54.54%)
			Bexarotene 150 mg + pralatrexate	11	• 11 (100) • 0 (0)	Mean: 62.27 (range: 42-82)	NR	
Talpur 2002[32]	• NR • Observational non-comparative • NA • Single centre • USA	Response rate, safety and tolerability	Bexarotene based regimen	16	• 14 (87.5) • 2 (12.5)	65 (43–79)	IIB: 1 (6.25) III: 9 (56.25) IVA: 4 (25) IVB: 2 (12.5)	Global ORR of 68.75% in patients treated with bexarotene based regimen
Rupoli 2016[33]	• Phase II • nRCT non-comparative • Multicentre • Italy	RR, EFS and safety	Bexarotene + PUVA	15	NR	NR	IB–IVA	Bexarotene plus PUVA combination therapy was associated with a global ORR in 60% of patients at a median follow up of 53 months

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment/ comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
Illidge 2013[34]	• Phase II • nRCT non-comparative • NR • Multicentre • UK	ORR at 24 weeks, response rate, PFS, OS, safety, change in mSWAT and QoL	Gemcitabine + bexarotene	36	NR	65 (38–83)	IB: 5 (13.9) IIA: 2 (5.6) IIB: 8 (22.2) III: 8 (22.2) IVA: 13 (36.1)	Higher global ORR at Week 12 (31.4%) compared with global ORR at Week 24 (14.3%) in the patients treated with gemcitabine plus bexarotene combination therapy Median PFS – 5.3 Median OS – 21.2 months (median follow-up 16.4 months)
Bunn Jr 1987[35]	• NR • nRCT non-comparative • NR • NR • NR	Response rate, safety	Recombinant interferon -alfa	20	NR	NR	II: 5 (25) III: 2 (10) IV: 13 (65)	At 6 months, a global ORR of 50% was associated with recombinant interferon alfa 50 mIU three times a week
Aviles 2015[36]	• NR • nRCT comparative • Open label • NR • NR	OS, safety Response rate, DOR, PFS	Interferon + methotrexate	201	• 201 (100) • 0 (0)	64.5 (36–71)	II B: 73 (36) IIIB: 57 (28) IV A: 40 (20) IV B: 29 (14)	Global CR was observed in 80% of patients treated with Interferon + retinoids combination OS - Significantly higher survival rate in patients treated with interferon plus
			Interferon + retinoids	176	• 176 (100) • 0 (0)	62.9 (43–75)	II B: 76 (42) IIIB: 36 (20) IV A: 35 (19)	

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment/ comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
							IV B: 31 (17)	methotrexate compared with interferon plus retinoids (i.e. 70% versus 67%; p=0.03) PFS - at five years of follow-up, no significant difference in PFS rate was observed between patients treated with interferon plus methotrexate (60%) versus interferon plus retinoids (62%; p=0.8)
Roenigk Jr 1990[37]	• Phase I • nRCT non-comparative • NR • Multicentre • NR	Response rate, DoR, TTR, safety	Interferon alpha-2a + PUVA	15	NR	NR	IB: 7 (63.6) IIB: 2 (18.2) III: 1 (9.1) IVB: 1 (9.1)	Interferon alpha-2a (6-30 mIU three times weekly) combination therapy with PUVA resulted in a global ORR of 90.9%
Foss 1992[38]	• Phase II • nRCT non-comparative • NR • NR • NR	Response rate, OS	Pentostatin + interferon alfa-2a	29	NR	NR	IV A: 8 (80) IVB: 2 (20)	Interferon alpha-2a (10–50 mIU three times a week) combination therapy with pentostatin (Nipent®) was associated with a global ORR of 30% Median OS - 15

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment/ comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
Kuzel 1995[39]	• Phase I/II • nRCT non-comparative • NR • NR • USA	Response rate, DoR, safety	Interferon alfa-2a + phototherapy	8	NR	NR	NR	Global ORR of 75% was observed in interferon alpha-2a (3–12 mIU three times a week) combination therapy with phototherapy treated population
Foss 1994[40]	• Phase II • nRCT non-comparative • NR • NR • NR	Response rate, TTP	Fludarabine + interferon Alfa-2a	21	NR	NR	NR	Interferon alpha-2a (5 mIU three times a week) combination therapy with fludarabine resulted in a global ORR of 50%
Kohn 1990[41]	• Phase II • nRCT non-comparative • NR • NR • NR	Response rate, response rate (blood, skin, lymph node, viscera), DoR, TTR, safety	Recombinant interferon -alfa	24	NR	60 (25–70)	NR	Recombinant interferon alfa (10–50 mIU/m^2) therapy was associated with a global ORR of 29% at the study end (Cut-off: 1 December 1988). The study reported a superior ORR in skin disease (25%) compared with blood (4.16%) and lymph nodes (12.5%)

Study name	• Study phase • Study design • Blinding • Study centre • Study country	List of endpoints	Treatment/ comparator	N	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Stages: n (%)	Efficacy outcomes (shared with MAVORIC)
								Median OS of patients receiving recombinant interferon alfa therapy was 13 months (range <1–>54)
McDonald 1978[42]	• NR • nRCT non-comparative • NR • Multicentre • USA	Response rate, DOR, safety	Methotrexate + Citrovorum factor	11	• 6 (100) • 0 (0)	Mean: 58.5 (range: 41–78)	NR	All 11 patients experienced a good to excellent response Complete remissions were induced in 7/11 patients

Based on Table 2 of the response to request for clarification[20]

CR = complete response; DOR = duration of response; EFS = event-free survival; IFN = interferon; IU = international unit; MF = Mycosis fungoides; mg = milligram; mSWAT = modified Severity Weighted Assessment Tool; MTX = methotrexate; NA = not applicable; NR = not reported; nRCT = non-randomised controlled trial; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PUVA = psoralen plus ultraviolet A therapy; QoL = quality of life; RCT = randomised controlled trial; SS = Sézary syndrome; TTNT = time to next treatment; TTP = time to progression; TTR = time to response; UK = United Kingdom; USA = United States of America

Table 3.4: Summary of vorinostat, bexarotene and interferon adverse events from non-RCTs

Study name	Treatment/ comparator	N	Any adverse event, n (%) Any grade Grade ≥3	Rash, n (%) Any grade Grade ≥3	Diarrhoea, n (%) Any grade Grade ≥3	Fatigue, n (%) Any grade Grade ≥3	Pyrexia, n (%) Any grade Grade ≥3	Peripheral neuropathy, n (%) Any grade Grade ≥3	Anaemia, n (%) Any grade Grade ≥3	Nausea, n (%) Any grade Grade ≥3	Pruritus, n (%) Any grade Grade ≥3	Thrombocytopenia, n (%) Any grade Grade ≥3	Vomiting, n (%) Any grade Grade ≥3
Vorinostat -based study													
Duvic 2007[43]	Vorinostat	37	NR NR	NR NR	18 (49)[$] NR	27 (73)[$] NR	NR 3 (8)	NR NR	4 (11)[$] 3 (8)	18 (49) NR	NR NR	20 (54)[$] 7 (19)	9 (24)[$] NR
Olsen 2007[44]	Vorinostat	74	NR 21 (28)[$]	NR NR	36 (48.6)[$] 0 (0)	34 (45.9) 4 (5.4)[$]	NR NR	NR NR	9 (12.2)[$] 1 (1.4)[$]	32 (43) 3 (4.1)[$]	10 (14) 1 (1)	16 (21.6)[$] 4 (5.4)[$]	11 (15) 1 (1)
Geskin 2010[45]	Vorinostat 200–400 mg-based regimens	14	NR NR	NR NR	2 (14.2) NR	2 (14.2) NR	NR NR	NR NR	6 (42.8) 2 (14.2)	2 (14.2) NR	NR NR	4 (28.5) 2 (14.2)	NR NR
Wada 2012[46]	Vorinostat	6	NR NR	NR NR	2 (33.3)[$] NR	NR NR	2 (33.3)[$] 0	NR NR	NR NR	4 (66.7)[$] 0 (0)	NR NR	4 (66.7)[$] 1 (16.7)[$]	3 (50)[$] NR
Kogge 2015[47]	Vorinostat	NR	NR NR	1 (7)[$] NR	2 (13)[$] NR	NR NR	1 (7)[$] NR	NR NR	7 (47)[$] 1 (7)[$]	3 (20)[$] NR	NR NR	3 (20)[$] NR	3 (20)[$] NR

Study name	Treatment/ comparator	N	Any adverse event, n (%) Any grade Grade ≥3	Rash, n (%) Any grade Grade ≥3	Diarrhoea, n (%) Any grade Grade ≥3	Fatigue, n (%) Any grade Grade ≥3	Pyrexia, n (%) Any grade Grade ≥3	Peripheral neuropathy, n (%) Any grade Grade ≥3	Anaemia, n (%) Any grade Grade ≥3	Nausea, n (%) Any grade Grade ≥3	Pruritus, n (%) Any grade Grade ≥3	Thrombocytopenia, n (%) Any grade Grade ≥3	Vomiting, n (%) Any grade Grade ≥3
Bexarotene-based studies													
Duvic 2017[28]	Bexarotene + pralatrexate	34	NR NR	NR NR	8 (24) 2 (6)	19 (56) 0 (0)	NR NR	NR NR	10 (29) 1 (3)	16 (47) 0 (0)	NR NR	NR NR	NR NR
Papadavid 2008[29]	PUVA + bexarotene 300 mg/day oral	9	6 (66.6) NR	NR NR	NR NR	NR NR	NR NR	NR NR	1 (11.1) NR	NR NR	NR NR	NR NR	NR NR
	PUVA + bexarotene 150 mg/day oral	5	5 (100) NR	NR NR	NR NR	NR NR	NR NR	NR NR	0 (0) NR	NR NR	NR NR	NR NR	NR NR
Talpur 2002[32]	Bexarotene based regimen	16	NR NR	NR NR	1 (6) NR	NR NR	NR NR	NR NR	11 (69) NR	0 (0) NR	NR NR	NR NR	NR NR
Illidge 2013[34]	Gemci-tabine + bexarotene	35	NR 25 (71.4)	NR 2 (5.7)	NR NR	NR 2 (5.7)	NR 1 (2.9)	NR NR	NR 1 (2.9)	NR NR	NR NR	NR 2 (5.7)	NR NR

Study name	Treatment/ comparator	N	Any adverse event, n (%) Any grade Grade ≥3	Rash, n (%) Any grade Grade ≥3	Diarrhoea, n (%) Any grade Grade ≥3	Fatigue, n (%) Any grade Grade ≥3	Pyrexia, n (%) Any grade Grade ≥3	Peripheral neuropathy, n (%) Any grade Grade ≥3	Anaemia, n (%) Any grade Grade ≥3	Nausea, n (%) Any grade Grade ≥3	Pruritus, n (%) Any grade Grade ≥3	Thrombocytopenia, n (%) Any grade Grade ≥3	Vomiting, n (%) Any grade Grade ≥3
Interferon based studies													
Bunn Jr 1987[35]	Recombi-nant inter-feron alfa	20	NR NR	NR NR	NR NR	NR NR	20 (20) $ NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR
Aviles 2015[36]	Interferon + metho-trexate	201	NR NR	NR NR	NR NR	NR NR	6 (3) NR	NR NR	NR NR	NR NR	NR NR	1 (0.5) NR	NR NR
	Interferon + retinoids	176	NR NR	NR NR	NR NR	NR NR	11 (6.3) NR	NR NR	NR NR	NR NR	NR NR	3 (1.7) NR	NR NR
Kohn 1990[41]	Recombi-nant inter-feron alfa	24	NR NR	NR NR	NR NR	NR NR	24 (24)[$] NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR

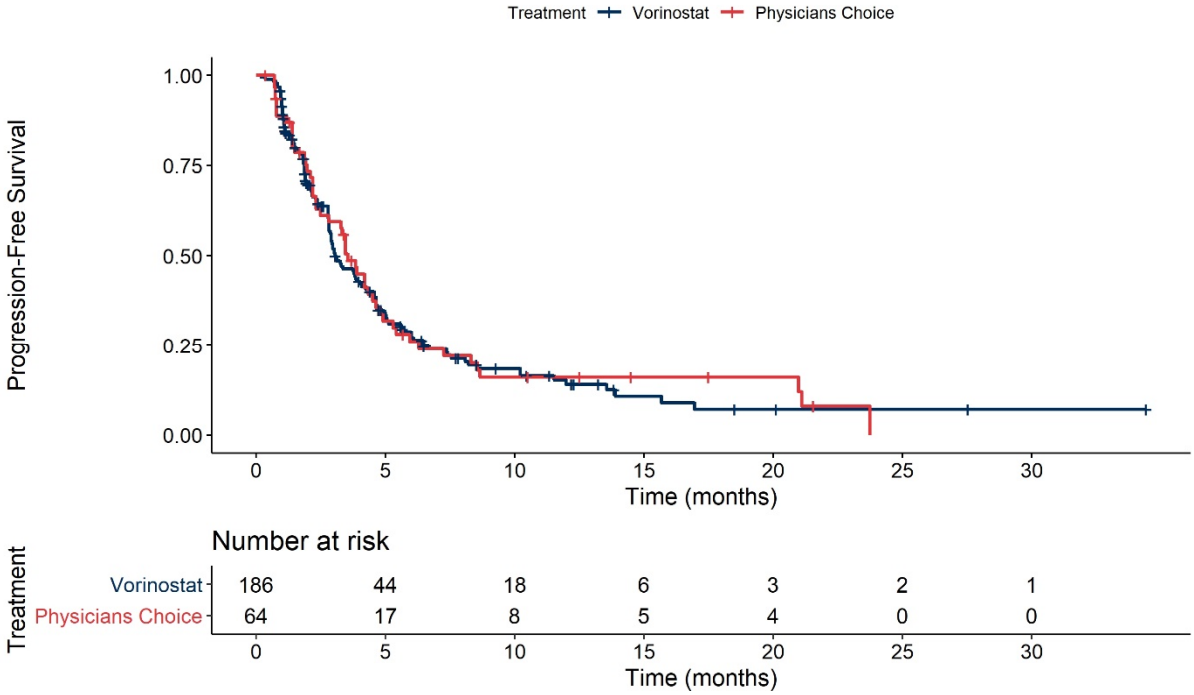
Based on Table 3 of the response to request for clarification[20]
[$] related to the drug
mg = milligram; NR = not reported; PUVA = psoralen plus ultraviolet light therapy; RCT = randomised controlled trial

Table 3.5: Baseline demographic and disease characteristics of patients in the ALCANZA and MAVORIC studies

	ALCANZA		MAVORIC	
	Brentuximab vedotin (n=64)	**Physician's choice of methotrexate or bexarotene (n=64)**	**Mogamulizumab (n=186)**	**Vorinostat (n=186)**
Age, median years (range)	62 (51–70)	59 (48-67)	63 ([redacted])	65 (56-72)
Male, n (%)	33 (52)	37 (58)	109 (59)	107 (58)
Race, n (%)				
White	56 (88)	53 (83)	125 (67.2)	135 (73)
Other	5 (8)	10 (16)	[redacted]	[redacted]
ECOG PS, n (%)				
0	43 (67)	46 (72)	106 (57.0)	104 (56)
1	18 (28)	16 (25)	78 (41.9)	82 (44)
2	3 (5)	2 (3)	2 (1.1)	0
Time from initial diagnosis, median months (range)	42.2 (12.8–87.4)	37.0 (12.3-102.7)	41.0 (17.4–78.8)	35.4 (16.2-68.2)
Disease type, n (%)				
MF	48 (75)	49 (77)	105 (56.5)	99 (53)
SS	N/A	N/A	81 (43.5)	87 (47)
Disease stage, n (%)				
IB-IIA	15 (31)	18 (37)	36 (19.4)	49 (26)
IIB	19 (40)	19 (39)	32 (17.2)	23 (12)
IIIA-IIIB	4 (8)	2 (4)	22 (11.8)	16 (9)
IVA1	0	1 (2)	73 (39.2)	82 (44)
IVA2	2 (4)	8 (16)	19 (10.2)	12 (6)
IVB	7 (15)	0	4 (2.2)	4 (2)
Lines of prior systemic therapy, median (range)	2 (1-4)	2 (1-3)	3 (2–5)	3 (2-5)

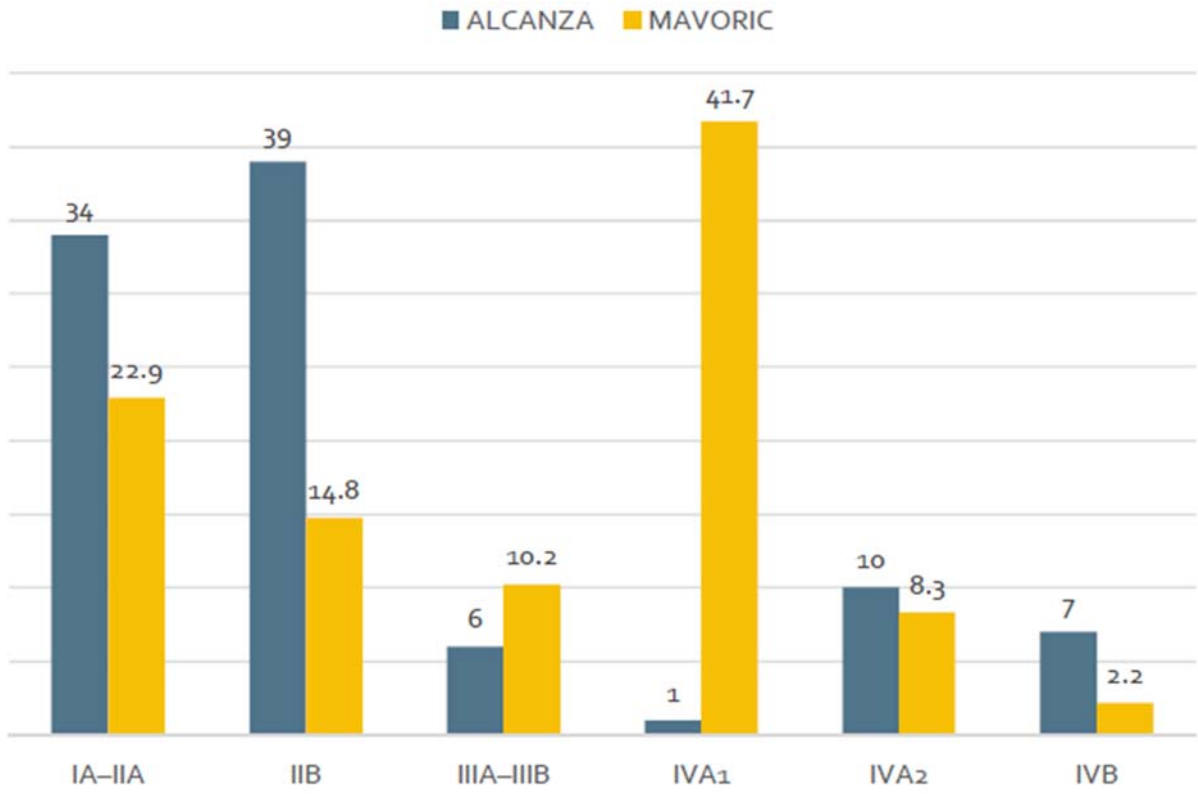
Based on Table 3 of the response to request for clarification[20]
ECOG = Eastern Cooperative Oncology Group; MF = mycosis fungoides; PS = performance status; SS = Sezary syndrome

Figure 3.1: Kaplan–Meier investigator-assessed progression-free survival curves for observed vorinostat (MAVORIC - ITT) versus physician's choice (ALCANZA - ITT) – 2016 data cut



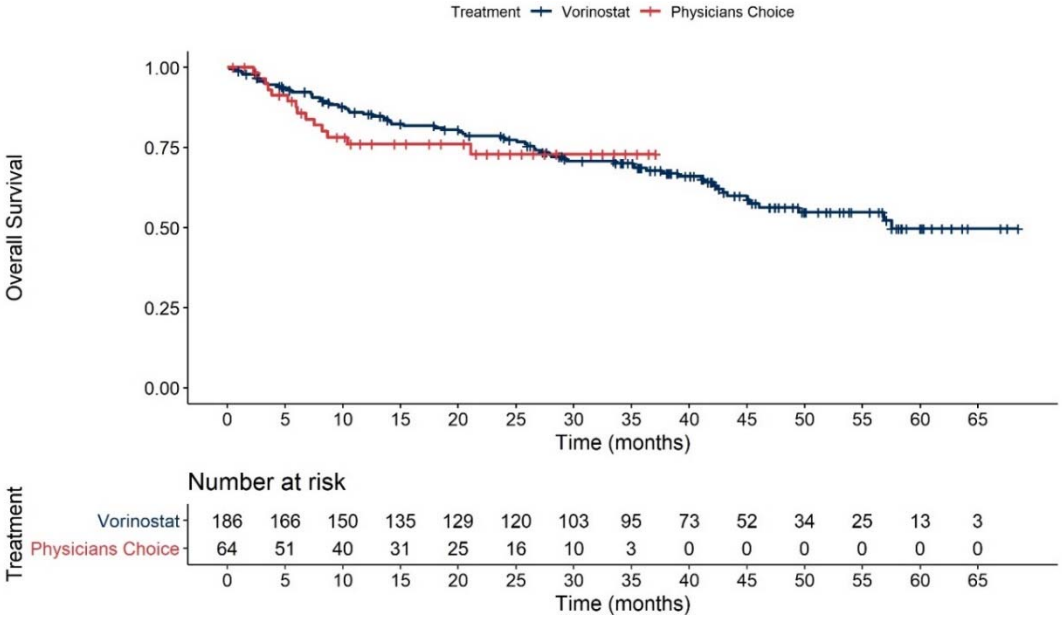
Based on Figure 2 of the response to request for clarification[20]
ITT = intention-to-treat

Figure 3.2: ALCANZA and MAVORIC populations by percentage of patients at given clinical stage



Based on Figure 1 of the response to request for clarification[20]
Intervention: MAVORIC – Mogamulizumab; ALCANZA – Brentuximab Vedotin
Comparator: MAVORIC – Vorinostat; ALCANZA – Physician's Choice (Methotrexate or Bexarotene)

Figure 3.3: Kaplan–Meier overall survival curves for observed vorinostat (MAVORIC - ITT) versus physician's choice (ALCANZA - ITT) – 2019 data cut*



Based on Figure 3 of the response to request for clarification[20]

* An updated data cut (2 March 2019) which focused on safety outcomes and collected only limited efficacy data (OS and time to discontinuation [TTD]) has been used for this analysis (this is consistent with the data used in the submission)

ITT = intention-to-treat; OS = overall survival; TTD = Time to discontinuation

Table 3.6: Skin responses for the treatments of interest

Treatment (Population)	Sample size	N responders	N evaluable	Proportion of ORR in skin (CR+PR)	Rate ratio (95% CI)
Vorinostat (ITT population)	186	29	186	0.16	0.72 (0.35, 1.49)
Physician's choice (ITT population)	64	13	64	0.20	

Based on Table 7 of the response to request for clarification[20]
Note: Rate ratio greater than 1 favours vorinostat. Rate ratio less than 1 favours physician's choice.
CI = confidence interval; CR = complete response; ITT = intention-to-treat; ORR = overall response rate; PR = partial response

Table 3.7: Time to response results from the MAVORIC and phase II/III study

	MAVORIC		Duvic et al. 2001[48]
	Mogamulizumab (n=186)	**Vorinostat (n=186)**	**Bexarotene 300 mg/m²/d (n=56)**
TTR, median (IQR)	3.3 months (2.0–6.4)	5.1 months (2.9–8.5)	180 days (14–197)

Based on Table 8 of the response to request for clarification[20]
IQR interquartile range; mg = milligram; TTR =time to response.

Table 3.8: Overview of adverse events: Safety population

	MAVORIC		Duvic et al. 2001[48]
	Mogamulizumab (n=184)	Vorinostat (n=186)	Bexarotene 300 mg/m^2/d (n=56)
Adverse Events (AEs), n (%)			
Any AEs	[redacted]	[redacted]	93 (99)
Serious Adverse Events, n (%)			
Drug-related Treatment-emergent SAEs	36 (19.6)	30 (16.1)	2 (4)
Discontinuation due to AEs, n (%)			
Drug-related TEAEs	[redacted]	[redacted]	4 (7)

Based on Table 9 of the response to request for clarification[20]
AE = adverse event; mg = milligram; SAE = serious adverse event; TEAE = treatment-emergent adverse event

ERG comment: The ERG is concerned by the use of vorinostat as a comparator in MAVORIC, the only study evaluating the effectiveness and safety of mogamulizumab in CTCL. As highlighted by the company, vorinostat is not licensed for the use in the UK and is not mentioned in the proposed treatment pathway.

In response to the request for clarification, the company discussed differences between MAVORIC and ALCANZA in the definition and schedule of assessment of PFS and ORR.[20] They concluded that *"the consequences of these differences are unknown. It might be anticipated that the reduced frequency of full GRS assessment and the need for lymph node progression confirmation through biopsy in the ALCANZA trial may delay the detection of progression and decrease the number of lymph node progression observations compared to the MAVORIC trial. It could also be anticipated that the confirmation of response based on skin assessment alone in ALCANZA could overestimate response compared to confirmation based on full Global Composite Response Score assessment. However, the 4-week sustained response need in MAVORIC could overestimate response compared to the 4-month sustained response need in ALCANZA".*[20]

The clinical expert working on the ERG report highlighted that the MAVORIC trials avoided using different comparator depending on the available drugs in the United States of America (USA) and centres outside the USA.[49] She acknowledged that vorinostat has some activity similar to methotrexate or bexarotene, and heterogeneity of treatment choice has demonstrated. While international consensus guidelines are available; the lack of comparative trials means that there is no clear algorithmic approach to treatment. Therefore, systemic treatment choice is currently guided by prognostic features, incorporating stage, available drugs and patient-specific factors such as previous treatment, age and comorbidities.

If vorinostat (MAVORIC) and physician's choice (ALCANZA) were truly comparable, it could be assumed that physician's choice would produce more favourable results for progression-free survival (PFS) and overall survival (OS), respectively, in ALCANZA (where patients are less severe in disease presentation) than vorinostat in MAVORIC. However, in response to request for clarification, the company have estimated hazard ratios for vorinostat versus physician's choice based on digitised Kaplan-Meier (KM) data (shown in see Figures 3.1 and 3.3), which show a slight PFS advantage for

physician's choice but an OS disadvantage for physician's choice compared with vorinostat (confidence intervals were wide for both), but the OS analysis may have been biased by crossover having been possible in both trials.[20] The ERG acknowledges the statement by the company regarding OS results, i.e. that "*the results may be biased and should therefore be interpreted with caution"*.[20] Based on the limited data available, the comparability of vorinostat and physician's choice cannot be established.

Overall, there is some uncertainty regarding the use of vorinostat as a proxy for *"established clinical management without mogamulizumab"*.[17]

3.4 Outcomes

ERG comment: This ERG report covers the outcomes defined in the NICE final scope, namely:

- Progression-free survival
- Response rates
- Overall survival
- Time to next treatment
- Health-related quality of life
- Adverse effects of treatment

The CS reported on two additional outcomes, time to treatment failure as well as next treatment-free survival, which were analysed post-hoc. These outcomes were not covered in this report, see section 4.2.5.

3.5 Other relevant factors

ERG comment: The economic analyses are mostly in line with the NICE scope, with concerns regarding population, comparator and caregivers' utilities, see above and section 5.2.8. Relevant results from subgroup analyses are reported in section 4.2.5.6.

4. Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D of the CS provided details of the systematic search of the literature used to identify clinical efficacy and safety literature.[50] It was reported that searches were conducted on 2 July 2019. A summary of the resources searched is provided in Table 4.1.

Table 4.1: Resources for the clinical efficacy and safety literature searches

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	Embase	embase.com	Not reported	2 July 2019
	MEDLINE		Not reported	
	MEDLINE In-Process	PubMed	Not reported	2 July 2019
	CENTRAL	Cochrane Library	Not reported	2 July 2019
	CDSR		Not reported	2 July 2019
	DARE		Not reported	2 July 2019
	HTA database		Not reported	2 July 2019
Conference proceedings	ASCO	Not reported	2017-2019	July 2019
	ASH		2017-2019	
	ESMO		2017-2019	
	ICML		2017-2019	
	ISCL / World Congress of Cutaneous Lymphomas		2017-2019	
	EORTC		2017-2019	
	WCD		2017-2019	
	USCLC		2017-2019	
	UKCLG		2017-2019	
	EMA		2017-2019	

Bibliographies of key systematic review and meta-analysis articles were screened to ensure that the initial searches captured all the relevant clinical studies.
ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; CDSR = Cochrane Database Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; DARE = Database of Abstracts of Reviews of Effects; EMA = European Medicines Agency; ESMO = European Society for Medical Oncology; HTA = Health Technology Assessment; ICML = International Conference on Malignant Lymphomas; ISCL = International Society of Cutaneous Lymphomas; UKCLG = United Kingdom Cutaneous Lymphoma Group; USCLC = United States Cutaneous Lymphoma Consortium; WCD = World Congress of Dermatology

ERG comment:

- The selection of databases searched was adequate, and searches were clearly reported and reproducible. The database name, host and date searched were provided. The date range of the searches was not reported.
- Searches were conducted in July 2019.
- An extensive range of conference proceedings was searched for the last two years (2017-2019). Details of the conferences searched, search strategies or search terms used, dates of searches, and results were not reported in the CS, but full details of the conference proceedings searches were provided in response to the ERG clarification letter.[20]
- MEDLINE and Embase were searched simultaneously using embase.com. This approach is not recommended. A simultaneous multi-file search such as this should include both MeSH (medical subject headings) and EMTREE subject headings to ensure that all subject indexing terms are searched; however, all of the search strategies only included EMTREE terms which may have impaired how well the strategies performed.
- MEDLINE In-process was searched via PubMed.
- Truncation and proximity operators were inconsistently used throughout.
- Study design filters were included for randomised controlled trials (RCTs) and observational studies so that both clinical efficacy and safety evidence could be identified. It is not clear if the study design filters were based on validated search filters, such as those published on the Information Specialists' Sub-Group (ISSG) Search Filters Resource website: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/
- The search strategies were designed to be sensitive as they included a facet of disease terms, but no facet of intervention terms. This approach attempts to identify all relevant interventions or comparators.
- The Cochrane Library searches were incorrectly reported: the CDSR search strategy and results were not reported at all; the Cochrane Central Register of Controlled Trials (CENTRAL) search strategy mistakenly repeated the MEDLINE In-process (PubMed) strategy; the company conducted the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) searches via the Centre for Reviews and Dissemination (CRD) interface, but misreported using the Cochrane Library. Details of the CDSR and CENTRAL search strategies were provided in response to the ERG clarification letter.
- The company did not search any clinical trials registers. Searches of ClinicalTrials.gov and/or World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) would have been useful for identifying completed and ongoing clinical trials.
- The PRISMA flow diagram of literature search results included 14 additional records identified from 'grey literature'. It is not clear if these records were identified from conference proceedings, reference checking or elsewhere.

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for RCTs and non-RCTs is presented in Table 4.2. The CS notes that the presented systematic review is an update of the original review conducted in February 2018.[1] According to the CS appendices, the eligibility criteria utilised a global perspective and, thus, were broader than the NICE scope.[50] However, in the decision problem (see section 3.1), the addressed population is narrower, focusing on adults with advanced MF or SS, rather than adults with any-stage MF or SS.[20]

Table 4.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Category	Inclusion criteria	Exclusion criteria
Population	Adult patients with any-stage R/R CTCL, including the subtypes MF and SS, who have been previously treated with at least one systemic therapy Population based on NICE scope: Adult patients with any-stage MF and SS, who have been previously treated with at least one systemic therapy.	• Healthy volunteers • Paediatric population • Disease other than R/R CTCL • Frontline therapy
Intervention	All pharmacological interventions and phototherapies for the treatment of R/R CTCL. Extractions for studies of interventions based on UK clinical practice: • Mogamulizumab • Brentuximab vedotin • Bexarotene • Methotrexate • Gemcitabine • Vorinostat • Interferon • CHOP regimen	Interventions not included in the list
Comparators	• Placebo • Best supportive care (author defined) • Any other pharmacological intervention • No comparator limit for single-arm trials • Standard of care in the UK	None
Outcomes	• Response rate • Global composite response • Progression-free survival • Overall survival • Time to treatment discontinuation • Mortality • Health-related quality of life • Incidence of adverse events • Study/ treatment discontinuation	Not reporting any of the outcomes included in the list
Study Design	• RCT • non RCT • Single-arm trials • Retrospective and prospective cohort studies • Real-world evidence studies • Systematic reviews	• Letters, comments and editorials • Case studies or case reports
Language	English language only	Non-English language
Countries	No limit	None

Based on Table D-6 of the CS appendices[50]
CHOP = gemcitabine; cyclophosphamide plus doxorubicin, vincristine, prednisolone; CS = company submission; CTCL = cutaneous T-cell lymphoma, MF = mycosis fungoides; NICE = National Institute for

Category	Inclusion criteria	Exclusion criteria
Health and Care Excellence; R/R = relapsed/refractory; RCT = randomised controlled trial; SS = Sézary syndrome; UK = United Kingdom		

ERG comment: The exclusion of non-English language studies possibly missed potentially relevant studies and the ERG asked the company to *"re-screen these references to ensure no relevant publication has been missed"*. [19] In response, the company provided a list of 191 references and stated that *"no relevant Non-English study has been found after re-screening the abstracts which were excluded based on language criteria"*.[20]

As discussed in section 3.1, there was a discrepancy between the population defined in the final scope issued by NICE and the eligibility criteria used in the CS (see Table 4.2 above).[1, 17]

4.1.3 Data extraction

According to the appendices of the CS, data were extracted from full text resources by one reviewer and then checked against the original article by another reviewer.[50]

ERG comment: The Cochrane Handbook for Systematic Reviews recommends that *"as a minimum, information that involves subjective interpretation and information that is critical to the interpretation of results (e.g. outcome data) should be extracted independently by at least two people"*.[51] Due to one reviewer completing data extraction and one person checking, there is a higher risk for errors.[51]

4.1.4 Quality assessment

The quality of included studies was assessed by the company.[1] The considered elements in the quality assessment included appropriate random assignment, adequate concealment of treatment allocation, similarity of groups at the outset of the study in terms of prognostic factors, and an inclusion of the intention-to-treat (ITT) analysis.

ERG comment: The ERG has no further comment regarding quality assessment, e.g. it is unclear how many people were involved in the quality assessment or how discrepancies were resolved.

4.1.5 Evidence synthesis

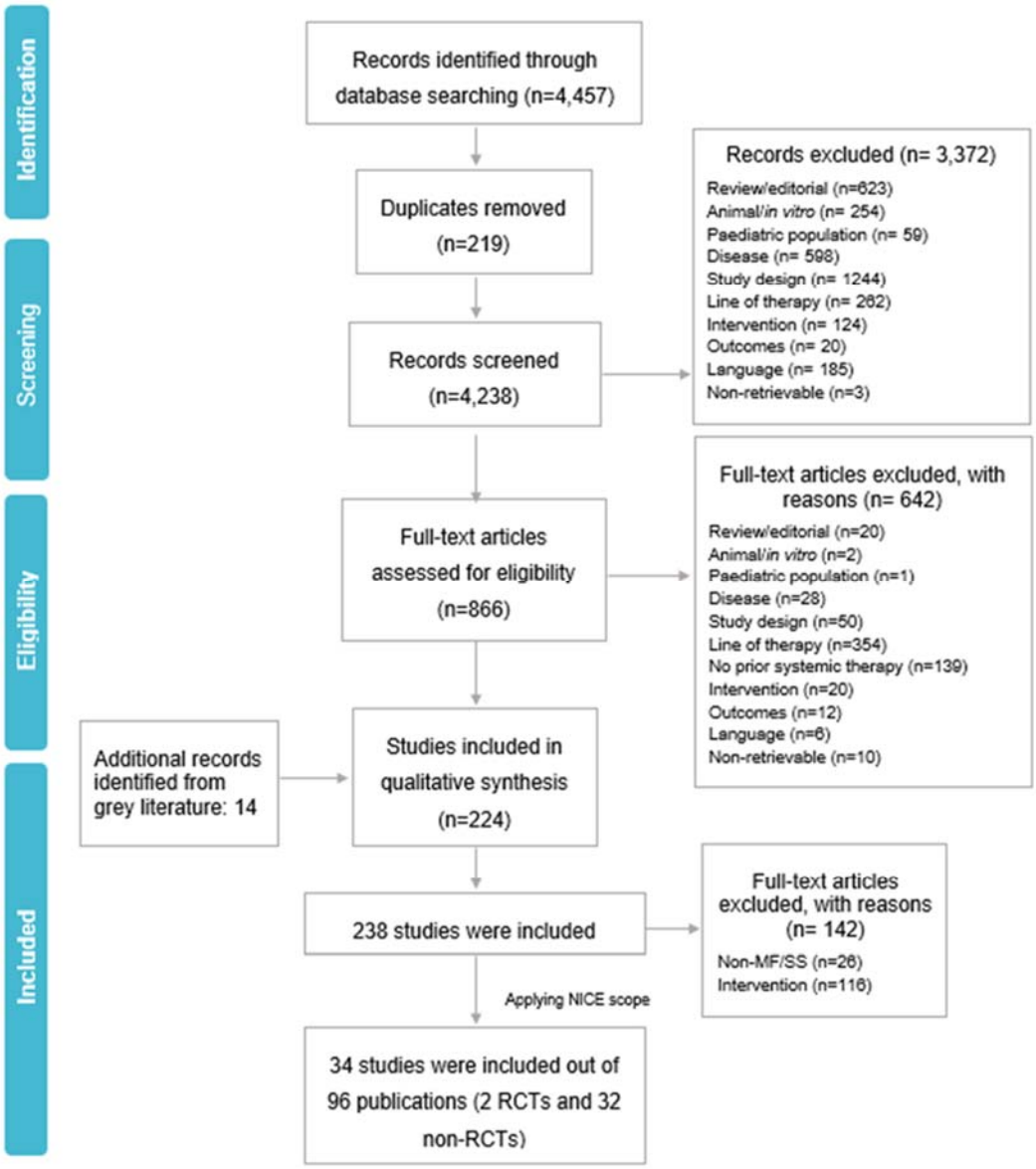
A single study, the MAVORIC trial, was included. Therefore, no evidence synthesis was completed.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 List of clinical effectiveness evidence

The SLR identified 4,238 records from database searches after the removal of duplicates. The number of included records after screening was 238 (including 14 additional references identified from grey literature), which were later narrowed to a final 96 records on 34 studies judged to be relevant to this appraisal. Of these, two studies were RCTs and 32 were observational studies. A PRISMA (Preferred reporting items for systematic reviews and meta-analyses) flow chart illustrating the selection of the studies is reported in Figure 4.1.

Figure 4.1: PRISMA flow chart for the selection of studies



Based on Figure D-1 of the CS appendices[50]
CS = company submission; MF = mycosis fungoides; PRISMA = Preferred reporting items for systematic reviews and meta-analyses; RCT = randomised controlled trial; SS = Sézary syndrome

Following review inclusion criteria (see section 4.1.2), two studies were identified, MAVORIC and ALCANZA.[52, 53] According to the response to clarification, the active treatment for ALCANZA was not relevant to the selected population.[20]

MAVORIC was the only study evaluating the effectiveness and safety of mogamulizumab in CTCL which was identified in the systematic literature review.[52]

The MAVORIC study is an international phase III open-label, randomised trial.[52] The objective was to evaluate the effectiveness of mogamulizumab compared to vorinostat in patients with stage IB-IVB MF and SS that had failed at least one previous course of systemic therapy. A description of the MAVORIC study is shown in Table 4.3.

As part of the relevant evidence, the CS cites the phase I/II trial of mogamulizumab in patients with CTCL conducted in the US which supported the development of the MAVORIC study.[1, 54]

Table 4.3: MAVORIC description

MAVORIC trial	
Design	Phase III multicentre, open-label, randomised, one-way crossover trial
Population	Patients aged ≥18 years with stage IB-IVB relapsed or refractory MF or SS
Intervention	Mogamulizumab 1.0 mg/kg IV on days 1, 8, 15 and 22 of the first cycle, and days 1 and 15 on subsequent cycles.
Comparator	Vorinostat 400 mg orally once daily.
Outcomes specified in the decision problem	Progression-free survival (PFS) assessed by the investigator; time to next treatment (TTNT); next treatment free survival; overall response rate (ORR) assessed by the investigator; duration of response (DOR); time to response (TTR); overall survival (OS); safety; quality of Life (QoL) measured using Skindex-29, FACT-G, EQ-5D-3L, Pruritus Likert scale and ItchyQoL)
Other reported outcomes	Time to treatment failure (TTF); PFS and ORR assessed by blinded independent review (BIR)
Post-hoc analyses outcomes	PFS, ORR and TTNT in patients with advanced disease (stage ≥IIB MF and all SS patients); ORR by disease compartment (skin, blood, lymph nodes, viscera); Skindex-29 and FACT-G – assessment of individual items; PFS and ORR by number of prior therapies; PFS, ORR and DOR by type of prior systemic therapy; ORR and safety after >351 days exposure to mogamulizumab; ORR and TTNT in patients with Stage IB-IIA disease

Based on Table 6 of the CS[1]
BIR = blinded independent review; CS = company submission; DOR = duration of response; EQ-5D-3L = European Quality of Life-5 Dimensions 3 levels; FACT-G = Functional Assessment of Cancer Therapy – General; IV = intravenous; kg = kilogram; MF = mycosis fungoides; mg = milligram; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life; SS = Sézary syndrome; TTF = time to treatment failure; TTNT = time to next treatment; TTR = time to response

ERG comment: As reported in appendix D of the CS the list of studies excluded from the systematic review was not provided.[50] However, the full list of 142 excluded studies was provided in response to request for clarification.[20]

Issues regarding the use of vorinostat, a treatment not licensed in the UK, as a comparator, are discussed in section 3.3 of this report.

4.2.2 Methodology of clinical effectiveness evidence

4.2.2.1 Eligibility criteria

As reported in the CS the eligibility criteria for inclusion in the MAVORIC study specified patients needed to have stage IB-IVB histologically confirmed relapsed or refractory MF or SS and be aged ≥18 years (in Japan, ≥20 years). Furthermore, patients had to have failed at least one previous systemic therapy, have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1 and adequate haematological, hepatic, and renal function.

In contrast, exclusion criteria restricted the entry of patients with large cell transformation, previous mogamulizumab or vorinostat treatment, central nervous system metastasis, active autoimmune disease, clinically significant uncontrolled intercurrent illness, and previous allogeneic transplant. To note, brief

exposure to vorinostat without evidence of progression or toxicity on treatment was allowed with sponsor approval.

The eligibility criteria for MAVORIC trial is summarised in Table 4.4 as reported in the CS.

Eligible participants were randomised 1:1 to either of the following:

- Mogamulizumab (1.0 mg/kg) administered as an intravenous (IV) infusion over at least one hour on days 1, 8, 15 and 22 of the first cycle and on days 1 and 15 of subsequent cycles.
- Vorinostat (400 mg) administered orally once daily with food beginning on day 1.

As stated by the CS, patients who progressed after at least two full treatment cycles of vorinostat or who were unable to tolerate vorinostat despite dose reduction, crossed over to be treated with mogamulizumab.[1]

Details of the sample size calculation and statistical analysis methods for MAVORIC are provided in Table 4.5. Definitions of the outcomes used in the MAVORIC trial are presented in section 4.2.5.

Table 4.4: MAVORIC eligibility criteria

Inclusion criteria	Exclusion criteria
Participants	
• Aged ≥18 years of age in all countries except Japan, where patients had to be ≥20 years of age • Women of childbearing potential must have had a negative pregnancy test within 7 days of receiving study medication • Willing to use appropriate method of contraception • Written informed consent	• Pregnant or lactating • Psychiatric illness, disability or social situation that would compromise the patient's safety or ability to provide consent, or limit compliance with study requirements
Previous or concomitant therapies	
Failed at least one prior course of systemic therapy (e.g. interferon, denileukin diftitox, bexarotene, photopheresis, anti-neoplastic chemotherapy, etc.). Psoralen plus ultraviolet light therapy (PUVA) was not considered a systemic therapy	• Prior treatment with mogamulizumab or vorinostat. Patients who were exposed to vorinostat for a short time, did not progress while on treatment, and did not have intolerable toxicity but were discontinued for another reason (e.g. comorbidity) were permitted to enter the study after discussion with the Medical Monitor • Had any cancer therapy within four weeks of randomization • History of allogeneic or autologous transplant • Systemic corticosteroid use, except to treat an infusion reaction • Topical corticosteroid use, except to treat acute rash • Receiving any immunomodulatory drug for concomitant or intercurrent conditions other than T-cell lymphoma within 4 weeks of treatment

Inclusion criteria	Exclusion criteria
Oncological characteristics	
• Histologically confirmed diagnosis of MF or SS • Patients with MF and a known history of non-complicated staphylococcus colonization/ infection were eligible provided they continued to receive stable doses of prophylactic antibiotics • Stage IB, II-A, II-B, III or IV disease • ECOG performance status of ≤1 • CD4+ cell count >200/mm^3	• Diagnosed with a malignancy in the past 2 years • Clinical evidence of central nervous system metastasis
Comorbidities	
Adequate haematological function: • ANC ≥1,500 cells/µl (≥1,500/mm^3) • Platelets ≥100,000 cells/µl (≥100,000/mm^3) • In patients with known bone marrow involvement, ANC ≥1,000 cells/µl (≥1,000/mm^3) and platelets ≥75,000 cells/µl (≥75,000/mm^3) Adequate hepatic function: • Bilirubin ≤1.5 times the specific institutional ULN, except for patients with Gilbert's syndrome • Aspartate transaminase (AST) and alanine transaminase (ALT) each ≤2.5 x ULN or ≤5.0 x ULN in the presence of known hepatic involvement by CTCL Adequate renal function: • Serum creatinine ≤1.5 x ULN or calculated creatinine clearance >50 ml/min using the Cockcroft-Gault formula	• Known active autoimmune disease (e.g. Graves' disease; systemic lupus erythematosus; rheumatoid arthritis; Crohn's disease; psoriasis) • Significant uncontrolled intercurrent illness including, but not limited to: • Uncontrolled infection requiring antibiotics • Clinically significant cardiac disease (class III or IV of the New York Heart Association [NYHA]) • Unstable angina pectoris • Angioplasty, stenting, or myocardial infarction within 6 months • Uncontrolled hypertension (systolic blood pressure (BP) >160 mmHg or diastolic BP >100 mmHg, found on two consecutive measurements separated by a 1-week period) despite two anti-hypertensive medications • Clinically significant cardiac arrhythmia or uncontrolled diabetes • Known or tests positive for HIV, HTLV-1, hepatitis B or hepatitis C disease • Active herpes simplex or herpes zoster

Based on Table 7 of the CS

ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; CD = cluster of differentiation; CS = company submission; CTCL = cutaneous T-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; HTLV-1 = human T-lymphotropic virus 1; MF = mycosis fungoides; min = minute; mm = millimetre; mmHg = millimetres of mercury; NYHA = New York Heart Association; PUVA = psoralen plus ultraviolet light therapy; SS = Sézary syndrome; ULN = upper limit of normal

Table 4.5: MAVORIC statistical methods

Sample size calculation
The sample-size and analysis of the primary outcome (PFS) was event-driven and 255 PFS events provided 90% power to detect a 50% increase in PFS based on a median PFS of 169 days on vorinostat. It was planned to randomise 317 patients to allow for a loss to follow-up of 10%.
Analysis populations
ITT – all patients randomly assigned to treatment and assigned a study number Efficacy evaluable – had received at least one dose of treatment, had a baseline and at least one post-baseline tumour assessment Safety – all patients who received at least one dose of study drug
Analysis methods
The primary analysis of all efficacy outcomes was based on the ITT population. Primary outcome (PFS assessed by the investigator): Mogamulizumab and vorinostat were compared using a Cox proportional hazards (PH) model adjusted for treatment, disease type, disease stage and region (USA, Japan, and Rest of the World). Groups were also compared using a stratified log-rank test at a one-sided 2.5% significance level. Median PFS was estimated using Kaplan-Meier methods as well as the estimated percentage surviving at six monthly intervals. Patients who withdrew for any reason or who initiated a new anticancer therapy before documented progression were censored at the time of their last efficacy assessment. Pre-specified subgroup analyses for PFS were: disease type; disease stage; blood involvement; region; age group; sex; race and lactate dehydrogenase level. Secondary outcomes: ORR – The difference in the percentage of patients achieving ORR was calculated and the 95% CI for this difference and the percentages per arm were estimated using exact methods. DOR and TTR (investigator assessed) were analysed using Kaplan-Meier methods OS – the analysis of OS used the same analysis methods as for PFS. To investigate the impact of crossover to mogamulizumab on survival estimates, additional analyses using an inverse probability of censoring weighting (IPCW) model, a rank-preserving structural failure time model (RPFST) and a two-stage approach.
Based on Table 7 of the CS and Kim, 2018[52] CI = confidence interval; CS = company submission; DOR = duration of response (time from first complete or partial response until progressive disease or death); IPCW = inverse probability of censoring weighting; ITT = intention-to-treat; PFS = progression-free survival; PH = proportional hazards; ORR = overall response rate; OS = overall survival; RPFST = rank-preserving structural failure time; TTR = time to response (time from randomisation to first confirmed CR or PR); USA = United States of America

ERG comment: Regarding the exclusion of subjects based on previous therapies, it is noted that subjects may have received skin directed treatment, including topicals and radiation within two weeks of randomisation. At the same time, the exclusion of subjects who had received autologous SCT was limited to the 90 days before the pre-treatment visit. More importantly, according to the protocol, subjects that had been previously treated with anti-CD4 antibody or alemtuzumab were eligible for inclusion provided their CD4+ cells were 200/mm^3 or higher.

Exceptions must also be noted in the exclusion of malignancies in the previous two years. These were for subjects with non-melanoma skin cancers; melanoma in situ; localised cancer of the prostate with current prostate-specific antigen of < 0.1 ng/ml; treated thyroid cancer; cervical carcinoma in situ or ductal/lobular carcinoma in situ of the breast within the previous two years and no current evidence of disease were eligible for enrolment. Similarly, subjects with history of large cell transformation (LCT)

but without current aggressive disease and no current evidence of LCT on pathology in skin or lymph nodes were also eligible for inclusion.

In addition to this, it is noted subjects with rapidly progressive malignant disease may have been enrolled at a later point prior discussion with the medical monitor. However, figures for these patients appear to have not been provided in the CS.[1]

The sample size calculation and analysis methods, including those used to assess the impact of crossover to mogamulizumab on overall survival, used appropriate methods and the ERG does not have any concerns.

The ERG has some concerns regarding the use of vorinostat as a comparator, see section 3.3.

4.2.2.2 Study flow

As explained in the CS, between 12 December 2012 and 29 January 2016, 372 participants across 61 sites in 11 countries (of which 16 were in Europe, including three in England) were randomly assigned to receive mogamulizumab (n=186) or vorinostat (n=186).[1] Of note, in the response to request for clarification the number sites was reported to be 59.[20]

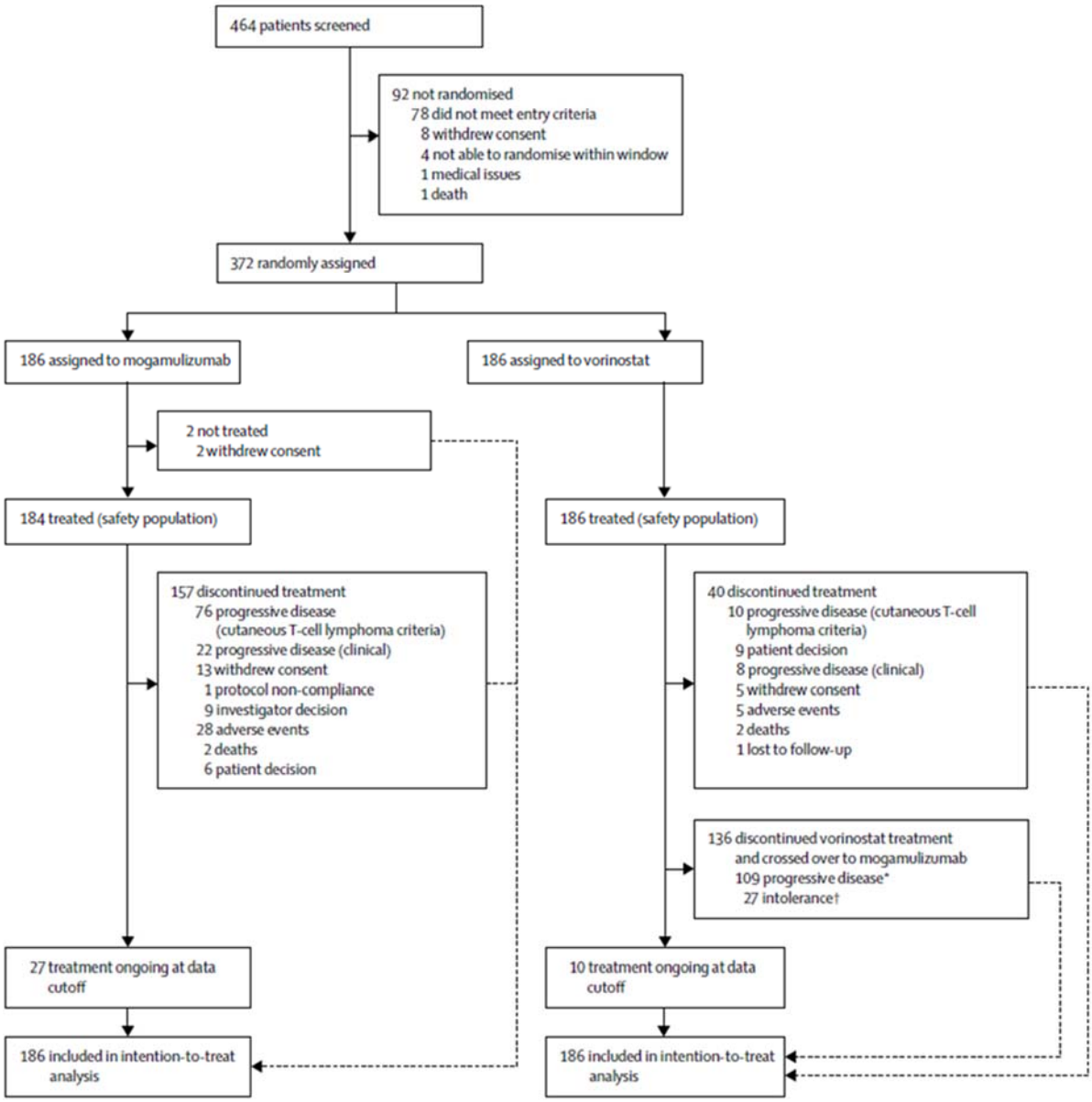
Overall, 204 participants with MF (54.8%) and 168 participants with SS (45.2%) were included. The safety population contained 370 participants including two who were randomised to mogamulizumab but did not receive the study treatment.[1]

Forty (21.5%) vorinostat patients and 157 (84.4%) mogamulizumab patients discontinued treatment. A total of 136 (73.1%) of the patients randomised to vorinostat crossed over to receive mogamulizumab, 109 due to disease progression and 27 due to reported intolerance. Of these 136 patients, three did not receive mogamulizumab due to adverse events unrelated to the vorinostat so 133 patients form the crossover population. The CONSORT flow-chart is presented in Figure 4.2.

The median duration of treatment exposure was 170 days [redacted] for mogamulizumab; 84 days [redacted] for vorinostat and [redacted] days [redacted] on mogamulizumab for the crossover group. Further details are given in Table 4.6.

The data in the section dedicated to the clinical effectiveness results of the MAVORIC trial are reported to be based on the 31 December 2016 cut-off unless otherwise stated.

Figure 4.2: MAVORIC participant flow-chart



Based on Figure D-2 of the CS appendices[50]

* of the 109 patients who crossed over to mogamulizumab because of disease progression, six had worsening disease or symptoms that did not meet the criteria for progression according to cutaneous T-cell lymphoma response criteria (clinical progression); † patients crossed over due to the following toxicities: fatigue (five patients); pulmonary embolism (four patients); thrombocytopenia (three patients); diarrhoea (three patients); asthenia (two patients); deep vein thrombosis (one patient); peripheral neuropathy (one patient); myalgia (one patient); blood creatinine increased (one patient); sepsis syndrome (one patient); chronic renal failure (one patient); dysgeusia (one patient); emotional distress (one patient); dermatitis (one patient); and skin rash (one patient)

CS = company submission

Table 4.6: Summary of treatment exposure in MAVORIC

	Randomised Treatment Period		Crossover
	Mogamulizumab (n=186)	**Vorinostat (n=186)**	**Mogamulizumab (n=136)[a]**
Extent of exposure (days)[b]			
Median (range)	170.0 [redacted]	84.0 [redacted]	[redacted]
Mean (SD)	245.2 (234.48)	144.3 (172.48)	[redacted]
Number of cycles initiated[c], n (%)			
Median (range)	[redacted]	[redacted]	[redacted]
1 cycle	[redacted]	[redacted]	[redacted]
2 cycles	[redacted]	[redacted]	[redacted]
3 cycles	[redacted]	[redacted]	[redacted]
4 cycles	[redacted]	[redacted]	[redacted]
5 cycles	[redacted]	[redacted]	[redacted]
6 cycles	[redacted]	[redacted]	[redacted]
7 cycles	[redacted]	[redacted]	[redacted]
8 cycles	[redacted]	[redacted]	[redacted]
9 cycles	[redacted]	[redacted]	[redacted]
10 cycles	[redacted]	[redacted]	[redacted]
11 cycles	[redacted]	[redacted]	[redacted]
12 cycles	[redacted]	[redacted]	[redacted]
13 cycles	[redacted]	[redacted]	[redacted]
Mogamulizumab infusions administered, median (range)	[redacted]	[redacted]	[redacted]
Dose intensity[d] (%), median (range)	97.49 [redacted]	95.12 [redacted]	[redacted]

Based on Table 18 of the CS[1]
[a] exposure results are based on 133 patients who crossed over to mogamulizumab and were treated
[b] 10 patients randomised to vorinostat were ongoing at data cut-off and had missing last dose date for vorinostat during the randomised treatment period. The last dose date has been imputed using the patient's last visit date during randomised treatment period
[c] a patient is considered to have initiated treatment for a cycle if the patient received any assigned study drug for that cycle
[d] % dose intensity of mogamulizumab was calculated as 100*(total actual dose/total duration of treatment/7)/(total planned dose/total planned weeks). % dose intensity of vorinostat was calculated as 100*(sum of [patient's actual dosage per dosing interval*actual days exposed per dosing interval])/(400*expected dose days), where expected dose days is last dose date - first dose date + 1.
CS = company submission; N/A = not applicable; SD = standard deviation

ERG comment: The design of the MAVORIC trial is defined as *"one-way crossover"*.[1] This meant that participants receiving the control treatment vorinostat could cross over to mogamulizumab if they progressed after at least two full cycles of vorinostat, or if they were unable to tolerate vorinostat despite dose reduction. This was to ensure that vorinostat patients were not discontinued prematurely and drop out of the trial. Allowing for crossover means that outcomes measured after progression such as overall survival may be biased by the fact that 73% of the vorinostat patients changed treatment. Additional analyses of OS accounting for crossover were performed, see section 4.2.5.3.

As the number of vorinostat cycles participants would have received was dependant on their progression or tolerance to vorinostat, the point at which they were switched to mogamulizumab varied. This is reflected in the wide range of vorinostat cycles that participants received (1-36). However, no analysis was reported on the potential impact that the number of vorinostat cycles may have had on the outcomes. Therefore caution needs to be applied in the interpretation of the results.

4.2.3 Quality assessment of the clinical effectiveness evidence

The quality assessment of MAVORIC is presented in Table 4.7.

Table 4.7: Quality assessment of MAVORIC

Study question	How is the question addressed in the study? (as reported in the CS)	Grade (Yes/No/Not Clear/ NA)	ERG comment
Was randomisation carried out appropriately?	Randomisation was conducted in a 1:1 ratio and was stratified by disease type (MF or SS) and disease stage (IB/II or III/IV).	Yes	Agreement
Was the concealment of treatment allocation adequate?	Randomisation was performed using a CTIVRS.	Yes	Agreement
Were the groups similar at the outset of the study in terms of prognostic factors?	Patient demographics were generally similar between treatment arms.	Yes	Agreement
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Open-label study design. Blinded independent review was also carried out to account for any potential bias.	No	Agreement
Were there any unexpected imbalances in dropouts between groups?		No	Agreement
Is there any evidence to suggest that the authors measured more outcomes than they reported?		No	Agreement
Did the analysis include an intention-to-treat analysis? If so, was the appropriate and were appropriate methods used to	The ITT population was used for the primary analysis. Standard censoring methods were used for the primary analysis.	Yes	Agreement

Study question	How is the question addressed in the study? (as reported in the CS)	Grade (Yes/No/Not Clear/ NA)	ERG comment
account for missing data?			
Based on Table 10 of the CS[1] CS = company submission; CTIVRS = Clin Trak Interactive Voice/Web Response System; ERG = Evidence Review Group; ITT = intention-to-treat; MF = mycosis fungoides; SS = Sézary syndrome			

ERG comment: The company noted that care providers, participants, and outcome assessors were not blinded to treatment allocation due to the open-label study design.[1] The primary analysis of PFS and response was based on investigator assessment as the investigators could physically examine the patients, but results based on a blinded independent review were also reported for comparison purposes.

4.2.4 Baseline characteristics

According to section B.2.3 of the CS, 58% of MAVORIC trial participants were male and 70% were white.[1] The median age was 63.5 years for mogamulizumab and 65.0 years for vorinostat. The median time from initial diagnosis was 41 months for mogamulizumab and 35.4 months for vorinostat overall. Stage IIB or higher accounted for 77% of the population and measurable blood involvement was 66% across both groups. Regarding the underlying disease, 54.8% of participants had mycosis fungoides (MF) and 45.2% had Sezary syndrome (SS). Table 4.8 illustrates the baseline characteristics as reported in the CS.

The median number of previous skin-directed therapies was three for both groups. Most of the randomised participants (66.8%) had not responded to their most immediate prior therapy[22] The CS also notes that all patients except one (in the vorinostat arm) had failed at least one prior systemic therapy.[1]

Table 4.8: MAVORIC baseline characteristics

Baseline characteristics	Mogamulizumab (n=186)	Vorinostat (n=186)
Median age, years (range)	63.5 ([redacted])	65.0 ([redacted])
<65 years, n (%)	99 (53.2)	89 (47.8)
Male, n (%)	109 (58.6)	107 (57.5)
Race, n (%)		
White	125 (67.2)	135 (72.6)
Black or African American	[redacted]	[redacted]
Other	[redacted]	[redacted]
Not reported	24 (12.9)	25 (13.4)
Underlying disease		
Mycosis fungoides	105 (56)	99 (53)
Sézary syndrome	81 (44)	87 (47)
ECOG performance status[a], n (%)		
0	106 (57.0)	104 (55.9)
1	78 (41.9)	82 (44.1)

Baseline characteristics	Mogamulizumab (n=186)	Vorinostat (n=186)
Time from initial diagnosis (months), median (IQR)[a]	41.0 (17.4–78.8)	35.4 (16.2–68.2)
Current clinical stage, n (%)		
IB–IIA	36 (19.4)	49 (26.3)
IIB	32 (17.2)	23 (12.4)
IIIA-IIIB	22 (11.8)	16 (8.6)
IVA_1	73 (39.2)	82 (44.1)
IVA_2	19 (10.2)	12 (6.5)
IVB[b]	4 (2.2)	4 (2.2)
Current sites of disease, n (%)		
Skin	[redacted]	[redacted]
Nodes	[redacted]	[redacted]
Viscera	[redacted]	[redacted]
Blood	[redacted]	[redacted]
Other (including bone marrow)	[redacted]	[redacted]
Blood involvement, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Previous CTCL therapies[c], n (%)		
Skin-directed therapies		
PUVA	[redacted]	[redacted]
Topical steroid	[redacted]	[redacted]
Bexarotene-topical	[redacted]	[redacted]
Radiotherapy	52 (28.0)	55(30.0)
Systemic therapies n (%)		
Alemtuzumab	19 (10)	16 (9)
Bexarotene-oral	107 (57.5)	110 (59.1)
Interferon-alpha	81 (43.5)	94 (50.5)
Methotrexate	[redacted]	[redacted]
ECP	[redacted]	[redacted]
Romidepsin	45 (24.2)	32 (17.2)
Nitrogen mustard	[redacted]	[redacted]
Doxorubicin HCL liposome	[redacted]	[redacted]
Pralatrexate	14 (7.5)	13 (7.0)
Carmustine	[redacted]	[redacted]
Brentuximab vedotin	16 (8.6)	4 (2.2)
Denileukin diftitox	[redacted]	[redacted]
Chlorambucil	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]

Baseline characteristics	Mogamulizumab (n=186)	Vorinostat (n=186)
IL-12	[redacted]	[redacted]
Other (skin-directed and systemic) n (%)	[redacted]	[redacted]
Median prior systemic therapies (IQR) n (%)	3.0 (2–5)	3.0 (2–5)
CR or PR to last prior CTCL therapy n (%)	[redacted]	[redacted]

Based on Table 8 of the CS,[1] Table P-1 of the CS Appendices,[50] and the response to request for clarification[20]
a Time from initial diagnosis (months) is calculated as (date of first dose of study medication - date of initial diagnosis + 1)/30. If the month and year of the diagnosis are provided but 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.
CR = complete response; CS = company submission; CTCL = cutaneous T cell lymphoma; ECOG = Eastern Cooperative Oncology Group; ECP = extracorporeal photopheresis; HCL = hydrochloride; IL = interleukin; IQR = interquartile range; PR = partial response; PUVA = psoralen plus ultraviolet light therapy

ERG comment: Assessing the generalisability of the results from MAVORIC (section B.2.13.1 of the CS), the CS compared the participants in MAVORIC with the population of the PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) dataset.[1] It concluded that *"MAVORIC patients are generally comparable to the PROCLIPI population, supporting the view that the MAVORIC population is generalizable to UK clinical practice"*.[1] However, it should be noted that PROCLIPI recruited participants from *"44 specialist centres worldwide"*, i.e. there is some uncertainty regarding the generalisability to UK clinical practice.[1]

In addition, the CS stated that the Haematological Malignancy Research Network (HMRN) dataset was also assessed but that *"…a number of legal and ethical issues prevented the dataset from being used within this submission: the progression data available in HMRN is very different to that in the MAVORIC study, a sharing agreement is not in place between HMRN and the manufacturer making data-sharing complicated and, as HMRN is an academic institution, non-commercial priorities meant the relevant data was not available in time"*.[1]

In response to the request for clarification, the company explained that the generalisability of prior treatments the participants received in the MAVORIC trial is comparable to the UK population as *"supported by a key clinical expert"*.[20]

According to the CS, 8.6% and 2.2% of participants receiving mogamulizumab and vorinostat, respectively, previously received BV thus limiting the number of participants that could have been determined to be refractory to BV. In order to meet the definition of population given in the decision problem addressed by the company (*"Adults with advanced mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma (i.e. stage ≥IIB MF and all SS) following at least one prior systemic therapy who are clinically ineligible for or refractory to treatment with brentuximab vedotin (BV)"*), a proportion of participants had to be assumed to be ineligible for treatment with BV. In the request for clarification, the ERG questioned the criteria which were employed to determine eligibility to BV.[19]

In response, the company stated that *"there is no single criterion or set of criteria that can be applied to determine eligibility for brentuximab vedotin (BV) treatment, or to predict patients that may be refractory to such treatment, prior to administration. Nonetheless, this is a patient group identified through individual patient assessment and informing treatment decisions in clinical practice, and clinical opinion is that the results of the MAVORIC trial are generalisable to this group"*.[20] Regarding CD 30, the response stated that *"although CD30 status could be considered a potential marker for BV*

eligibility (as BV is only licensed for use in CD30+ patients), CD30 is not a predictive factor for treatment response to mogamulizumab (or vorinostat), and therefore CD30 status was not a pre-specific subgroup of interest to the MAVORIC trial".[20]

Overall, the number of participants considered to be *"ineligible for BV"* as well as how this status was determined remains unclear.

The ERG notes how the inclusion of participants with complete or partial response appears opposed to the definition of the population originally stated in the trial, i.e. *"relapsed or refractory".*[1] However, this may still be interpreted in line with the scope, i.e. *"following at least one prior systemic therapy".*[17]

4.2.5 Efficacy outcomes

This ERG report covers the results defined in the NICE final scope (see section 3), namely:

- Progression-free survival (see section 4.2.5.1)
- Response rates (see section 4.2.5.2)
- Overall survival (see section 4.2.5.3)
- Time to next treatment (see section 4.2.5.4)
- Health-related quality of life (see section 4.2.5.5)
- Adverse effects of treatment (see section 4.2.6)

The CS reported on two additional outcomes, time to treatment failure as well as next treatment-free survival, which were analysed post-hoc. These outcomes were not covered in this report.

Relevant results from subgroup analyses are reported in section 4.2.5.6.

In response to request for clarification, the company provided definitions of the outcomes used in the MAVORIC trial (Table 4.9).[20]

Table 4.9: Outcomes used in the MAVORIC trial

Outcome	Definition
Progression-free survival (PFS)	The primary efficacy variable was PFS based upon the assessment by the Investigator, defined as the time from the day of randomisation to a treatment arm until documented PD or death due to any cause. Documented disease progression included disease progression in any compartment based on the Investigator's assessment per CTCL response criteria or documented disease progression reported during the follow-up period. The date of progression was the earliest date at which documented disease progression could be declared. As per the response criteria used (Olsen 2011),[3] for subjects who exhibited conditions of PD but continued on study treatment due to a questionable clinical impression, the subject was not considered to have progressed unless PD was confirmed at least four weeks after the date of the initial questionable PD. In this case, the initial date was used as the date of PD. If the questionable clinical impression of PD was not confirmed, the subject was not deemed to have documented PD at the time of initial questionable PD.
Overall response rate (ORR)	ORR was defined as the proportion of subjects who were responders (confirmed CR or PR) based on the Investigator's assessment. Confirmed CR or PR was defined as documented CR or PR based on the Investigator's assessment of overall response per Global Composite Response Score that was subsequently confirmed by two or more consecutive observations for a minimum of four weeks. In the case where a subject had successive visit responses of CR, N/A, CR, then, as long as the time between the two visits of CR was greater than four

Outcome	Definition
	weeks, the subject was defined as a responder. Subjects lacking valid data to assign a response status were included in the denominator for response rate calculation based on the ITT Set and, hence, were considered non-responders.
Best overall response	Best overall response was defined as the best response recorded across all time points from the start of treatment until disease progression/recurrence or end of treatment. The subject's best response assignment was dependent on the achievement of both measurement and confirmation criteria.
Duration of response (DOR)	For subjects with confirmed response (CR or PR), DOR was defined as the time from the date that criteria for CR/PR (whichever was first recorded) were met until the first date that PD or death was objectively documented. Subjects who did not relapse were censored at the day of their last tumour assessment (from any compartment).
Time to response (TTR)	For subjects who achieved a best overall response of CR or PR during the randomised treatment period, the TTR was summarised descriptively. TTR was defined as the time from the date of randomisation to the date that criteria for CR/PR (whichever was first recorded) were first met. Subjects who did not respond over the course of the study had a missing value for TTR.
Overall survival (OS)	OS was defined as the time from the date of randomisation until the date of death of the subject due to any cause. Subjects who were still alive at the end of the survival follow-up period or were lost to follow-up at the time of analysis were censored on the last date the subject was known to be alive.
Time to next treatment (TTNT)	TTNT was defined as time from the start date of randomised treatment (end date of mogamulizumab treatment for crossover patients) to the start date of next systemic treatment (excluding topical steroids or focal radiation).
Time to treatment failure (TTF)	TTF was defined as the time from the day of randomisation to a treatment arm until discontinuation of randomised treatment due to any reason except for those subjects who discontinued randomised treatment due to one year on treatment with a CR. Subjects who experienced an overall CR and discontinued randomised treatment after one year of treatment were censored at the last dose date of the randomised treatment. Subjects who were randomised but did not take any study drug were censored at the last documented visit date.
Skindex-29 Score	The Skindex-29 instrument measures the effect of skin disease on health-related quality of life (Chren 1996).[55] It is composed of 29 items assessing three domains: emotions, symptoms, and functioning. The items are scored on a five-point Likert-type scale (never, rarely, sometimes, often, all the time). Responses to each item are transformed to a linear scale of 100 (never=0, rarely=25, sometimes=50, often=75, all the time=100) for the purpose of scale score calculation. A scale score is the mean of a subject's responses to the items in a given scale and the composite Skindex-29 score is calculated as the average of the three scale scores to measure the overall impact on quality of life. Higher scores indicate a higher impact of skin disease.
FACT-G total score	The FACT-G is a validated instrument for assessing health-related quality of life in subjects with cancer (Webster 2003).[56] The FACT-G consists of 27 items in the following 4 domains: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). The total FACT-G score is obtained by summing individual subscale scores. Response scores on negatively-phrased questions are reversed before summing. Higher scores for the scales and subscales indicate better quality of life.
EQ-5D-3L index score	The EuroQol/EQ-5D is a standardised, reliable and validated instrument to measure health-related quality of life. The EQ-5D self-reported questionnaire

Outcome	Definition
	includes the EQ-5D descriptive system and a visual analogue scale (VAS). The EQ-5D 3 level version (EQ-5D-3L) descriptive system comprises the following dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The EQ-5D index score is calculated based on the descriptive system using a set of item weights (value sets) to derive a single score ranging from -0.109 to 1, with 1 representing full health. The value sets for the US were used for the calculation of the EQ-5D index score (Shaw 2005).[57] The EQ-5D self-reported questionnaire also includes a visual analogue scale (VAS), which records the respondent's self-rated health status on a graduated (0-100) scale, with 100 = best imaginable health state and 0 = worst imaginable health state.
Based on Table 12 of the response to request for clarification[20] CR = complete response; CTCL = cutaneous T-cell lymphoma; DOR = duration of response; EQ-5D = European Quality of Life-5 Dimensions; EQ-5D-3L = European Quality of Life-5 Dimensions 3 levels; EWB = emotional well-being; FACT-G = Functional Assessment of Cancer Therapy – General; ITT = intention-to-treat; FWB = functional well-being; N/A = not applicable; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; PWB = physical well-being; SWB = social/family well-being; TTF = time to treatment failure; TTNT = time to next treatment; TTR = time to response; VAS = visual analogue scale	

4.2.5.1 Progression-free survival

Progression free survival (PFS) as assessed by the investigator was defined as the primary endpoint of the MAVORIC study. At the time of data cut-off (31 December 2016), 110 PFS events occurred in the mogamulizumab arm and 131 in the vorinostat arm.[1] The median PFS with mogamulizumab (7.7 months, 95% confidence interval (CI) 5.67 to 10.33 months) was significantly greater than with vorinostat (3.1 months, 95% CI 2.87 to 4.07 months) with a corresponding hazard ratio (HR) of 0.53 (95% CI 0.41 to 0.69). These results are also supported by the comparison of the point estimates for the proportion of patients without progression of disease at 6, 12, 18 and 24 months (Table 4.10).

According to the CS appendices, the median PFS for those participants who crossed to mogamulizumab from vorinostat (n=133) was 8.9 months (95% CI 5.4 to 14.8 months) and for all the participants who received mogamulizumab (n=319) was 8.4 months (95% CI 6.1 to 10.3 months).[50]

Table 4.10 shows the results for PFS assessed by both the investigator and blinded independent review (BIR) while the Kaplan-Meier (KM) plot is shown in Figure 4.3.

Table 4.10: Progression-free survival results

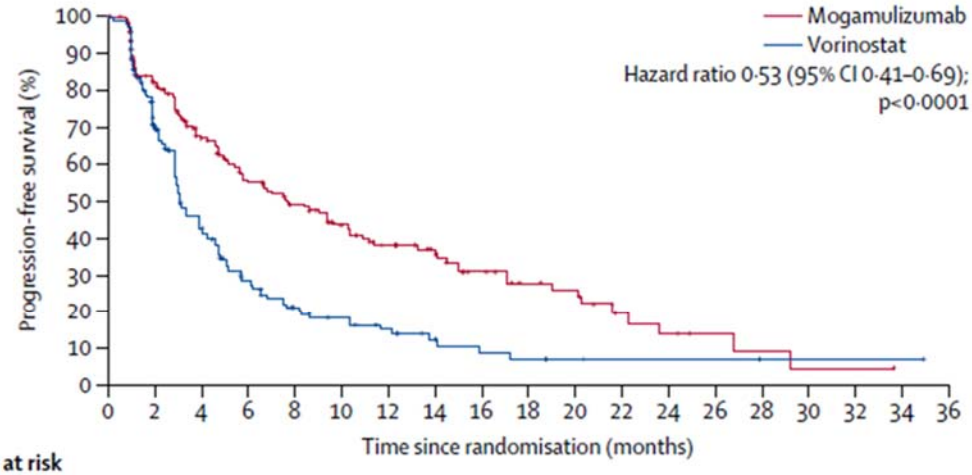
	By investigator		By blinded independent review	
	Mogamulizumab (n=186)	**Vorinostat (n=186)**	**Mogamulizumab (n=186)**	**Vorinostat (n=186)**
Patients with PFS event, n (%)	110 (59.1)	131 (70.4)	[redacted]	[redacted]
Progressive disease	104 (55.9)	128 (68.8)	[redacted]	[redacted]
Death	6 (3.2)	3 (1.6)	[redacted]	[redacted]
Patients censored n (%)	76 (40.9)	55 (29.6)	[redacted]	[redacted]
PFS (months)				
Median (95% CI)	7.70 (5.67 to 10.33)	3.10 (2.87 to 4.07)	6.70 (5.63 to 9.37)	3.83 (3.00 to 4.70)
HR (95% CI)	0.53 (0.41, 0.69)		0.64 (0.49, 0.84)	
Log rank P-value	<0.0001		0.0007	
Q1[a]	2.9	1.9	[redacted]	[redacted]
Q3[a]	20.1	6.6	[redacted]	[redacted]
Percentage of patients alive without progressive disease at each 6-month interval (95% CI)				
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 11 of the CS[1] and Table O-2 of the CS appendices[50]

[a] Q1 is after 25% of patients had progressed or died, Q3 is after 75% of patients had progressed or died.

CI = confidence interval; CS = company submission; HR = hazard ratio; PFS = progression-free survival; Q = quartile

Figure 4.3: Kaplan-Meier plot for PFS results (investigator-assessed, ITT population)



Number at risk (number censored)																			
Mogamulizumab	186	138	100	77	65	50	39	32	22	16	14	7	5	3	2	1	1	0	0
	(0)	(16)	(30)	(36)	(40)	(49)	(53)	(59)	(64)	(68)	(69)	(73)	(73)	(75)	(75)	(75)	(75)	(76)	(76)
Vorinostat	186	111	61	36	23	18	13	8	5	4	3	2	2	2	1	1	1	1	0
	(0)	(23)	(33)	(39)	(43)	(45)	(47)	(50)	(51)	(51)	(52)	(53)	(53)	(53)	(54)	(54)	(54)	(54)	(55)

Based on Figure 5 of the CS[1]
CI = confidence interval; CS = company submission; ITT = intention-to-treat; PFS = progression-free survival

ERG comment: The analysis of PFS showed a significant reduction in the risk of progression of 47% (95% CI 31 to 59%) with mogamulizumab compared to vorinostat. The results of the investigator and independent review PFS assessments were similar.

The ERG consulted a clinical expert about the choice of outcome measures, specifically the choice of TTNT or PFS. Her response stated that the *"assessment of progression in these patients is difficult regardless whether you use PFS or TTNT, as you sometimes have variable skin symptoms, some areas get better, other get worse. Normally you would only start a different therapy if there definite progression, so it is a more stringent or relevant effectivity assessment"*.[49] It might therefore be concluded that assessment of progression is associated with some uncertainty.

4.2.5.2 Response rate

The results for the overall response rate (ORR), best overall response, duration of response (DOR) and time to response (TTR) are presented in section B.2.6.2 of the CS as well as in appendix O.1 of the CS.[1, 50]

The CS reported a risk difference (RD), erroneously reported as rate ratio in the CS, of 23.1 (95% CI 12.8 to 33.1%) for the ORR of mogamulizumab relative to vorinostat as assessed by the investigator. Similarly, the analysis by BIR also favoured mogamulizumab with a difference of 19.4% (95% CI 9.0 to 29.4%).[1]

Results for ORR, DOR and TTR are presented in Table 4.11. The median DOR was 14.1 months with mogamulizumab and 9.1 months with vorinostat but no statistical analysis was performed.

The response rate (ORR, DOR and TTR) was also evaluated by disease compartment by the investigator. The results are reported in Table 4.12 and all analyses of ORR favour mogamulizumab. Forty-four percent of patients receiving mogamulizumab had at least a 50% improvement in skin response compared to 22% in the vorinostat arm.

Table 4.11: Response rates results

	By investigator		Mogamulizumab after crossover	By BIR	
	Mogamulizumab (n=186)	Vorinostat (n=186)	(n=133)	Mogamulizumab (n=186)	Vorinostat (n=186)
ORR (confirmed CR + PR), n (% [95% CI])	52 (28.0 [21.6 to 35.0])	9 (4.8 [2.2 to 9.0])	41 (31.0 [redacted]	43 (23.0 [17.3 to 29.8])	7 (4 [1.5 to 7.6])
ORR risk difference (95% CI)	23.1 (12.8 to 33.1)		NR	19.4 (9.0 to 29.4)	
DOR (months), median (IQR)	14.1 (8.4–19.2)	9.1 (5.6–NE)	NR	54 (29.0)	13 (7.0)
TTR (months), median (IQR)	3.3 (2.0–6.4)	5.1 (2.9–8.5)	NR	3 (1.6)	0
Best overall response (CR + PR), n (%)	65 (34.9)	12 (6.5)	[redacted]	[redacted]	[redacted]
Confirmed CR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CR, n (%)	5 (2.7)	0	[redacted]	[redacted]	[redacted]
Confirmed PR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stable disease, n (%)	80 (43.0)	115 (61.8)	[redacted]	[redacted]	[redacted]
Progressive disease, n (%)	1 (0.5)	6 (3.2)	[redacted]	[redacted]	[redacted]
Not accessible, n (%)	40 (21.5)	53 (28.5)	[redacted]	[redacted]	[redacted]

Based on Table 12 of the CS,[1] Table O-1 of the CS appendices,[50] and the CSR[22]

BIR = blinded independent review; CI = confidence interval; CR = complete response; CS = company submission; CSR = clinical study report; DOR = duration of response; IQR = interquartile range; NR = not reported; ORR =overall response rate; PR = partial response; TTR = time to treatment response

Table 4.12: Response rate by disease compartment: ITT population

Response by compartment	Mogamulizumab	Vorinostat
Overall ORR (confirmed CR + PR)	**(n=186)**	**(n=186)**
n (% [95% CI])[a]	52 (28.0 [21.6 to 35.0])	9 (4.8 [2.2 to 9.0])
Skin	**(n=186)**	**(n=186)**
ORR (confirmed CR + PR), n (%)	78 (41.9)	29 (15.6)
P-value	[redacted]	
DOR (months), median (range)	20.6 (11.2–NE)	10.7 (4.8–NE)
TTR (months), median (range)	3.0 (1.9–4.7)	2.7 (1.1–5.6)
Blood	**(n=122)**	**(n=123)**
ORR (confirmed CR + PR), n (%)	83 (68.0)	23 (18.7)
P-value	[redacted]	
DOR (months), median (range)	25.5 (15.9–NE)	NE
TTR (months), median (range)	1.1 (1.0–1.2)	1.9 (1.0–2.1)
Lymph nodes	**(n=124)**	**(n=122)**
ORR (confirmed CR + PR), n (%)	21 (16.9)	5 (4.1)
P-value	[redacted]	
DOR (months), median (range)	15.5 (15.5–15.5)	NE
TTR (months), median (range)	3.3 (2.8–6.8)	2.9 (1.1–8.5)
Viscera	**(n=3)**	**(n=3)**
ORR (confirmed CR + PR), n (%)	0 (0)	0 (0)

Based on Table 13 of the CS[1] and Table 16 of the response to request for clarification[20]
[a] Footnote included in the original source but not reported by the company
CI = confidence interval; CR = complete response; CS = company submission; DOR = duration of response; ITT = intention-to-treat; NE = not estimable; ORR = overall response rate; PR = partial response; TTR = time to response

In section B.2.13.1 of the CS, the company highlighted that the response to vorinostat during MAVORIC was lower than expected.[1] This is attributed to the fact the skin-only response for vorinostat was 12.4% (approximately half of the result in the registrational trial) and that in the MAVORIC study, response rate was based upon the global composite response assessment whilst in the registrational trial this was primarily based on the skin response only.[1] The company explained that potential reasons include *"advances in, and increasing familiarity with, skin assessment techniques, changes in assessment criteria, and very large differences in size and number of sites and design of the Phase III versus Phase II studies"*.[1]

ERG comment: In the request for clarification, the ERG asked for other potential differences between the phase II and phase III studies regarding the patients treated with mogamulizumab.[19]

In response, the company provided a summary of response rates by disease compartment for mogamulizumab-treated patients only (Table 4.13).[20] The mogamulizumab participants reported a lower response in blood and lymph nodes but a similar response in the skin compartment, which indicates that the effectiveness of mogamulizumab according to the trial data is probably conservative.

Table 4.13: Summary of response rate by disease compartment for mogamulizumab-treated patients

Response by compartment for patients treated with mogamulizumab	MAVORIC	Phase I/II study
Skin	**(n=186)**	**(n=38)**
ORR (confirmed CR + PR), n (%)	78 (41.9)	16 (42.1)
Blood	**(n=122)**	**(n=19)**
ORR (confirmed CR + PR), n (%)	83 (68.0)	18 (94.7)
Lymph nodes	**(n=124)**	**(n=28)**
ORR (confirmed CR + PR), n (%)	21 (16.9)	7 (25.0)
Viscera	**(n=3)**	**(n=N/A)**
ORR (confirmed CR + PR), n (%)	0 (0)	NR
Based on Table 16 of the CS[1] and the response to request for clarification[20] CR = complete response; CS = company submission; N/A = not applicable; ORR = overall response rate; PR = partial response		

4.2.5.3 Overall survival

Overall survival (OS) was an exploratory outcome of the MAVORIC trial. Updated OS results using a data cut-off of 2 March 2019 were provided in the appendices of the CS and the clarification letter response.[20, 50] MAVORIC was not powered to estimate OS and maturity was not achieved. Therefore, there is some uncertainty associated with the OS results.

The primary analyses excluded patients who had received an allogenic stem cell transplant (aSCT). The ERG requested OS results including aSCT patients although the company stated that the analysis including these patients is likely to be affected by informative censoring (post-censoring survival is different to patients not receiving an aSCT.[19, 20] These results are presented in Table 4.14 and the KM curve for OS for the primary analysis is in Figure 4.4 and for the population including stem cell transplant (SCT) in Figure 4.5. The median OS was [redacted] months for mogamulizumab and [redacted] months for vorinostat with a corresponding HR of [redacted] showing no statistically significant difference in OS.

Additional analyses of the OS were also performed, see Table 4.14. These analyses used IPCW adjustment and two-stage adjustment in order to adjust for the impact on OS of the 133 vorinostat patients who crossed over to mogamulizumab during the trial. Although these analyses had HRs which were more favourable to mogamulizumab none of the analyses of OS showed statistically significant differences between treatments.

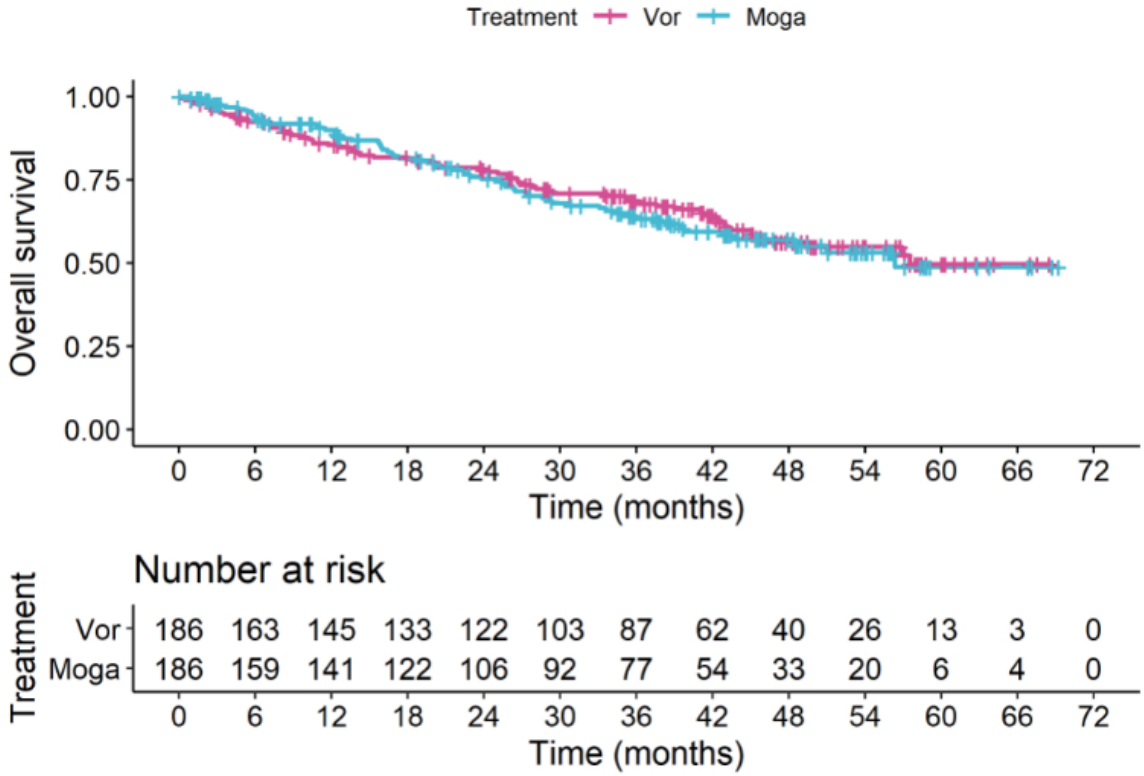
Table 4.14: Overall survival results

	Mogamulizumab (n=186)	Vorinostat (n=186)
OS results without crossover adjustment		
OS (months), median (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
OS results with IPCW adjustment		
OS (months), median (95% CI)	[redacted]	[redacted]

	Mogamulizumab (n=186)	Vorinostat (n=186)
Hazard ratio (95% CI)	[redacted]	
OS results with two-stage adjustment		
OS (months), median (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
OS results including aSCT		
OS (months), median (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
OS results including aSCT with IPCW adjustment		
OS (months), median (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
OS results including aSCT with two-stage adjustment		
OS (months), median (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	

Based on Tables 17, 19, and 21 of CS appendix V[58] and Tables 17, 19 and 21 of appendix 3 of the response to the request for clarification[59]
Note: Hazard ratios were adjusted for disease stage, disease type and region
aSCT = allogenic stem cell transplant; CI = confidence interval; CS = company submission; IPCW = inverse probability of censoring weighting; NE = not estimable; OS = overall survival

Figure 4.4: KM plot for OS results (2 March 2019)



Based on Figure O-O-1 of the CS appendices[50]

CS = company submission; KM = Kaplan-Meier; Moga = mogamulizumab; OS = overall survival; Vor = vorinostat

Figure 4.5: KM plot for OS results including aSCT

Based on Figure 41 of appendix 3 of the response to the request for clarification[59]
aSCT = allogenic stem cell transplant; KM = Kaplan-Meier; KW-0761 = mogamulizumab; OS = overall survival

ERG comment: In the request for clarification, the ERG asked the company for an OS analysis that included patients who received aSCT.[19] In their interpretation of these results (Table 4.14), the company highlighted how these analyses were affected by informative censoring (i.e. the reason for censoring could be related to outcome as patients receiving aSCT are likely to have a different survival to those not receiving it). Due to this aSCT patients were excluded from the OS analysis and their survival was estimated based on external data (for use in the economic model) as the company stated that an analysis of OS treating censoring as uninformative may be biased due to longer survival in those patients receiving aSCT (25 patients received aSCT and four died).

The ERG notes how the Food and Drug Administration (FDA) has highlighted the potential complications of aSCT after mogamulizumab within the warning and precautions to be considered by prescribers.[60]

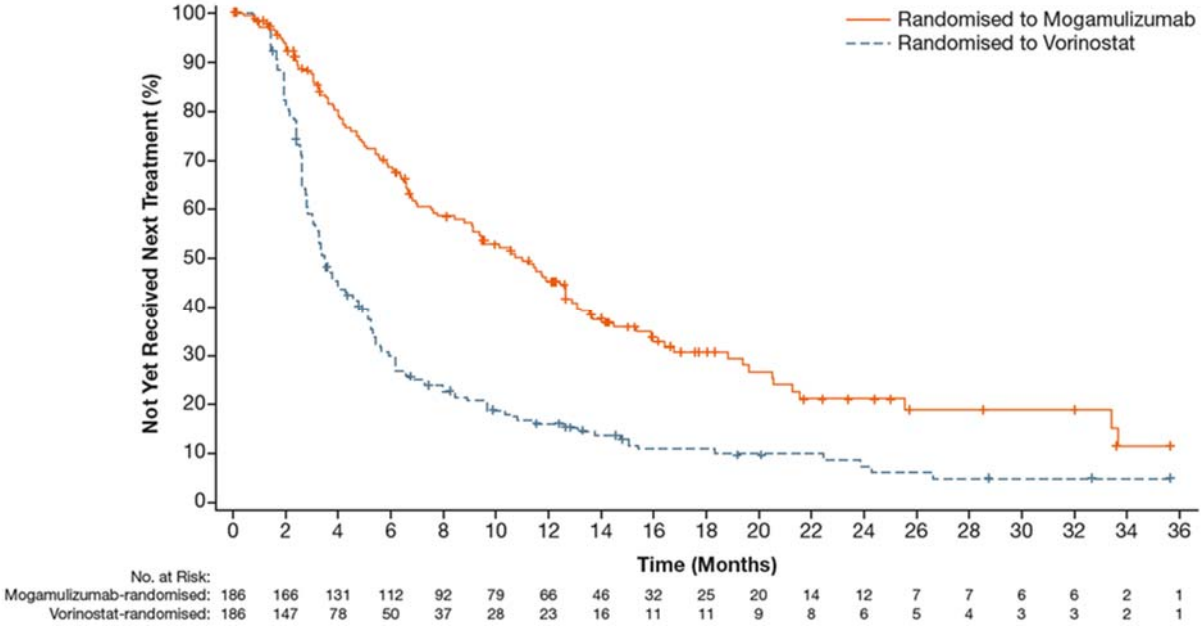
The results for OS should be considered with caution due to the high proportion (73%) of vorinostat patients who subsequently crossed over to mogamulizumab after progression or due to treatment intolerance. Additional analyses accounting for treatment crossover were performed following the methods recommended by NICE Decision Support Unit (DSU) technical support document (TSD) 16 but these methods all require assumptions which may not be satisfied in practice (e.g. all possible confounding variables are included in the model).[61]

4.2.5.4 Time to next treatment

Time to next treatment (TTNT) was defined as the period *"...from end of randomised treatment (including end date of mogamulizumab treatment for crossover patients) to next systemic treatment"*.[1] Survival and treatment data were collected every three months (+/- 14 days). As reported in the appendix of the CS, TTNT excluded topical steroids or focal radiation.[50]

The median TTNT for mogamulizumab was statistically significantly longer than for vorinostat at 11.0 months (95% CI 8.8 to 12.6 months) compared to 3.2 months (95% CI 3.1 to 4.3 months). The KM plot is presented in Figure 4.6.

Figure 4.6: KM plot for time to next treatment (TTNT)



Based on Figure 16 of the CS[1]
CS = company submission; KM = Kaplan-Meier; TTNT = time to next treatment

Results for a further analysis investigating TTNT in those patients who discontinued their randomised treatment using the data from the March 2019 cut-off were provided in a supporting document.[62] Details are provided in Table 4.15. The mean TTNT for mogamulizumab was [redacted] months compared to [redacted] months for vorinostat.

Table 4.15: TTNT after subsequent therapies per study design subgroup

Population	n	Mean (days)	SD	Median
Randomised to mogamulizumab	[redacted]	[redacted]	[redacted]	[redacted]
Randomised to vorinostat crossed-over to mogamulizumab	[redacted]	[redacted]	[redacted]	[redacted]
Vorinostat only	[redacted]	[redacted]	[redacted]	[redacted]
Pooled Mogamulizumab (randomised + crossover)	[redacted]	[redacted]	[redacted]	[redacted]

Based on supporting document, submitted as part of the CS[62]
CS = company submission; SD = standard deviation; TTNT = time to next treatment

ERG comment: The ERG would like to point out how relevant information for an unbiased analysis may have been lost by excluding therapies such as topical steroids and focal radiation on the TTNT

outcome. The clinical expert explained that local radiotherapy for palliation is particularly effective in MF patients as part of their palliative care when there is limited disease progression.[49]

4.2.5.5 Health-related quality of life

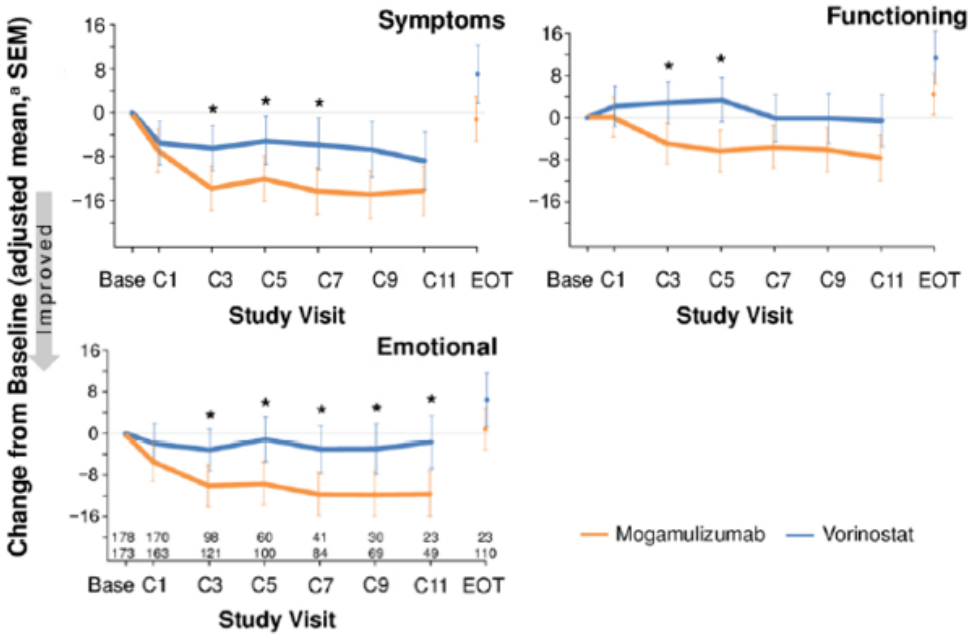
The MAVORIC trial evaluated quality of life (QoL) using three instruments: Skindex-29, FACT-G (Functional Assessment of Cancer Therapy – General) and EQ-5D-3L (European Quality of Life-5 Dimensions 3 levels). Pruritis was evaluated using the ItchyQoL and Pruritus Likert scale. All outcome measures had high completion rates of over [redacted]% throughout the trial. The results up to treatment cycle 11 were summarised in the CS.[1]

Mean Skindex-29 scores for individual domains by treatment group and cycle are shown in Figure 4.7. After six months, mogamulizumab had a greater reduction (improvement) in overall score of -12.6 (95% CI -15.94 to -9.29) compared to vorinostat (mean change -6.0, 95% CI -9.39 to -2.52). For individual domains, significant differences favouring mogamulizumab were seen at treatment cycle three or later for the symptoms, functioning and emotional subscales.

Figure 4.8 shows results for FACT-G. Statistically significant differences favouring mogamulizumab were seen for the physical and emotional subscales at treatment cycle one and for the functional subscale at treatment cycle 3. After six months, mogamulizumab had a greater improvement in overall score of 4.6 (95% CI 2.14 to 7.04) compared to vorinostat (mean change -2.3, 95% CI -4.84 to 0.21).

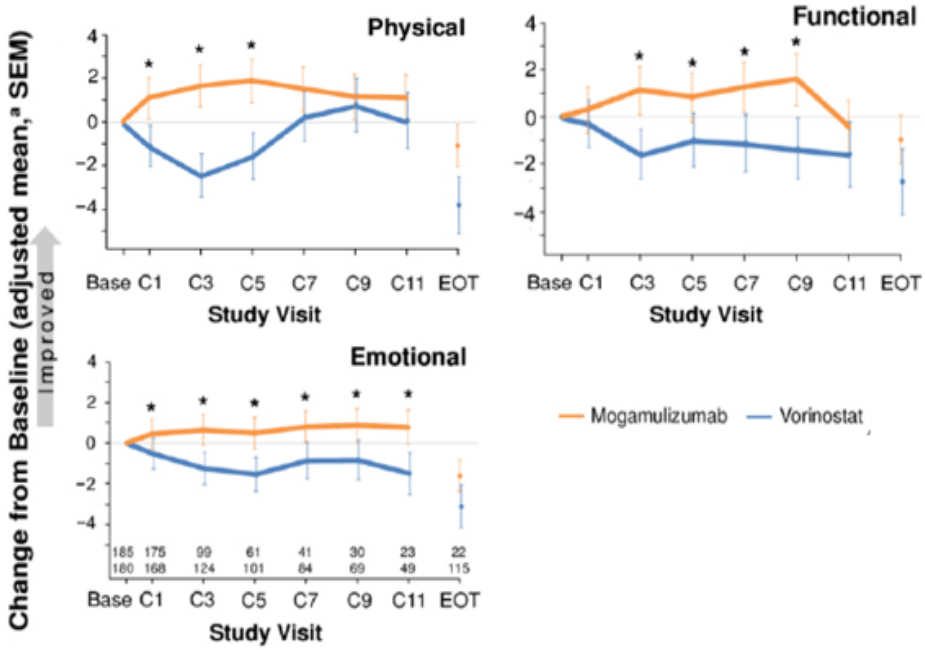
Figure 4.9 shows the percentages of patients with a clinically meaningful improvement in EQ-5D-3L score by treatment cycle. This covers five dimensions: mobility, self-care, usual activities, pain or discomfort; anxiety or depression; as well as a visual analog scale (VAS) of self-rated health from 0 to 100. A change on the VAS of 8 to 12 is a minimally clinically important difference for cancer patients. After six months the mogamulizumab group had a significantly greater increase in overall EQ-5D-3L score (mean change 0.06, 95% CI 0.028 to 0.085) compared to vorinostat (mean change 0.02, 95% CI -0.008 to 0.052).

Figure 4.7: Skindex-29 results by treatment cycle



Based on Figure 11 of the CS[1]
[a] P<0.05
CS = company submission; EOT = end of treatment; SEM = standard error of mean

Figure 4.8: FACT-G results by treatment cycle

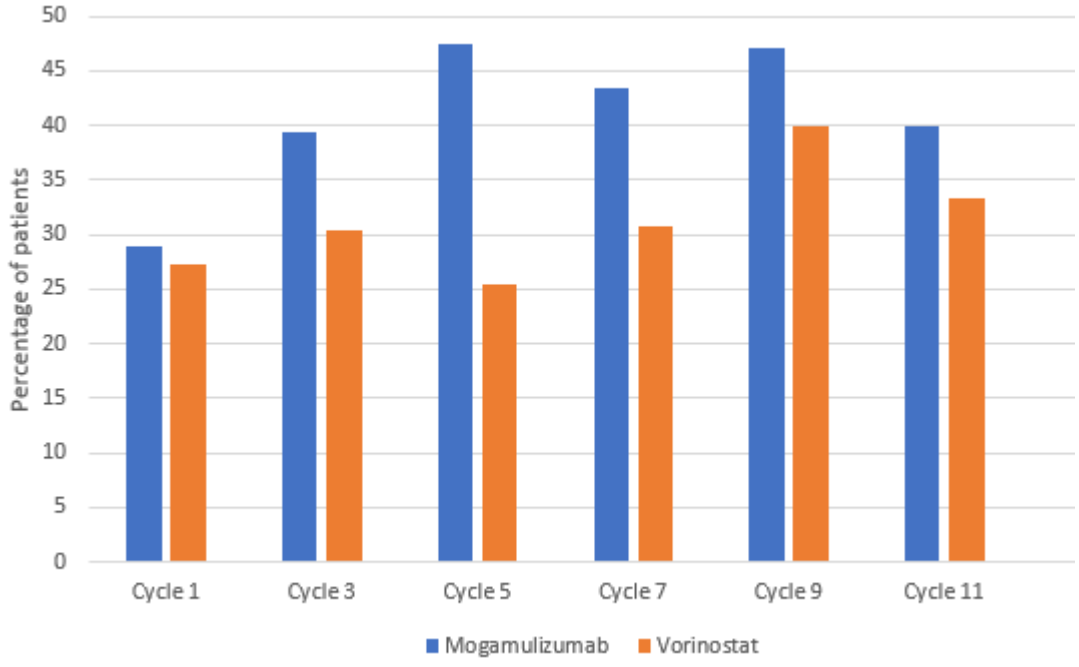


Based on Figure 8 of the CS[1]

[a] P<0.05

CS = company submission; EOT = end of treatment; FACT-G = Functional Assessment of Cancer Therapy – General; SEM = standard error of mean

Figure 4.9: Percentage of patients with clinically meaningful improvements in EQ-5D-3L score



Based on Figure 10 of the CS[1]

[a] P<0.05

CS = company submission; EQ-5D-3L = European Quality of Life-5 Dimensions 3 levels; FACT-G = Functional Assessment of Cancer Therapy – General; SEM = standard error of mean

4.2.5.6 Subgroup analyses

Subgroup analyses for the primary outcome, PFS, are shown in a forest plot in Figure 4.10. This shows the investigator-assessed results by baseline characteristics such as gender, age, race, disease type, disease stage and geographical region. Mogamulizumab improved PFS compared to vorinostat for most subgroups apart from patients with MF, stage Ib/II disease, those with no blood involvement and those negative for C-C chemokine receptor type 4 (CCR4).

Subgroup results for MF and SS patients for ORR, DOR and TTR are reported in Table 4.16.

Results for PFS, TTNT and OR for stage ≥IIB patients are shown in Table 4.17. This subgroup 77% of the trial population. There were 150/186 and 137/186 participants in the mogamulizumab and vorinostat groups respectively. The HR for the PFS in this subgroup was 0.43 (95% CI 0.31 to 0.58). Results for TTNT and ORR in stages IIA and IB for MF participants are shown in Table 4.18.

Table 4.16: ORR, DOR and TTR results per disease subgroup

	Mycosis fungoides (n=204)		Sézary syndrome (n=186)	
	Mogamulizumab (n=105)	Vorinostat (n=99)	Mogamulizumab (n=99)	Vorinostat (n=87)
ORR (confirmed CR + PR), n (% [95% CI])	[redacted]	[redacted]	[redacted]	[redacted]
Risk difference (95% CI)	[redacted]		[redacted]	
DOR (months), median (IQR)	13.1 (4.7–18.0)	9.1 (5.6–NE)	17.3 (9.4–19.9)	6.9 (6.9–6.9)
TTR (months), median (range)	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 12 of the CS[1] and the CSR[22]
CS = company submission; CSR = clinical study report; DOR = duration of response; IQR = interquartile range; ORR = overall response rate; TTR = time to response

Table 4.17: PFS, TTNT and ORR results for stage ≥IIB

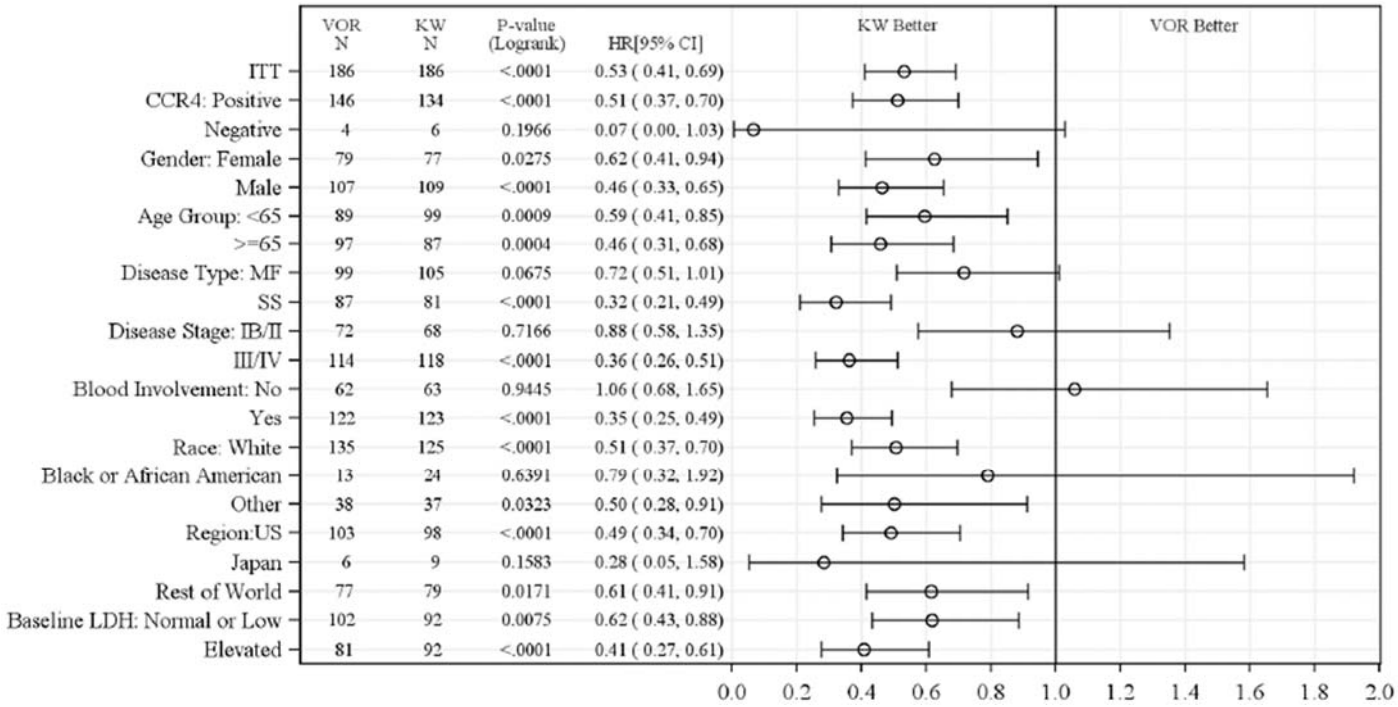
	Mogamulizumab (n=150)	Vorinostat (n=137)
Patients with PFS event, n (%)	86 (57.3)	101 (73.7)
Median PFS, months (95% CI)	9.40 (5.73 to 14.03)	3.07 (2.87 to 3.90)
HR (95% CI)	0.43 (0.31 to 0.58)	
TTNT (months), median (95% CI)	11.00 (7.73 to 13.63)	3.47 (2.87 to 4.53)
HR (95% CI)	0.36 (0.27 to 0.48)	
ORR (confirmed CR + PR), n (% [95% CI])	45 (30.0 [22.8 to 38.0])	4 (2.9 [0.8 to 7.3])
Difference (95% CI)	27.1 (19.1 to 35.5)	

Based on Table 16 of the CS[1]
CI = confidence interval; CR = complete response; CS = company submission; HR = hazard ratio; ORR = overall response rate; PFS = progression-free survival; PR = partial response; TTNT = time to next treatment

Table 4.18: TTNT and ORR results for stages IIA and IB for MF subgroup

	Stage IB		Stage IIA	
	Mogamulizumab (n=15)	**Vorinostat (n=27)**	**Mogamulizumab (n=21)**	**Vorinostat (n=22)**
TTNT (months), median (95% CI)	11.5 (1.43 to 15.97)	3.1 (2.73 to 5.30)	10.1 (5.53 to12.63)	4.87 (2.37 to 7.97)
ORR (confirmed CR + PR), n (% [95% CI])	3 (20.0 [4.3 to 48.1])	5 (18.5 [6.3 to 38.1])	4 (19.0 [5.4 to 41.9])	0 (0 [0.0 to 15.4])
Based on Table O-7 of the CS appendix[50] CI = confidence interval; CR = complete response; CS = company submission; ORR = overall response rate; PR = partial response; TTNT = time to next treatment				

Figure 4.10: Forest plot of PFS subgroup results (investigator-assessed)



Based on Figure E-1 of the CS appendices[50]

CCR4 = C-C chemokine receptor type 4; CS = company submission; HR = hazard ratio; ITT = intention-to-treat; KW = mogamulizumab; LDH = lactate dehydrogenase; MF = mycosis fungoides; PFS = progression-free survival; SS = Sézary syndrome; US = United States (of America); Vor = vorinostat

ERG comment: The ERG notes that PFS and ORR were not significantly improved with mogamulizumab in neither the subgroup of patients with MF nor in those patients with stage IB/II disease.

4.2.6 Safety outcomes

The CS emphasised the incidence of the treatment-emergent adverse events (TEAEs) within the MAVORIC trial, noting similarities between the mogamulizumab and vorinostat treatment groups of [redacted]% and [redacted]%, respectively.[1] The most common TEAEs experienced in the safety population of mogamulizumab included infusion-related reactions, drug eruption, diarrhoea, and fatigue.[50] Patients originally assigned to the vorinostat treatment arm, experienced TEAEs including diarrhoea, nausea, thrombocytopenia, and fatigue.[50] However, patients who crossed over from vorinostat to mogamulizumab experienced TEAEs similar to patients who had been originally assigned to receive mogamulizumab. The reported incidence of drug-related TEAEs was [redacted]% for mogamulizumab and [redacted]% for vorinostat.[1] The CS noted that the incidence of TEAEs was similar for patients who had crossed over to the mogamulizumab treatment from vorinostat, however, this number was not specified.[1]

The AEs experienced more often were in the vorinostat group than the mogamulizumab group included diarrhoea, nausea, and fatigue, which were rated at a mild or moderate level of severity.[50] The CS appendices noted that three grade ≥3 infusion-related reactions and eight grade ≥3 drug eruption events were experienced among patients in the mogamulizumab group.[50] This was stated to be attributed to the differing modes of administration.

A total of 12 patients died due to AEs, which comprised of nine patients who received vorinostat and three who received mogamulizumab.[1] The company further specified that of the three deceased patients who received mogamulizumab, two of the deaths were speculated to be related to treatment, while one was related to disease progression.[1] Of the nine patients who received vorinostat, three of the deaths were suspected to be related to treatment, while six were considered to be unrelated to treatment.[1] The CS reported [redacted] patients who had crossed-over from the vorinostat to mogamulizumab group had experienced AEs resulting in death.[1] Patients who received mogamulizumab had a higher incidence of treatment emergent serious adverse events (SAEs) of 37.5% when compared to the vorinostat group with a reported incidence of 24.7%.[1]

The company provided a table depicting the SAEs experienced in the mogamulizumab and the vorinostat groups in the appendix, see Table 4.21 below.[50]

Table 4.19: Overview of adverse events, safety population

	Pre-treatment and randomised treatment period		Cross-over patients
	Mogamulizumab (n=184)	Vorinostat (n=186)	Mogamulizumab (n=136)
Adverse Events (AEs), n (%)			
Any AEs	[redacted]	[redacted]	[redacted]
Any TEAEs	[redacted]	[redacted]	[redacted]
Drug-related TEAEs	[redacted]	[redacted]	[redacted]
NCI/CTCAE grade 3, 4, 5 AEs, n (%)			
Any Grade 3, 4, 5 AEs	[redacted]	[redacted]	[redacted]

	Pre-treatment and randomised treatment period		Cross-over patients
	Mogamulizumab (n=184)	Vorinostat (n=186)	Mogamulizumab (n=136)
Any Grade 3, 4, 5 TEAEs	[redacted]	[redacted]	[redacted]
Drug-related Grade 3, 4, 5 TEAEs	[redacted]	[redacted]	[redacted]
AEs with Outcome of Death	[redacted]	[redacted]	[redacted]
Serious adverse events, n (%)			
Any SAEs	[redacted]	[redacted]	[redacted]
Treatment-emergent SAEs	69 (37.5)	46 (24.7)	[redacted]
Drug-related Treatment-emergent SAEs	36 (19.6)	30 (16.1)	[redacted]
Discontinuation due to AEs, n (%)			
Any AEs	[redacted]	[redacted]	[redacted]
Any TEAEs	35 (19.0)	43 (23.1)	[redacted]
Drug-related TEAEs	[redacted]	[redacted]	[redacted]

Based on CS Table 19[1]
[a] includes one patient with TEAE with outcome of death that occurred during crossover and >30 days after the last dose of vorinostat, but was related to vorinostat
[b] includes two patients with non-TEAEs with outcome of death
AE = adverse event; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Table 4.20: Most common TEAEs (Grade 1–2, ≥10% of patients; grade 3–5, ≥2% of patients) in either treatment group by system organ class and preferred term, safety population

System organ class Preferred term	Mogamulizumab (N=184)		Vorinostat (N=186)	
	Grade 1–2, n (%)	Grade 3–5, n (%)	Grade 1–2, n (%)	Grade 3–5, n (%)
Blood and lymphatic system disorders				
Thrombocytopenia[a]	25 (14)	0 (0)	63 (34)	13 (7)
Gastrointestinal Disorders				
Abdominal pain	7 (4)	0 (0)	21 (11)	0 (0)
Constipation	20 (11)	1 (1)	32 (17)	2 (1)
Diarrhoea	42 (23)	1 (1)	106 (57)	9 (5)
Nausea	27 (15)	1 (1)	76 (41)	3 (2)
Vomiting	11 (6)	0 (0)	23 (12)	1 (1)
General disorders and administration site conditions				
Asthenia	10 (5)	0 (0)	23 (12)	4 (2)
Fatigue	40 (22)	3 (2)	59 (32)	11 (6)
Peripheral oedema	27 (15)	0 (0)	26 (14)	1 (1)
Pyrexia	30 (16)	1 (1)	11 (6)	0 (0)
Infections and infestations				
Cellulitis	2 (1)	4 (2)	6 (3)	4 (2)
Pneumonia[b]	2 (1)	8 (4)	0 (0)	3 (2)

System organ class Preferred term	Mogamulizumab (N=184)		Vorinostat (N=186)	
	Grade 1–2, n (%)	Grade 3–5, n (%)	Grade 1–2, n (%)	Grade 3–5, n (%)
Sepsis	1 (1)	3 (2)	1 (1)	5 (3)
Upper respiratory tract infection	19 (10)	0 (0)	7 (4)	2 (1)
Injury, poisoning and procedural complications				
Infusion related reaction	58 (32)	3 (2)	1 (1)[c]	0 (0)
Investigations				
Aspartate aminotransferase increased	6 (3)	2 (1)	11 (6)	1 (1)
Blood creatinine increased	6 (3)	0 (0)	52 (28)	0 (0)
Weight decreased	10 (5)	1 (1)	31 (17)	2 (1)
Metabolism and nutrition disorders				
Decreased appetite	12 (7)	2 (1)	44 (24)	2 (1)
Musculoskeletal and connective tissue disorders				
Muscle spasm	9 (5)	0 (0)	27 (15)	2 (1)
Nervous system disorders				
Dizziness	12 (7)	0 (0)	19 (10)	0 (0)
Dysgeusia	6 (3)	0 (0)	53 (28)	1 (1)
Headache	23 (13)	0 (0)	28 (15)	1 (1)
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism	0 (0)	0 (0)	0 (0)	7 (4)
Skin and subcutaneous tissue disorders				
Alopecia	13 (7)	0 (0)	36 (19)	0 (0)
Drug eruption[d]	36 (20)	8 (4)	1 (1)	0 (0)
Vascular disorders				
Hypertension	9 (5)	8 (4)	13 (7)	12 (6)

Based on Table F-2 of the CS appendices[50]
[a] adverse events reported as thrombocytopenia and decreased platelet count are combined into this row
[b] adverse events reported as pneumonia, influenzal pneumonia, legionella pneumonia, pneumococcal pneumonia, atypical pneumonia, and bronchopneumonia are combined into this row
[c] one patient 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)
[d] skin rashes that were assessed by the investigator or sponsor as possibly, probably, or definitely related to study drug
CS = company submission; TEAE = treatment-emergent adverse event

ERG comment: The company noted that grade ≥3 infusion-related reactions and grade ≥3 drug eruption events were likely attributed to differing administration methods.[1] The listed system organ classes are consistent with the CSR.[22]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparisons were performed.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparisons were performed.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness has been undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted as part of the systematic review to identify clinical efficacy and safety studies. A good range of databases and resources, including conference proceedings, were searched and the searches were transparent and reproducible. One set of searches was conducted to identify both efficacy and safety evidence. The searches included RCTs and observational study design filters in order to identify both efficacy and safety evidence. Searches were conducted in July 2019. The ERG was concerned about the overall quality of the searches conducted, as truncation and proximity operators were used inconsistently; MEDLINE and Embase were searched simultaneously without including both MeSH and EMTREE subject heading indexing terms, which may have impaired how well the strategies performed; the date ranges of searches were not reported; and the Cochrane Library searches were not accurately reported. However, the searches were adequate, and given the range of resources searched, it was unlikely that any relevant studies were missed.

The main source of effectiveness evidence was the MAVORIC trial (section 4.2.2). It was an RCT which should be considered to be an appropriate design to estimate the effectiveness of mogamulizumab vs. a comparator. However, there are concerns regarding the appropriateness of the comparator, vorinostat, to the scope and UK clinical practice. Furthermore, when estimating the effectiveness vs. vorinostat, crossover (switching) from vorinostat to mogamulizumab was permitted, occurring in 73.1% of cases. Therefore, outcomes measured after progression such as OS could be biased. Other outcomes, including PFS, might also be biased given that the trial was also open-label (section 4.2.3).

"Approximately 80% of patients" represented the population defined in the decision problem. In addition to issues related to the narrower definition, there is some doubt as to the generalisability of MAVORIC trial to this population. Specifically, a criterion for the company decision problem population is those *"who are clinically ineligible for or refractory to treatment with brentuximab vedotin (BV)"*. However, even after request for clarification, the number of participants considered to be *"ineligible for BV"* as well as how this status was determined remains unclear.

PFS assessed by blinded independent review (BIR) results favoured mogamulizumab over vorinostat (hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.49 to 0.84). However, as attested by clinical expert opinion, there is some uncertainty regarding progression assessment and results were not statistically significant for MF patients and those with disease stage IIB/II.

A number of measures of response rates are reported which generally favour mogamulizumab over vorinostat (see section 4.2.5.2 for details).

The results for the OS (BIR assessed) also favoured mogamulizumab (risk difference 19.4%, 95% CI 9.0 to 29.4). Because the company stated that the skin only response for mogamulizumab in MAVORIC was lower than in the *"registrational study"*, the ERG sought clarification, which showed that skin only response in MAVORIC (41.9%) was very similar to that in the phase I/II study (42.1%). It should be noted that OS was an exploratory outcome of the MAVORIC trial. The results for this outcome varied depending on the approach used to type of adjustment for switching and the censoring of participants receiving allogenic stem cell transplant (aSCT). The result of the analysis without crossover adjustment, but censoring for aSCT favoured vorinostat, although it was not statistically significant (HR [redacted]). These methods are discussed in detail in section 5.2.6.

Critically, the ERG highlights the risk of bias for all the outcomes measured after progression that have resulted from the specific study design and flow of participants where 73% of vorinostat patients switched to mogamulizumab.

The median TTNT for mogamulizumab was statistically significantly longer than for vorinostat at 11.0 months (95% CI 8.8 to 12.6 months) compared to 3.2 months (95% CI 3.1 to 4.3 months).

The analyses to evaluate the changes in quality of life were made using three instruments Skindex-29, FACT-G (Functional Assessment of Cancer Therapy – General) and EQ-5D-3L (European Quality of Life-5 Dimensions 3 levels). Results favoured mogamulizumab over vorinostat, although follow-up was only up to 11 cycles, i.e. less than 12 months.

An overview of adverse events (AEs) in the safety population is provided in Table 4.19. The CS noted the incidence of treatment-emergent AEs to be comparable between the two treatment groups. The listed adverse events were found to be consistently reported with the clinical study report (CSR), with the most commonly reported AEs in the mogamulizumab group was infusion-related reactions while in the vorinostat group this was diarrhoea and fatigue.

The ERG notes the warning issued by the Food and Drug Administration (FDA) for the potential complications of aSCT after mogamulizumab.

5 Cost effectiveness

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

Appendices G, H and I of the CS report the literature searches used to identify cost effectiveness, health-related quality of life (HRQoL) and healthcare resource use studies. One overarching search strategy was used to identify cost effectiveness, HRQoL and healthcare resource use evidence in the following databases: EconLit, NHS Economic Evaluation Database (EED) and the health technology assessment (HTA) Database. Three separate Embase and MEDLINE (embase.com) searches were conducted for each section: cost effectiveness, HRQL and healthcare resource use. Searches were conducted on 17 June 2019, and limited by date range to 2009 onwards. It is not clear why this date limit was used. A summary of the resources searched is provided in Table 5.1. The CS reported that a targeted literature search in PubMed was conducted to identify health state utilities for states describing the burden of caring for a partner with CTCL: this targeted search was reported in appendix M of the CS.[50]

Table 5.1: Resources for the cost effectiveness, health-related quality of life and healthcare resource use literature searches

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	Embase	Not reported	Not reported	17 June 2019
	MEDLINE			
	MEDLINE In-Process	Not reported	Not reported	17 June 2019
	EconLit	EBSCO	Not reported	17 June 2019
	NHS EED	Not reported	Not reported	17 June 2019
	HTA		Not reported	17 June 2019

EED = Economic Evaluation Database; HTA = Health Technology Assessment Database; NHS = National Health Service

ERG comment:

- MEDLINE and Embase were searched simultaneously using embase.com. This approach is not recommended.[63] A search such as this should include both MeSH and EMTREE subject headings to ensure that all subject indexing terms are searched; however, all of the economic search strategies only included EMTREE terms which may have impaired how well the strategies performed.
- Database date ranges were not explicitly reported for any of the economic related searches.
- Database host providers were not reported. The EconLit database host provider (EBSCO) appears in the search strategy itself, rather than in the methods.

- The economic searches were limited by date to 2009 onwards. It was not clear why this date limit was used.
- The CS reported that MEDLINE In-Process was searched using PubMed. This is inaccurate, as the search limit used in PubMed identifies 'Ahead of print' and recently added records, not in-process records: (publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint). Therefore in-process records were actually excluded from the company's PubMed search.
- The company reported searching NHS EED and the HTA database via the Cochrane Library. This is incorrect as NHS EED and HTA are no longer available on the Cochrane Library. The company conducted the NHS EED and HTA searches via the CRD interface, and misreported using the Cochrane Library.
- Truncation and proximity operators were inconsistently used throughout.
- The search strategies used in MEDLINE In-Process (PubMed), EconLit, and NHS EED/HTA only included a population facet of search terms, and so were sensitive enough to identify studies for all of the economic sections (cost effectiveness, health-related quality of life and healthcare resource use). The embase.com search strategies included an additional facet of search terms for each of the economic sections (cost effectiveness, health-related quality of life and healthcare resource use); three separate searches were conducted in embase.com.
- It is not clear if the search facets used to identify cost effectiveness, health-related quality of life and healthcare resource use were based on validated search filters, such as those published on the ISSG Search Filters Resource website: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/
- The PRISMA flow diagrams for the cost effectiveness and healthcare resource use literature search results included four additional records identified from 'HTA search'. However, the results of the HTA database search are included in the 'Records identified through database searching'. It is not clear how these four additional HTA records were identified.
- A targeted literature search in PubMed was conducted to identify health state utilities for states describing the burden of caring for a partner with CTCL. The targeted search was reported in appendix M: date range, search date and search results were not reported.[50]

5.1.2 Inclusion/exclusion criteria used in the study selection

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 5.2.

Table 5.2: Eligibility criteria for the systematic literature reviews

PICOS	Inclusion criteria	Exclusion criteria
Patient population	Adult patients with any-stage R/R CTCL	• Healthy volunteers • Paediatric population • Disease other than R/R CTCL • Frontline therapy
Intervention	All pharmacological interventions and phototherapies for R/R CTCL treatment	• Non-pharmacological interventions • Radiation therapy
Comparator	No restrictions	None
Outcomes(s) 1	• Incremental costs, life years gained and quality-adjusted life years, and any other	• Cost-only studies • Burden of illness

PICOS	Inclusion criteria	Exclusion criteria
(Published economic evaluations)	measure of effectiveness reported together with costs • Incremental cost effectiveness ratio, health states • Sensitivity analysis (including variability reported around the parameters) and model assumptions	
Outcomes(s) 2 (Utility studies)	• Utility values (SF-6D, EQ-5D®, HUI, etc.) • Health-related quality of life mapped health utility index score • Disutility values • Caregiver burden • Patient burden	Studies not reporting utility/ disutility values
Outcomes(s) 3 (Cost/resource use studies)	Cost and resource use data such as direct costs, indirect costs, total costs, length of hospitalization/ hospital stay, physician visits, etc.	Studies not reporting cost and resource use data
Study design 1 (Cost effectiveness analysis studies)	Full economic evaluations: • Cost consequence • Cost minimisation • Cost effectiveness • Cost utility • Cost benefit • Budget impact • Systematic reviews	• Letters, comments and editorials • Studies reporting only clinical data • Case reports or case series
Study design 2 (Utility studies)	• RCTs, non-RCTs, and observational studies reporting utility data • Economic evaluations reporting utility values • Systematic reviews	• Letters, reviews, comment, or editorials • Case reports or case series
Study design 3 (Cost/resource use studies)	• Cost and resource use studies • Cost studies • Resource use studies • Economic evaluations reporting cost and resource use • Systematic reviews	• Letters, comments and editorials • Studies reporting only clinical data • Case reports or case series
Based on appendices G, H and I of the CS[50] CS = company submission; CTCL = cutaneous T-cell lymphoma; EQ-5D = European Quality of Life-5 Dimensions; HUI = health utility index; PICOS = population, intervention, comparator, outcomes and study design; RCT = randomised controlled trial; R/R = relapsed/refractory; SF-6D = short form – 6 dimensions		

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies.

5.1.3 Identified studies

The systematic literature review (SLR) identified five cost effectiveness studies which met the eligibility criteria. Most of the cost effectiveness evidence was identified from HTA submissions.[64-68] Of the four included HTAs, two were submitted to the Pharmaceutical Benefits Advisory Committee (PBAC) for brentuximab vedotin and vorinostat, one was the TA577 submission to NICE for brentuximab vedotin and one was submitted to the Medical Services Advisory Committee (MSAC) for extracorporeal photopheresis. No published cost effectiveness analyses of mogamulizumab for the treatment of MF or SS were identified.

The utility search did not identify any relevant article. However, four publications were identified from the grey literature searches. Ultimately, three unique studies were included from these four publications. Of the three included studies, one was the NICE brentuximab vedotin HTA submission,[68] one was the MSAC extracorporeal photopheresis HTA submission,[65] and one was the MAVORIC RCT comparing mogamulizumab to vorinostat.[52]

The search for studies reporting cost and resource use identified eight publications that were relevant for the UK. Cost and resource evidence included four HTAs,[65-68] one economic evaluation,[64]and two cost and/or resource studies.[69, 70]

ERG comment: The rationales for excluding cost effectiveness studies after full paper reviewing are considered and appropriate given the defined in- and exclusion criteria.

5.1.4 Interpretation of the review

The CS provides an overview of the included cost effectiveness, utility and resource use and costs studies, but no specific conclusion was formulated. No previous cost effectiveness analysis of mogamulizumab was identified. Some cost and utility data were derived from the TA577 submission.

ERG comment: The company identified no economic evaluations addressing the decision problem it wished to target. Searches and eligibility criteria were appropriate and therefore it is unlikely that relevant studies were missed.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.3: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Partitioned survival analysis with three different treatment pathways (no aSCT, aSCT after current/and subsequent treatments)	To be in line with previous NICE TA 577 and to incorporate aSCT	B.3.2
States and events	Disease control (on treatment), disease control (off treatment), subsequent treatment, aSCT disease free, aSCT progressed, end stage care, dead	NTFS was seen as clinically more meaningful than PFS	B.3.2
Comparators	ECM		B.3.2

	Approach	Source/Justification	Signpost (location in CS)
Population	Patients with advanced disease (stage ≥IIB MF and all SS patients) only	Subgroup of population with marketing authorisation, with a higher unmet need	B.3.2
Treatment effectiveness	Based on NTFS and OS	MAVORIC: NTFS was regarded as more clinically meaningful than the primary endpoint (PFS)	B.3.3
Adverse events	Accounted for in terms of their costs (not HRQoL), based on frequency and impact and derived from MAVORIC	Utility data from MAVORIC were assumed to include impact of AEs on HRQoL	B.3.3
Health related QoL	Utilities were estimated for progression-free and progressed disease states based on EQ-5D-3L data collected in MAVORIC. A mixed effects model was used to estimate utilities per health state. A vignette study was used to estimate the impact of the carer burden on caregivers' HRQoL.	In line with NICE reference case. The company stated that caregivers are also affected by the disease.	B.3.4
Resource utilisation and costs	Drug acquisition and administration costs, costs associated with treatment-related adverse events, with disease management and patient observation and end of life care were included, based on multiple sources.	Unit prices were based on National Health Service (NHS) reference prices, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF 2019) and the eMIT tool; consistent with NICE reference case.	B.3.5
Discount rates	Discount of 3.5% for utilities and costs	Consistent with NICE reference case	
Subgroups	No subgroups		
Sensitivity analysis	DSA, PSA and scenario analyses were performed.		B.3.8

aSCT = allogeneic stem cell transplant; BNF = British National Formulary; CS = company submission; DSA = deterministic sensitivity analysis; ECM = established clinical management; eMIT = Drugs and pharmaceutical electronic market information tool; EQ-5D-3L = European Quality of Life-5 Dimensions 3 levels; HRQoL = health-related quality of life; MF = mycosis fungoides; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NTFS = next treatment free survival; OS = overall survival; PFS = progression-free survival; PSA = probabilistic sensitivity analysis; PSSRU = Personal Social Services Research Unit; SS = Sezary syndrome; TA = technology appraisal

5.2.1 NICE reference case checklist

Table 5.4: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	No, narrower than NICE scope	
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Partly	The comparator evidence was based on a comparator, vorinostat, which is not licensed in Europe and not listed in the scope or considered by the company to be routinely used in the NHS. There was uncertainty about representative treatments in this population.
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	After clarification response this was sufficient
Synthesis of evidence in outcomes	Systematic literature review (SLR)	Yes	
Measure of health effects	Quality adjusted life years (QALYs)	Yes	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Partly	Carer utilities were derived using a vignette study
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Yes	
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic modelling	Yes	
HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review			

5.2.2 Model structure

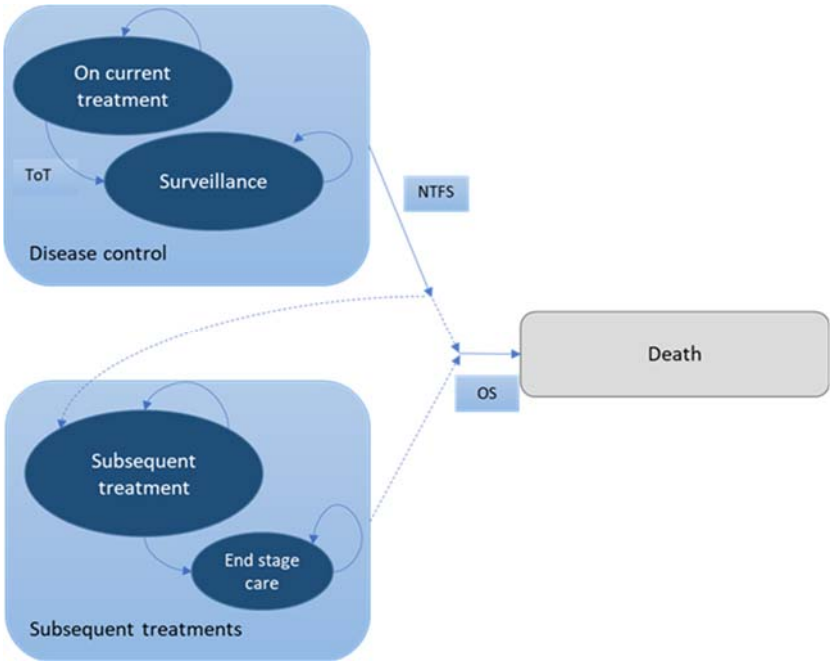
The company developed a partitioned survival model in Microsoft Excel.[71] The company stated that two changes were made to the traditional partitioned survival approach[1]:

- Inclusion of the potential for patients to receive aSCT
- The use of disease control or TTNT instead of progression determining the health states

The inclusion of aSCT led to the modelling of three separate patient pathways: 1) for patients who do not undergo aSCT, 2) patients who undergo aSCT after the current treatment, and 3) patients who undergo aSCT after subsequent treatments.

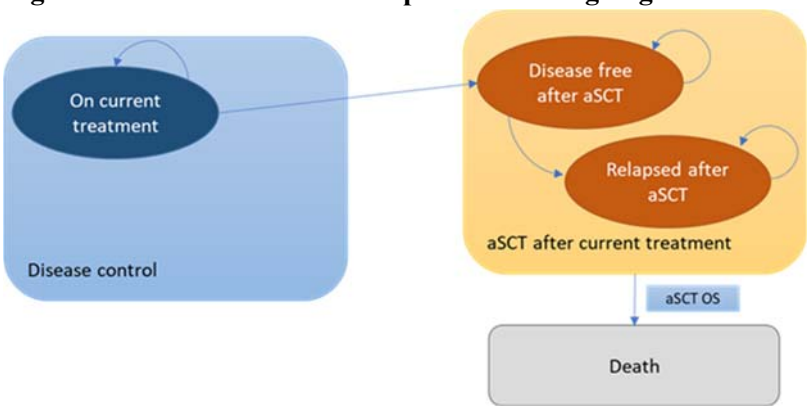
- Re 1) Patients who do not undergo aSCT all started in the 'On current treatment' health state. Patients could move to the dead state any time (based on OS and general population mortality). When treatment stopped, patients moved to the 'Surveillance' health state when their symptoms did not necessitate starting a new treatment immediately, and to the 'subsequent treatment' health state where they received symptomatic care and increased monitoring due to the progression of their disease (based on NTFS). In the last six months of life, end stage care was modelled with increased resource use and reduced quality of life (Figure 5.1).
- Re 2) Patients who undergo aSCT after current treatment all started in the 'On current treatment' health state, where they remained until a pre-specified time point (18 weeks) when they were scheduled to receive aSCT. For patients who received mogamulizumab, a 50-day wash-out period was assumed to reduce the risk of transplant complications, and aSCT was therefore modelled to take place seven weeks after the pre-specified time point. After aSCT, patients could stay disease-free or relapse. Patients could die at any time point (Figure 5.2).
- Re 3) The pathway of patients who undergo aSCT after a subsequent treatment was similar to those who do not undergo aSCT, i.e. they started 'on treatment' and moved to other states according to OS and NTFS. However, at a pre-specified time-point (after [redacted] in mogamulizumab and after [redacted] in ECT) all patients in the 'subsequent treatment' health state received aSCT and could experience a disease-free period or relapse. Again, patients could die at any time point (Figure 5.3).

Figure 5.1: Model structure for patients who do not undergo aSCT



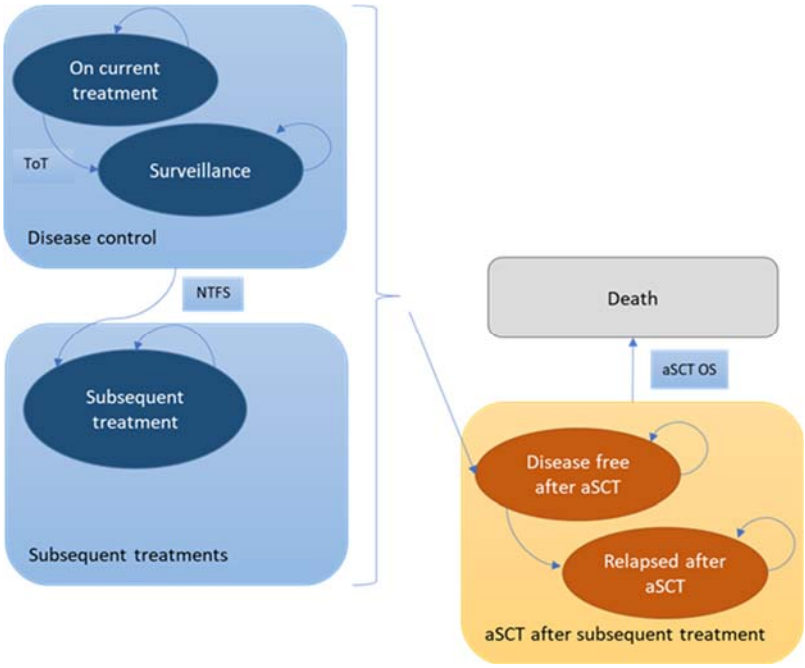
Based on Figure 20 of the CS[1]
aSCT = allogenic stem cell transplant; CS = company submission: NTFS = next treatment-free survival; OS = overall survival; ToT = time on treatment

Figure 5.2: Model structure for patients undergoing aSCT after their current treatment



Based on Figure 21 of the CS[1]
aSCT = allogenic stem cell transplant; CS = company submission: OS = overall survival; ToT = time on treatment

Figure 5.3: Model structure for patients undergoing aSCT after a subsequent treatment



Based on Figure 22 of the CS[1]
aSCT = allogenic stem cell transplant; CS = company submission: OS = overall survival; ToT = time on treatment

ERG comment: The main concerns of the ERG relate to: a) implementation of aSCT in the company's model, b) the variability in timing of aSCT not being reflected in the company's model, c) the implementation of the wash-out period for mogamulizumab, and d) using a NTFS-based model instead of a progression-based model.

a. The ERG's main concern with the inclusion of the three aSCT pathways was that a proportion of patients was artificially added to the model population that had zero mortality and remained in the disease control state (the "aSCT after current treatment" pathway) without subtracting these patients from the ones in the disease control state in the "no aSCT" pathway. The model population was therefore biased: it had an over-representation of patients in the disease control health state compared to what was observed in MAVORIC, which is likely to cause an underestimation of overall mortality in the model. This caused a bias in favour of the treatment arm with the higher proportion of aSCT after current treatment. The proportions of patients assumed to receive aSCT after current treatment were [redacted] for mogamulizumab and [redacted] for ECM. A possible implementation that would have prevented this issue would have been to subtract the proportion of those patients receiving aSCT after current treatment from those in the disease control health state and reallocating these patients to the remaining health states.

   Another issue around aSCT was that experts consulted in the company's advisory board voiced the *"concern that treatment with mogamulizumab could potentially compromise eligibility for transplantation (as a gold standard curative treatment)"*.[14] In the minutes it is furthermore stated that *"it was also suggested that Kyowa Kirin should move away from proposing mogamulizumab as a bridge to transplant, as data in this area is lacking and would not benefit Kyowa Kirin at the appraisal stage"*.[14] The company had implemented a wash-out period but not provided further evidence that aSCT could be used after current treatment with mogamulizumab after that wash-out period. The ERG clinical consultant stated that the wash-out period would likely address any concerns about safety, but also stated that it is a very small minority of these patients that is eligible for aSCT.[49] To address the implementation problem in the company's model, in the ERG base-case,

aSCT after current treatment was disabled for both treatment arms, but the company's implementation of aSCT after subsequent treatments was maintained (in line with trial evidence and given that this was correctly implemented). The ERG's clinical consultant agreed this was a reasonable approach.[49]

b. In the economic model, patients could undergo aSCT after current treatment or after subsequent treatments. The company used pre-specified time points (18 weeks for patients receiving aSCT after current treatment and [redacted] (mogamulizumab) and [redacted] (ECM) for patients receiving aSCT after subsequent treatments). This was not in line with ERG clinical consultant's opinion, who stated that the time point of receiving aSCT after current treatment was variable and depending on how well the patient responded to current treatment. The ERG considered that the implementation of fixed time points in the model was not in line with clinical practice.

c. The company stated that patients in the mogamulizumab arm who were eligible for aSCT after current treatment required a 50-day wash-out period. However, this was not reflected in the economic model in which utilities and costs pertaining to aSCT were both accrued directly after stopping current treatment. Hence, the ERG adjusted the model by keeping patients in the "Disease Control (on treatment)" state during the wash-out period instead of moving them to the "aSCT after current treatment" state already while removing mogamulizumab-related treatment costs during the wash-out period. This did not affect the ERG's base-case.

d. In contrast to TA577 in which PFS was used, health states in the economic model were defined based on disease control and the need for new treatments (NTFS).[68, 71] The company argued that this endpoint was more closely aligned with symptoms and disease control, and as a result a better proxy for treatment changes, HRQoL and resource utilisation.[1] Although the ERG agreed with the company's arguments, the ERG also considered that there may still be uncertainty as to whether NTFS is the better endpoint, with PFS having been chosen as the primary endpoint in MAVORIC, and therefore included the progression-based model as a scenario.

5.2.3 Population

The European Medicines Agency (EMA) marketing authorisation for mogamulizumab is for the treatment of adult patients with MF or SS who have received at least one prior systemic therapy.[72, 73] The patient population considered in the economic model was restricted to patients with advanced disease (stage ≥IIB MF and all SS patients) only, which is a subgroup of the final scope issued by NICE and the MAVORIC trial.[17, 71]

ERG comment: The main concern of the ERG relates to: the modelled population being a subgroup of the MAVORIC trial and the NICE scope. In the economic model, the company considered patients with advanced disease (stage ≥IIB MF and all SS patients) only, which is a subgroup of the population in the MAVORIC trial and the final NICE scope. Therefore, the ERG included a scenario in which the ITT population was used. It is worth highlighting that the direction in which the incremental cost effectiveness ratio (ICER) changes with a change of population used in the model is contingent on the crossover adjustment method used (which highlights the large impact of the uncertainty around OS on the ICER).

5.2.4 Interventions and comparators

As per its marketing authorisation, mogamulizumab was modelled with a posology of 1 mg/kg as an intravenous infusion administered weekly on days 1, 8, 15 and 22 of the first 28-day cycle, followed by

infusions every two weeks on days 1 and 15 of every subsequent 28-day cycle. Based on clinical inputs and benefits from the MAVORIC trial, a 24-month stopping rule was implemented.[1]

Patients with advanced MF and SS are currently treated with ECM, which comprises a number of treatments (Table 5.5).[1] However, evidence for vorinostat was used to inform the comparator in the economic model, because vorinostat was the active comparator in the MAVORIC trial. Vorinostat is not licensed for use in Europe and is not used as standard of care in the UK. The company stated that vorinostat showed similar outcomes (in terms of PFS) to those observed in the ALCANZA trial's physician's choice arm[53] and the bexarotene phase II pivotal trial,[18] and was therefore judged to be a reasonable proxy for ECM without mogamulizumab.

Table 5.5: Composition of ECM arm

Treatment	Proportion	Treatment schedule and dosing
Methotrexate	[redacted]	25 mg, one day per week
Bexarotene	[redacted]	300 mg/m^2 daily
Interferon alfa-2a* (peginterferon)	[redacted]	180 mcg once a week
Gemcitabine	[redacted]	1,000 mg/m^2 on day 1 and 8 of 21-day cycle
CHOP	[redacted]	Cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 on day 1, prednisolone 40 mg/m^2 on days 1-5 of 21-day cycle
Liposomal doxorubicin	[redacted]	20 mg/m^2 twice monthly
Etoposide	[redacted]	120-240 mg/m^2 for five days every month
Prednisolone	[redacted]	40 mg/m^2 on days 1-5 of 21-day cycle
PUVA	[redacted]	2 per week for 14 weeks
ECP	[redacted]	On 2 consecutive days every 28 days
TSEBT	[redacted]	4 per week for 4 weeks (may be repeated once)

Based on Table 22 of the CS[1]
* As interferon alfa-2a has been withdrawn from the market and the stores are being used up, it is substituted with pegylated derivatives of interferon alfa (peginterferon)
CHOP = combination of cyclophosphamide, doxorubicin, vincristine and prednisolone; CS = company submission; ECM = established clinical management; ECP = extracorporeal photopheresis; mcg = microgram; mg = milligram; PUVA = psoralen plus ultraviolet light therapy; TSEBT = total skin electron beam therapy

ERG comment: The main concerns of the ERG relate to: a) relative treatment effectiveness based on a proxy for UK standard of care and b) the composition of the ECM arm.

a) Relative treatment effectiveness was based on a proxy: MAVORIC did not compare mogamulizumab to current standard care in the UK but to vorinostat, which is not licensed in the EU (European Union). As discussed in section 3.3, the company argued that vorinostat could *"be considered a reasonable proxy for current standard of care in the NHS, based on a naïve comparison of results from the vorinostat arm of the MAVORIC study and the physician's choice arm (methotrexate or bexarotene i.e. UK standard treatments) of the ALCANZA study as well as comparison to Phase II bexarotene data"*.[1] The ERG requested an analysis using the data from the ALCANZA study to inform the comparator's treatment effectiveness but the company did not provide this analysis, citing two reasons: 1) the ALCANZA trial population differed from the target

population in the present appraisal, and 2) the ALCANZA treatment effectiveness was biased by crossover (which was not appropriately adjusted for in TA577).[19, 20]

As for 1), the company helpfully provided an overview of differences in the populations (Table 3.5).[20] If vorinostat and physician's choice were truly comparable, it would therefore be expected that physician's choice would produce more favourable PFS and OS in ALCANZA (where patients are less severe in disease presentation) than vorinostat in MAVORIC. However, in response to request for clarification, the company have estimated hazard ratios for vorinostat versus physician's choice based on digitised KM data (shown in see Figures 3.1 and 3.3), which show a slight PFS advantage for physician's choice indeed, but an OS disadvantage for physician's choice compared with vorinostat (confidence intervals were wide for both), but the OS analysis may have been biased by crossover having been possible in both trials.[20] Based on the limited data available and this analysis, the comparability of vorinostat and physician's choice cannot be established.

As for 2), incorporating unadjusted ALCANZA physician's choice treatment effectiveness in the cost effectiveness analysis would have enabled a comparison of ICERs using unadjusted data (with the unadjusted MAVORIC vorinostat analysis), but the ERG acknowledges that this may not have provided a lot of information given the differences in patient population. It was therefore not possible for the ERG to assess the size of the bias introduced by the lack of relative treatment effectiveness data with the appropriate comparator. In response request for clarification, the company did, however, include a scenario incorporating adverse events, health state costs, time on treatment (ToT), dose intensity and utilities informed using data from physician's choice (i.e. methotrexate or bexarotene) arm from the ALCANZA (ITT) study.[20] In this scenario, the company stated that the ICER decreased by 3.5%[20]. Although the ERG acknowledges the difficulties faced by the company, the lack of direct comparator data for the ECM arm remains a major concern in the appraisal of mogamulizumab.

b) The ECM arm composed of several treatment options (Table 5.5) and was based on clinical expert opinion through a short survey and in-depth interviews.[20] Based on the ERG's clinical consultants' opinion, it appeared that not all treatment options in the ECM arm were appropriate comparators for mogamulizumab in the UK.[49] Methotrexate, bexarotene and interferon alfa-2a are typically used as first or second line treatments and therefore not an appropriate comparator for mogamulizumab, which is proposed as a third line treatment. Furthermore, PUVA is a topical treatment that is usually given to patients with earlier disease and ECP and TSEBT are only used in respectively SS and MF and are therefore no direct comparators. Hence, the ERG explored the impact of using a different treatment mix in ECM and found that it was likely small.

5.2.5 Perspective, time horizon and discounting

The analysis took a NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was 1 week with a time horizon of 30 years.[1]

ERG comment: In contrast to submission TA577, in which a time horizon of 45 years was used, a time horizon of 30 years was used in the model during initial submission as this was assumed to be the maximum life expectancy of patients based on clinical expert interviews.[14, 68] Nevertheless, in the company's base-case analysis, [redacted] of the patients in the mogamulizumab arm were still alive after 30 years. In response to clarification question B2 and in line with the request of the ERG, the company extended the time horizon to 45 years keeping the age specific mortality from the general population as

the maximum limit.[20] This prolonged time horizon resulted in a marginally lower ICER. The extended time horizon was also incorporated in the ERG base-case.

5.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness used for intervention and comparators are: the MAVORIC trial, which informs OS, NTFS, PFS, ToT, proportion of patients undergoing aSCT after subsequent treatments and dose intensity; data used in TA577 from the London supra-regional centre to inform estimates of disease-free survival (DFS) and OS for patients undergoing aSCT; and expert opinion to inform proportions of patients undergoing aSCT after current treatment (mogamulizumab or ECM). The company's base-case uses a post-hoc analysis on data from MAVORIC only including patients with advanced disease, instead of using the ITT population.

5.2.6.1 Overall survival

5.2.6.1.1 Adjusting for crossover

The MAVORIC study was not powered to detect OS differences between treatment arms (only 23% of patients had an OS event). In addition, the crossover design of MAVORIC allowed patients randomised to the vorinostat arm to switch to mogamulizumab treatment if they had at least two cycles of treatment and showed confirmed disease progression or had intolerable toxicity (grade ≥3 adverse events, excluding inadequately treated nausea, vomiting, diarrhoea, and alopecia), despite dose reduction and appropriate management of side-effects. The company stated that, given that 72.6% of patients switched from the vorinostat arm to the mogamulizumab arm, unadjusted OS data were heavily confounded by the crossover design. For all OS analyses, patients who received aSCT were excluded.

Two different methods described in the NICE Decision Support Unit (DSU) technical support document (TSD) 16 were followed to adjust for crossover: the inverse probability of censoring weights (IPCW) and the two-stage estimation (TSE) method.[61] Results of the two methods are shown in Figures 23 and 26 and Tables 24 and 28 of the CS.[1] The company considered that the TSE method did not account for any spill over effects of mogamulizumab on the next treatment and therefore chose the IPCW method in the base-case.

The rank-preserving structural failure time (RPSFT) approach was also explored. As with the unadjusted data, the RPSFT method resulted in OS estimates that favoured vorinostat, as shown in appendix R of the CS.[50] The company stated that the point estimate of the hazard ratio was considered to be *"counter-intuitive"*.[1] Furthermore, the company considered there to be two assumptions underlying this method, which may not be fulfilled: that of the common treatment effect, and that of a time-invariant treatment effect. The company did not perform any extrapolations with the resulting analysis.

5.2.6.1.2 Survival analysis

Using the IPCW method for crossover adjustment, the exponential and the generalised gamma survival models made the best statistical fit for the mogamulizumab and vorinostat arms respectively, based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) criteria (Table 25 of the CS).[1] The company stated that the generalised gamma applied to the vorinostat arm had a long plateau, which was not considered realistic for the comparator ECM in the UK.[1] The company used expert opinion and external data to choose distributions: three publications with data from MF/SS patients and data from the Hospital Episode Statistics (HES) database, noting that survival estimates from those studies may not be generalisable to this decision problem because patients were less heavily pre-treated and had an under-representation of SS patients compared with the MAVORIC trial.[10, 23, 74] The company

compared these external data to extrapolations using six different distributions (Table 27 of the CS) and chose the lognormal and the exponential models for mogamulizumab and vorinostat arms respectively.[1]

Using the TSE method for crossover adjustment, the exponential model made the best statistical fit for both mogamulizumab and vorinostat arms (Table 29 of the CS), but the company explored the lognormal and exponential models respectively in their scenario analyses.[1]

Mortality estimates in the model were capped at a minimum of general population mortality, data for which were obtained from the Office of National Statistics (ONS).[75]

5.2.6.1.3 Next-treatment-free survival

The NTFS data were nearly complete. Parametric survival models were fitted independently, because it was uncertain whether the proportional hazard assumption held. The lognormal made the best statistical fit for the mogamulizumab arm and the generalised gamma for the vorinostat arm (Table 31 of the CS).[1] The generalised gamma was chosen for both arms in the company's base-case. Subsequent treatments and their distribution are shown in Table 46 of the CS.[1]

5.2.6.2 Allogeneic stem cell transplant

5.2.6.2.1 Patients receiving aSCT

Patients could receive aSCT if they had achieved good PR or CR and could be eligible at two time points: after current treatment (mogamulizumab or ECM) or after subsequent treatment. The design of the MAVORIC trial did not allow patients to be bridged to aSCT prior to progression. The proportions of patients receiving aSCT after current treatment were therefore based on estimates from a clinician survey ([redacted] for the mogamulizumab group and [redacted] for the ECM group). The time to receive aSCT after current treatment (18 weeks after initiation of treatment) was based on NICE TA577.[68] A wash-out period of 50 days after mogamulizumab treatment stop was assumed.[1]

After subsequent treatment, the proportions of patients receiving aSCT ([redacted] for the mogamulizumab group and [redacted] for the vorinostat group) and the timing of aSCT ([redacted] for the mogamulizumab group and [redacted] for the vorinostat group) were based on MAVORIC in the base-case, and based on a clinician survey in scenario analysis (Table 32 of the CS).[1]

5.2.6.2.2 Disease free survival and overall survival after aSCT

Disease-free survival (DFS) and OS estimates for patients who received aSCT were obtained from the London supra regional centre as reported in TA577.[68] PFS data were redacted in TA577 and could therefore not be used.[68] Kaplan-Meier (KM) data of DFS and OS were shown in Figures 32 and 33 of the CS, respectively.[1] The company stated that the *"minimal intensity"* aSCT data used in NICE TA577 were determined by the committee as appropriate to reflect contemporary NHS England practice across the UK, and that this was assumed to hold for this appraisal as well.[1] The KM curves were digitalised and standard parametric survival models were fitted to the obtained *"patient-level"* data (Figures 34 and 35 in the CS).[1] The Gompertz model made the best statistical fit for both DFS and OS (Table 33 in the CS).[1] The company chose the Gompertz model for DFS and the (second-best fitting) lognormal model for OS.[1] The reason for choosing the lognormal model for OS was to be in line with TA577, where the log-normal model fit was selected based on the time point where the DFS curve converged with the OS curve, i.e. the time point at which all relapsed patients were implied to have died.[1, 68]

5.2.6.3 Dose intensity

The mean dose intensity reported during the randomised treatment period of MAVORIC was 97.5% for mogamulizumab, and the company assumed the same dose intensity for ECM.[1]

5.2.6.4 Time on treatment

Given the complete nature of the data for the time on treatment (ToT), KM data were used directly to capture mogamulizumab and vorinostat ToT. ToT for vorinostat was used to inform ECM ToT, except for those components of ECM that are given for a shorter duration, e.g. TSEBT or PUVA, where the mean shorter, limited duration was included.

5.2.6.5. ERG comment

The main concerns of the ERG relate to: a) treatment effectiveness based on post-hoc analysis in sub-population, b) relative treatment effectiveness based on a proxy for UK standard of care, c) comparator's OS estimates confounded by crossover, d) uncertain OS extrapolations, e) potential bias in OS by excluding patients undergoing aSCT, f) extrapolation of NTFS, g) uncertain proportions of patients receiving aSCT, h) extrapolation of DFS after aSCT (see sections 5.2.6.5.1 to 5.2.6.5.8).

5.2.6.5.1 Treatment effectiveness based on post-hoc analysis in sub-population

Treatment effectiveness in the company's base-case was informed by a post-hoc analysis including only advanced disease patients instead of using the ITT population. Results from this analysis are therefore to be interpreted with caution. A scenario based on the ITT population resulted in a moderate increase in the ICER. It is not possible to quantify the potential selection bias in the company's post-hoc analysis. The ERG uses the ITT population analysis in a scenario.

5.2.6.5.2 Relative treatment effectiveness based on a proxy for UK standard of care

Relative treatment effectiveness was based on a proxy: MAVORIC did not compare mogamulizumab to current standard care in the UK but to vorinostat, which is not licensed in the EU. It was impossible for the ERG to assess the size of bias that may be introduced by this (see sections 3.3 and 5.2.4 for further details).

5.2.6.5.3 Comparator's OS estimates confounded by crossover

The comparator OS estimates derived from MAVORIC were confounded by crossover and different adjustment methods had vastly different results. The ERG agreed with the company's assessment that adjusting for crossover to estimate OS was indicated in this case: patients would not have the option of switching to mogamulizumab in current clinical practice. However, the ERG considers that it is difficult to choose a most appropriate adjustment method and that all of them appear to be biased. A recent publication by Sullivan et al. 2020 offered reporting recommendations for crossover adjustment methods.[76] These were not yet published at the time of the CS, and it is understandable that these were not fully followed, but this made it difficult for the ERG to fully assess the methods used and their implementation.

One conclusion that can be drawn based on the CS is that OS is associated with additional uncertainty because of crossover in MAVORIC (the reported adjustment methods resulted in large differences in ICERs) and that any extrapolation of OS and resulting model outcomes should be interpreted with extreme caution. All established crossover adjustment methods are based on strong assumptions. The RPSFT model, results of which were only provided in response to the request for clarification, had the highest ICERs, even higher than those obtained without any adjustment.[20] The company's main arguments against this method were that it produced a *"counter-intuitive point estimate (due to the assumption of a time-invariant treatment effect on the HR scale) with considerable uncertainty, and the implausibility of the "common treatment effect" assumption in this setting"*.[20]

However, the unadjusted KM data from MAVORIC (Figure 41 in appendix V of the CS) show a survival benefit for patients that switch to mogamulizumab later (those that were randomised to

vorinostat), which may support a common treatment effect assumption.[58] The company further noted that *"the RPSFTM methodology has a tendency to increase the magnitude of the treatment effect away from the point of no difference (i.e. HR = 1)"*.[1] The ERG accepts that the RPSFT method may not result in clinically plausible estimates taking into account clinical expert opinion that treatment with mogamulizumab may result in an OS advantage, or at least in similar OS to that obtained with ECM.

The IPCW method for crossover adjustment produced the most favourable OS results for mogamulizumab amongst the explored methods. This method relies on the *"no unmeasured confounders"* assumption.[1] The company used stabilised weights, obtained from a logistic regression model. Based on the information provided by the company it was not possible to fully assess how these weights were obtained. However, it appears that some *"extreme weights"* were obtained for those patients randomised to vorinostat that did not switch but were potentially eligible for switching.[58] The company did not provide the proportion of patients who did not switch out of those eligible for switching, which, if low, is an indicator for the IPCW method potentially being biased. The proportion of patients switching in the advanced population was 71.5% (133 patients in that subgroup).[50] According to TSD 16 and other literature, weights larger than 10 could mean that the IPCW method produces biased results.[61, 76, 77] This, paired with a potentially high proportion of patients that switched compared to those eligible for switching, may indicate that the use of IPCW could be inappropriate in this setting. Finally, the ERG was concerned that there may not be plausible clinical explanation for results of the IPCW method that exhibited a significant drop in patients at risk at approximately 6 months (Figure 23 of the CS),[1] which was also described as *"very dramatic"* by one of the experts consulted by the company.[13] The other expert consulted by the company mentioned that the IPCW (when using the exponential model) resulted in a rather low 10-year OS estimate, and that the TSE estimate was *"more likely"* but this expert mentioned the caveat that the population was more severe.[13]

The company also explored the TSE method. The company's arguments against using the TSE method were that 1) OS extrapolations lacked plausibility when comparing its extrapolated OS with external data and 2) the method did not account for spill-over effects (benefit carried over to subsequent treatment period) that mogamulizumab may provide.

As for 1) the TSE method provided OS estimates no less in line with external data presented in Table 27 of the CS than the IPCW method – in general these comparisons are to be interpreted with caution because of the differences in patient populations between studies.[1] These comparisons are further hampered by significant differences in OS estimates between the different sources for external data. The ERG therefore considers that the TSE method should not be ruled out based on comparisons with the external data presented.

As for 2) the company cited their post-hoc analyses on TTNT data (also of subsequent treatments) as well as clinical expert opinion to support the claim of such spill-over effects.[1] TTNT is indeed longer for patients who were treated with mogamulizumab than for patients treated with vorinostat (also for subsequent treatments). However, there may not be sufficient evidence to support this. The ERG acknowledges that the TSE method not only requires the *"no unmeasured confounders"* assumption (as the IPCW method does) but also requires the existence of a *"secondary baseline"*, that is the time after which switching was allowed.[1] Progression status was one of the main criteria for switching, and the majority of patients appeared to have switched because of progression, which supports the existence of a secondary baseline. Furthermore, for the TSE method, the *"no unmeasured confounders"* assumption is important at the time of the secondary baseline, which may be more easily satisfied than at other time points where other variables may not have been measured (required for the IPCW method).[1]

Figure 5.4 shows OS for patients randomised to vorinostat using the unadjusted data, the IPCW method, and the TSE method, and in comparison with mogamulizumab OS in the advanced population. Based on this figure, the ERG's clinical consultant stated that the TSE method resulted in clinically most plausible OS estimates for the ECM arm, that unadjusted data were not in line with clinical practice and that the IPCW method resulted in OS estimates that were lower than those in clinical practice.[49] The company provided an attempt at external validation, stating that OS with vorinostat in MAVORIC should not exceed that in other studies, which all included a less severe patient population. Whilst OS estimates obtained using the IPCW and the TSE method broadly fit that criterion, the ERG considered that comparability was indeed hampered by the differences in patient population and treatment between the studies. In addition, the company cited two clinical experts, whose estimates were broadly in line with those of the TSE method.[1]

Based on all these considerations, the ERG considered that OS may be better reflected by the TSE method, but acknowledges that there is large uncertainty about OS, and the crossover adjustment method. Hence, the ERG chose the TSE method for crossover adjustment in the ERG base-case, and explored the impact of choosing the IPCW method in a scenario. To reflect the methodological uncertainty over the crossover adjustment method, the ERG explored in a scenario the impact of model averaging over the two methods, assuming that the IPCW method had a probability of 30% of being correct, and the TSE a probability of 70% of being correct. These weights were assumptions, informed by the feedback by the clinical consultant.[49] To reflect the large uncertainty induced by crossover in MAVORIC, the ERG also used the KM data without any adjustment method for crossover in a scenario.

Figure 5.4: OS estimates for ECM and mogamulizumab in MAVORIC advanced population

Based on CS economic model[71]
ECM = established clinical management; IPCW = inverse probability of censoring weighting; OS = overall survival; TSE = two-stage estimation

5.2.6.5.4 Uncertain OS extrapolations

OS was an exploratory, not a primary, endpoint in MAVORIC and as such MAVORIC was not powered to estimate OS, and maturity was not achieved (see sections 4.2.5.3 and 5.2.6.1.1) All OS extrapolations were therefore highly uncertain. The choice of parametric survival model for modelling OS had a high impact on model outcomes and was associated with substantial uncertainty. To demonstrate an example of the potential impact, choosing the models with the best statistical fit instead of the company's model choices for modelling OS, and using the company's base-case settings increased the ICER to £54,325 per QALY gained, an increase of approximately £20,000. The company provided justification for deviating from the models with best statistical fit: for the ECM arm the generalised gamma would provide a potentially unrealistically high long-term OS, lacking in clinical plausibility ([redacted] of patients still alive at 20 years). For the mogamulizumab arm, the company stated that, based on visual inspection, the lognormal distribution fitted the data better than the (based on AIC and BIC best-fitting) exponential at the first half of the curve, where more data were available.[20] It may be worth highlighting that the lognormal was the model with the best long-term OS prediction for mogamulizumab. Furthermore, the company argued that mogamulizumab had a potential disease-modifying effect, which could be captured in a longer tail of mogamulizumab compared with ECM. The company did not present evidence for such a disease-modifying effect.[1] Given the substantial uncertainty, the ERG therefore preferred the model with the best statistical fit (exponential) for modelling OS in the mogamulizumab arm in its base-case.

The ERG used the TSE method in their base-case. In their scenario using the TSE method, the company chose the exponential distribution in the ECM arm, which was indeed the model exhibiting the best statistical fit.[1] If the TSE method were used for adjusting for cross-over, the mogamulizumab arm would remain unchanged and the same model for OS extrapolation should be used. Indeed, the company's choice of the lognormal remained unchanged, and the ERG preferred the use of the exponential in this analysis. For the ECM arm, the exponential would have the best fit and this is implemented in the company's and ERG's base-case.

5.2.6.5.5 Potential bias in OS by excluding patients undergoing aSCT

OS estimates may further be biased by the exclusion of patients who had received aSCT after subsequent treatments for the purposes of OS analysis: there may be selection bias because of unobserved confounders playing a role in patients receiving aSCT. The size of this bias cannot be assessed but the company provided two scenarios in which these patients were not excluded from the survival analysis: 1) where OS estimates without aSCT excluded were used only in the model pathway for patients never undergoing aSCT, *"and patients were only allowed to receive aSCT after subsequent treatments to correspond with the MAVORIC trial protocol"*.[1] In this scenario, OS was likely over-estimated because the *"no aSCT"* pathway benefited from longer OS from MAVORIC including aSCT OS and the "*aSCT after subsequent treatment"* pathway benefited from prolonged OS as well. 2) OS estimates without aSCT excluded were used in the pathways for those never undergoing aSCT, and those having aSCT after subsequent therapies (the proportion of patients having aSCT after current treatments were set to nought).[1] This scenario was incorrect as patients receiving aSCT after subsequent treatment could be in all preceding health states, including the mogamulizumab treatment health state. The impact of both scenarios on the ICER was modest, but neither one of them truly reflected the use of MAVORIC data without the exclusion of aSCT patients. As a result, it was difficult to assess the impact of the exclusion of aSCT patients from MAVORIC OS analyses on the ICER.

5.2.6.5.6 Extrapolation of NTFS

The company selected the generalised gamma for extrapolation of NTFS in both treatment arms. However, the lognormal model made the better statistical fit for the mogamulizumab arm and therefore the ERG chose the lognormal for modelling NTFS in the mogamulizumab arm.

5.2.6.5.7 Uncertain proportions of patients receiving aSCT

The proportion of patients receiving aSCT is subject to uncertainty. The proportion of patients receiving aSCT after subsequent treatments was taken from MAVORIC. In MAVORIC, patients were not allowed to have aSCT after current treatment, and in clinical practice some of these patients would have received aSCT sooner in the treatment pathway (after current treatment). Furthermore, the ERG's clinical consultant considered that patients included in trials often have fewer comorbidities and are therefore more likely than the population seen in clinical practice to receive aSCT. It therefore appears likely that the proportions of patients receiving aSCT after subsequent treatments are an over-estimate. The clinical expert stated that *"fitness and suitability for transplant reduces with further lines of therapy and response to next line therapy are invariable reduced and of shorter duration"* and that the proportion of patients eligible for aSCT with current practice may be less than 5% overall, below the company's estimate of [redacted]% in the ECM group and [redacted]% in the mogamulizumab group (for both after current and subsequent treatments respectively).[49] Based on these considerations, and to avoid the over-representation of patients in the disease control state induced by the company's modelling of aSCT after current treatment as detailed in section 5.2.2, the ERG disabled aSCT after current treatment in its base-case.

5.2.6.5.8 Extrapolation of DFS after aSCT

Extrapolation of DFS and OS after aSCT based on digitised KM data from the London supra regional centre as reported in TA577 may be biased because data on censoring was not available and the long plateau in the KM estimates may be assigned a higher weight than it should when assuming no censoring. The company did not provide a scenario changing the assumptions about censoring. The Gompertz distribution used for DFS (chosen in company's base-case) placed the most emphasis on that plateau. The ERG therefore considered that it may be more appropriate to select the lognormal for DFS, in line with OS, and incorporated this in the ERG base-case.

5.2.7 Adverse events

The source of evidence for treatment adverse events used for intervention and comparator was the safety population of the MAVORIC trial (see Table 34 in the CS for number of AEs in each treatment arm).[1] The company assumed the same AE rate for ECM as for vorinostat. Only grade 3 and 4 AEs were assumed to have important impact on the costs and quality of life. The impact of AEs on HRQoL was, however, not included in the model.

ERG comment: The main concerns of the ERG relate to: a) whether vorinostat AEs were a reasonable proxy for AEs for people treated with ECM and b) the exclusion of HRQoL impact of AEs.

a) The ERG considered that it was questionable whether vorinostat AEs were a reasonable proxy for AEs that patients may experience when treated with ECM. The company pointed out that the influence of AEs on the ICER was minimal and provided a comparison of AEs in MAVORIC and the ALCANZA trial. This comparison was hampered by the differences in patient populations in MAVORIC and ALCANZA. The ERG agreed that any differences in AEs observed in clinical practice compared to what was observed in MAVORIC would likely not have a significant impact on the ICER.

b) The HRQoL impact of AEs was not explicitly modelled, however, treatment-specific utility values were used for the mogamulizumab and ECM arms in the model. These values were directly derived from MAVORIC and the company therefore argued that the HRQoL impact of AEs was likely captured. The ERG agreed with this assessment.

5.2.8 Health-related quality of life

The utility values for the economic model were based on the EQ-5D-3L data from MAVORIC. The UK tariff was applied to the MAVORIC EQ-5D-3L questionnaire data to generate patient-specific EQ-5D-3L utility data.[78] The MAVORIC data were analysed using longitudinal mixed models; post-baseline EQ-5D utility scores were regressed on fixed effects of (i) baseline EQ-5D utility score, (ii) randomised treatment, (iii) current treatment, and (iv) progression status (yes versus no), as well as all possible interaction terms. The final model (see Table 35 of the CS) was free of interaction terms, and included neither current nor randomised treatment status as they were not found to be independent predictors of patient utility.[1] Mean adjusted cycle-specific utilities as well as mean utilities for the on-treatment period and the last observation as observed in the MAVORIC trial were estimated (Table 36 of the CS).[1]

The company stated that utilities for the post-treatment period or for the time patients received subsequent therapies were difficult to obtain as according to protocol patients were administered the EQ-5D-3L instrument during each treatment cycle, and at the end of treatment visit. The last observation values for mogamulizumab in post-progression were therefore used in the subsequent treatment health state. This value was similar to the one obtained from the ALCANZA trial for progressed patients, which was used in TA577 (0.61 and 0.64 in the advanced population for predicted and observed values respectively, and 0.66 and 0.68 in the ITT population for predicted and observed values respectively). Given the substantial proportion of patients crossing over to mogamulizumab in the vorinostat arm, the company argued that utility values calculated from the trial for the post-vorinostat period were biased by the impact of mogamulizumab received as a subsequent treatment and therefore no differential utility value was used for the subsequent treatment health state between mogamulizumab and comparator treatment.[1]

Data from TA577 were used for utility values associated with subsequent aSCT (0.42 in the first two weeks, 0.60 from week 3 to month 4, and 0.77 from three months onwards[79]) and for end-stage care (0.38).[68, 79] In alternative scenario analyses, data from TA577 were used for utility values of progression-free (0.689) and for post-progression (0.61).[68, 80]

Given the significant high demand on carers' and family resources of advanced CTCL, a vignette study to evaluate carer utilities was undertaken.[81] Carer disutilities were based on a vignette study, in which vignettes were informed by a targeted review of qualitative studies with individuals with CTCL and/or their caregivers and interviews with CTCL specialists. Vignettes were scored by subjects from the general population and valued using the van Hout mapping algorithm.[82] Three health state vignettes were developed to describe the experience of caring for an individual with advanced CTCL, i.e. one described caring for an individual who was receiving second line treatment, one describing an individual on third line treatment, and one describing an end of life state. A carer utility gain was included in the model using the utility value of the incremental difference between caring for a patient in second line of treatment versus caring for a patient in third line of treatment (utility values of [redacted]) for the time spent in the "Disease control"-state by using the incremental time spent by patients in the mogamulizumab arm versus the ECM arm. Hence, caregivers' utilities were assumed to be related to the time spent in the disease control state for both treatments.

5.2.8.1 Health-related quality of life data identified in the review

According to the CS, the SLR identified three unique studies for inclusion, one being limited to a disutility estimate for adverse effects as a result of treatment with interferon alfa 2 beta, methotrexate or alemtuzumab.[1] The MAVORIC data and TA577-reported ALCANZA patient utility data appeared to be the only published or directly available evidence for health state utility estimates in CTCL.

A summary of utility values used in the base-case cost effectiveness analysis is provided in Table 5.6.

Table 5.6: Health state utility values

State	Utility value	Reference	Justification
On Tx, cycle 1-2, mogamulizumab	[redacted]	Patient-reported EQ-5D data from the pivotal RCT (MAVORIC trial)	Trial data
On Tx, cycle 3-4, mogamulizumab	[redacted]		
On Tx, cycle 5-6, mogamulizumab	[redacted]		
On Tx, cycle 7-8, mogamulizumab	[redacted]		
On Tx, cycle 9-10, mogamulizumab	[redacted]		
On Tx, cycle 11-12, mogamulizumab	[redacted]		
On Tx, cycle 12+, and Surveillance, mogamulizumab	[redacted]		
On Tx, cycle 1-2, ECM	[redacted]		
On Tx, cycle 3-4, ECM	[redacted]		
On Tx, cycle 5-6, ECM	[redacted]		
On Tx, cycle 7-8, ECM	[redacted]		
On Tx, cycle 9-10, ECM	[redacted]		
On Tx, cycle 11-12, ECM	[redacted]		
On Tx, cycle 12+, and Surveillance, ECM	[redacted]		
Subsequent treatments, mogamulizumab and ECM	[redacted]	Patient-reported EQ-5D data from the pivotal RCT for mogamulizumab	Due to cross-over, similar data for mogamulizumab and ECM
End-stage care	[redacted]	SLR	Also used for decision making in TA577
Post-SCT (first two weeks)	[redacted]		
Post-SCT (week 3 to month 4)	[redacted]		

State	Utility value	Reference	Justification
Post-SCT (3 months onwards)	[redacted]		
Career utility gain	[redacted]	New vignette study	
Based on Table 38 of the CS [1] ECM = established clinical management; EQ-5D = European Quality of Life-5 Dimensions; RCT = randomised controlled trial; TA = technology assessment; Tx = treatment			

5.2.8.2 Adverse event related disutility values

Despite that the company mentioned that only grade 3 and 4 AEs were included as they have important impact on the costs and quality of life, no adverse event related disutilities were taken into account in the model. Only costs were applied for AEs as a lump sum at the start of treatment.

ERG comment: The main concerns of the ERG relate to: a) the use of cycle-specific utility values over the first 12 weeks; b) lack of transparency on how utility values were derived; c) the absence of impact of adverse events on health state utilities; d) concerns regarding the inclusion of caregivers' disutilities.

Re a) The ERG questioned the company's use of cycle-specific utility values in the first 12 weeks paired with a counter-intuitive pattern of utility values over time (for example for mogamulizumab, increase in cycle 5, decrease in cycle 7, increase in cycle 9). In response to clarification question B12, the company stated that *"there is a trend of the utilities increasing over time while patients are on mogamulizumab"*.[20] Furthermore, the company stated that this may be due to the response to treatment and the subsequent potential reduction or disappearance of symptoms, and that differences between individual cycles were small and not statistically significant (probably only by chance).[20] The ERG was also concerned that the use of cycle-specific utilities may be less robust, increase noise (e.g. as each parameters is separately estimated in the PSA) and add overall uncertainty to the model. The company implemented a scenario analysis using health-state specific utilities. In response to clarification question B12, the company stated that, for this scenario, the single health state utilities for the disease control health state were estimated as the average of all observations if at those visits the subject did not progress.[20] Hence, these health state specific (not cycle-specific) utilities were used in the ERG base-case.

Re b) It was not entirely clear to the ERG how cycle-specific, on treatment, and last observation post-progression utilities were derived as utilities in the MAVORIC trial were only collected while patients were on treatment (including patients crossing over to mogamulizumab) and during one additional visit after stopping treatment. In response to clarification question B14, the company provided some more explanation regarding the derivation of utilities for each state.[20] From this explanation, it was still not entirely clear to the ERG how on treatment utilities were derived (especially from the vorinostat arm). The company stated that, for on treatment utilities, the mean utilities were taken from observations for visits where the subject was assigned to mogamulizumab or vorinostat; i.e. for subjects randomised to mogamulizumab this was all on-treatment visits, and for subjects randomised to vorinostat this was the crossover visits only (if the subject crossed over).[20] From this statement, it appeared that only visits after cross-over were considered for the vorinostat arm, which appears incorrect. The ERG could not correct these utility values but explored using the same utility values for both treatment arms in a scenario to assess the potential size of impact on the ICER.

Re c) No AE-related disutilities were taken into account in the model and costs were applied as a lump sum at the start of treatment. In response to clarification question B15, the company stated that *"the impact of all adverse events on quality of life for both treatment arms are included in the utility values used in the model and no additional disutility was required to be included for adverse events"*.[20]. The ERG considers this argument to be reasonable given that utilities were estimated treatment-dependent and grade 3 and 4 AEs were relatively common in both groups and hence, difficult to estimate independently of current health states of patients.

Re d) The ERG considered that the inclusion of caregivers' utilities did not appear to be in accordance with the NICE's Reference Case for the Methods of Technology Appraisal as this states that *"the measurement of changes in health-related quality of life should be reported directly from patients and the utility of these changes should be based on public preferences using a choice-based method"*.[83] A study including only vignette health states was conducted to estimate carer disutilities. The ERG acknowledges, however, that guidance regarding the inclusion of caregivers' utilities is lacking. This was also emphasised by a recent report by the decision support unit commissioned by NICE in which it was stated that it is unclear when and how carer health effects should be included in economic evaluations.[84] The company's approach of only adding a utility gain for carers of patients in the disease control health state probably avoided some of the flaws of other implementation methods (such as implementing carer utilities throughout patients' lifetimes, which would add an additional benefit of patient survival). However, as it was unclear whether caregivers' utilities should be included and how they should be included in an economic evaluation, the ERG has excluded carers' utilities as part of the ERG base-case but included them in a scenario analysis.

5.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs, treatment administration costs, subsequent treatment costs (including aSCT, subsequent treatment costs after aSCT and subsequent treatments) and costs of managing grade 3/4 adverse events.

Unit costs for non-drug resources were obtained from the National Schedule of Reference Costs 2017-2018[85] and the Personal Social Services Research Unit (PSSRU) report,[86] and unit costs of drugs were obtained from the British National Formulary (BNF 2019)[87] and the Drugs and pharmaceutical electronic market information tool (eMIT 2019)[88] for generic products.

Resource use related to secondary care was based on the HES database, while resource use related to community care and treatments was based on published literature including information identified by a systematic literature review, and data from previous NICE TAs and expert opinion.

5.2.9.1 Resource use and costs data identified in the review

According to Appendix I of the CS, the SLR identified eight studies reporting cost and resource use evidence including three studies from the UK.[50]

5.2.9.2 Treatment costs

The average cost per administration of mogamulizumab was calculated by multiplying the recommended dose for mogamulizumab based on the MAVORIC trial (1 mg/kg), by the mean weight for European patients in the MAVORIC trial, which was 76.77 kg and the discounted price per vial of [redacted] The cost of a single vial containing 20 mg of mogamulizumab is £1,329, but [redacted] The average cost per administration was thus calculated to be [redacted] with dose banding (see Table 39 of the CS).[1] A scenario analysis, which assumed no wastage due to perfect vial sharing was conducted (leading to the mean cost per administration of [redacted] Comparator

treatment dosing was taken from TA577, the KOL survey and the London Cancer Alliance 2019[89] and comparator drug costs were reported in Table 40 of the CS.[1]

The first administration of peginterferon, and each administration of mogamulizumab, gemcitabine and liposomal doxorubicin was assumed to cost the same as the administration of simple parenteral chemotherapies, while CHOP was assumed to require the complex parenteral administration. The first administration of all other drug therapies was assumed to cost the same as the delivery of oral chemotherapies.

5.2.9.3 Health state costs

Resource use associated with patient observation and disease management for MF/SS was derived from the HES database.[90] It should be noted that in TA577, health state costs were based on expert opinion and were heavily criticised by the ERG and the committee.[68] To reduce the uncertainty of these estimates, a retrospective study was conducted using the HES database containing details of all inpatient admissions, Accident and Emergency (A&E) attendances and outpatient appointments at NHS hospitals in England.[90] The retrospective study was used for different time periods for inpatient/outpatient care. Costs per patient-week from diagnosis and from death are reported in Tables 42 and 43 of the CS, respectively.[1] For community-based costs, resource use from the NICE TA577 using ERG's preferred scenario was multiplied with current unit costs.[68]

The cost of aSCT was based on the methodology used in NICE TA567, which was using UK data.[91] The transplant cost, £35,472.26, is the weighted average of three NHS Reference Costs 2017/18 Total healthcare resource group (HRG; SA38A, SA39A and SA40Z), while the follow-up costs, £42,239.35, for two years were based on the UK Stem Cell Strategy Oversight Committee 2004 inflated to 2017/2018. The costs of treatments after aSCT were estimated based on NICE TA577.[68] The cost of subsequent treatment for patients without and with aSCT was £5,891 and £2,415, respectively.

Subsequent treatments (modelled as a health state) after mogamulizumab and ECM were assumed to be the same and were derived from a clinician survey and interviews. Length of subsequent treatments were based on expert opinion and literature (see Tables 46 and 47 from the CS).[1] Health state related costs are reported in Table 5.7.

Table 5.7: Health state related costs

Health state	Costs	Cost components considered	Reference resource use
Disease control	Inpatient-outpatient service + community based costs	[redacted] per week	HES database + NICE TA 577 (Table 44 of the CS)[68, 90]
Subsequent treatments		[redacted] per week	
End-stage care		[redacted] per week	
aSCT	Transplant costs and follow-up	77,712	NHS Reference Costs 2017/18 Total HRGs: weighted average of SA38A, SA39A and SA40Z, Assumed follow-up costs from TA567[91]

Health state	Costs	Cost components considered	Reference resource use
Cost of subsequent treatment after aSCT		5,405	NICE TA577[68]
Based on Table 44 of the CS[1] aSCT = allogenic stem cell transplant; CS = company submission; HRG = healthcare resource group; NICE = National Institute for Health and Care Excellence; TA = technology appraisal			

5.2.9.4 Adverse event related costs

AE costs (see Table 45 of the CS) were calculated based on the reported incidence of relevant grade 3-4 AEs reported in the MAVORIC trial.[1] Costs for each of the AEs were taken from previous TAs (TA306, TA567, TA584, TA600).[1] The cost for sepsis was a weighted average of related codes in NHS reference costs (WJ06A-J).[85] Expert opinion was required for aspartate aminotransferase increase, constipation, dysgeusia, headache, infusion related reactions, muscle spasm and peripheral oedema.[1]

ERG comment: The main concerns of the ERG relate to: a) the length of subsequent treatments; b) 24-month stopping rule; c) the list of included interventions in ECM.

Re a) It was not entirely clear to the ERG how the length of treatment for subsequent therapies and subsequent treatment costs modelled was determined based on expert opinion and interviews. In response to clarification question B18, the company elaborated on this process and provided scenario analyses in which the effect of treatment duration of each comparator, and the use of bexarotene as the main comparator was varied.[20] This showed only a small impact on the ICER (marginally lower ICERs compared to the company's base-case).

Re b) A 24-month treatment stopping rule for mogamulizumab was assumed in the model, which is neither in line with the licence nor with the evidence from the MAVORIC study.[71] In response to clarification question B7, the company also stated that at 24 months approximately [redacted] of patients would be still receiving mogamulizumab in the advanced population.[20] As treatment effect was derived from this trial and as some patients were still on treatment after 24 month, effectiveness was likely over-estimated in the trial compared to what it would be in practice when such a stopping rule was to be enforced. Treatment costs are thus lower in the model without adjusting the likely lower treatment effect. The ERG considers that applying the stopping rule on treatment costs with adjusting treatment effectiveness will lead to biased outcomes. Hence, the ERG excluded the stopping rule in the ERG base-case.

Re c) The proportion of patients using different comparators within the ECM arm was based on expert opinion elicited using a short survey either by mail or face-to-face interviews.[1] As both the type of treatments included in the ECM and the proportions of each comparator were not observed in a clinical study, the ERG consulted an independent expert who in turn expressed an opinion regarding the included comparators. This led to some discrepancies, for example, the expert consulted by the ERG regarded methotrexate, bexarotene, and interferon alfa-2a (peginterferon) as first or second line treatments only. It is not clear to the ERG what the cause is for these differences. Appendix U of the CS does not specify the country in which the clinical consultants work.[50] Clinical experts who participated in the UK CTCL advisory board meeting were based in the UK, however, it was unclear whether those experts also participated in the interviews held to determine treatment mix for ECM.[14] If

the consultants are working outside the UK this may be an explanation for the discrepancies. To conclude, the ERG is concerned about the representativeness of the treatment mix in the ECM arm but the impact of this on the ICER is likely small, as discussed in section 5.2.4.

6 Cost effectiveness results

6.1 Company's cost effectiveness results

In the deterministic base-case analysis, total LYs and QALYs gained were larger for mogamulizumab than for ECM. Incremental QALYs (2.83) were mainly driven by QALY gains in the subsequent treatment health state, where patients in both arms spent most time (by an increment of [redacted] life years (LYs) for mogamulizumab versus ECM). Total costs were also higher for mogamulizumab than for ECM. Incremental costs ([redacted]) mainly resulted from higher drug costs and monitoring costs after subsequent treatment. The deterministic ICER amounted to £33,819 per QALY gained (Table 6.1).

6.2 Company's sensitivity analyses

The company performed a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analyses (DSA) to explore the uncertainty surrounding the base-case results.

Compared with the deterministic results, the PSA with 1,000 iterations showed similar incremental QALYs and slightly lower costs, which resulted in an ICER of [redacted] (Table 6.1). The cost effectiveness acceptability curve in the economic model showed that mogamulizumab had a 22% and 98% probability of being cost effective at willingness-to-pay (WTP) thresholds of £30,000 and £50,000, respectively.

The company performed DSAs by varying key model parameters between their upper and lower confidence interval limits or standard error. The ICER was most sensitive to the utility after subsequent treatments, mogamulizumab OS log-normal, and mogamulizumab administration costs. In all of these DSAs, the ICER exceeded the WTP threshold of £30,000.

6.2.1 Scenario analyses

The company conducted several scenario analyses. The results for mogamulizumab versus ECM showed ICERs ranging between £28,661 and £45,872 per QALY gained. The three most influential scenarios that increased the ICER were using the two-stage adjustment to correct for cross-over with full variable set (£45,872) and restricted variable set (£44,123), and using the Weibull distribution for OS for both arms (£42,900). The three most influential scenarios that decreased the ICER were applying a 0% discount rate to costs and health outputs (£28,661), applying per mg costing (perfect vial sharing) for mogamulizumab (£32,837) and using the loglogistic distribution for NTFS (£33,492).

Table 6.1: Deterministic and probabilistic base-case results (discounted)

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Deterministic	[redacted]	3.69	2.83	£33,819
Probabilistic	[redacted]	3.69	2.83	£33,611
ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year				

ERG comment: The main concerns of the ERG relate to the additional requested scenario analyses or adjustments to the base-case. Although the company provided most of the additional requested scenario

analyses, some requested analyses or adjustments were not provided. The ERG requested the following scenarios/base-case adjustments:

1. extended time horizon (clarification question B2; analysis performed but updated model not provided)[20]
2. a scenario analysis in which all parameters for the comparator (standard care) were all informed using data from physician's choice (i.e. methotrexate or bexarotene) from the ALCANZA study (clarification question B3; a scenario was provided using part of the ALCANZA data)[20]
3. a scenario analysis using PFS and OS instead of NTFS and OS (clarification question B4; scenario analysis provided)[20]
4. scenario analysis with RPSFT model for crossover adjustment (clarification question B5; scenario analysis provided)[20]
5. scenario in which treatment waning is applied to mogamulizumab OS, NTFS and PFS (clarification question B7d; scenario provided)[20]
6. scenario in which there is no stopping rule (clarification question B7e; scenario provided)[20]
7. a scenario in which DFS and OS after aSCT are estimated in a way that includes censoring and in which only the KM data approximately up to 24 months are used (clarification question B10; scenario not provided)[20]
8. a scenario using a gamma distribution for all cost parameters (clarification question B21; analysis performed but updated model not provided)[20]
9. the inclusion of ToT estimates in the PSA (clarification question B22; not incorporated into PSA but alternative scenario analyses presented)[20]

Furthermore, the company provided additional (non-requested) scenario analyses in which the effect of treatment duration of each comparator, and the use of bexarotene as the main comparator was varied (in response to clarification question B18).[20] Overall, the ERG was satisfied with the company's response to most of the requested analyses. However, the company was not able to provide important additional analyses looking at the impact of the possible biased KM data for DFS and OS after aSCT (given the possibility of censoring) and survival models based on the ALCANZA study.

6.3 Model validation and face validity check

6.3.1 Face validity

The model structure and inputs (i.e. survival estimates, current treatment practice for MF/SS, proportion of patients using aSCT, and whether mogamulizumab changes treatment pattern) were validated using five in-depth interviews with one clinical oncology consultant and two dermatology consultants.[13] Additionally, an advisory board meeting was conducted.[14]

6.3.2 Internal validity

A model validator not involved in the original programming checked the calculation and reference formulas, and an additional team member checked the values of numbers supplied as model inputs.[1]

6.3.3 Cross validity

After the clarification phase, in response to clarification question B23, the company provided cross-validation of the submitted cost effectiveness analysis compared with NICE TA577.[20, 68] This cross-validation was limited to model structure and major assumptions, estimates such as proportions receiving aSCT, health state utilities, and costs.

6.3.4 External validity

To assess clinical plausibility of the overall survival curves excluding patients with aSCT used in the model, estimates were compared to published observational data, data from the HES database and clinical expert opinion (see above). To this extent, the company identified three publications: Agar 2010[10], Kim 2003[74], and Talpur 2012[23].

In the HES database, survival was available for 82 MF and 14 SS patients after one prior systemic treatment.[90] The company stated however that the published data and the HES database included populations with better expected survival, less heavily pre-treated patients, and lower proportion of patients with stage IV disease.[1]

ERG comment: The main concerns of the ERG relate to: a) the lack of cross-validation regarding survival curves and b) the fit of the IPCW cross-over adjustment to the external validation data.

a) The company did not provide possible explanations for different results especially in the comparator group (regarding OS and PFS, life-years (LYs) and QALYs gained, and health state and comparator costs) compared with NICE TA577.[68]

b) During the clarification phase, the ERG requested that the company provide justification for why the IPCW method was chosen in the base-case instead of the TSE method (clarification question B5).[19] In response to this request, the company argued that the presented survival estimates from the available observational data was expected to be a high upper limit of the expected survival.[20] Additionally, the company pointed out that TSE estimates appear to be above these upper thresholds of 1 to 20 year survival from the observational data. The ERG is not fully convinced by these arguments as it notes that, while some of the estimates in the TSE method are indeed higher compared to some of the observational data, the estimates appear to fit relatively well to the most recent identified paper by Talpur 2012 et al. (with lower TSE survival estimates, as expected in a more severe population) and fit relatively well to estimates of experts.[23]

7 Evidence Review Group's additional analysis

7.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 7.1 summarises the main issues highlighted by the ERG in section 5.2, indicates the expected direction of bias introduced by these issues and whether these are examined in ERG analysis either in the base-case or as a scenario conditional on the base case.

Table 7.1: Main ERG critique of company's submitted economic evaluation

Issue: numbered if included in ERG base-case (BC)	Likely direction of bias introduced in ICER[a]	ERG analyses (BC or scenario)	Addressed in company analysis?
Model structure (section 5.2.2)			
6. Incorrect implementation of patients receiving aSCT after current treatment	+	BC	-
Variability in timing of aSCT not reflected	+/-	-	-
2. Wash-out period not fully considered in modelling of aSCT after current treatment in the mogamulizumab trace	-	BC	-
Population, interventions and comparators, perspective and time horizon (sections 5.2.3 to 5.2.5)			
Subgroup of advanced population used (not ITT)	+/-	Scenario	Scenario
Comparator evidence based on proxy (vorinostat)	+/-	-	Scenarios
Composition of ECM arm	+/-	-	-
5. Time horizon is not lifetime	-	BC	Scenario
Treatment effectiveness and extrapolation (section 5.2.6)			
7. OS estimates confounded by crossover: IPCW method used in CS	+	BC & scenarios	Scenarios
8. OS uncertain extrapolations: choice of lognormal in CS	+	BC	Scenarios
OS estimated excluding patients with aSCT	+/-	-	Scenarios
9. Extrapolation of NTFS: choice of generalised gamma in CS	-	BC	Scenarios
6. Proportions of patients receiving aSCT uncertain	+/-	BC	Scenarios
10. Extrapolation of DFS after aSCT: choice of Gompertz DFS	+	BC	Scenarios
Health-related quality of life (section 5.2.8)			
11. Caregivers' utilities	-	BC	Scenario
12. Utilities in first 12 weeks: choice of cycle-specific	+	BC	Scenario

Issue: numbered if included in ERG base-case (BC)	Likely direction of bias introduced in ICER[a]	ERG analyses (BC or scenario)	Addressed in company analysis?
3. Error in utility of PFS in TA577 scenario	?	BC	-
Resources and costs (section 5.2.9)			
4. 24- months stopping rule does not match the evidence or licence	+	BC	Scenario
1. Error in cost calculations for monitoring and subsequent treatments after aSCT in both mogamulizumab and ECM traces (cell link error).	-	BC	-

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator

aSCT = allogenic stem cell transplant; BC = base-case; CS = company submission; DFS = disease-free survival; ECM = established clinical management; ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; IPCW = inverse probability of censoring weighting; ITT = intention-to-treat; MJ = matters of judgement; NTFS = next treatment-free survival

Based on all considerations in section 5.2 (summarised in Table 7.1), the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016)[92]:

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

7.1.1 Fixing errors

1. Error in cost calculations for monitoring and subsequent treatments after aSCT in both mogamulizumab and ECM traces (cell link error). The ERG corrected the error.
2. Wash-out period not fully considered in modelling of aSCT after current treatment in the mogamulizumab trace. The ERG corrected the error.
3. Error in utility of PFS in TA577 scenario. The ERG corrected the error.

7.1.2 Fixing violations

4. 24-months stopping rule does not match the evidence or licence (section 5.2.9). The ERG disabled the stopping rule.
5. Time horizon is not lifetime (section 5.2.5). The ERG used the company's alternative setting of the time horizon to 45 years.
6. Incorrect implementation of patients receiving aSCT after current treatment (section 5.2.2). The ERG disabled aSCT after current treatment.

7.1.3 Matters of judgement

7. OS estimates confounded by crossover: IPCW method used in CS (section 5.2.6). The ERG used the TSE method instead of IPCW for adjusting for crossover.
8. OS uncertain extrapolations: choice of lognormal in CS (section 5.2.6). The ERG used the exponential model for extrapolating mogamulizumab OS instead the of lognormal.
9. Extrapolation of NTFS: choice of generalised gamma in CS (section 5.2.6). The ERG used the lognormal model instead of the generalised gamma for mogamulizumab NTFS.
10. Extrapolation of DFS after aSCT: choice of Gompertz: The ERG used the lognormal model instead of the Gompertz for DFS after aSCT.
11. Caregivers' utilities: The ERG disabled caregivers' utilities.
12. Utilities in first 12 weeks choice of cycle-specific: The ERG used a single health state-specific utility for 'on treatment' (and not cycle-specific)

Results are presented in Table 7.2.

7.1.4 Additional sensitivity analyses

Additional sensitivity analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. Exploratory analyses conditional on the ERG base-case included:

1. Include caregiver utilities as per company's modelling
2. PFS model structure instead of NTFS

3. ITT population instead of advanced disease
4. IPCW method used for crossover adjustment
5. Model averaging using 30% IPCW / 70% TSE method
6. Use of OS estimates without crossover adjustment

Results are presented in Table 7.3.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Table 7.2 shows how individual adjustments impact the results plus the combined effect of all aforementioned adjustments simultaneously, resulting in the (deterministic) ERG base-case. The 'fixing error' adjustments were combined and the other ERG analyses were performed also incorporating these 'fixing error' adjustments given the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues. The exploratory scenario analyses are presented in Table 7.3. These are all conditional on the ERG base-case. The submitted model file contains technical details on the analyses performed by the ERG (e.g. the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

Table 7.2: Deterministic (unless indicated) ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Mogamulizumab	[redacted]	4.60	[redacted]	2.83	£33,819
ECM	[redacted]	1.78			
CS base-case with errors 1-3 corrected by ERG					
Mogamulizumab	[redacted]	4.61	[redacted]	2.83	£33,326
ECM	[redacted]	1.78			
Fixing violation (4, no stopping rule assumed)					
Mogamulizumab	[redacted]	4.61	[redacted]	2.83	£37,850
ECM	[redacted]	1.78			
Fixing violation (5, time horizon of 45 years)					
Mogamulizumab	[redacted]	4.64	[redacted]	2.85	£33,250
ECM	[redacted]	1.78			
Fixing violation (6, 0% aSCT after current treatment assumed)					
Mogamulizumab	[redacted]	4.49	[redacted]	2.91	£33,874
ECM	[redacted]	1.58			
Matter of judgement (7, OS: use TSE method instead of IPCW)					
Mogamulizumab	[redacted]	4.61	[redacted]	1.70	£45,026
ECM	[redacted]	2.91			
Matter of judgement (8, OS: use exponential instead of lognormal for mogamulizumab)					
Mogamulizumab	[redacted]	3.99	[redacted]	2.21	£38,550
ECM	[redacted]	1.78			
Matter of judgement (9, NTFS: use lognormal instead of gengamma for mogamulizumab)					
Mogamulizumab	[redacted]	4.59	[redacted]	2.81	£33,640
ECM	[redacted]	1.78			

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Matter of judgement (10, DFS after aSCT: use lognormal instead of Gompertz)					
Mogamulizumab	[redacted]	4.61	[redacted]	2.83	£33,956
ECM	[redacted]	1.78			
Matter of judgement (11, OS: no caregiver utilities assumed)					
Mogamulizumab	[redacted]	4.43	[redacted]	2.65	£35,547
ECM	[redacted]	1.78			
Matter of judgement (12, single utility-specific health states for "on treatment")					
Mogamulizumab	[redacted]	4.63	[redacted]	2.83	£33,340
ECM	[redacted]	1.80			
ERG base-case (deterministic)					
Mogamulizumab	[redacted]	3.63	[redacted]	0.85	£100,690
ECM	[redacted]	2.78			
ERG base-case (probabilistic)					
Mogamulizumab	[redacted]	3.66	[redacted]	0.86	£98,856
ECM	[redacted]	2.80			

aSCT = allogenic stem cell transplant; CS = company submission; ECM = established clinical management; DFS = disease-free survival; ECM = established clinical management; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IPCW = inverse probability of censoring weighting; NTFS = next treatment-free survival; OS = overall survival; QALY = quality-adjusted life year; TSE = two-stage estimation

Table 7.3: Deterministic (unless indicated) scenario analyses conditional on ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Mogamulizumab	[redacted]	3.63	[redacted]	0.85	£100,690
ECM	[redacted]	2.78			
Scenario (1, caregiver utilities assumed)					
Mogamulizumab	[redacted]	3.81	[redacted]	1.03	£83,382
ECM	[redacted]	2.78			
Scenario (2, PFS model structure instead of NTFS model structure)					
Mogamulizumab	[redacted]	3.49	[redacted]	0.87	£99,046
ECM	[redacted]	2.63			
Scenario (3, ITT population instead of advanced disease only)					
Mogamulizumab	[redacted]	3.84	[redacted]	0.96	£82,837
ECM	[redacted]	2.89			
Scenario (4, OS: use IPCW method instead of TSE method)					
Mogamulizumab	[redacted]	3.63	[redacted]	2.04	£51,223
ECM	[redacted]	1.60			
Scenario (5, probabilistic, OS: use 30% IPCW and 70% TSE method)					
Mogamulizumab	[redacted]	3.66	[redacted]	1.22	£74,229

ECM	[redacted]	2.44			
Scenario (6, OS: use no crossover adjustment)					
Mogamulizumab	[redacted]	3.63	[redacted]	-0.31	Dominated
ECM	[redacted]	3.95			

ECM = established clinical management; ECM = established clinical management; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IPCW = inverse probability of censoring weighting; ITT = intention-to-treat; NTFS = next treatment-free survival; PFS = progression-free survival; OS = overall survival; QALY = quality-adjusted life year; TSE = two-stage estimation

Many uncertainties were identified. Some of these, although not all, were explored in the PSA, or through scenario analysis, and were shown to be impactful, especially the cross-over adjustment method chosen, OS extrapolations and incorporation of aSCT. Some issues could not be explored using PSA or scenarios, namely: the comparator effectiveness being based on a proxy, and the implementation issue with aSCT after current treatment. An overview of the uncertainties in different model aspects and their potential impact on cost effectiveness findings, as filled in in the TRUST tool[93], is shown in appendix 1.

7.3 ERG's preferred assumptions

The ERG's preferred assumptions are those that were outlined in section 7.2, where the individual effect of each change to the model was shown and the cumulative effect of all ERG preferred assumptions in the ERG base-case. The cumulative of the ERG's preferred assumptions are shown below.

Table 7.4: ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company base-case	6.1	£33,819
1 to 3.Corrections made by ERG		£33,326
No stopping rule	5.2.9	£37,850
Prolonged time horizon	5.2.5	£37,737
No aSCT after current treatment	5.2.2	£38,563
TSE method for crossover adjustment	5.2.6	£54,090
Exponential for mogamulizumab OS	5.2.6	£79,949
Lognormal for mogamulizumab NTFS	5.2.6	£82,042
Lognormal for DFS after aSCT	5.2.6	£83,282
No caregiver utilities	5.2.8	£100,544
No cycle-specific utilities	5.2.8	£100,690

aSCT = allogenic stem cell transplant; DFS = disease-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; NTFS = next treatment-free survival; OS = overall survival; QALY = quality-adjusted life year; TSE = two-stage estimation

7.4 Conclusions of the cost effectiveness section

The CS is overall of high quality and transparently described.[1] The company's model is functional and allows for exploration of multiple relevant scenarios.[71] The submission appears complete in terms of the studies included and data used. The submission is mostly in line with the NICE reference case, with some concerns: most prominently, the comparative evidence informing this appraisal did not include a relevant comparator in the UK (see section 3.2). Secondly, the company included caregiver utilities, which were based on a vignette study. It should also be noted that the company's decision problem is

narrower than the NICE scope (with only the advanced population used in the CS, see section 3.1) Overall, the company's ICER is very uncertain and likely biased, an product of issues with the evidence, uncertainty about methods and model assumptions. It is worth noting that the main driver of cost effectiveness is overall survival, largely as a result of the large number of patients switching treatment in the main trial, and that any estimates of it are very uncertain

The company identified no economic evaluations addressing the decision problem it wishes to target. Searches and eligibility criteria were appropriate and therefore it is unlikely that relevant studies were missed. In the absence of economic evaluations for this decision problem, the company developed a de novo economic evaluation. The company's economic evaluation met most of the NICE reference case criteria, except for the inclusion of caregivers' utilities, which were based on a vignette study. It is worth highlighting that the company's decision problem is narrower in focus than NICE's scope, focusing on patients with advanced disease (stage ≥IIB MF and all SS patients). This meant that clinical effectiveness was based on a subgroup of MAVORIC; the ITT population was used in an exploratory analysis. Due to lack of evidence on any appropriate UK comparator, which might be regarded as ECM, the company used evidence on relative treatment effectiveness comparing mogamulizumab to a proxy used in MAVORIC, i.e. vorinostat, which is not licensed in the EU, is not in the NICE scope and was identified by the company as not ECM.

The ERG appreciated the difficulty in obtaining appropriate comparative evidence as well as the company's efforts to establish that evidence on vorinostat could be used to inform the ECM arm in the model, but considered that the lack of direct comparator data for the ECM arm remained a major concern in the appraisal of mogamulizumab. The partitioned survival analysis using different pathways to reflect the possibility of patients receiving aSCT was deemed an appropriate reflection of clinical practice in theory. However, the company's technical implementation probably introduced bias in the model population, which the ERG considered not reflective of clinical practice. There were also safety concerns about aSCT after treatment with mogamulizumab, which the company attempted to address by including a wash-out period in their model. Other concerns about the modelling of aSCT included that the variability of timing of aSCT was not reflected and that proportions of patients receiving aSCT were uncertain and probably over-estimated in the model. The company used NTFS instead of PFS (the primary endpoint in MAVORIC), based on it being more closely aligned with symptoms and disease control, which was therefore considered a better proxy for treatment changes, HRQoL and resource utilisation. After consultation with a clinical expert, the ERG agreed on this, but explored the impact of using a PFS-based model instead. OS was based on MAVORIC, but it was only an exploratory, not a primary, endpoint. As such, MAVORIC was not powered to estimate OS, and maturity was not achieved. All OS extrapolations were therefore highly uncertain. The choice of parametric survival model for extrapolation of OS had a high impact on model outcomes and was associated with substantial uncertainty. However, the main problem with estimating the effectiveness of mogamulizumab versus vorinostat was that the comparator OS estimates, derived from MAVORIC, were confounded by crossover, which required adjustment in statistical analyses. Different adjustment methods had vastly different results. All methods relied on assumptions that may not be fulfilled. Based on critical appraisal of the methods and consultation with a clinical expert, the ERG considered the TSE method to best reflect comparator OS, but with the caveat of uncertainty. The alternative, the IPCW method, was used in an exploratory analysis. There was a lack of clarity in the estimation of utility values based on MAVORIC, which was not completely resolved. Furthermore, the inclusion of caregivers' utilities, whilst not unprecedented, lacked guidance on whether their inclusion was appropriate and, if so, how this should be done. The implementation of a 24-months stopping rule was not in line with MAVORIC or the licence and the ERG therefore preferred not to use it.

Based on these considerations, the ERG made multiple changes to the model, including fixing errors, fixing violations and matters of judgement. It is important to note that both the company's and ERG's ICERs suffered from large uncertainty and should be interpreted with caution.

8 End of life

In the CS, the company did not include any statement regarding mogamulizumab meeting the end of life criteria defined by NICE.[1, 50]

9 References

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Appendix 1: The TRansparent Uncertainty ASsessmenT tool

Table A1.1: The TRansparent Uncertainty ASsessmenT tool (TRUST)

	Item	Sources of uncertainty					Impact on cost effectiveness			
		Lack of transparency	Methods	Imprecision	Bias	Unavailability	NOT in PSA	NOT in Scenario analysis	Impact on cost effectiveness	Remarks
Context / scope	PICOTP	No	Yes	N/A	Yes	No	N/A	No	Likely low	Methods: Narrower population than in scope, ITT analysis used in scenario, Biases: comparator treatment mix based on EO and comparator evidence based on a proxy, time horizon was short
Model structure	Health states and how they relate to each other	No	Yes	N/A	Yes	N/A	Yes	No	Likely high	Methods: incorrect implementation of aSCT after current treatment and wash-out period, Bias: there may be safety concerns about aSCT after mogamulizumab, proportions may be biased
Selection of evidence	Identification and selection of sources for evidence on effectiveness, safety, utilities & costs	No	No	N/A	No	No	N/A	N/A	Likely no impact	

		Item	Sources of uncertainty					Impact on cost effectiveness			
			Lack of transparency	Methods	Imprecision	Bias	Unavailability	NOT in PSA	NOT in Scenario analysis	Impact on cost effectiveness	Remarks
Model	**Inputs**	Transition probabilities / time to event / accuracy estimates	No	No	No	Yes	Yes	Yes	Yes	Likely high	Bias: censoring assumption about OS and DFS after aSCT (not explored), Unavailability: proportions of patients receiving, and time points of, aSCT in UK clinical practice, after current treatment, safety concerns about aSCT after mogamulizumab treatment may lead to no aSCT possible after mogamulizumab (not explored)
		Relative effectiveness estimate	No	No	Yes	Yes	No	Yes	No	Likely high	Imprecision: MAVORIC was not powered to detect OS differences, Bias: OS and NTFS based on post-hoc analyses (scenario for ITT, scenario with aSCT included), crossover design of MAVORIC and different adjustment methods are biased (scenarios with different methods), extrapolation of OS (scenarios),
		Adverse events	No	No	No	Yes	No	Yes	No	Likely no impact	Bias: AEs estimated based on proxy to comparator
		Utilities	Yes	Yes	No	Yes	No	Yes	No	Likely high	Transparency: Estimation of utility values unclear, Methods: vignette study for

		Item	Sources of uncertainty					Impact on cost effectiveness			
			Lack of transparency	Methods	Imprecision	Bias	Unavailability	NOT in PSA	NOT in Scenario analysis	Impact on cost effectiveness	Remarks
											derivation of caregivers' utilities, Bias: lack of guidance re caregiver utilities
		Resource use & costs	No	No	No	Yes	No	Yes	No	Likely high	Bias: stopping rule not in accordance with evidence or licence, treatment mix of comparator unclear (small impact)
	Implementation	Technical implementation	No	Yes	N/A	N/A	N/A	N/A	N/A	N/A	Incorrect implementation of aSCT
Outcomes		ICER, costs, life-years, QALYs gained	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

AE = adverse events; aSCT = allogeneic stem cell transplant; DFS = disease free survival; EO = expert opinion; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; N/A = Not applicable; NTFS = next treatment-free survival; OS = overall survival; PICOTP = Population, Intervention, Comparison, Outcomes, Time, Perspective; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; TRUST = The TRansparent Uncertainty ASsessmenT tool; UK = United Kingdom

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Mogamulizumab for treated mycosis fungoides or Sézary syndrome T-cell lymphoma [ID1405]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm** on **Monday 30 March** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Critique on SLR search methodology -1

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 14 of the ERG report it states: *The ERG was concerned about the overall quality of the searches conducted, as truncation and proximity operators were used inconsistently; MEDLINE and Embase were searched simultaneously without including both MeSH and EMTREE subject heading indexing terms, which may have impaired how well the strategies performed; the date ranges of searches were not reported; and the Cochrane Library searches were not accurately reported. However, the searches were adequate, and given the range of resources searched, it was unlikely that any relevant studies were missed.* Similar statements are made on pages 46, 79 and 82 This is mis-leading given the searches were comprehensive and robust which utilised the study design filter adapted from with the Information Specialists'	Kyowa Kirin requests that the ERG update the sentence to: *The ERG is aware that MEDLINE and Embase were searched simultaneously including only EMTREE subject heading indexing terms which is much broader than MeSH but searching only EMTREE may have impaired how well the strategies performed. However, the searches were adequate, and given the range of resources searched, it was unlikely that any relevant studies were missed.*	The implication from the statement in the ERG report is that searches were not accurately conducted. However, truncation and proximation characters as highlighted by ERG was only used in study design facet and not in the disease facet. The study design facet is adapted from the Information Specialists' Sub-Group (ISSG) Search Filters Resource website using the syntaxes available in EMBASE.com. As mentioned in the Appendix D of the CS, no time limits were applied for the clinical effectiveness which was searched from the database inception date. In clarification to response A2, the date range and the detailed search strategies for Cochrane library was already clarified.	Not a factual error. The ERG report highlighted issues regarding the quality and reporting of the searches. However, it concluded that the searches were adequate, and "it was unlikely that any relevant studies were missed".

Sub-Group (ISSG) Search Filters Resource website.			

Issue 2 Critique of SLR methodology -2

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On pg 81 of the ERG report, in Table 5.1 *Date range of the electronic databases were not reported* This is misleading since searches were limited from 2009 onwards	Kyowa Kirin requests that the Table 5.1 of the ERG report should be amended to include *Date range – 2009 - 2019*	All the economic evidence for systematic review of cost-effectiveness and cost-resource was limited from 2009 onwards to capture the most recent evidence base.	Not a factual error. Date range of searches not reported, no justification of date limit.

Issue 3 Data not marked as AIC as per company submission

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG comment</th></tr>
<tr><td>Values in Table 3.8 page 43 not marked as AIC</td><td>Kyowa Kirin requests that the ERG mark values as AIC, amended table as follows:
<table>
<tr><th></th><th colspan="2">MAVORIC</th><th>Duvic et al. 2001[48]</th></tr>
<tr><th></th><th>Mogamulizumab (n=184)</th><th>Vorinostat (n=186)</th><th>Bexarotene 300 mg/m²/d (n=56)</th></tr>
<tr><td colspan="4">Adverse Events (AEs), n (%)</td></tr>
<tr><td>Any AEs</td><td>[redacted]</td><td>[redacted]</td><td>93 (99)</td></tr>
<tr><td colspan="4">Serious Adverse Events, n (%)</td></tr>
<tr><td>Drug-related Treatment-emergent SAEs</td><td>36 (19.6)</td><td>30 (16.1)</td><td>2 (4)</td></tr>
<tr><td colspan="4">Discontinuation due to AEs, n (%)</td></tr>
<tr><td>Drug-related TEAEs</td><td>[redacted]</td><td>[redacted]</td><td>4 (7)</td></tr>
<tr><td colspan="4">Based on Table 9 of the response to request for clarification[20]
AE = adverse event; mg = milligram; SAE = serious adverse event; TEAE = treatment-emergent adverse event</td></tr>
</table></td><td>The data have not been published</td><td>AiC marking has been amended.</td></tr>
<tr><td>Values in Table 4.10 page 64 not</td><td>Kyowa Kirin requests that the ERG mark values as AIC, amended table as follows:
<table>
<tr><th></th><th colspan="2">By investigator</th><th colspan="2">By blinded independent review</th></tr>
<tr><th></th><th>Mogamulizumab (n=186)</th><th>Vorinostat (n=186)</th><th>Mogamulizumab (n=186)</th><th>Vorinostat (n=186)</th></tr>
</table></td><td>The data have not been published</td><td>AiC marking has been</td></tr>
</table>

marked as AIC	Patients with PFS event, n (%)	110 (59.1)	131 (70.4)	[redacted]	[redacted]		amended.
	Progressive disease	104 (55.9)	128 (68.8)	[redacted]	[redacted]		
	Death	6 (3.2)	3 (1.6)	[redacted]	[redacted]		
	Patients censored n (%)	76 (40.9)	55 (29.6)	[redacted]	[redacted]		
	PFS (months)						
	Median (95% CI)	7.70 (5.67 to 10.33)	3.10 (2.87 to 4.07)	6.70 (5.63 to 9.37)	3.83 (3.00 to 4.70)		
	HR (95% CI)	0.53 (0.41, 0.69)		0.64 (0.49, 0.84)			
	Log rank P-value	<0.0001		0.0007			
	Q1[a]	2.9	1.9	[redacted]	[redacted]		
	Q3[a]	20.1	6.6	[redacted]	[redacted]		
	Percentage of patients alive without progressive disease at each 6-month interval (95% CI)						
	6 months	[redacted]	[redacted]	[redacted]	[redacted]		
	12 months	[redacted]	[redacted]	[redacted]	[redacted]		
	18 months	[redacted]	[redacted]	[redacted]	[redacted]		
	24 months	[redacted]	[redacted]	[redacted]	[redacted]		
	30 months	[redacted]	[redacted]	[redacted]	[redacted]		
	Based on Table 11 of the CS[1] and Table O-2 of the CS appendices[50] [a] Q1 is after 25% of patients had progressed or died, Q3 is after 75% of patients had progressed or died. CI = confidence interval; CS = company submission; HR = hazard ratio; PFS = progression-free survival; Q = quartile						

<table>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Table 4.11 Page 66- the following data should be marked as AIC and redacted from the published ERG report</td><td>Kyowa Kirin requests that the ERG mark values as AIC, amended table as follows:
<table>
<tr><th>Mogamulizumab after cross-over</th><th colspan="2">By BIR</th></tr>
<tr><th>(n=136)</th><th>Mogamulizumab (n=186)</th><th>Vorinostat (n=186)</th></tr>
<tr><td>41 (31.0 [redacted]</td><td>43 (23.0 [17.3 to 29.8])</td><td>7 (4 [1.5 to 7.6])</td></tr>
<tr><td>NR</td><td colspan="2">19.4 (9.0 to 29.4)</td></tr>
<tr><td>NR</td><td>54 (29.0)</td><td>13 (7.0)</td></tr>
<tr><td>NR</td><td>3 (1.6)</td><td>0</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td>The data are not yet published and are AIC</td><td>AiC marking has been amended.</td></tr>
<tr><td>Table 4.15 Page 71 - the following data should be</td><td>Kyowa Kirin requests that the ERG mark values as AIC, amended table as follows:

Table 0.1: TTNT after subsequent therapies per study design subgroup</td><td>The data are not yet published and are AIC</td><td>AiC marking has been</td></tr>
</table>

marked as AIC and redacted from the published ERG report	**Population**	**n**	**Mean (days)**	**SD**	**Median**			amended.
	Randomised to mogamulizumab	[redacted]	[redacted]	[redacted]	[redacted]			
	Randomised to vorinostat crossed-over to mogamulizumab	[redacted]	[redacted]	[redacted]	[redacted]			
	Vorinostat only	[redacted]	[redacted]	[redacted]	[redacted]			
	Pooled Mogamulizumab (randomised + crossover)	[redacted]	[redacted]	[redacted]	[redacted]			
	Based on supporting document, submitted as part of the CS[62] CS = company submission; SD = standard deviation; TTNT = time to next treatment							

Issue 4 Incorrect definition of TTNT

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Table 4.9, Page 61 TTNT is defined as ”TTNT was defined as time from the start date of first subsequent treatment to the start date of second subsequent therapy” This is the definition of time to next next treatment (TTNNT) in other areas of the report the TTNT definition has been cited correctly “	Kyowa Kirin requests that the ERG report should be amended to: TTNT is defined as “time from the start date of randomised treatment (end date of mogamulizumab treatment for crossover patients) to the start date of next systemic treatment (excluding topical steroids or focal radiation)”	Incorrect definition needs to be corrected	Corrected as suggested. It should be noted that the cited definition was (incorrectly) used in Table 12 of the response to request for clarification.

Issue 5 Incorrect presentation of comparative data

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG comment</th></tr>
<tr>
<td>In Table 4.16, Page 74

Data within the first two rows of this table has been presented incorrectly and therefore the Risk Difference which is presented is misleading
<table>
<tr><th rowspan="2"></th><th colspan="2">Mogamulizumab (n=186)</th><th colspan="2">Vorinostat (n=186)</th></tr>
<tr><th>MF (n=105)</th><th>SS (n=81)</th><th>MF (n=99)</th><th>SS (n=87)</th></tr>
<tr><td>ORR (confirmed CR + PR), n (% [95% CI])</td><td>13 (12.4 [6.8-20.2])</td><td>5 (5.1[1.7-11.4])</td><td>30 (37.0 [26.6 to 48.5])</td><td>2 (2.3 [0.3 to 8.1])</td></tr>
<tr><td>Risk difference (95% CI)</td><td colspan="2">7.3 (-6.5 to 21.0)</td><td colspan="2">34.7 (19.9 to 48.4)</td></tr>
</table>
</td>
<td>Kyowa Kirin requests that the ERG report should be amended to:
<table>
<tr><th rowspan="2"></th><th colspan="2">MF</th><th colspan="2">SS</th></tr>
<tr><th>Moga (n=105)</th><th>Vorinostat (n=99)</th><th>Moga (n=99)</th><th>Vorinostat (n=87)</th></tr>
<tr><td>ORR (confirmed CR + PR), n (% [95% CI])</td><td>13 (12.4 [6.8-20.2])</td><td>5 (5.1[1.7-11.4])</td><td>30 (37.0 [26.6 to 48.5])</td><td>2 (2.3 [0.3 to 8.1])</td></tr>
<tr><td>Risk difference (95% CI)</td><td colspan="2">7.3 (-6.5 to 21.0)</td><td colspan="2">34.7 (19.9 to 48.4)</td></tr>
</table>
Source CSR Tables 14.2.2.1.4
</td>
<td>Incorrect definition needs to be corrected</td>
<td>Table 4.16 has been amended accordingly.</td>
</tr>
</table>

Issue 6 aSCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
<u>Implementation of aSCT after current treatment in the model</u> ERG Report page 17 *Incorrect implementation of patients receiving aSCT after current treatment (section 5.2.2). The ERG disabled aSCT after current treatment.* ERG Report page 89 *The ERG's main concern with the inclusion of the three aSCT pathways was that a proportion of patients was artificially added to the model population that had zero mortality and remained in the disease control state (the "aSCT after current treatment" pathway) without subtracting these patients from the ones in the disease control state in the "no aSCT" pathway.*	These sections should be removed from the ERG report.	The proportion of patients receiving aSCT after current treatment (as well as the proportion of patients receiving aSCT after subsequent treatments) has been subtracted from the total population number to derive the number of patients entering the "no aSCT" pathway – see cell AD21 on the PF Moga sheet of the economic model.	Not a factual error. The overall model population is different (likely less severe) than the trial population, as explained in the text. We are aware of the subtraction but that does not solve the issue that one pathway contains the trial population (minus the patients with aSCT after subsequent treatment), one pathway with patients having aSCT after subsequent treatment (it is fine until here), and a third pathway with patients having aSCT after current treatment. The model is then averaged over these three pathways, resulting in a patient population that is biased.
<u>Effect of excluding aSCT patients on OS bias</u> ERG Report page 98, section 5.2.6.5.5 *OS estimates may further be biased by the exclusion of patients who had received aSCT after subsequent treatments for the purposes of OS analysis:*	This sentence should be deleted from the Report.	OS of patients receiving aSCT in the trial was modelled using external data due to informative censoring of these patients. Not excluding them from the analyses of OS for patients not receiving	Not a factual error.

there may be selection bias because of unobserved confounders playing a role in patients receiving aSCT.		aSCT would have double counted their benefit. The OS for those not undergoing aSCT was one of the model inputs. It was not used to compare mogamulizumab with ECM, thus so selection bias does not play a role. If it was a comparison, which is not the case, the resulting bias would be against mogamulizumab, as those receiving aSCT are in better health state and have better prognosis, excluding them would reduce the effectiveness. Mogamulizumab results in more aSCT, excluding aSCT patients would exclude more patients with better prognosis in the mogamulizumab arm, reducing its effectiveness more.	
<u>Effect of excluding aSCT patients</u> ERG Report page 14 section 1.2, page 79 section 4.6 *The results for this outcome varied depending on the approach used to type of adjustment for switching and the censoring of participants receiving allogenic stem cell transplant (aSCT).*	The second part of the sentence should be deleted: *The results for this outcome varied depending on the approach used to type of adjustment for switching ~~and the censoring of participants receiving allogenic stem cell transplant (aSCT)~~.*	The censoring of patients has very minor effect, mainly due to the small number of patients receiving aSCT. The ICER excluding aSCT patients (base case) was £33,819/QALY, and the ICER including aSCT patients (scenario analysis) was £32,836/QALY.	Not a factual error.

Extrapolation of DFS ERG Report page 17 section 1.4, page 11 Table 7.1, page 113 section 7.1.3 *Extrapolation of DFS after aSCT: choice of Gompertz: The ERG used the lognormal model instead of the generalised gamma for DFS after aSCT.* Page 99, section 5.2.6.5.8 *Extrapolation of DFS and OS after aSCT based on digitised KM data from the London supra regional centre as reported in TA577 may be biased because data on censoring was not available and the long plateau in the KM estimates may be assigned a higher weight than it should when assuming no censoring. The company did not provide a scenario changing the assumptions about censoring. The Gompertz distribution used for DFS (chosen in company's base-case) placed the most emphasis on that plateau. The ERG therefore considered that it may be more appropriate to select the lognormal for DFS, in line with OS, and incorporated this in the ERG base-case.*	1. Typo in the text. It should read: *Extrapolation of DFS after aSCT: choice of Gompertz: The ERG used the lognormal model instead of Gompertz ~~the generalised gamma~~ for DFS after aSCT.* 2. The following sentence should be rephrased: *The company could ~~did~~ not provide a scenario changing the assumptions about censoring, as the data was not available.* While important uncertainties exist as correctly pointed out by the ERG, in line with the available evidence and clinical plausibility the most appropriate distribution is the Gompertz.	The first quotation has a typo. The data and conclusion underlying the extrapolation of DFS and OS was taken from the TA577, where the details are either not available or marked as confidential, thus not available to Kyowa Kirin. Therefore, we could not provide the censoring data unfortunately, as we do not have access to it. During TA577 the issue of the plateau was also discussed, updated data (data cut 2 in Addendum of updated evidence for the consideration of the NICE Appraisal Committee) was submitted. "*As in the original dossier based on data cut 1, the Gompertz curve is the only curve that reflects the decreasing probability of relapse with time reducing over time to a zero probability (a plateau) for the updated Morris 2018 data (data cut 2). The longer follow-up and larger patient pool, supports the Gompertz curve as the most clinically plausible outcome and the most aligned with expectations in clinical practice (i.e. patients who have not*	1. This typo was corrected. 2. Not a factual error.

		relapsed within 12 months of alloSCT would likely be in long-term remission, with very few events expected beyond this point). This is in line with generally expected outcomes of an alloSCT and has been well documented across different cancers, particularly lymphomas." The ERG pointed out the uncertainties remaining around this evidence, conducted scenario analyses, and clinical expert were consulted. After the consultation, the Committee concluded as per the FAD: *"The committee acknowledged there were limitations in the evidence, including its small sample size and relevance to clinical practice because few patients had a transplant directly after having brentuximab vedotin. However, it was aware that there are limited data on transplants for people with advanced CTCL, and that disease that had not relapsed within 15 months of treatment was likely to remain in long-term remission. The committee concluded that the company's approach to modelling outcomes after transplant was appropriate for decision making."*	

		Kyowa Kirin, has followed the advice of the Committee based on the data and clinical expert opinion as we were relying on the same data. Additionally, Kyowa Kirin reproduced the analyses for the data cut 1 (only these curves were available) and has reached the same conclusion, that based on the statistical fit and clinical validation, Gompertz distribution provides the best fit and therefore should be chosen.	
<u>Timing of aSCT</u> ERG Report page 90 Section 5.2.3 *This was not in line with ERG clinical consultant's opinion, who stated that the time point of receiving aSCT after current treatment was variable and depending on how well the patient responded to current treatment. The ERG considered that the implementation of fixed time points in the model was not in line with clinical practice.*	The sentences should be revised as: *There is uncertainty around the mean according to ~~This was not in line with~~ ERG clinical consultant's opinion, who stated that the time point of receiving aSCT after current treatment was variable and depending on how well the patient responded to current treatment. ~~The ERG considered that the implementation of fixed time points in the model was not in line with clinical practice.~~*	There is limited data on the time point of patients receiving aSCT after current treatment, however on average 18 weeks was assumed to be in line with clinical practice according to expert opinion and was included in TA577. This was accepted as a reasonable assumption. While, as the ERG described it, after any treatment (including mogamulizumab, brentuximab or ECM) the timing of aSCT can vary patient by patient, the use of a mean time point in the model is a reasonable simplification and in line with the average clinical practice. The question of using a mean as opposed to individual level data is a modelling question, and not a clinical validity issue. In this case,	Not a factual error.

		the use of individual time point with the help of patient level simulation, would not provide additional information.	

Issue 7 Crossover adjustment

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Counterintuitive results with TSE between populations ERG Report page 90 Section 5.2.3 *It is worth highlighting that the direction in which the incremental cost effectiveness ratio (ICER) changes with a change of population used in the model is contingent on the crossover adjustment method used (which highlights the large impact of*	The sentence should read as: *It is worth highlighting that the direction in which the incremental cost effectiveness ratio (ICER) changes with a change of population used in the model with the TSE is counterintuitive ~~contingent on the crossover adjustment method used (which highlights~~ results ~~large impact of the uncertainty~~*	The issue highlighted here underlines the main problem with the TSE results, which are not in line with our understanding of the clinical pathway after progression or subsequent treatment. Using the ERG base case, while mogamulizumab has an advantage in the Disease control and the aSCT health states, the TSE estimates indicate a reduced survival on subsequent treatments. Using the TSE crossover adjustment, in the [redacted] This contrast with the clinical experts' understanding of the effect of mogamulizumab, and also their direct experience in clinical practice, that mogamulizumab leads to a more indolent disease, with increased time with disease control even on subsequent treatments. It also contrasts with the evidence available on longer time to next treatment on the subsequent treatments with mogamulizumab vs. ECM (please see section B.2.6.4 in MS). When using ITT population, despite mogamulizumab being less effective (in terms of PFS, OS, response) predicted life-years on subsequent treatments are higher on mogamulizumab, leading to a better ICER. This counterintuitive result suggests clinical implausibility for the Subsequent treatment results using TSE, and the resulting impact on the ICER is just an artefact of these implausible predictions. **Table 2. Undiscounted life-years results with TSE adjustment** **Undiscounted life-years** | **Disease control** | **Subsequent treatment** | **After aSCT** | **Total**	Not a factual error.

the uncertainty around OS on the ICER).	*~~around OS on the ICER~~).*		

Advanced population using ERG base case				
Mogamulizumab	[redacted]	[redacted]	[redacted]	6.45
ECM	[redacted]	[redacted]	[redacted]	4.90
Incremental	[redacted]	[redacted]	[redacted]	1.55
ITT population using ERG base case				
Mogamulizumab	[redacted]	[redacted]	[redacted]	6.91
ECM	[redacted]	[redacted]	[redacted]	5.10
Incremental	[redacted]	[redacted]	[redacted]	1.81

This is not the case with the IPCW crossover adjustment.

Table 3. Undiscounted life-years results with IPCW adjustment

Undiscounted life-years	**Disease control**	**Subsequent treatment**	**After aSCT**	**Total**
Advanced population using ERG base case				
Mogamulizumab	[redacted]	[redacted]	[redacted]	6.45
ECM	[redacted]	[redacted]	[redacted]	2.72
Incremental	[redacted]	[redacted]	[redacted]	3.74
ITT population using ERG base case				
Mogamulizumab	[redacted]	[redacted]	[redacted]	6.91

		ECM	[redacted]	[redacted]	[redacted]	3.75	
		Incremental	[redacted]	[redacted]	[redacted]	3.15	
Choice of method by the Manufacturer ERG Report page 93 Section 5.2.6.1.1 *The company considered that the TSE method did not account for any spill over effects of mogamulizumab on the next treatment and therefore chose the IPCW method in the base-case.*	The sentence should read as: *The company considered that the results with TSE method did not account for any spill over effects of mogamulizumab on the next treatment and were not in line with the observational data and the experience of clinical experts, therefore chose the IPCW method in the base-case.*	The submission acknowledged, similarly to the ERG's conclusion, that all methods involve uncertainty, thus the choice between the methods was based on clinical validity of the predictions generated using each method using expert opinion and external, observational data.					Not a factual error.
Drop in risk with the IPCW method ERG Report page 96 Section 5.2.6.5.3 *Finally, the ERG was concerned*	The sentence should read as: *Finally, the ERG was concerned that ~~there may not be plausible clinical explanation for~~*	This dramatic drop in risk at 6 months is a statistical artefact of the MAVORIC trial protocol, and as such does not require clinical explanation. This drop is due to the MAVORIC trial design allowing patients to crossover only after two full cycle of treatment and an additional minimum 2 weeks waiting period. The survival curve can be assumed to be smoother in clinical practice without this artificial drop. The single distributions correct for this drop.					Not a factual error.

that there may not be plausible clinical explanation for results of the IPCW method that exhibited a significant drop in patients at risk at approximately 6 months (Figure 23 of the CS),[1] which was also described as "very dramatic" *by one of the experts consulted by the company*	*results of the IPCW method that exhibited a significant drop in patients at risk at approximately 6 months (Figure 23 of the CS),[1] which was also described as* "very dramatic" *by one of the experts consulted by the company, however the MAVORIC trial, which allowed patients to crossover first only at this time point, should be taken into consideration.*		
Comparison of crossover adjusted results to observational data ERG Report page 96 and 97 Section 5.2.6.5.3 *the TSE method provided OS estimates no less*	These sentences should be rephrased, so that apply only for the results with the IPCW method. *the TSE method provided OS estimates ~~no~~ less in line with external data*	The below graph shows the observational data and the expert opinion (dotted lines) and the adjusted MAVORIC results (solid lines). For the comparison with the predicted survival estimates, please note that survival estimates from the available observation data and expert opinion is expected to be a high upper limit of the expected survival for the MAVORIC advanced population. This is due to the external data including: • Populations with lower proportion of patients with SS (7-15% vs. 47% in the MAVORIC trial) • Lower proportion of patients with stage IV disease (6-7% vs. 52% in the MAVORIC trial) • Less heavily pre-treated patients.	Not a factual error.

in line with external data presented in Table 27 of the CS than the IPCW method *Whilst OS estimates obtained using the IPCW and the TSE method broadly fit that criterion, the ERG considered that comparability was indeed hampered by the differences in patient population and treatment between the studies. In addition, the company cited two clinical experts, whose estimates were broadly in line with those of the TSE method.*	*presented in Table 27 of the CS than the IPCW method* *Whilst OS estimates obtained using the IPCW ~~and the TSE method~~ broadly fit that criterion, the ERG considered that comparability was indeed hampered by the differences in patient population and treatment between the studies. ~~In addition, the company cited two clinical experts, whose estimates were broadly in line with those of the TSE method.~~*	The TSE estimates are higher than the survival estimates for a healthier population from most of the observational studies and the data from expert opinion at the 1-year, 3-year and 5-year time points, while lower or similar at the 10-year and 20-year time points. The IPCW results lower than the external data at the 3-year, 5-year and 10-year time points also at the 3-year, the 5-year and the 10-year time points (with the exception of the HES data to which it is similar ay year 3) and similar at the 20-year timepoint.	

		[redacted] [redacted] 1 [redacted]	

Comparison of methods ERG Report page 96 Section 5.2.6.5.3 *Furthermore, for the TSE method, the "no unmeasured confounders" assumption is important at the time of the secondary baseline, which may be more easily satisfied than at other time points where other variables may not have been measured (required for the IPCW method).*	This sentence should be deleted.	While, as the ERG described, the secondary baseline was progression, progression status was also the most important predictor of crossover for IPCW, thus this sentence is not correct.	Not a factual error.

Issue 8 Comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Comparison with Reference case ERG Report page 86 Table 5.4	Instead of "No", "Partly" should be written	The therapies included as comparators in the economic evaluation were	Amended this according to the company's request.

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case			
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	[redacted]	The comparator evidence was based on a comparator, vorinostat, which is not licensed in Europe and not listed in the scope or considered by the company to be routinely used in the NHS. There was uncertainty about representative treatments in this population.		the therapies routinely used in the NHS as per Reference case. The distribution and resource use and cost consequences of these therapies were included based on their use in the NHS. Based on limited evidence, their efficacy and safety were assumed to be similar to that of vorinostat. Thus, while the MAVORIC trial did not use comparator therapies that are routinely used in the NHS, the economic evaluation did, just with a higher uncertainty around the efficacy and safety inputs.	Of note, the ERG does not really consider this as factually wrong - the submission does not include evidence on the clinical effectiveness and safety of an appropriate comparator in UK clinical practice. However, the ERG acknowledges that the company tried to incorporate costs of the appropriate comparator.
<u>Comparison with ALCANZA trial</u> ERG Report page 92 Section 5.2.3 *If vorinostat and physician's choice were truly comparable, it would therefore be expected that physician's choice would*				Comparison of the OS results from ALCANZA and MAVORIC trials should be deleted. *If vorinostat and physician's choice were truly comparable, it*	Any comparison of OS between MAVORIC and ALCANZA trials is not informative due to the high rates of crossover (73% in	Not a factual error. Despite cross-over, it is reasonable to have expectations about OS in a less severe

produce more favourable PFS and OS in ALCANZA (where patients are less severe in disease presentation) than vorinostat in MAVORIC. However, in response to request for clarification, the company have estimated hazard ratios for vorinostat versus physician's choice based on digitised KM data (shown in see Figures 3.1 and 3.3), which show a slight PFS advantage for physician's choice indeed, but an OS disadvantage for physician's choice compared with vorinostat	*would therefore be expected that physician's choice would produce more favourable PFS ~~and OS~~ in ALCANZA (where patients are less severe in disease presentation) than vorinostat in MAVORIC. ~~However, in response to request for clarification,~~ the company have estimated hazard ratios for vorinostat versus physician's choice based on digitised KM data (shown in see Figures 3.1 ~~and 3.3~~), which show a slight PFS advantage for physician's choice indeed~~, but an OS disadvantage for physician's choice~~ compared with vorinostat*	MAVORIC and 46% in ALCANZA trials). Additionally, any potential OS advantage of the better population in the ALCANZA trial could have been offset by the higher crossover rate for vorinostat. Therefore, only PFS is informative, which shows what was expected, as described by the ERG Report.	patient population, independent of treatment.

Issue 9 Caregiver utilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
<u>Exclusion of caregiver utilities</u> ERG Report page 103 Section 5.2.9 *The company's approach of only adding a utility gain for carers of patients in the disease control health state probably avoided some of the flaws of other implementation methods (such as implementing carer utilities throughout patients' lifetimes, which would add an additional*	Based on the evidence available, caregiver burden should be included as part of the base case.	Kyowa Kirin welcomes the comments, that our method avoided some of the flaws of the other implementation methods, and accepts, that there are uncertainties inherent in vignette studies. However, the evidence provided (the published literature, expert opinion and the vignette study) all show that MF and SS have profound impact on caregivers' quality of life, unlike other cancer	Not a factual error.

benefit of patient survival). However, as it was unclear whether caregivers' utilities should be included and how they should be included in an economic evaluation, the ERG has excluded carers' utilities as part of the ERG base-case but included them in a scenario analysis.		indications. Additionally, mogamulizumab can delay or prevent patients reaching the most advanced stages of the disease, when the caregiver burden is greatest. The ERG also states on page 21 of the Report, that "The significant burden of disease on the patient, caregiver and healthcare system is clearly demonstrated with multiple accounts of personal experience.". The importance of caregiver burden has also been stressed in TA577, however there was a lack of values for the impact. Kyowa Kirin following the recent DSU guidance addressed this data gap and undertook a study to evaluate caregiver utilities. These values have been implemented using a conservative approach. Thus, caregiver utilities should be included in the economic evaluation as part of the base case.	

Issue 10 Additional issues

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 1.4 Outcomes included in CS are incomplete	Kyowa Kirin requests that the ERG change this to:	To aid in both the accuracy and clarity of the document	Not a factual error.

• Time to next treatment	• Time to next treatment/ Next treatment-free survival.		The bulleted list summarises the outcomes that were a) defined in the NICE scope *and* b) included in the CS.
Incomplete sentence on paragraph 3 of Page 27 *"patients in MAVORIC were more than those in ALCANZA (median lines of prior therapy: 3 versus 2, respectively)*	Kyowa Kirin requests that the ERG change this to: "Patients in MAVORIC were more heavily pre-treated than those in ALCANZA (median lines of prior therapy: 3 versus 2, respectively)"	To aid in both the accuracy and clarity of the document.	Not a factual error. Cited sentence not included in the ERG report.
Incorrect abbreviation of TTNT The ERG consulted a clinical expert about the choice of outcome measures, specifically the choice of TTNT or PFS. Her response stated that the *"assessment of progression in these patients is difficult regardless whether you use PFS or **TNTT**, as you sometimes have variable skin symptoms, some areas get better, other get worse. Normally you would only start a*	Incorrect abbreviation of TTNT The ERG consulted a clinical expert about the choice of outcome measures, specifically the choice of TTNT or PFS. Her response stated that the *"assessment of progression in these patients is difficult regardless whether you use PFS or **TTNT**, as you sometimes have variable skin symptoms, some areas get better, other get worse. Normally you would only start a*	To aid in both the accuracy and clarity of the document	Typo corrected

different therapy if there definite progression, so it is a more stringent or relevant effectivity assessment".	*different therapy if there definite progression, so it is a more stringent or relevant effectivity assessment*".		
The figures quoted below are for the mogamulizumab arm of the trial and not the vorinostat arm of the MAVORIC trial as per Table 8 in the company submission *"40% of physician's choice patients in ALCANZA were stage IIB compared with 17.2% in the vorinostat arm of MAVORIC, conversely, 39.2% of patients in the vorinostat arm of MAVORIC patients were stage IVA1 with there being no stage IVA1 patients in the physician's choice arm of ALCANZA patients, the advanced stage population of MAVORIC could therefore be considered more severe than that of ALCANZA. "*	Kyowa Kirin requests that the ERG report should be amended to: "39% of physician's choice patients in ALCANZA were stage IIB compared with 12.4% in the vorinostat arm of MAVORIC, conversely, 44.1% of patients in the vorinostat arm of MAVORIC patients were stage IVA1 with there being 2% stage IVA1 patients in the physician's choice arm of ALCANZA patients, the advanced stage population of MAVORIC could therefore be considered more severe than that of ALCANZA"	The error needs correcting as the data presented is incorrect	Not a factual error. The quote is correctly citing the response to question 4.c of the response to request for clarification.
Table 4.11 page 66 reports (n=136) for Mogamulizumab	Outcomes are for the 133 patients that crossed over from vorinostat and received mogamulizumab, therefore	Incorrect value should be corrected	Changed accordingly.

patients after crossover but it should be (n=133). Of the 186 patients randomly assigned to vorinostat, 136 crossed over to mogamulizumab therapy, however three patients approved for crossover did not receive mogamulizumab because of adverse events unrelated to vorinostat.	Kyowa Kirin requests that the ERG change the table cell should read: **Patients receiving mogamulizumab after crossover** **(n=133)**		
Description in table 4.3 of the MAVORIC trial does not exactly reflect Table 6 in the company submission. It does not include 'Multicentre'	Kyowa Kirin requests that the ERG report should be amended to: Phase III multicentre, open-label, randomised, one-way crossover trial	To accurately reflect the description of the trial.	Changed accordingly.
Statement in paragraph 2 page 97 contains a typo To reflect the large uncertainty induced by crossover in MAVORC, the ERG also used the KM data without any adjustment method for crossover in a scenario	Kyowa Kirin requests that the ERG report should be amended to: To reflect the large uncertainty induced by crossover in MAVORIC, the ERG also used the KM data without any adjustment method for crossover in a scenario	To accurately reflect the description of the trial.	Typo corrected.
<u>Utility error</u>	This sentence should be deleted from the Report.	In the scenario analyses the ERG preferred scenario was used (0.69), which was described in the ERG Report Addendum page 9:	Not a factual error.

ERG Report page 17, section 1.4, page 111 Table 7.1, page 113 *Error in utility of PFS in TA577 scenario. The ERG corrected the error.*		Incremental QALYs decrease in Scenario 1 as a result of increasing the time spent in active therapy following progression at the expense of time spent in the end-stage care state. The utility value applied for the active therapy state is relatively high (0.64) versus the utility value applied for end-stage care (0.38) and is similar to the PFS utility used in the ERG's revised company base case (0.69). This means that the QALY gain accrued in the pre-progression state for treatment with BV due to longer PFS is largely offset for treatment with PC by the QALYs accrued from spending longer in the active therapy state. Incremental QALYs in Scenario 3 increase versus the ERG's revised company base case due to the modelled OS gain. There is no impact on incremental QALYs in Scenario 2. The model for the ALCANZA scenario submitted for clarifications questions, should only be used with the Disease control scenario, the other scenarios are not updated and should not be used	
<u>Cost calculation of mogamulizumab</u> ERG Report page 103 Section 5.2.9.2 *The average cost per administration of mogamulizumab was calculated by multiplying the recommended dose for mogamulizumab based on the MAVORIC trial (1 mg/kg), by the mean weight for European patients in the MAVORIC trial, which was 76.77 kg and the discounted price per vial*	The description should be updated with the base case calculations.	The described calculation method was only used for the scenario analysis using per mg cost calculation. The base case used cost calculation with wastage using dose banding according to NHS England guidelines. Wastage with dose banding used by NHS England for monoclonal antibodies allows a 10% discrepancy in the administered dose, therefore patients whose required dose is less than 10% higher than the dose available in a given number of vials, can still receive only those vials without the need to open a new vial. For patients above the 10% limit, a new vial would be opened, leaving some of the contents unused and discarded. According to this, weight bands were estimated (taking into account the mean relative dose intensity). Each weight band required different number of vials, each with their costs. The distribution of European patients according to these weight bands in the MAVORIC trial was multiplied by the cost of the vials for each band.	Not a factual error. Dose banding is mentioned in the sentence after and it is made clear that the no wastage calculation is only used in a scenario.
<u>Washout period</u> Page 117 Section 7.4 *There were also safety concerns about aSCT after treatment with mogamulizumab,*	The sentence should be updated: *There were also safety concerns about aSCT after treatment with*	The 7-week washout period was used in the model, as the SmPC states, that "A higher risk of transplant complications has been reported if mogamulizumab is given within a short time frame (approximately 50 days) before HSCT."	This has been amended in executive summary and conclusion.

which the company attempted to address by including a wash-out period in their model, which was not evidence-based.	*mogamulizumab, which the company attempted to address by including a wash-out period in their model, in line with the SmPC ~~which was not evidence-based~~.*		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Mogamulizumab for treated mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: May 2020

1. Summary of the technical report

1.1 In summary, the technical team considered the following:

Issue		Likely impact on ICER	Technical team's preliminary judgement
1	**Population**	Small*	The subgroup with severe disease is likely to be a clinically relevant population and is in line with the company's proposed positioning
2	**Comparator**	Unclear*	Using the MAVORIC trial to model mogamulizumab compared with standard care results in uncertainty in the treatment effect for the standard care arm because the trial compared mogamulizumab with vorinostat
3a	**Cross-over adjustment**	Substantial	It is unclear whether the IPCW or the TSE method to adjust for cross-over is most appropriate and further clinical input is required
3b	**Extrapolation of overall survival**	Substantial	The ERG's OS extrapolation using an exponential curve for both treatment arms is preferred because the company's use of different parametric models needs substantial justification
4	**Allogenic stem cell transplant (aSCT)**	Small*	It is appropriate to remove aSCT after current treatment to avoid over-estimating the proportion of patients in the 'disease control' health state
5	**Stopping rule for mogamulizumab**	Substantial	A 2-year stopping rule for mogamulizumab is not appropriate because it is not evidence-based
6	**Utility values**	Moderate	It is appropriate to use health state specific utilities and exclude carer utility values to reduce uncertainty in the cost-effectiveness model
*The impact on the cost-effectiveness results could not be assessed for all areas of uncertainty in each issue. These areas include the use of various lines of treatment in the modelled population, the use of an unlicensed treatment as a proxy for standard care in the NHS and the timing and proportions having aSCT in clinical practice			

1.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The clinical evidence for overall survival is immature

- There was a high level of cross-over in the trial and adjustment methods are associated with uncertainty
- The estimated treatment effect in the standard care arm is based on vorinostat (a treatment not licensed in the UK)

1.3 The cost-effectiveness results include a commercial arrangement (patient access scheme) for mogamulizumab.

1.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) between £51,223 to £100,690 per QALY gained (see table 8).

1.5 The company did not submit any data for the end-of-life criteria

1.6 The technology is likely to be considered innovative

1.7 No equality issues were identified (see table 10)

2. Topic background

2.1 **Disease background**

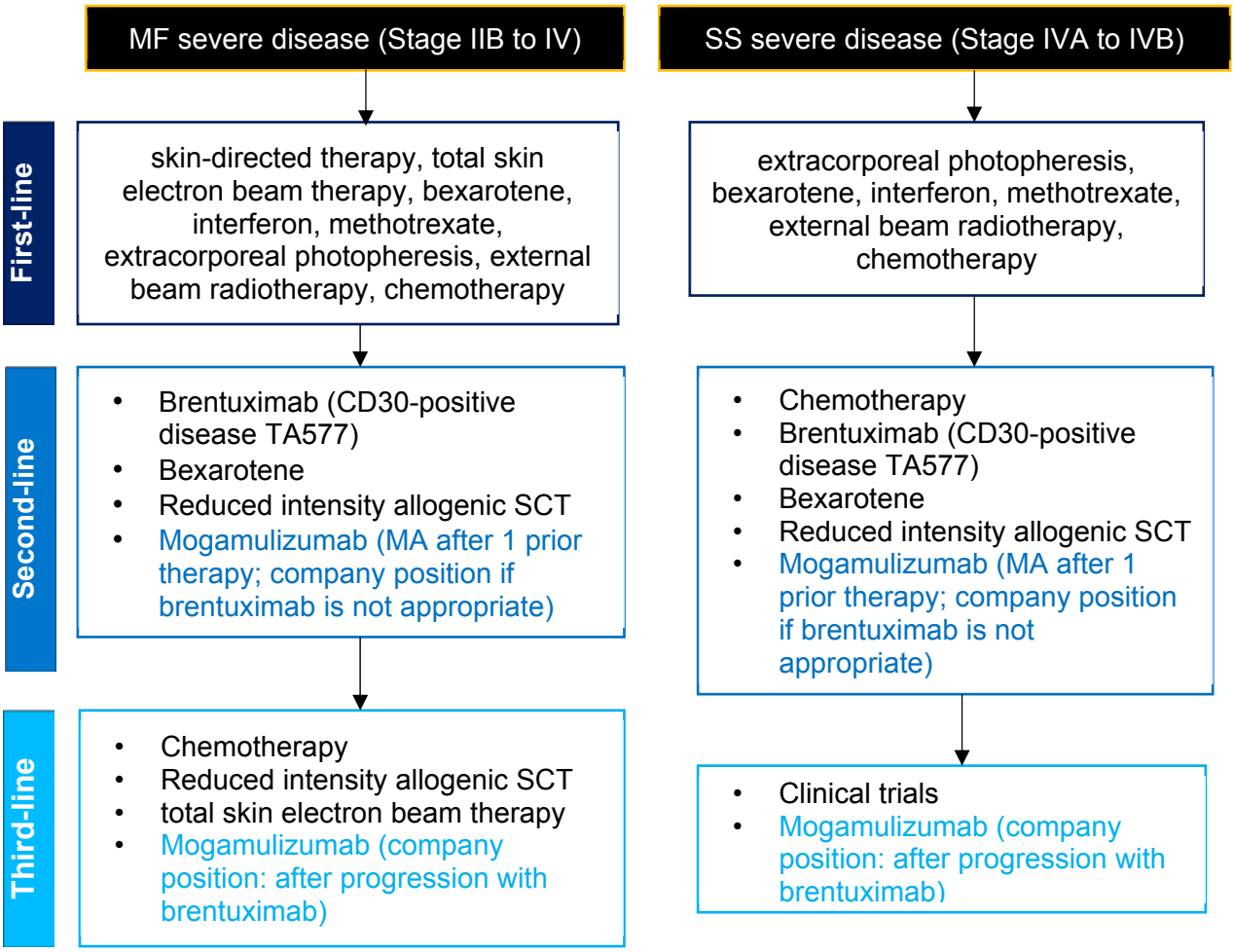
- Cutaneous T-cell lymphoma (CTCL) is a rare type of non-Hodgkin's lymphoma that affects the skin.
  - Mycosis fungoides (MF) is the most common type of CTCL
  - Sézary syndrome (SS) is closely related to MF and refers to a condition when cancerous T-cells (Sézary cells) are found in the blood as well as the lymph nodes
- It is caused by the uncontrolled growth of T-lymphocytes in the skin:
  - Many types of CTCL start as flat red patches or plaques on the skin, which progress to skin tumours
  - Some people experience swelling of the lymph nodes
- Between 2009 and 2013, 1,659 people were newly diagnosed with CTCL of which around 55% were MF

- The majority of people diagnosed with cutaneous T-cell lymphoma are over the age of 50 but it can also affect young people

2.2 Mogamulizumab

Marketing authorisation (received Jan 2019)	The treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.
Mechanism of action	Mogamulizumab is a defucosylated, humanized IgG1 kappa immunoglobulin that selectively binds to C-C chemokine receptor type 4 (CCR4), a G-protein-coupled receptor for C-C chemokines that is involved in the trafficking of lymphocytes to various organs including the skin, resulting in depletion of the target cells.
Administration	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.
Price	The list price is £1,329 per vial (20mg of mogamulizumab in 5ml, corresponding to 4mg/mL), the course of a treatment is £57,109. Simple discount PAS approved

2.3 Treatment pathway for severe disease (based on clinical guideline from the British Association of Dermatologists and UK Cutaneous Lymphoma Group)

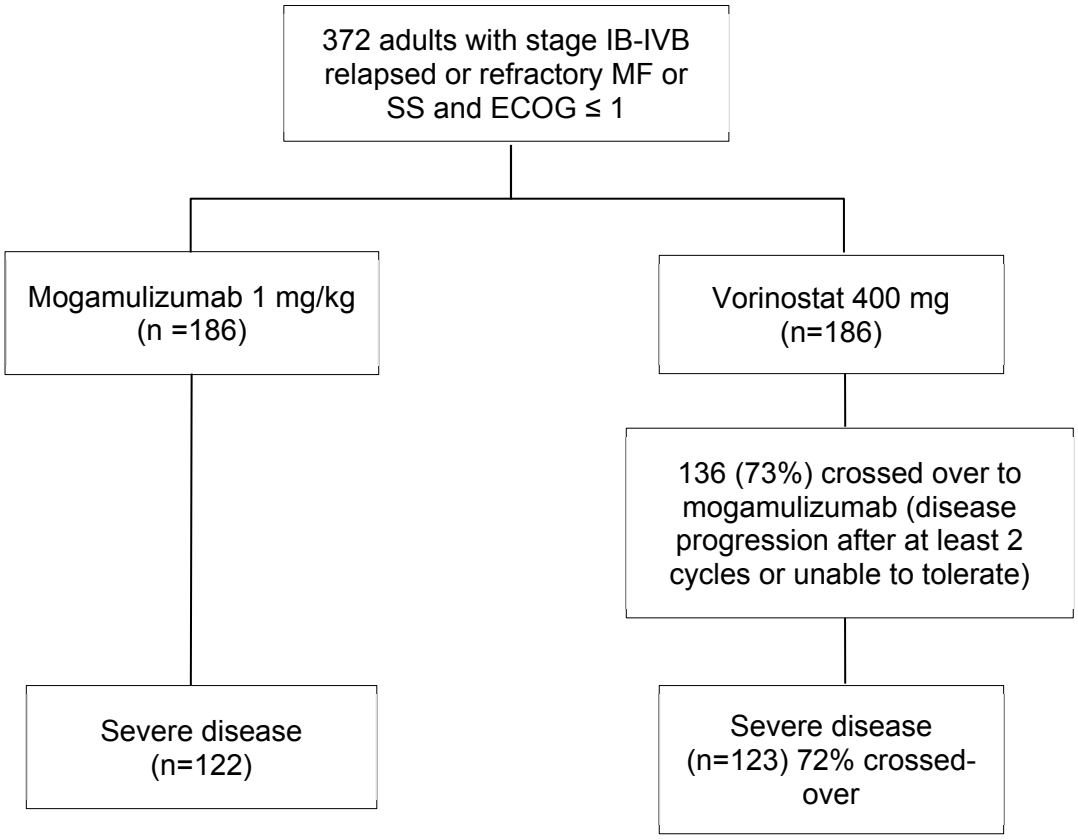


Prognosis in MF and SS severe disease (clinical guideline from the British Association of Dermatologists and UK Cutaneous Lymphoma Group)

Stage	Overall survival (%)		Progression-free survival (%)	
	5-year	10-year	5-year	10-year
IIB	40–65	34	52	42
IIIA	47	37	47	38
IIIB	40	25	18	27
IVA1	37	18	38	17
IVA2	18	15	23	20
IVB	18	-	18	-

2.4 Summary of clinical evidence

Flow diagram of MAVORIC trial (primary data source used in the model)



Summary of ALCANZA trial (secondary data source not used in the model)

- Phase 3 trial comparing brentuximab with physician's choice (methotrexate or bexarotene). Used as main trial in TA577 but results were confounded by treatment switching
- Included 128 adults with ECOG 0-1 and:
  - CD30+ MF who received at least 1 previous systemic therapy, or
  - CD30+ primary cutaneous anaplastic large cell lymphoma (subtype of CTCL) who received at least 1 previous systemic therapy or radiotherapy
  - No patients with SS were included

2.5 Key trial results from MAVORIC

Outcome	MAVORIC ITT population (n=372)		MAVORIC severe disease (n=245)	
	Mogamulizumab	Vorinostat	Mogamulizumab	Vorinostat
Median PFS	7.70 (5.67 to 10.33)	3.10 (2.87 to 4.07)	9.4 (5.8 to 14.1)	2.9 (2.8 to 3.8)
PFS	HR 0.53 (0.41 to 0.69)		HR 0.42 (0.30 to 0.58)	
Median OS unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
IPCW		[redacted]		[redacted]
TSE		[redacted]		[redacted]
OS unadjusted	[redacted]		[redacted]	
IPCW	[redacted]		[redacted]	
TSE	[redacted]		[redacted]	
Median NTFS	9.6 (7.0 to 11.8)	3.37 (3.1 to 4.0)	[redacted]	[redacted]
Median TOT	5.6 (4.4 to 7.1)	2.9 (2.4 to 3.3)	[redacted]	[redacted]

All OS data excludes patients who had an aSCT

Abbreviations: IPCW, NTFS, next treatment-free survival; IPCW, Inverse Probability of Censoring Weights; PFS, progression-free survival; OS, overall survival; TOT, time one treatment; TSE, two-stage estimation

Kaplan Meier from MAVORIC subgroup with severe disease (excludes aSCT and no cross-over adjustment)

Data source: Figure 5 in company submission appendix V

2.6 Model structure

The company model included 3 separate treatment pathways (see figures 1 to 3):

- Treatment pathway 1 – no allogenic stem cell transplant (aSCT)
  - All patients start in the 'on current treatment' health state and can move to the dead state any time (based on OS and general population mortality)
  - When treatment is stopped, patients move to:
    - ◊ 'surveillance' health state if symptoms were controlled without treatment
    - ◊ 'subsequent treatment' health state if there is disease progression (based on next treatment-free survival [NTFS])
  - In the last six months of life, end stage care was modelled with increased resource use and lower quality-of-life
- Treatment pathway 2 – aSCT after current treatment with mogamulizumab or standard care
  - All patients start in 'on current treatment' health state until a pre-specified time point (18 weeks) at which point they have an aSCT
  - There is a 50-day wash out period for those on mogamulizumab (to reduce the risk of transplant complications) so aSCT is done 7 weeks after the pre-specified time point
  - After aSCT, patients stay disease-free or relapse and can move to the dead state any time
- Treatment pathway 3 – aSCT after subsequent treatment
  - This is similar to treatment pathway 1 because all patients start 'on treatment' and move to other states according to OS & NFTS
  - At a pre-specified time point ([redacted] for mogamulizumab and [redacted] for standard care) all patients in 'subsequent treatment' have an aSCT
  - After aSCT, patients stay disease-free or relapse and can move to the dead state at any time

Figure 1. Model structure 1 – no aSCT

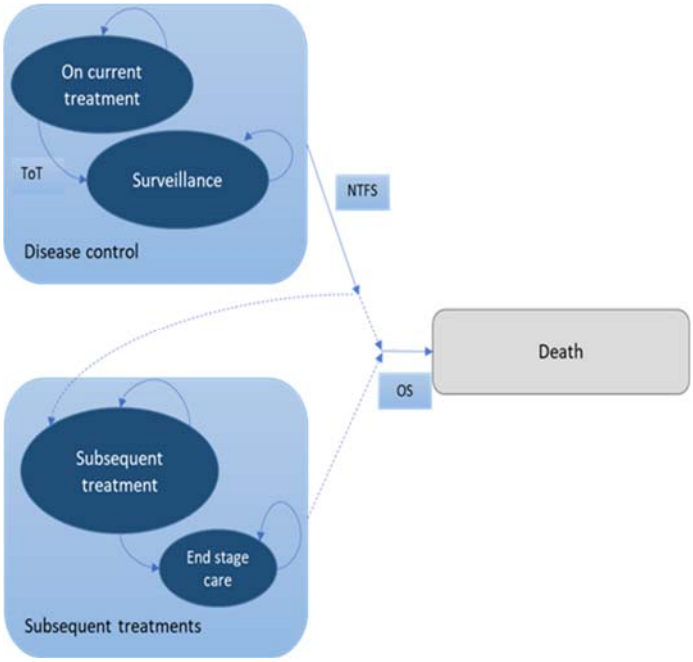


Figure 2. Model structure 2 – aSCT after current treatment

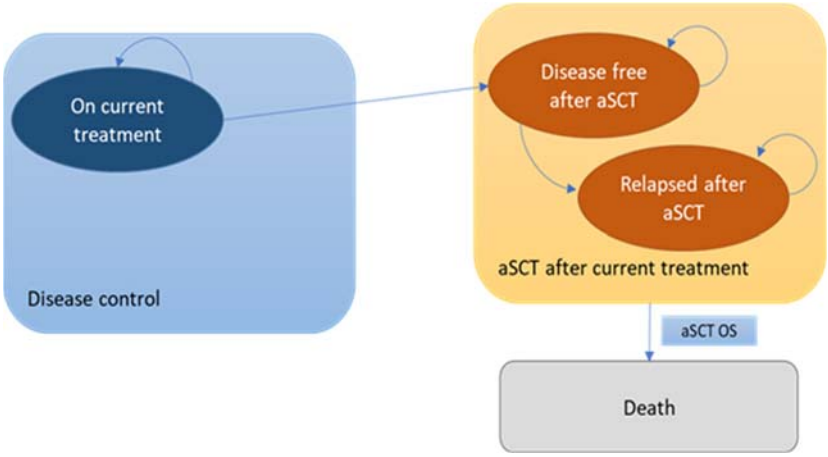
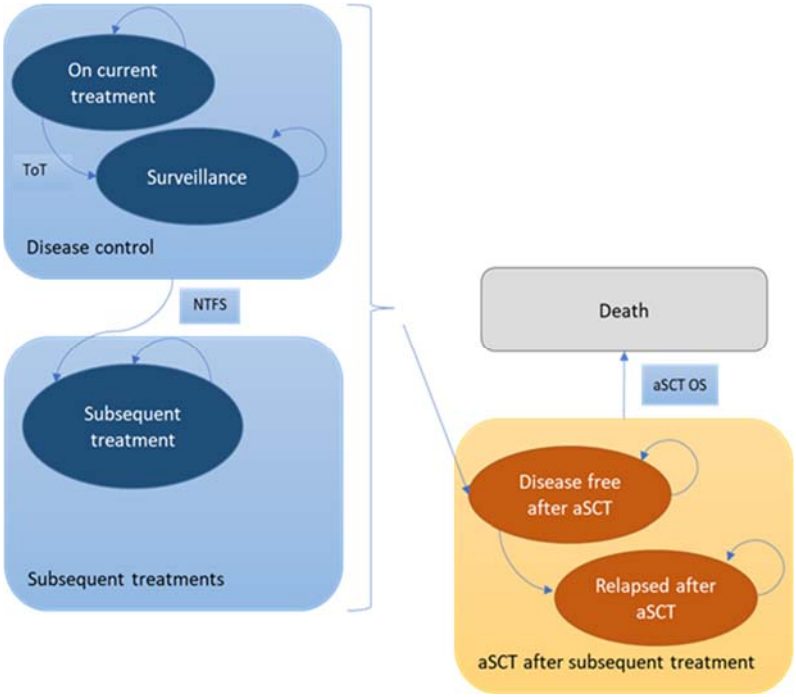


Figure 3. Model structure 3 – aSCT after subsequent treatment



3. Key issues for consideration

Issue 1 – Population

<table>
<tr><td>Questions for engagement</td><td>1. In clinical practice, is mogamulizumab likely to be used for people with severe disease (defined as stage ≥IIB for MF and all patients with SS) after 1 prior treatment and after disease progression with brentuximab or if it is inappropriate (see section 1.2 treatment pathway)?
a. Is this subgroup a clinically relevant population for the NHS in England?
b. Are trial results from the subgroup with severe disease in MAVORIC generalisable to the NHS in England (see table 2 for baseline characteristics)?</td></tr>
<tr><td>Background/description of issue</td><td>The company have positioned mogamulizumab as a treatment option after brentuximab vedotin or if it is not appropriate (NICE TA577 only recommends brentuximab for people with CD30-positive cutaneous T-cell lymphoma) and for people with severe disease. This is narrower than the full marketing authorisation (see table 1).
Table 1. Summary of population in MA and evidence
<table>
<tr><th>Marketing authorisation (MA)</th><th>NICE scope</th><th>Company’s proposed positioning</th><th>MAVORIC trial</th><th>Company base case</th></tr>
<tr><td>Adults with MF or SS who have received at least one prior systemic therapy</td><td>Same as MA</td><td>Adults with advanced MF or SS (i.e. stage ≥IIB MF and all SS) after at least one prior systemic therapy who are clinically ineligible for or refractory to treatment with brentuximab vedotin</td><td>Adults with MF or SS (Stage IB, II-A, II-B, III or IV) after at least 1 prior therapy with ECOG 0 or 1</td><td>Subgroup from MAVORIC (severe disease stage ≥IIB MF and all SS patients)</td></tr>
</table>
Table 2. Baseline characteristics of ITT population and severe disease subgroup from MAVORIC
<table>
<tr><th>Characteristic</th><th>ITT (n=372)</th><th>Severe disease (n=287)</th></tr>
</table>
</td></tr>
</table>

Median age	[redacted]	65-67 (26-101)
Male	[redacted]	173 (60.3)
ECOG 0	[redacted]	155 (54.0)
ECOG 1	[redacted]	130 (45.3)
Stage IB–IIA	[redacted]	0
Stage IIB	[redacted]	55 (19.2)
Stage IIIA-IIIB	[redacted]	38 (13.2)
Stage IVA1	[redacted]	155 (54.0)
Stage IVA2	[redacted]	31 (10.8)
Stage IVB[a]	[redacted]	8 (2.8)
Median prior systemic therapies (range)	[redacted]	[redacted]
MF	[redacted]	[redacted]
SS	[redacted]	[redacted]

[a] two patients in the ITT population (one in each treatment group) were noted to have stage IVB disease at baseline but did not have measurable visceral disease at baseline
Abbreviations: ITT, intention-to-treat; ECOG, Eastern Cooperative Oncology Group
Data source: Table 10 in clarification response, see tables 2.1 and 2.2 in ERG report for disease severity ratings

Table 3. Number of previous systemic therapies in MAVORIC (severe disease)

Number of previous systemic therapies	Mogamulizumab	Vorinostat
0	0 (0.0)	0 (0.0)
1	17 (16)	18 (19)
2	27 (25)	25 (26)

3	20 (19)	22 (23)
4	16 (15)	9 (9)
5	5 (5)	11 (12)
≥ 6	22 (21)	11 (12)
Data source: Table P-1 in company submission appendix Systemic therapies might have been used as monotherapy or in combination with other agents		

The company explained that its proposed positioning (see table 1) is in line with the expected use in clinical practice in the NHS and represents the population with the greatest unmet need.

The ERG advised that in MAVORIC, the subgroup analyses of people with severe disease (defined as stage ≥IIB for MF and all patients with SS) were post-hoc analyses. The ERG also explained that the company's model included people having various different lines of treatment (see table 3) and because regimens could have been taken in combination, it is difficult to determine the percentage at each line of therapy.

The clinical expert explained that the company's proposed positioning would generally cover third-line treatment but noted that brentuximab is only licensed for people with CD-30 positive disease (around 15 to 20%). For those with CD-30 negative disease who would not be eligible for brentuximab, mogamulizumab would be a second-line treatment option. In clinical practice, severe disease is defined as refractory disease with worsening disease, high symptom burden and poor health-related quality of life.

The technical team is concerned that the subgroup with severe disease from MAVORIC is a post hoc analysis and may not be generalisable to the NHS in England. The technical team also notes that the modelled population includes patients at various lines of treatment and this may impact estimated costs and treatment outcomes.

Why this issue is important	A scenario analysis using the full intention-to-treat population in MAVORIC increased the company's base case ICER from £33,819 to £35,643 per QALY gained but lowered the ERG base case from £100,690 to £82,837 per QALY gained. The change of population in the model is contingent on the crossover adjustment method used and this differed in the company and ERG base case (see issue 3a)

Technical team preliminary judgement and rationale	The technical team considers that the subgroup with severe disease is likely to be a clinically relevant population and is in line with the company's proposed positioning. The technical team would like to invite the company to provide further details on the proportion of patients at each line of treatment in the modelled population and to consider modelling the cost-effectiveness of mogamulizumab separately for each line of treatment and by disease type (MF and SS)

Issue 2 – Comparator

Questions for engagement	2. What treatments are currently used in the NHS in England for people with severe disease after brentuximab vedotin or if it is not appropriate? a. What proportion of patients would have each treatment (see table 4)? b. Is vorinostat likely to be clinically comparable to standard care in the NHS in England? 3. Would you expect symptoms to be controlled after current treatment is stopped? If so, approximately how long would symptom control last until further treatment is needed?
Background/description of issue	There is no trial evidence directly comparing mogamulizumab with standard care in the UK. The MAVORIC trial compared mogamulizumab with vorinostat, a treatment that is not used or licensed in the UK. **The company** assumes that vorinostat is a suitable proxy for standard care in the UK because it showed similar outcomes (in terms of PFS) compared with the physician's choice arm (methotrexate or bexarotene i.e. UK standard treatments) of the ALCANZA study. The company's model comparing mogamulizumab with standard care also estimated the treatments used in standard care based on clinical expert opinion through a short survey and in-depth interview (see table 4). **Table 4. Comparators included in the standard care arm**

Treatment	Proportion
Methotrexate	[redacted]
Bexarotene	[redacted]

Interferon alfa-2a* (peginterferon)	[redacted]
Gemcitabine	[redacted]
CHOP	[redacted]
Liposomal doxorubicin	[redacted]
Etoposide	[redacted]
Prednisolone	[redacted]
PUVA	[redacted]
ECP	[redacted]
TSEBT	[redacted]
Abbreviations: CHOP, Gemcitabine; cyclophosphamide plus doxorubicin, vincristine, prednisolone; ECP, Extracorporeal photopheresis; PUVA, Psoralen plus ultraviolet light therapy; TSEBT, Total skin electron beam therapy	

The ERG advised that if vorinostat and physician's choice were truly comparable, it would be expected that physician's choice would produce more favourable PFS and OS in ALCANZA (because patients have less severe disease) than vorinostat in MAVORIC. The company's estimated hazard ratios for vorinostat versus physician's choice based on digitised KM data show slightly improved PFS but worse OS for physician's choice compared with vorinostat (confidence intervals were wide for both). However, the OS analysis of both trials may have been biased by crossover. Based on the limited data available and this analysis, the comparability of vorinostat and physician's choice cannot be established.

Clinical advice to the ERG suggested that methotrexate, bexarotene and interferon alfa-2a are typically used as first or second-line treatments and are therefore not an appropriate comparator for mogamulizumab, if it is proposed as a third-line treatment. In addition, psoralen plus ultraviolet light therapy is a topical treatment that is usually given to patients with earlier disease and extracorporeal photopheresis and total skin electron beam therapy are only used in SS and MF respectively and are therefore not direct comparators.

The clinical expert explained that current treatment is generally in line with the guideline from the British Association of Dermatologists and UK Cutaneous Lymphoma Group but recently interferon

	has become unavailable because both companies that produce it have stopped its production. The clinical expert advised that this has been very challenging because there is a lack of treatment options for refractory disease and emphasised the importance of mogamulizumab. **The technical team** is concerned that there are no data to directly compare mogamulizumab with standard care in the NHS in England. The size of the bias associated with this is not known.
Why this issue is important	The ERG explored the impact of using a different treatment mix in the standard care arm and found that the impact on the cost-effectiveness analyses were likely to be small (exact ICERs not reported).
Technical team preliminary judgement and rationale	Using the MAVORIC trial to model mogamulizumab compared with standard care results in uncertainty in the treatment effect for the standard care arm because the trial compared mogamulizumab with vorinostat. However, there are no data to directly compare mogamulizumab to standard care. The treatments included in the standard care arm in the company's base case may differ to those used in clinical practice in the NHS in England but this is unlikely to have a large impact on the cost-effectiveness results.

Issue 3a – Cross-over adjustment

Questions for engagement	4 Which cross-over adjustment method provides the most clinically plausible OS estimates for the standard care arm to represent people with severe disease in the NHS in England (see figure 4)? a. Is a large drop in survival at around 6 months clinically plausible for this subgroup with severe disease?
Background/description of issue	The MAVORIC study was not powered to detect OS differences between treatment arms (only 23% of patients had an OS event). In addition, the crossover design of MAVORIC allowed patients randomised to the vorinostat arm to switch to mogamulizumab if they had at least two cycles of treatment and showed confirmed disease progression or had intolerable toxicity, despite dose reduction. In the ITT population, 73% of patients in the vorinostat arm crossed-over to treatment with mogamulizumab (72% in severe disease subgroup).

	Treatment switching methods aim to reconstruct individual patient data for overall survival in the standard care arm as if there had been no crossover. **Figure 4. OS estimates after adjusting for cross-over for subgroup with severe disease in MAVORIC**  **The company** preferred to use the IPCW method to adjust for cross-over and compared OS estimates to published external data (HES data and clinical expert opinion). However, the company recognised that the external data sources included a population with a better expected survival compared with MAVORIC because they had a lower proportion of people with SS (47% in MAVORIC compared with 7-15% in HES). Based on clinical opinion, the company suggested that OS estimates using the TSE method were not

clinically plausible. The company further stated that post-hoc analyses of time to next treatment (TTNT) data and clinical expert opinion suggests that mogamulizumab has a spill-over effect, (that is, it provides benefit on next treatment) which is not seen in estimated treatment effect from the TSE models.

The company also clarified that cross-over took place at around 6 months and this should be taken into consideration when interpreting the large drop in patients at risk at 6 months using the IPCW method

The ERG advised that the OS estimates for standard care from MAVORIC were confounded by crossover and different adjustment methods had vastly different results (see table 5) but considered that all adjustment methods were biased. The ERG explained that the company did not submit sufficient information to fully assess all crossover adjustment methods. Therefore, the ERG considered that OS is associated with additional uncertainty because of treatment switching in MAVORIC and that any extrapolation of OS and resulting model outcomes should be interpreted with extreme caution.

Clinical expert advice to the ERG suggested that the TSE method resulted in the most clinically plausible OS estimates for the standard care arm, unadjusted data were not in line with clinical practice and that the IPCW method resulted in OS estimates that were lower than those in clinical practice (see figure 4).

The ERG preferred the TSE method for crossover adjustment and explored the impact of choosing the IPCW method in a scenario. To reflect the methodological uncertainty over the crossover adjustment method, the ERG explored in a scenario the impact of averaging over the two methods, assuming that the IPCW method had a 30% chance of being correct, and the TSE had a 70% chance of being correct.

The clinical expert advised that for people eligible for second-line treatment current average overall survival would be around 1 year to 18 months and for people eligible for third-line treatment, this would be around 6 months or less. The survival time from diagnosis is around 3 to 5 years.

The technical team is concerned that the choice of method to adjust for cross-over has a large impact on the cost-effectiveness results and is associated with substantial uncertainty.

Table 5. Summary of cross-over adjustment methods for severe disease subgroup

Method	Company	ERG
No adjustment HR [redacted]	Unadjusted data were heavily confounded by the crossover design	Adjusting for cross-over is appropriate

	RPSFTM HR [redacted]	Assumptions were not met. This method gave a counter-intuitive HR as it favoured vorinostat.	RPSFT method may not result in clinically plausible estimates given that clinical experts suggest mogamulizumab may result in an OS advantage, or at least in similar OS compared with standard care.
	IPCW HR [redacted]	Used stabilised weights obtained from a logistic regression model	This method produces the most favourable OS results for mogamulizumab and it's not possible to fully assess how weights were obtained. It appears that some extreme weights were used for patients having vorinostat who were potentially eligible to switch but did not (company did not provide this). If there was a low proportion of patients who did not switch despite being eligible, it may indicate that IPCW was potentially biased.
	TSE HR [redacted]	Not considered appropriate because 1) OS extrapolations lacked plausibility compared with external data and 2) the method did not account for potential spill-over effects (benefit carried over to subsequent treatment period) of mogamulizumab.	1) OS estimates were as similar to the company's external data as the IPCW method therefore the TSE method should not be ruled out based on comparison with external data 2) No sufficient evidence to support 'spill-over' effect for mogamulizumab

Why this issue is important	A scenario analysis using the TSE method to adjust for cross-over in MAVORIC increased the company's base case ICER from £33,819 to £45,872 per QALY gained. The ERG scenario analysis assuming 30% IPCW and 70% TSE to adjust for cross-over lowered the ERG base case from £100,690 to £74,229 per QALY gained.
Technical team preliminary judgement and rationale	There is substantial uncertainty because all adjustment methods are associated with bias. It is unclear whether the IPCW or the TSE method to adjust for cross-over is most appropriate and further clinical input is required

Issue 3b – Extrapolation of overall survival

Questions for engagement	5 In current clinical practice, what is the average survival time for people eligible for second-line treatment? a. approximately what proportion of people would you expect to survive at 5 and 10 years? b. What is the average survival for people with severe disease in the NHS? 6 In current clinical practice, what is the average survival time for people eligible for third-line treatment? a. approximately what proportion of people would you expect to survive at 5 and 10 years? b. What is the average survival for people with severe disease in the NHS? 7 Is the company or ERG extrapolation of OS most clinically plausible (see figures 5 and 6 and table 6)?
Background/description of issue	Overall survival in MAVORIC was not a primary endpoint therefore MAVORIC was not powered to detect OS differences between treatment arms and the data were not mature. **Table 6. Summary of preferred OS extrapolations and cross-over adjustment**

			Proportion alive, years (%)					Proportion alive, years (%)			
	Cross over	**Moga**	**1**	**3**	**5**	**10**	**Standard care**	**1**	**3**	**5**	**10**
MAVORIC	IPCW	Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]

Company base case	IPCW	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Best statistical fit		Exponential	[redacted]	[redacted]	[redacted]	[redacted]	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
MAVORIC	TSE	Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]
ERG preferred	TSE	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Observational data (table 27 in company submission)											
HES[1]	NA	NA	-	-	-	-	NA	57	31	25	-
Talpur[2] 2012	NA	NA	-	-	-	-	NA	91	68	51	34
Kim[3] 2003	NA	NA	-	-	-	-	NA	67	40	32	15
Agar[4] 2010	NA	NA	-	-	-	-	NA	-	-	37	22
Guideline[5]	NA	NA	-	-	-	-	NA			18-65	15-34

Note: Data for the company base case was taken from the company submission model, data for the ERG preferred analysis was taken from the ERG corrected model

*IPCW: 57 months for mogamulizumab and 28 months for standard care; TSE: 33 months for standard care

[1] data from England from 2010 to 2019, in the HES database survival data was only available for 82 MF and 14 SS patients after one prior systemic treatment; [2] study of 1,263 patients with MF/SS, seen between 1982-2009 data for stage IIB to IV; [3] assessed data on 525 patients collected from 1958 to 1999 with MF/SS; [4] uses the ICARSIS database, which contains data on 1,502 patients with MF/SS collected from 1980 to 2009; [5] from table 2 in the clinical guideline for MF and SS (range from stage IIB to IVB, no details on line of treatment)

Abbreviations: Moga, mogamulizumab; IPCW, Inverse Probability of Censoring Weights; TSE, two-stage estimation

Figure 5. Company preferred OS extrapolation with IPCW cross-over adjustment (severe disease)

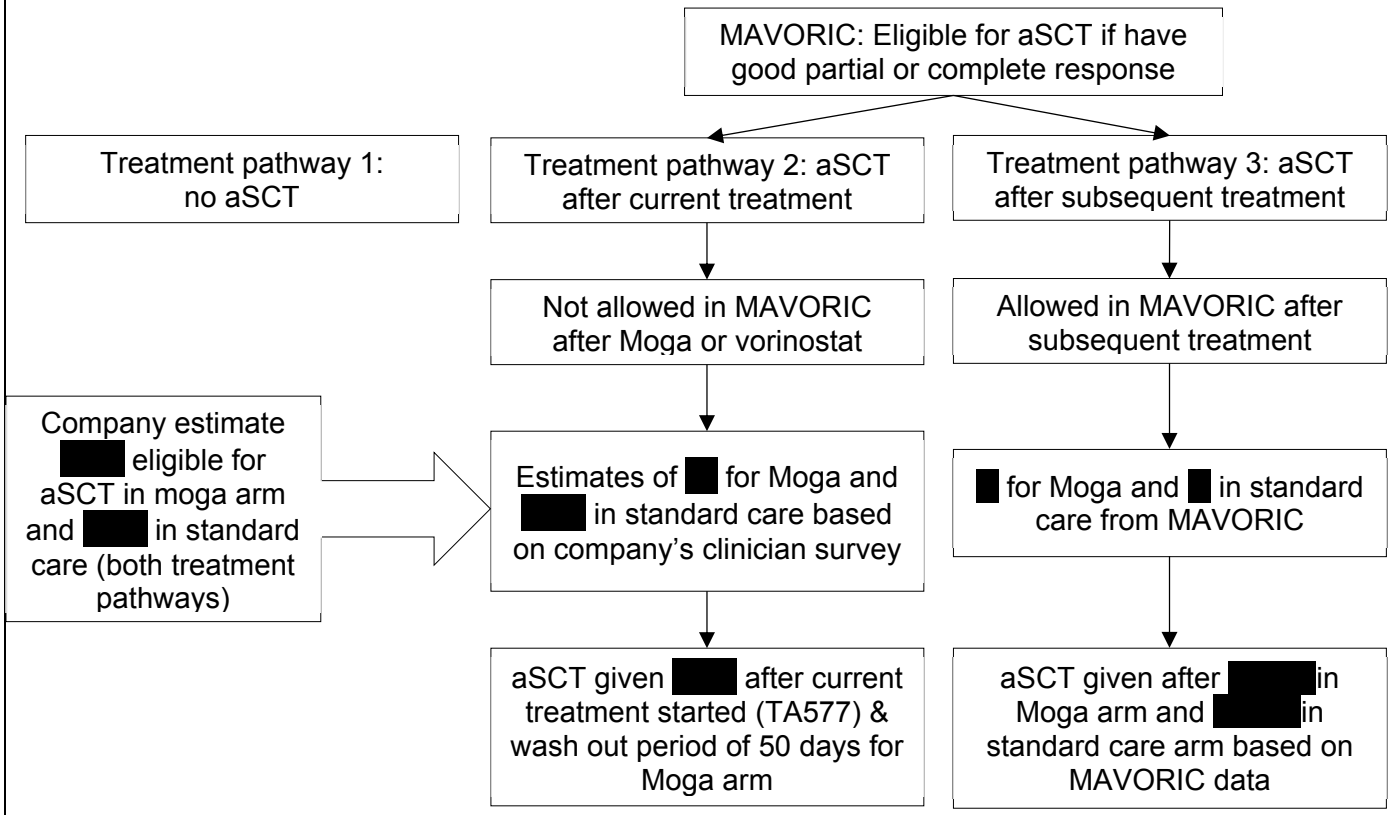
Figure 6. ERG preferred OS extrapolation with TSE cross-over adjustment (severe disease)

	 **The company** noted that although generalised gamma had the best statistical fit for the standard care arm, it had a long plateau, which was not considered realistic in the UK. The company used expert opinion and external data to choose its preferred distributions: three publications with data from MF/SS patients and data from the Hospital Episode Statistics (HES) database. **The ERG** preferred the TSE cross-over adjustment and an exponential extrapolation for both treatment arms but noted considerable uncertainty because MAVORIC was not powered to estimate OS and the data was not mature. **The clinical expert** explained that for people eligible for third-line treatment, around 50% would be expected to survive at 1 year and this would drop to around 10% by 5 years. **The technical team** are concerned that the choice of OS extrapolation and cross over adjustment (see issue 3a) have a large impact on the cost-effectiveness results and are associated with considerable

	uncertainty. The technical team note that the company's use of different parametric models to extrapolate survival requires substantial justification (see DSU technical support document 14). Although, the ERG preferred extrapolation may over-estimate survival in the standard care arm compared with current clinical practice in the NHS in England, it may be more methodologically appropriate.
Why this issue is important	A scenario analysis using alternative distributions to extrapolate OS increased the company's base case ICER from £33,819 to between £33,955 to £49,553 per QALY gained The ERG's scenario analysis using the company's preferred IPCW cross-over adjustment and the ERG preferred OS extrapolation reduces the ERG base case from £100,690 to £51,223 per QALY gained.
Technical team preliminary judgement and rationale	The technical team prefer the ERG's OS extrapolation using an exponential curve for both treatment arms because using different parametric models would need substantial justification. However, the survival estimates in the standard care arm may be higher than expected compared with clinical practice. In addition, there is substantial uncertainty because the trial was not powered to estimate OS and the data is immature. The technical team would like to invite the company to report updated survival data from HES (including any further baseline characteristics or descriptions of the sample and a breakdown of overall survival at 1, 6, 12, 18 months and yearly thereafter) and to provide data that addresses the end-of-life criteria because this is not included in the company submission.

Issue 4 – Allogenic stem cell transplant (aSCT)

Questions for engagement	8 At what point in the treatment pathway are patients likely to have an allogeneic SCT (aSCT)? Would eligibility for aSCT be based on fixed time points or depend on a patient's response to treatment? a. Approximately what proportion of people who are eligible for second or third-line treatment are likely to have an aSCT? 9 In your clinical opinion, is treatment with mogamulizumab likely to impact on a patient's eligibility for aSCT?

Background/description of issue	The company used 3 separate treatment pathways (see section 2.6 for model structure and description and figure 7 below) **Figure 7. Allogenic SCT by treatment pathway** 

	The company believed that mogamulizumab could result in bridging to aSCT and estimated the proportions who would have it after mogamulizumab or standard care using a short clinician survey from 1 clinical oncology consultant and 2 dermatology consultants (see appendix U of company submission). **The ERG** removed aSCT as a treatment option after current treatment in its base case to avoid over-estimating the proportion of patients in the 'disease control' health state but noted that this was not in line with current clinical practice. It would have preferred to have seen a model with corrections to the implementation of aSCT after current treatment. The ERG advised that there was other uncertainty because: • Clinical advice to the ERG suggested the proportion of people assumed to be eligible for an aSCT in MAVORIC was overestimated compared with clinical practice because patients in trials often have fewer comorbidities and are more likely to have an aSCT. In clinical practice, the proportion eligible for aSCT would be expected to be less than 5%. • Clinical advice to the ERG suggested the use of pre-specified time points for aSCT was not in line with clinical practice and this would be based on how well the patient responded to current treatment rather than at fixed time-points. However, the ERG noted that this would require a major structural change to the model. • OS estimates may be biased by the exclusion of patients who had an aSCT after subsequent treatments. This is because there may be selection bias from unobserved confounders playing a role in patients who had aSCT and the size of this bias cannot be assessed **The clinical expert** suggested that patients would be eligible for aSCT if they have advanced, refractory disease and it's usually used after the first remission because a second remission is not as common. There are additional criteria that patients must meet to be considered eligible, for example they should be young, fit enough for transplant and have no co-morbidities **The technical team** is concerned that the proportion of people having aSCT and its timing in the trial and in the model may not reflect current clinical practice in the NHS in England. The technical team also recognised the ERG's concerns that structural changes to the model may be needed if aSCT is not used after fixed time points in clinical practice in the NHS. However, the technical team notes that this is not likely to have a large impact on the ICER.
Why this issue is important	An ERG scenario analysis removing aSCT after current treatment increased the company's base case ICER from £33,819 to £33,874 per QALY gained.

Technical team preliminary judgement and rationale	The technical team preferred to remove aSCT after current treatment to avoid over-estimating the proportion of patients in the 'disease control' health state but would like to see a model with corrections to the implementation of aSCT after current treatment. This had a minor impact on the ICER.

Issue 5 – Stopping rule for mogamulizumab

Questions for engagement	10 In your clinical opinion, would a 2-year stopping rule for mogamulizumab be appropriate?
Background/description of issue	The SPC states that mogamulizumab treatment should be continued until disease progression or unacceptable toxicity and no stopping rule was used in the MAVORIC trial. In MAVORIC [redacted] of patients in the subgroup with severe disease and [redacted] in the ITT population were having mogamulizumab at 2 years. **The company's** base case used a 2-year stopping rule for mogamulizumab based on clinical input and clinical benefits from the MAVORIC trial. The company suggest that the likely treatment effect with a 2-year stopping rule would be similar to that observed in the trial because only a small proportion were having mogamulizumab after 2 years. **The ERG** advised that the treatment effect from MAVORIC was likely to be over-estimated in the trial compared with clinical practice that included a 2-year stopping rule because some patients in MAVORIC were still on treatment after 2 years. The ERG considered that applying the stopping rule on treatment costs and using an adjusted treatment effectiveness would lead to biased outcomes. Therefore, the ERG preferred to remove the stopping rule because it was not based on the evidence. **The clinical expert** suggested that a 2-year stopping rule was inappropriate if patients were still benefitting from treatment. The expert explained that although only a small proportion of people would be expected to continue treatment after 2 years, there is currently a lack of alternative treatment options therefore a stopping rule would not be acceptable in the NHS. **The technical team** is concerned that a 2-year stopping rule is not appropriate given that it is not included in the SPC or the trial. The technical team also recognise that there is no evidence that uses a 2-year stopping rule for mogamulizumab and shows the impact on the treatment effect.
Why this issue is important	Applying a 2-year stopping rule has a large impact on the ICER. The company's base case increases from £33,819 to £38,349 per QALY gained when removing the 2-year stopping rule.

Technical team preliminary judgement and rationale	A 2-year stopping rule for mogamulizumab is not appropriate because it is not evidence-based.

Issue 6 – Utility values

Questions for engagement	11 In your clinical opinion, is a patient's health-related quality of life generally stable while on treatment? 12 Compared with other cancers, do you think MF and SS has a similar impact on carers?
Background/description of issue	EQ-5D-3L data was collected in MAVORIC while patients were on treatment (including patients crossing over to mogamulizumab) and during one additional visit after stopping treatment. A vignette study (n=100) was used to evaluate carer utilities. Vignettes were informed by a targeted review of qualitative studies of people with cutaneous T-cell lymphoma and/or their caregivers and interviews with specialists. Vignettes were scored by people from the general population and valued using the van Hout mapping algorithm.

Table 7. Summary of utility values

	Mogamulizumab	Standard care	TA577
Cycle 1 to 12	[redacted]	[redacted]	-
Cycle 12 +	[redacted]	[redacted]	-
Subsequent treatment	[redacted]		-
End stage	[redacted]		0.38
Post aSCT first 2 weeks	[redacted]		0.42
Post aSCT week 3 to month 4	[redacted]		0.60
Post aSCT 4 month onward	[redacted]		0.77
Carer utility gain while in disease control state	[redacted]	N/A	N/A
PFS	[redacted]		0.68
Progressed	[redacted]		0.61

	Note: cycle-specific, subsequent treatment and health state based (PFS and progressed) utility values based on MAVORIC Abbreviations: aSCT, allogenic stem cell transplant Data source: Table 38 company submission and company model **The company** used cycle-specific utility values for the first 12 weeks and then applied an average thereafter (see table 7). The company clarified that there was a trend of utilities increasing over time while on mogamulizumab but differences between individual cycles were small and not statistically significant. The company also explained that for on-treatment utilities, the mean values were taken from observations where the patient was assigned to mogamulizumab or vorinostat; i.e. for patients randomised to mogamulizumab this was all on-treatment visits, and for patients randomised to vorinostat this was the crossover visits only (if the patient crossed over). The company also considered it appropriate to include utility values for carers because of the significant demand on carers' and family resources. Its base case included a carer utility gain for time spent within the disease control health state in the mogamulizumab arm. **The ERG** explained its concerns around the utility values used in the company's model: • the use of cycle-specific utility values for the first 12 weeks was questionable because there was a counter-intuitive pattern of utility values over time (for example for mogamulizumab, increase in cycle 5, decrease in cycle 7, increase in cycle 9). The ERG was also concerned that the use of cycle-specific utilities may be less robust, increase noise (e.g. as each parameter is separately estimated in the PSA) and add overall uncertainty to the model. • the lack of transparency on how 'on treatment' utilities were derived (especially for the vorinostat arm) because it appeared that only visits after cross-over were considered, which appears incorrect • the inclusion of caregivers' disutilities was not in line with the NICE methods guide because it relied on a vignette study The ERG preferred to use health state specific (not cycle-specific) utilities in its base case and exclude carer utility values. **The clinical expert** explained that cutaneous T-cell lymphoma is very disabling for patients and their carers because it is disfiguring and symptoms include open wounds (which may smell), social isolation, pain, depression. The expert also emphasised that disease was terminal.

	The technical team is concerned that the methods used to derive carer utilities may not be robust and that health state utility values were not used consistently during the treatment period.
Why this issue is important	A scenario analysis using the post-progression utility value accepted in TA577 (0.61) and excluding carer utilities increased the company's base case ICER from £33,819 to £35,767 and £36,065 per QALY gained respectively.
Technical team preliminary judgement and rationale	It is appropriate to use health state specific utilities and exclude carer utility values to reduce uncertainty in the cost-effectiveness model.

4. Issues for information

Tables 8 to 10 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 8: Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	ICER	Change from base case
Company base case	**–**	£33,819	
1. ERG correction of errors and other minor changes (see table 10)	Technical team agree with ERG changes (see table 10)	£34,197	+£378
All ICERs below include all assumptions from 1			
2. Remove 2-year stopping rule for mogamulizumab	Issue 6	£38,718	+£4,899

Alteration	Technical team rationale	ICER	Change from base case
3. No aSCT after current treatment	Issue 5	£34,576	+£757
4. Use IPCW or TSE cross-over adjustment	Issue 3a (key model driver)	£34,197 to £46,483*	+£378 to +£12,664*
5. Use ERG preferred OS extrapolation (exponential for both arms)	Issue 3b (key model driver)	£39,792	+£378
6. Remove caregiver utilities	Issue 6	£36,278	+£2,459
7. Use single health-state specific utility values for 'on treatment'	Issue 6	£34,211	+£392
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£51,223 to £100,690***	**+£17,404 to +£66,871***
*The TSE method for cross-over adjustment increases the ICER. The technical team's preferred ICER using IPCW cross-over adjustment is £51,223 per QALY gained and £100,690 using the TSE method			

Table 9: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Immature evidence base	Median overall survival in the trial has not yet been reached (23% of patients had an OS event)	Impact on the cost-effectiveness estimates are unknown
Treatment effect for standard care	The estimated treatment effect in the standard care arm is based on vorinostat (a treatment not licensed in the UK)	Impact on the cost-effectiveness estimates are unknown
Cross-over in MAVORIC	72% of patients randomised to the vorinostat arm crossed over to treatment with mogamulizumab and there was a large drop	The IPCW and TSE methods to adjust for cross-over are explored (see table 8)

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	in the number of people at risk at around 6 months. The company clarified this was around the time of the first cross-over and this should be taken into consideration when interpreting the large drop in survival.	

Table 10: Other issues for information

<table>
<tr><th>Issue</th><th>Comments</th></tr>
<tr><td>Extrapolation of next treatment-free survival and disease-free survival after aSCT</td><td>The company and ERG used the following extrapolation methods. The technical team accepted the ERG's methods but note that these do not have a large impact on the cost-effectiveness results.
<table>
<tr><th>Outcome</th><th>Company base case</th><th>ERG</th></tr>
<tr><td>Next treatment-free survival</td><td>Generalised gamma</td><td>Lognormal for mogamulizumab</td></tr>
<tr><td>Disease-free survival after aSCT</td><td>Gompertz</td><td>Lognormal</td></tr>
</table></td></tr>
<tr><td>Other ERG changes</td><td>The ERG also amended the time horizon to 45 years and corrected 3 errors (2 errors related to the implementation of aSCT and 1 error related to the PFS utility used in TA577). The technical team considered all corrections to be appropriate and noted they did not have a large impact on the cost-effectiveness results.</td></tr>
<tr><td>Equality considerations</td><td>No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.</td></tr>
<tr><td>End-of-life</td><td>The company did not report any information for the end-of-life criteria</td></tr>
</table>

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Mogamulizumab for treated mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma [ID1405]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm** on **Friday 5 June 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

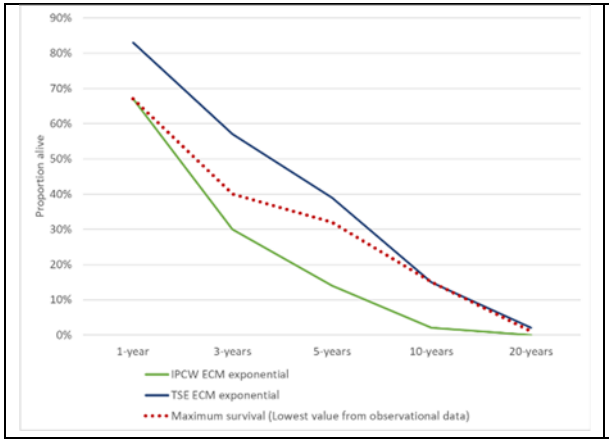
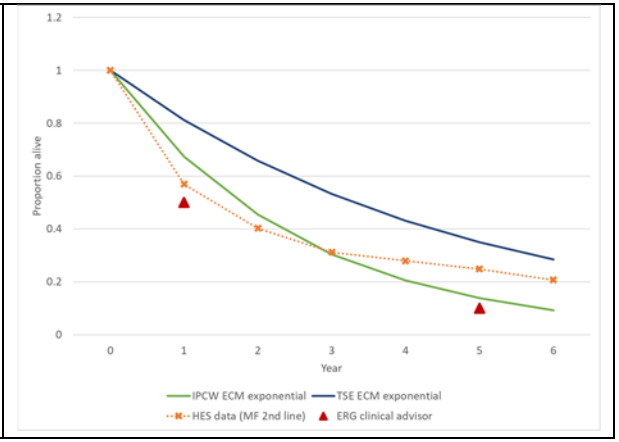
Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Kyowa Kirin Ltd.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable

Questions for engagement

Issue 1: Population	
1. In clinical practice, is mogamulizumab likely to be used for people with severe disease (defined as stage ≥IIB for MF and all patients with SS) after 1 prior treatment and after disease progression with brentuximab or if it is inappropriate (see section 1.2 of technical report on the treatment pathway)? a. Is this subgroup a clinically relevant population for the NHS in England? b. Are trial results from the subgroup with severe disease in MAVORIC generalisable to the NHS in England (see table 2 in technical report for baseline characteristics)?	In the pivotal MAVORIC study, approximately 80% of patients represented this subgroup. These patients have substantial reductions in overall survival and a greater burden of disease, hence represent a proportion of the total population with a great unmet need. Of these advanced patients, those who are ineligible for brentuximab vedotin based on clinical judgement or who have previously received brentuximab vedotin and have become refractory to this treatment represent patients with the greatest unmet need and the potential future clinical practice in the UK. This subgroup is both clinically relevant for the NHS in England and the MAVORIC trial is generalisable to NHS in England based on in-depth interviews with three clinical experts in England who have experience in treating MF/SS patients and with mogamulizumab: • Consultant in Clinical Oncology in England • Dermatology consultant, Professor of Cutaneous Oncology in England • Consultant Dermatologist in England For more details, please see the Appendix U in Manufacturer Submission and the full interviews submitted in the reference pack.

Issue 2: Comparator	
2. What treatments are currently used in the NHS in England for people with severe disease after brentuximab vedotin or if it is not appropriate? a. What proportion of patients would have each treatment (see table 4 in technical report)? b. Is vorinostat likely to be clinically comparable to standard care in the NHS in England?	In response to NICE, ERG and NHS England, and after additional clinical validation Kyowa Kirin has revised the base case comparator and length of comparator treatment. Using bexarotene as the main comparator and the appropriate length of treatment, resulted in an approximate £5,000/QALY decrease in the ICER. Scenario analyses looking at [redacted] methotrexate use and [redacted] pegylated interferon use resulted in minor changes. Please see section II of the **additional analyses submitted with this response** for more details. Vorinostat is considered a reasonable proxy for standard of care currently used in the NHS according to the clinical experts, as well as evidence in the literature. The approval of bexarotene, a key comparator for this submission, was based on a Phase II study of 193 cutaneous T-cell lymphoma patients; of these patients 93 had advanced stage disease refractory to prior systemic therapy (Eisai 2006). The efficacy data in this study showed an **overall response rate** in the skin of 31%; this is similar to the ORR of 29.7% seen in the skin compartment in the vorinostat arm of the MAVORIC study. The use of vorinostat as a proxy for standard of care is further supported when considering the progression-free survival curves for vorinostat from the MAVORIC study and the physician's choice arm (i.e. methotrexate or bexarotene) from the ALCANZA study (Prince 2017). Progression-free survival curves from the intention-to-treat population of these studies overlap thus confirming clinicians' comments that vorinostat should be considered a proxy for English standard of care. For further details, please see section B.2.9 of the Manufacturer Submission.

3. Would you expect symptoms to be controlled after current treatment is stopped? If so, approximately how long would symptom control last until further treatment is needed?	Due to its mechanism of action (see MS Section Error! Reference source not found.), patients can experience benefit from mogamulizumab after stopping treatment and after progression. This can be seen in the analyses of the treatment-free period in the MAVORIC trial using time to next treatment (see MS Section Error! Reference source not found.). Clinical experts suggested that, time to next treatment is more aligned with symptom control, thus time to next treatment acts as a good proxy for the length of symptom control: "Progression as defined in the MAVORIC trial: • Can indicate changes in quality of life • However not sensitive enough, e.g. patients' quality of life can deteriorate prior to progression requiring treatment change, or after progression • Treatment change is a better proxy for quality of life" (9th September 2019) "Treatment-free period reflects the higher response rates, but also better response (longer and better quality of response), so you can do 'watch and wait'. Time to next treatment thus reflects the rate, quality and durability of response and is clinically important. […] Progression-free survival is technical. A minimal disease occurrence, such as a small rash can trigger it. This results in a situation, where the patient might have progressed, but is still doing ok. Time to next treatment is clinically more meaningful.[…] Quality of life is influenced mostly by response and duration of response, thus time to next treatment is a good proxy. Resource use depends on time to next treatment, and what that next treatment is based on response" (3rd October 2019) "Clinical benefit usually comes from symptom alleviation and increased life expectancy. Treatment discontinuation is not really a good predictor, as it depends why the patient stops the treatment. It could be due to progressive disease but could be due to complete response. Time until next treatment is a good predictor." (14th October 2019).
Issue 3a: Cross-over adjustment	

4. Which cross-over adjustment method provides the most clinically plausible OS estimates for the standard care arm to represent people with severe disease in the NHS in England (see figure 4 in technical report)? a. Is a large drop in survival at around 6 months clinically plausible for this subgroup with severe disease?	While statistically both inverse probability of censoring weighted (IPCW) and two-stage estimation (TSE) methods are potential options, both the external validation against observational data from the UK Hospital Episode Statistics (HES) and published data from Kim 2003, Talpur 2012 and Agar 2010 support the use of IPCW adjustment for crossover adjustment. Additionally, the shorter predicted survival with the TSE method on subsequent treatments after mogamulizumab compared to on subsequent treatments after the comparator, and the lower life-years for the advanced population despite the better results from the MAVORIC trial compared to the intention-to-treat population are clinically implausible. Survival estimates with IPCW/TSE from 2+ line of treatment are compared below to published observational data from diagnosis for a better patient population (time measures from diagnosis as opposed to from start of 2nd line treatment, lower proportion of SS patients, lower proportion of more advanced patients, and less heavily pre-treated) and UK HES data from 2nd line treatment. Survival estimates with IPCW are below the maximum threshold of the observational data and in line with the HES database findings, while results with the TSE are likely to overestimate the survival.  

	For further details please see the **additional analyses attached**, the Manufacturer Submission section B.3.3.1 and the Clarification answers. The large drop in risk at 6 months is not a clinical issue. It is a statistical artefact of the MAVORIC trial protocol. MAVORIC trial design allowed patients to crossover only after two full cycle of treatment and an additional minimum 2 weeks waiting period. The survival curve can be assumed to be smoother in clinical practice without this artificial drop. The single distributions used correct for this drop.
Issue 3b: Extrapolation of overall survival	

5. In current clinical practice, what is the average survival time for people eligible for second-line treatment?
    a. approximately what proportion of people would you expect to survive at 5 and 10 years?
    b. What is the average survival for people with severe disease in the NHS?

For the proportion of patients surviving at the different timepoints from the UK Hospital Episode Statistics (HES) database and from the MAVORIC trial using inverse probability of censoring weighted (IPCW) and two-stage estimation (TSE) adjustment are presented below:

Crossover adjustment	Source (comparison to MAVORIC patients)	1-year	3-years	5-years
-	HES database (MF patients, staging not available, 2nd line)	57%	31%	25%
IPCW	For Established Clinical Management arm from model	67%	30%	14%
TSE	For Established Clinical Management arm from model	83%	57%	39%

Median survival from the UK Hospital Episode Statistics (HES) database and from the MAVORIC trial using IPCW/TSE adjustment are presented below:

Median survival from:	Source	Median survival	Comments
From the start of 2nd line systemic treatment	HES database	1.3 years	Weighted by the distribution of MF/SS in MAVORIC trial*
From the start of 2nd+ line systematic treatment	For Established Clinical Management arm from model with IPCW	1.8 years	-
	For Established Clinical Management arm from model with TSE	3.4 years	-

	In both cases the results with the IPCW adjustment are aligned with the UK HES data, while the TSE adjustment is likely to overestimate survival.
6. In current clinical practice, what is the average survival time for people eligible for third-line treatment? a. approximately what proportion of people would you expect to survive at 5 and 10 years? b. What is the average survival for people with severe disease in the NHS?	Kyowa Kirin is not aware of any published data for survival for patients eligible for third line treatment. The UK Hospital Episode Statistics Database has limited number of patients in third line treatment (95 in mycosis fungoides and 17 in Sézary disease between 1st October 2010 and 31st March 2019). The median survival was 1.1 years for mycosis fungoides and 1.0 year for Sézary disease. However, it would not be clinically appropriate to have mogamulizumab placed as 3rd+ line therapy (that is, much later lines of therapy than license). This is because the disease modifying benefits of mogamulizumab would not be realised clinically if used 3rd+ line for these patients.
7. Is the company or ERG extrapolation of OS most clinically plausible (see figures 5 and 6 and table 6 in the technical report)?	The exponential and the lognormal extrapolations are very close with a high uncertainty. In the mogamulizumab arm, Akaike and Bayesian Information Criteria for all distributions are very close ([redacted] and [redacted] respectively). However, using visual inspection, lognormal distribution (which with log-logistic distribution has the second lowest Akaike and Bayesian Information Criteria) fits better than the exponential curve (with slightly lower Akaike Information Criterion ([redacted] vs. [redacted]) and Bayesian Information Criterion ([redacted] vs. [redacted]) at the first half of the curve, where more data are available. Additionally, the evidence shows a potentially disease modifying effect for mogamulizumab, which would result in a longer tail, as opposed to Established Clinical Management (vorinostat) arm. (Please see additional analyses for more details on the disease modifying effect of mogamulizumab.)
Issue 4: Allogenic stem cell transplant (aSCT)	

8. At what point in the treatment pathway are patients likely to have an allogeneic SCT (aSCT)? Would eligibility for aSCT be based on fixed time points or depend on a patient's response to treatment?
    a. Approximately what proportion of people who are eligible for second or third-line treatment are likely to have an aSCT?

In the MAVORIC trial, [redacted] of patients randomised to mogamulizumab and [redacted] of vorinostat patients have received allogenic stem cell transplant. While allogenic stem cell transplant was only allowed after subsequent treatment in the MAVORIC trial design, in clinical practice app. [redacted] of patients would be receiving it after current treatment according to the clinical experts. This was exactly in line with the findings from the HES database, which showed [redacted] of MF/SS patients receiving allogenic stem cell transplant after second-line treatment.

Timing and comparator	UK expert opinion (mean of 3 experts)	UK HES database	MAVORIC trial
Immediately after mogamulizumab	[redacted]	NA	NA
After subsequent treatment to mogamulizumab	[redacted]	NA	[redacted]
Immediately after current clinical practice	[redacted]	[redacted]	NA
After subsequent treatment to current clinical practice	[redacted]	No data available	[redacted]

9. In your clinical opinion, is treatment with mogamulizumab likely to impact on a patient's eligibility for aSCT?

The ERG mentioned safety concerns regarding allogenic stem cell transplant after mogamulizumab. However, these safety concerns are for a limited time. As the Summary of Product Characteristics states, "higher risk of transplant complications has been reported if mogamulizumab is given within a short time frame (approximately 50 days) before HSCT." Consequently a 7-week washout period was used in the model. This is in line with the NICE Overview of discussions with key stakeholders about technical aspects of the case: "have experience using mogamulizumab as a bridge to stem cell transplant in a few patients and it doesn't impact eligibility although need to wait 8 weeks before all HSCT to reduce impact on GvHD".

Issue 5: Stopping rule for mogamulizumab

10. In your clinical opinion, would a 2-year stopping rule for mogamulizumab be appropriate?	According to expert opinion: "based on proportions of patients in MAVORIC post 24 months (approximately 14% of patients would be still receiving mogamulizumab in the advanced population and 10% in the ITT population) that stopping therapy at 24 months would still provide clinical benefit to the vast majority of patients receiving mogamulizumab"..
Issue 6: Utility values	

11. In your clinical opinion, is a patient's health-related quality of life generally stable while on treatment?	While there is uncertainty, the MAVORIC trial shows an increase in utilities while on treatment (see graph below). However due to the uncertainty, Kyowa Kirin revised the base case to include stable health state utilities. 

12. Compared with other cancers, do you think MF and SS has a similar impact on carers?	Both the published literature and the expert interviews indicated greater burden on carers than in other indications. This is in line with the conclusions from NICE TA577. The vignette study conducted by Kyowa Kirin also showed, that not only caregiver utilities are low but they are significantly lower in 3rd line treatment vs. 2nd line treatment: EQ-5D values: 0.366 (95% CI: 0.322-0.411) vs. 0.559 (95% CI: 0.511-0.607) respectively. While there are discussions around the correct implementation of carer utilities, Kyowa Kirin has used a conservative approach that avoided the pitfalls listed by ERG. The model included carer utilities as decrements only for the disease control health state and assumed not to affect any of the subsequent health states, thereby potentially underestimating the effect of carer burden. Please see Manufacturer Submission Section B.3.4 for further details on published studies, expert opinion, the vignette study, and the implementation of the results from the vignette study.

Technical engagement response

Mogamulizumab for treated mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma [ID1405]

Additional Manufacturer analyses

In response to the Technical Engagement Meeting on 13th May 2020, Kyowa Kirin describes in detail below four additional analyses regarding:

- Crossover adjustment
- Revised base case for comparator and length of comparator treatment
- End of life criteria
- Inclusion of aSCT after current treatment

Additional background data is available in the appendices.

I. Crossover adjustment

While statistically both inverse probability of censoring weighted (IPCW) and two-stage estimation (TSE) methods are potential options, both the external validation against observational data and clinical plausibility support the use of IPCW adjustment for crossover adjustment.

Additional analyses as per NICE/ERG request

At the request of NICE ERG, Kyowa Kirin has investigated crossover further. 20% of the crossover from vorinostat to mogamulizumab was due to intolerance, while the rest due to progression. The lag between progression and switching among those who have crossed over due to progression is short (Figure 1). Thus, statistically both inverse probability of censoring weighted (IPCW) and two-stage estimation (TSE) methods are potential options. As a result, external validation and clinical plausibility is crucial.

Figure 1. Lag between progression and switch

External validation

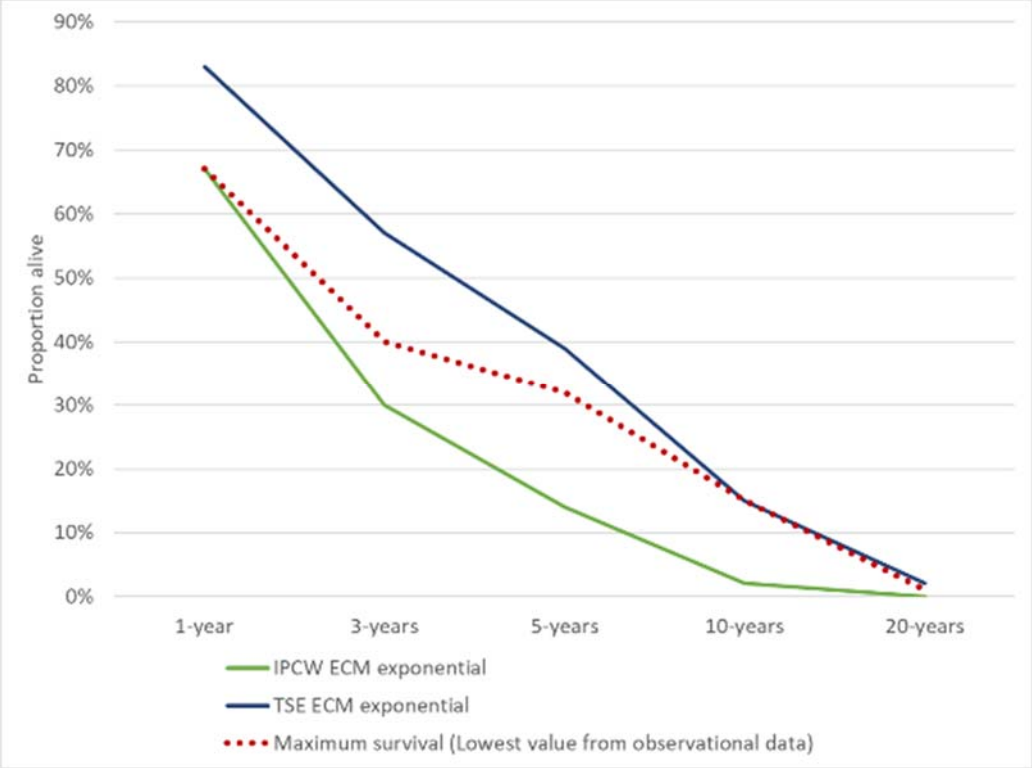
As described in the submission (please see section B.3.3.1 of the Manufacturer submission), three published observational studies and a UK Hospital Episode Statistics (HES) database study conducted by Kyowa Kirin are available for external validation. However, the observation studies assessed life expectancy from initial cutaneous T-cell lymphoma (CTCL) diagnosis and apply for a population with substantially higher life expectancy than the target population, as they include populations with

- Substantially lower proportion of patients with SS (7-15% vs. 47% in the MAVORIC trial) ,
- Substantially lower proportion of patients with stage IV disease (6-7% vs. 52% in the MAVORIC trial),
- Substantially less heavily pre-treated patients.

As a result, survival estimates from the available observational data is expected to be a high upper limit of the expected survival for the MAVORIC advanced population. The HES database study is much closer to the target population, as it looks at survival from the second line systemic treatment. (Additional information requested for the HES data is available in Appendix 3.)

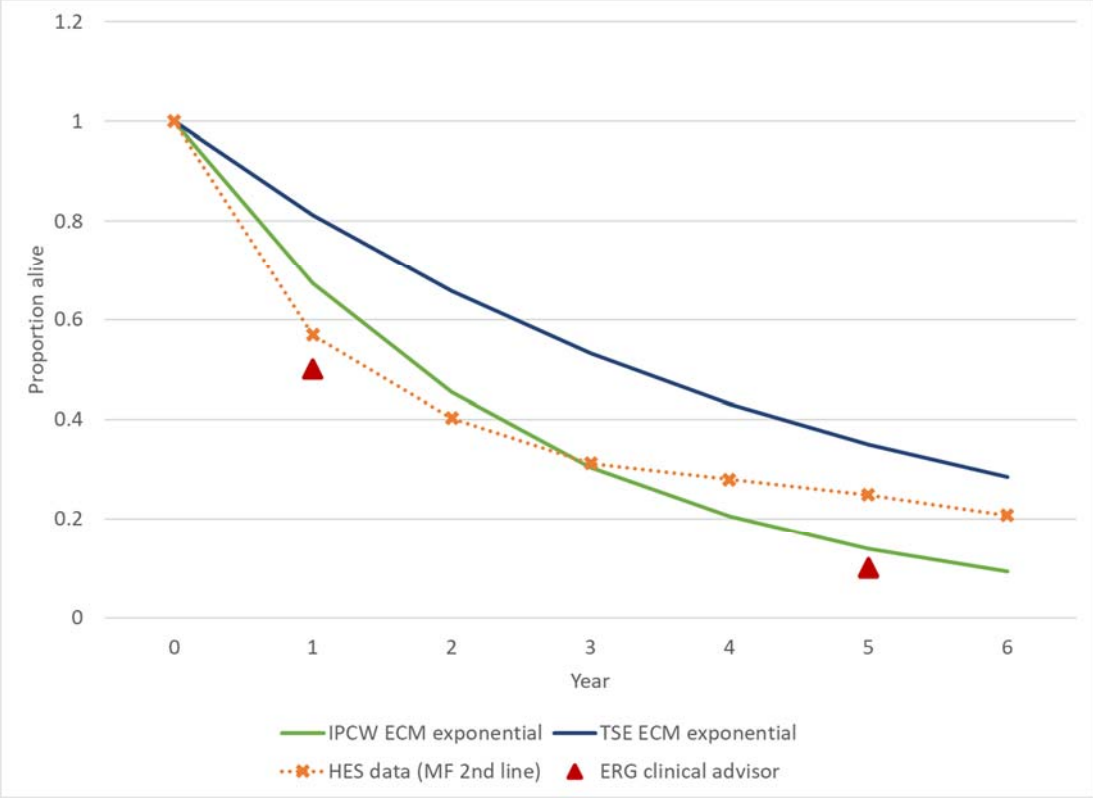
Comparing survival of the advanced population with IPCW and TSE adjustment to the observational data, IPCW is below the higher upper limit of the published data from diagnosis and in line with the UK HES data from second-line treatment (Figure 2). Similarly, the median survival of the advanced population with IPCW adjustment (1.8 years) is closer to the median survival for MF/SS from the HES database (1.3 years) and below the median survival from diagnosis from the observational studies (Table 1). Median survival from 2+ line of treatment with TSE adjustment however is more than double than that from the HES data and in line with the survival from diagnosis. This suggests, that the IPCW method results are in line with the clinical practice and the TSE method is likely to greatly overestimates overall survival results.

Figure 2. Survival estimates with IPCW, TSE adjustments and the observational data and in line



Notes: Based on Table 27 of Manufacturer Submission

Figure 3. Survival estimates with IPCW, TSE adjustments and the HES database findings



Notes: Based on Table 27 of Manufacturer Submission; ERG clinical advisor: "For people eligible for third-line treatment survival may be around 50% at 1 year and drop to 10% at 5 years"; HES data has <10 patients from year 5; Number of patients with SS is 14 in the database

Table 1. Median survival with crossover adjustments and observational data

Median survival from:	**Source**	**Median survival**	**Comments**
From diagnosis	Weighted average of survival by stages from Kim et al. 2003	2.2 years	Weighted by the distribution of stages in MAVORIC trial* Lower proportion of SS patients
	Weighted average of survival by stages from Agar et al. 2010	3.8 years	Weighted by the distribution of stages in MAVORIC trial* Lower proportion of SS patients
From the start of 2nd line systemic treatment	HES database	1.3 years	Weighted by the distribution of MF/SS in MAVORIC trial*
From the start of 2nd+ line systematic treatment	For ECM arm from model with IPCW	1.8 years	-
	For ECM arm from model with TSE	3.4 years	-

*Weighting described in Table 2.

Table 2. Estimation of weighted median survivals

Source	Weighted average	Data labels	Data					
HES database	1.3 years	MF/SS	MF	SS				
		Median survival (years)	1.5	1.0				
		Weight from MAVORIC trial (Kim et al. 2018)	55%	45%				
Kim et al. 2003	2.2 years	Stage	IIB/III	IV				
		Median survival (years)	4	1.5				
		weight from MAVORIC trial (Kim et al. 2018)	28%	72%				
Agar et al. 2010	3.8 years	Stage	IIB	IIIA	IIIB	IVA1	IVA2	IVB
		Median survival (years)	4.7	4.7	3.4	3.8	2.1	1.4
		Weight from MAVORIC trial (Kim et al. 2018)	17%	6%*	6%*	60%	9%	3%

*Assumes equal distribution between stages IIIA and IIIB.

Clinical plausibility

Clinical plausibility of the results with IPCW and TSE adjustment was also assessed. The TSE method, in the advanced population, predicts longer survival on subsequent treatments after vorinostat (Established Clinical Management (ECM) in the model) than on subsequent treatments after mogamulizumab (please see numbers marked red with red circle in Table 3). This is more pronounced using the ERG scenario of exponential distribution for the extrapolation of both treatment arm (incremental undiscounted life years on subsequent treatment between mogamulizumab and vorinostat: [redacted]). This is clinically unlikely given the mechanism of action of mogamulizumab. The clinical experts suggested, that mogamulizumab is disease modifying:

- "Mogamulizumab has better response rate and longer duration of response. The hypothesis is, that even if the patient has progressed, the disease became indolent. That is, even if the disease has crossed the threshold for the progression criterion, the disease was slower after mogamulizumab. "
- "Mogamulizumab has a potential benefit post-progression as it is disease modifying."
- "Additionally, mogamulizumab changes the underlying biology of the disease, e.g. there is anecdotal evidence, that when the disease comes back, it does in a modified and slower way. "

(Please see more information in Appendix U of the Manufacturer submission. Interview reports were submitted by Kyowa Kirin in the reference pack.)

Exploratory post-hoc analysis of the MAVORIC trial suggested by the clinical expert seems to support the assumption that treatment with mogamulizumab slows disease progression as time to next treatment after subsequent treatments was also found to be longer after mogamulizumab treatment compared to vorinostat treatment (see Manufacturer submission section B.2.6).

Similarly, with TSE adjustment, the results between populations are not in line with the mechanism of action for mogamulizumab described above: while mogamulizumab results in better incremental life-years in the Disease control health state in the advanced population compared to the ITT

population in line with the results from the MAVORIC trial, the TSE adjustment results in a decrease of life-years in the subsequent treatment health state and overall in the advanced population (please see numbers marked with green circle in Table 3).

Table 3. Undiscounted life-years with IPCW and TSE crossover adjustment

	Disease control	Subsequent treatment	After aSCT	Total
TSE: Advanced population using ERG base case				
Mogamulizumab	[redacted]	[redacted]	[redacted]	6.45
ECM	[redacted]	[redacted]	[redacted]	4.90
Incremental	[redacted]	[redacted] *	[redacted]	1.55
TSE: ITT population using ERG base case				
Mogamulizumab	[redacted]	[redacted]	[redacted]	6.91
ECM	[redacted]	[redacted]	[redacted]	5.10
Incremental	[redacted]	[redacted]	[redacted]	1.81
IPCW: Advanced population using ERG base case				
Mogamulizumab	[redacted]	[redacted]	[redacted]	6.45
ECM	[redacted]	[redacted]	[redacted]	2.72
Incremental	[redacted]	[redacted]	[redacted]	3.74
IPCW: ITT population using ERG base case				
Mogamulizumab	[redacted]	[redacted]	[redacted]	6.91
ECM	[redacted]	[redacted]	[redacted]	3.75
Incremental	[redacted]	[redacted]	[redacted]	3.15

*Using the ERG scenario of exponential distribution for the extrapolation of OS for mogamulizumab, this is [redacted].

II. Revised base case

In response to criticism by NICE ERG and NHS England, and after additional clinical validation Kyowa Kirin revised the base case comparator and length of comparator treatment. [redacted] These resulted in an approximate £8,000/QALY decrease in the ICER to £25,724/QALY [redacted]. Scenario analyses for uncertainties identified by the ERG report and in the technical engagement discussion result in ICERs ranging from £22,365 to £32,845.

Comparator

There is currently no gold standard treatments for the population mogamulizumab is likely to be used in, for people with severe disease (defined as stage ≥IIB for MF and all patients with SS) after 1 prior treatment and after disease progression with brentuximab or if it is inappropriate.

ERG highlighted issues with the selection of the appropriate comparator:

"Based on the ERG's clinical consultants' opinion, not all treatment options in the ECM arm were appropriate comparators for mogamulizumab in the UK.[49] Methotrexate, bexarotene and interferon alfa-2a are typically used as first or second line treatments and therefore not an appropriate comparator for mogamulizumab, which is proposed as a third line treatment. Furthermore, PUVA is a topical treatment that is usually given to patients with earlier disease and ECP and TSEBT are only

used in respectively SS and MF and are therefore no direct comparators. Hence, the ERG explored the impact of using a different treatment mix in ECM and found that it was likely small." (ID1405 Mogamulizumab ERG report post-FAC v0.3 270420 AS [ACIC]; p92)

Additionally, "recently interferon has become unavailable because both companies that produce it have stopped its production" (Technical report).

NHS England came to the same conclusion that interferon alfa-2a is not a 2+ line treatment option and excluded methotrexate due to the uncertainty surrounding its use. As a result, NHS England recommended bexarotene as comparator for the target population of 2+ line of treatment.

Based on the Technical Engagement Meeting 13th May, Kyowa Kirin has sent two additional questions regarding the use of bexarotene as the most commonly used treatment, and the proportion of patients using methotrexate to the 3 UK clinical experts, who have completed the interviews also and have experience in treating MFF/SS patients and with mogamulizumab. (Please see Appendix 1 for the questions and the full answers.)

The clinicians agreed that interferon is not available, as mentioned by the ERG and NHS England also. While pegylated interferon is sometimes used instead, there is lack of data on its efficacy. Methotrexate is used mostly in stage III erythrodermic disease and in first line as mentioned by the ERG's clinical expert, so by the time they are eligible for mogamulizumab, over 85% of patients will have already received methotrexate. In line with NHS England recommendations, bexarotene is the most common comparator for this population, although in SS the picture is less clear.

As a result, Kyowa Kirin has revised the base case to include bexarotene as the main comparator.

In addition, the ERG requested on the Technical Engagement Meeting, to include a scenario with methotrexate included as an additional comparator. Only one clinician responded to the question on methotrexate use, however the other two clinicians have provided data in the interviews conducted prior to the model development (please see detailed responses in Manufacturer responses to Clarification questions). The mean value from the three replies ([redacted]) was included for a scenario analysis. An additional scenario including pegylated interferon use ([redacted] based on the initial interviews) was also estimated.

Length of treatment

In the submission, the conservative assumption was used that the comparator treatment duration cannot be longer than the time on vorinostat. Time on treatment with vorinostat however is shorter than the duration seen with some of the comparators used in the UK, e.g., bexarotene, methotrexate or interferon alpha-2a. Thus, this assumption underestimated the length of treatment with comparators and as a result underestimated the cost of comparators. ERG has critiqued this approach, and Kyowa Kirin has updated the base case to address this issue in line with NHS England budget impact analysis submission (Table 4).

Table 4. Treatment duration for comparators

Treatment	Mean duration of treatment	Source	Implementation
Bexarotene	48 weeks	NHS England budget impact analysis submission	Exponential distribution fitted to the mean
Methotrexate	48 weeks	NHS England budget impact analysis submission	Exponential distribution fitted to the mean
Interferon alpha-2a	12 months	NHS England budget impact analysis submission	Exponential distribution fitted to the mean

Patient access scheme

[redacted]

Results

The revised base case results in an ICER of £25,724/QLY using the submission base case (Table 5). (Additional results are available in Appendix 4.) Including changes recommended by NICE ERG (time horizon extended to 45 years, extrapolation of NTFS with lognormal model for mogamulizumab, single health state utility assuming no change in utilities while on treatment), that have high uncertainty due to the limited data leads to an ICER of £25,993/QALY. The addition of methotrexate or pegylated interferon results in minor changes (Table 6).

Table 5. Results with the revised base case [redacted]

	ICER with submission base case (£/QALY)	Change from baseline	ICER with changes recommended by NICE ERG*	Change from baseline
Baseline: Conservative assumptions: bexarotene, INF, methotrexate, topical treatments as comparators, tx duration same as vorinostat	£33,819	-	£34,075	-
Step 1: Treatment duration from NHS England	£32,215	-£1,604	£32,487	-£1,588
Step 2: Bexarotene as comparator and treatment duration from NHS England	£27,247	-£6,572	£27,517	-£6,558
Step 3: [redacted]	£25,724	-£8,095	£25,993	-£8,082

*These changes include extended time horizon, extrapolation of NTFS (lognormal model for mogamulizumab), single health state utility (no change in utilities while on treatment)

Table 6. Scenario analyses of the revised base case [redacted]

Comparators	ICER with submission base case (£/QALY)	Change compared to revised base case	ICER with changes recommended by NICE ERG*	Change compared to revised base case
Revised base case	£25,724	-	£25,993	-
Comparators: [redacted] methotrexate, [redacted] bexarotene	£27,143	£1,419	£27,413	£1,420
Comparators: [redacted] pegylated interferon, [redacted] bexarotene	£26,999	£1,275	£27,268	£1,275
No 24-month stopping rule	£29,932	£4,208	£30,203	£4,210
Mogamulizumab OS extrapolated with exponential model	£28,830	£3,106	£29,229	£3,236
TSE crossover adjustment	£32,383	£6,659	£32,845	£6,852
No aSCT after current treatment	£26,269	£545	£26,550	£557
Caregiver utilities excluded	£27,432	£1,708	£27,570	£1,577
With reduced community-based disease management costs similarly to inpatient/outpatient costs	£22,512	-£3,212	£22,579	-£3,414
With 50% reduced community-based disease management costs	£22,365	-£3,359	£22,559	-£3,434

*These changes include extended time horizon, extrapolation of NTFS (lognormal model for mogamulizumab), single health state utility (no change in utilities while on treatment)

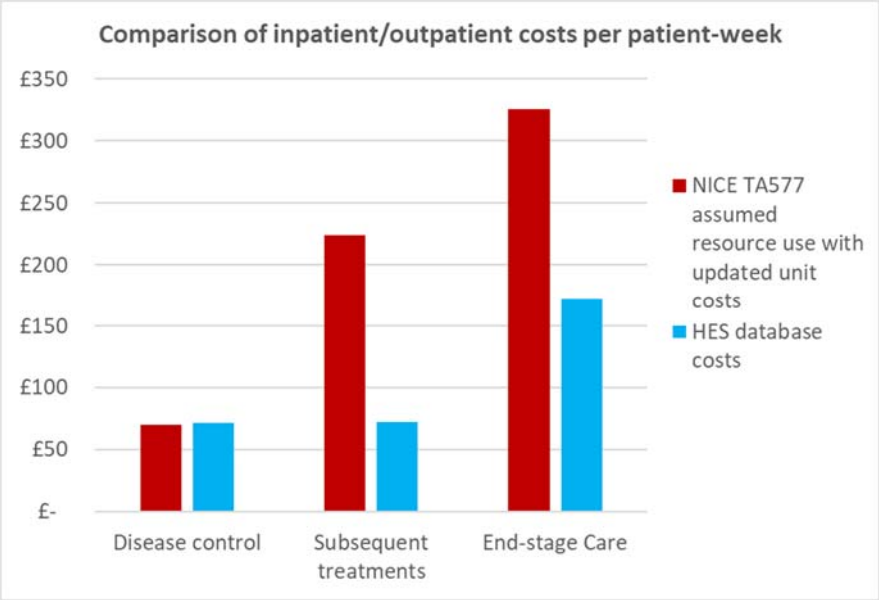
III. Additional scenario analyses around disease management costs

There is a lack of data and uncertainty around community-based health care costs in MF/SS. Kyowa Kirin used a conservative approach by including costs from NICE TA577, that were criticised for being overestimated. Scenario analyses exploring the uncertainty reduced the ICER by approximately £3,000/QALY to £22,365 and £22,579 per QALY [redacted].

MF/SS has a significant burden on healthcare resource use due to the intensive management of the disease. As a result, disease management costs are high and influential. Disease monitoring in the 'Subsequent treatments' and 'End-stage care' states are among the ten most influential inputs according to the deterministic sensitivity analyses. In the previous NICE TA for MF/CC (TA577) semi-

structured interviews were used to determine disease management costs, which were criticised as being overestimated. Kyowa Kirin aimed to reduce uncertainty by conducting a HES database study to assess the MF/SS cost of inpatient/outpatient services. The results from the HES database confirmed the ERG criticism. Costs from the HES database were still high, however were substantially lower than previously assumed after progression/subsequent treatment and in end-stage care (Figure 4). (For detailed estimation of the updated TA577 unit costs, please see Appendix 2, for HES database costs, please see Manufacturer submission, and Answers to clarification questions.)

Figure 4. Comparison of inpatient/outpatient costs per patient-week



However, no data were available for community-based costs, thus the costs from TA577 updated with current unit costs were used. As these were also criticised to be overestimated similarly to the inpatient/outpatient costs, two additional scenario analyses were conducted. One scenario assumed the community-based costs were overestimated by the same proportion as the inpatient/outpatient costs (Table 7) and the other scenario assumed, that they were overestimated by 50%. These assumptions reduced the ICER by an approximate £3,000/QALY (Table 9).

Table 7. Difference between costs from NICE TA577 and HES database

Inpatient/outpatient costs	Disease control / Pre-progression	Subsequent treatments / Post-progression	End-stage Care
NICE TA577 assumed resource use with updated unit costs	£70	£224	£325
HES database costs	[redacted]	[redacted]	[redacted]
HES costs / NICE TA577 assumed costs	[redacted]	[redacted]	[redacted]

Table 8. Calculation of disease management costs for the scenario analyses

	Disease control / Pre-progression	Subsequent treatments / Post-progression	End-stage Care
TA577 Total costs excluding inpatient-outpatient costs	£124	£125	£717
Inpatient/outpatient costs from HES	[redacted]	[redacted]	[redacted]
Total costs per week using HES database for inpatient-outpatient costs	[redacted]	[redacted]	[redacted]
Total costs per week using HES database for inpatient-outpatient costs assuming same overestimation for community-based costs as for inpatient/outpatient services	[redacted]	[redacted]	[redacted]
Total costs per week using HES database for inpatient-outpatient costs assuming 50% overestimation community-based costs	[redacted]	[redacted]	[redacted]

Table 9. Results of the scenario analyses with reduced community-based costs [redacted]

Scenario	Base case	With reduced community-based disease management costs similarly to inpatient/outpatient costs	With 50% reduced community-based disease management costs
Revised base case	£25,724	£22,512	£22,365
Revised base case with changes according to ERG recommendations*	£25,993	£22,579	£22,559

*These changes include extended time horizon, extrapolation of NTFS (lognormal model for mogamulizumab), single health state utility (no change in utilities while on treatment)

IV. End of life (EoL) criteria

Depending on the calculation method, for advanced population with 2+ line of treatment, the median life expectancy is 12.0-20.9 months, and the mean undiscounted life-years from the model in the submission base case is 37.2 months. The extension of life is 64 months in the base case, and even in the worst case 19 months.

Kyowa Kirin welcome NICE and committee's thoughts on EoL and accordingly have provided additional data to review this further.

We do understand that mogamulizumab is a systemic treatment for advanced disease in stage ≥II MF and all SS, however with EoL, it would not be clinically appropriate to have mogamulizumab placed as 3rd+ line therapy (that is, much later lines of therapy than license). This is because the disease modifying benefits of mogamulizumab would not be realised clinically if used 3rd+ line for these patients.

The clinically relevant population for mogamulizumab are advanced MF and SS patients following at least one prior systemic therapy. This includes patients starting from second-line treatment. **Error! Reference source not found.** describes the evidence for the end of life criteria for this population. ITT population of the MAVORIC trial is included as per NICE ERG request as sensitivity analyses. Populations for later lines of treatment were not assessed as they are not in line with the unmet need in MF/SS and the clinical opinion.

Table 10 presents the life expectancy in the target population and in the scenario analyses with the ITT population of the MAVORIC trial and additional scenarios by NICE ERG. Both analyses are done using IPCW crossover adjustment. Unadjusted values do not represent the current patient population, as they include a large proportion of patients on mogamulizumab, thus are not presented here. Crossover adjustment with TSE is clinically implausible (see Section I.), thus values with TSE are not presented here either. Table 11 presents the life extension in the base case and worst-case scenario analysis.

Table 10. Life expectancy (requirement: normally less than 24 months)

Source and method	Result
Base case: Advanced population	
From UK HES database: Median survival from start of second line systemic treatment	MF: 18 months SS: 12 months
From model predictions Median survival for ECM arm in submission base case	20.9 months
From model predictions Mean undiscounted life-years for ECM arm in submission base case	37.2 months
Scenario analysis: ITT population	
From model predictions Median survival for ECM arm	29.7 months
From model predictions Mean undiscounted life-years for ECM arm	49.0 months
Scenario analyses: no aSCT after current treatment, 45-year time horizon	
From model predictions Median survival for ECM arm	20.9 months
From model predictions Mean undiscounted life-years for ECM arm	32.6 months

Table 11. Extension to life (requirement: normally of a mean value of at least an additional 3 months with robust estimates)

Source and method	Incremental undiscounted life-years
Base case: Advanced population	
Manufacturer submission base case	64 months
Scenario analyses: Worst case scenario	
Worst case scenario (TSE adjustment, exponential distribution for mogamulizumab, no aSCT after current treatment)	19 months*
Scenario analyses: ITT population	
Manufacturer submission base case	56.4 months
Worst case scenario (TSE adjustment, exponential distribution for mogamulizumab, no aSCT after current treatment)	21.7 months*

*Please note the TSE adjustment produces clinically implausible results between ITT and advanced populations (see section I. for more details)

V. The use of aSCT after current treatment

According to the UK HES database and clinical experts, aSCT is used after current treatment, both after Established Clinical Management (ECM), and after a washout period, after mogamulizumab. Scenario analyses requested by NICE ERG exploring the timing and the implementation had very minor effect on the ICER.

While aSCT was not included in the MAVORIC trial design, it is part of the clinical practice with an approximate [redacted] receiving it after current treatment according to the clinical experts (Table 12). This was exactly in line with the findings from the HES database, which showed [redacted] of MF/SS patients receiving aSCT after second-line treatment.

Table 12. Use of aSCT after current and subsequent treatment

Timing and comparator	Average	UK KOL1	UK KOL2	UK KOL3
Immediately after mogamulizumab	[redacted]	[redacted]	[redacted]	[redacted]
After subsequent treatment to mogamulizumab	[redacted]	[redacted]	[redacted]	[redacted]
Immediately after current clinical practice	[redacted]	[redacted]	[redacted]	[redacted]
After subsequent treatment to current clinical practice	[redacted]	[redacted]	[redacted]	[redacted]

Safety concerns

The ERG mentioned safety concerns regarding aSCT after mogamulizumab. However, these safety concerns are for a limited time. As the SmPC states, “higher risk of transplant complications has been reported if mogamulizumab is given within a short time frame (approximately 50 days) before HSCT.” Consequently a 7-week washout period was used in the model. This is in line with the NICE Overview of discussions with key stakeholders about technical aspects of the case: “have experience using mogamulizumab as a bridge to stem cell transplant in a few patients and it doesn’t impact eligibility although need to wait 8 weeks before all HSCT to reduce impact on GvHD”.

Timing concerns

NICE ERG has also commented on timing concerns: "[…] the time point of receiving aSCT after current treatment was variable and depending on how well the patient responded to current treatment. The ERG considered that the implementation of fixed time points in the model was not in line with clinical practice."

Using an average fixed timepoint is a reasonable simplification, and a necessary simplification for a cohort model. The use of a variable timepoint would require a patient level simulation, which would increase complexity without significant changes in the results and increase uncertainty. Kyowa Kirin however included scenario analyses to test the effect of using different time points, than the 18 weeks used in the NICE TA577. The use of different timing however has minimal effect of the results (Table 13).

Implementation concerns

NICE ERG has pointed out two potential concerns with the implementation:

1. *"proportion of patients was artificially added to the model population that had zero mortality and remained in the disease control state (the "aSCT after current treatment" pathway) without subtracting these patients from the ones in the disease control state in the "no aSCT" pathway"*
2. How patients receiving aSCT after current treatment would have changed the efficacy of those in the MAVORIC trial who did not receive aSCT, but could have with a different trial design

The proportion of patients receiving aSCT after current treatment (as well as the proportion of patients receiving aSCT after subsequent treatments) has been subtracted from the total population number to derive the number of patients entering the "no aSCT" pathway, so the patients themselves have not been double counted.

Regarding the second concern, in the MAVORIC trial [redacted] of patients in the mogamulizumab arm and [redacted] patients in the vorinostat arm received aSCT after subsequent treatment. Within the cost-effectiveness model, based in expert elicitation, an additional [redacted] of patients in the mogamulizumab arm and [redacted] patients in the vorinostat arm were assumed to receive aSCT after current treatment (Table 12).

OS for patients receiving aSCT was estimated based on external data. The patients who actually received aSCT in the trial were removed to avoid 'double counting' the effect of aSCT. NICE ERG has requested to implement a scenario "by excluding a proportion of the best responders, and therefore increasing the proportions of patients with partial response)". However, this was not possible for the 'additional' patients who were modelled as receiving aSCT, as we do not know who they were. It is likely that the patients who would have received aSCT have a better prognosis than the remaining patients. To account for this, we have down weighted the patients who demonstrated a complete/partial response according to the proportion of patients who were modelled as receiving aSCT (in excess of those observed in the trial). On the basis that an additional [redacted] of patients in the mogamulizumab arm received an aSCT, and in the advanced population 30% (please Section B.2.7 in Manufacturer Submission for further details) achieved a complete or partial response (Leoni et al. 2019), patients who demonstrated a complete/partial response in the mogamulizumab arm were down weighted to [redacted] % (estimated from [redacted]. Patients in the vorinostat arm were not similarly

down weighted as the weights for these patients had already been adjusted as part of the IPCW analysis. In this sense this sensitivity analysis is conservative.

This resulted in only minor change in the ICER (Table 13).

Table 13. Scenario analyses for aSCT after current treatment [redacted]

Scenario	ICER (£/QALY)
Revised base case	£25,724
Revised base case with down weighting patients	£26,634
Revised base case with aSCT at 13 weeks (base case 18 weeks)	£25,618
Revised base case with aSCT at 23 weeks (base case 18 weeks)	£25,904

References

Leoni M, Ito T, Jones T and Li J. Efficacy and Safety of Mogamulizumab in Previously Treated, Advanced-Stage Mycosis Fungoides and Sézary Syndrome Patients: A Post Hoc Analysis of the MAVORIC Study. International Society for Pharmacoeconomics and Outcomes Research EU (ISPOR-EU). Copenhagen, Denmark. 6–9 November, 2019 2019. PCN54.

Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol. 2003; 139(7):857-66.

Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol*. 2010; 28(31):4730-9.

Appendix 1: Additional questions to clinical experts and full responses

Three UK clinical experts have been emailed, who have completed the interviews also and have experience in treating MFF/SS patients and with mogamulizumab:

- One UK Consultant in Clinical Oncology
- One UK Dermatology consultant, Professor of cutaneous oncology
- One UK Consultant Dermatologist

The following two questions have been sent:

- Would you agree, that since recently interferon has become unavailable, and due to the common use of methotrexate in earlier lines, for the target population of mogamulizumab (patients with advanced MF/SS following at least one prior systemic therapy (median number of prior treatments in MAVORIC trial was 3) who are clinically ineligible for, or refractory to, treatment with brentuximab vedotin), bexarotene is the most commonly used treatment?
- What proportion of these patients would use methotrexate?

The following replies were received:

- Clinical expert 1's reply:

  "1) I agree that alpha interferon is more difficult to prescribe and most of our existing patients are switching to pegylated interferon as an alternate although there is lack of data on efficacy in CTCL.

  2) Methotrexate (MTX) is rarely used in early stage disease and is generally less effective than Bexarotene for stage I-II. Paradoxically MTX is most effective in stage III erythrodermic disease although the explanation for this is not known.

  3) I would agree that Bexarotene is the commonest used therapy for patients who are likely eligible (according to the criteria in the statement below) for Mogamulizumab.

  4) Possibly 30% [could use methotrexate] but could be higher – certainly not above 50%."

- Clinical expert 2:

  "We use bexarotene more for patch / plaque and methotrexate only for erythroderma (IIIA OR B not IV)

  IVA1 ECP +/- bexarotene, IVA2 gemcitabine

  We are using pegylated IFN"

- Clinical expert 3 focused on Sézary Disease only:

  "1. We now use Pegylated interferon in place of interferon and this used as commonly as Bexarotene, neither of which are used very often in Sézary. – answer no.

1. Over 75% of Sézary patients will received methotrexate as their first systemic therapy. By the time they are eligible for Mogamulzimab, over 85% will have received mtx"

Appendix 2. Updated disease management costs from NICE TA577

Table 14. Updated health state costs from the NICE TA577

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	All resource use unless otherwise noted are taken from: NICE TA577 FAD - Committee Papers Table 7: Resource use assumptions. ERG scenario 3
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
Hospital outpatient									
Clinical nurse specialist	100%	0.19	100%	0.38	100%	0.25	90.00	PSSRU 2018 - Band 5 hospital nurse cost per hour of patient contact	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Dermatologist visit	0%	0.00	100%	0.50	50%	0.17	114.00	NHS reference costs 2018 - Dermatology consultant-led	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Oncologist outpatient visit	100%	0.19	100%	0.38	0%	0.00	104.00	NHS reference costs 2018 - Medical oncology non-consultant-led	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Consultant oncologist visit	100%	0.19	100%	0.54	100%	0.17	173.00	NHS reference costs 2018 - Medical oncology consultant-led	NICE TA 577, Company submission, Table 49
Psychologist	0%	0.00	0%	0.00	5%	0.25	109.00	PSSRU 2018 - Consultant: psychiatric - cost per working hour	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Hospital inpatient									
Dermatology day centre or oncology ward	0%	0.00	0%	0.00	20%	0.11	806.00	NHS reference costs 2018 - JC41Z Major skin procedures day case	NICE TA 577, Company submission, Table 49
Home visit									

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	All resource use unless otherwise noted are taken from: NICE TA577 FAD - Committee Papers Table 7: Resource use assumptions. ERG scenario 3
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
District nurse visit	100%	0.25	100%	0.25	100%	0.25	36.00	PSSRU 2018 - Nurse (GP practice) per hour	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Macmillan nurse/social services	0%	0.00	0%	0.00	100%	0.25	224.00	7 * PSSRU 2018 - Social work assistant cost per hour of client-related work	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Palliative care support team	0%	0.00	0%	0.00	100%	0.25	43.00	PSSRU 2018 - Occupational therapist per hour (community occupational therapist)	NICE TA 577, ERG Erratum in Appraisal consultation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Investigations and tests									
Complete blood count	100%	0.25	100%	0.67	0%	0.00	2.51	NHS reference costs 2018 - DAPS05: Haematology	
Liver function test	100%	0.25	100%	0.33	0%	0.00	1.11	NHS reference costs 2018 - DAPS04: Clinical Biochemistry	
Urea and electrolytes test	100%	0.25	100%	0.33	0%	0.00	1.11	NHS reference costs 2018 - DAPS04: Clinical Biochemistry	
LDH (lactate dehydrogenase)	0%	0.00	100%	0.33	0%	0.00	1.11	NHS reference costs 2018 - DAPS04: Clinical Biochemistry	
CT scan	50%	0.08	50%	0.17	0%	0.00	139.15	NHS reference costs 2018: RD27Z - Computerised Tomography Scan	

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	All resource use unless otherwise noted are taken from: NICE TA577 FAD - Committee Papers Table 7: Resource use assumptions. ERG scenario 3
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
								of more than Three Areas (outpatient)	
PET scan	50%	0.08	50%	0.17	0%	0.00	139.15	NHS reference costs 2018: RD27Z - Computerised Tomography Scan of more than Three Areas (outpatient)	
Skin and wound care									
Radiotherapy	0%	0.00	0%	0.00	90%	0.11	992.92	2*NHS reference costs 2018- SC25Z: Deliver a Fraction of Total Body Irradiation	NICE TA 577, Company submission, Table 49
Betnovate	0%	0.00	0%	0.00	80%	0.34	4.12	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 49	NICE TA 577, Company submission, Table 49
Dressings									
Localised coverage	37.5%	49.00	37.5%	49.00	37.5%	7.00	6.25	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 45	NICE TA 577, ERG Erratum in Appraisal consulation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Mepitel dressings	0%	0.00	0%	0.00	12.5%	21.00	14.25	Unit based on NICE TA577 ACD document: Committee Papers	NICE TA 577, ERG Erratum in Appraisal consulation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	All resource use unless otherwise noted are taken from: NICE TA577 FAD - Committee Papers Table 7: Resource use assumptions. ERG scenario 3
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
								Company Submission Document B Table 49	
Mepilex large sheet dressings	0%	0.00	0%	0.00	12.5%	14.00	63.64	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 49	NICE TA 577, ERG Erratum in Appraisal consulation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Mepilex small dressings	0%	0.00	0%	0.00	12.5%	21.00	10.17	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 49	NICE TA 577, ERG Erratum in Appraisal consulation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Mepilex heels	0%	0.00	0%	0.00	12.5%	14.00	12.87	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 49	NICE TA 577, ERG Erratum in Appraisal consulation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Elasticated garments	0%	0.00	0%	0.00	12.5%	1.00	26.12	Unit based on NICE TA577 ACD document: Committee Papers Company Submission	NICE TA 577, ERG Erratum in Appraisal consulation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33

	Pre-progression		Post-progression		End-stage Care		Cost (£) per unit	Unit cost reference	All resource use unless otherwise noted are taken from: NICE TA577 FAD - Committee Papers Table 7: Resource use assumptions. ERG scenario 3
	% of all patients	Frequency per week	% of all patients	Frequency per week	% of all patients	Frequency per week			
								Document B Table 49	
Medium Allevyn	0%	0.00	0%	0.00	37.5%	49.00	17.36	Unit based on NICE TA577 ACD document: Committee Papers Company Submission Document B Table 49	NICE TA 577, ERG Erratum in Appraisal consulation documents (https://www.nice.org.uk/guidance/ta577/documents/appraisal-consultation-document), Table 33
Other drug treatment (pain relief)									
Oramorph	0%	0.00	0%	14.00	100%	14.00	0.27	BNF 2019	
Oromorph (breakthrough pain / iv)	0%	0.00	80%	1.00	80%	0.25	0.09	BNF 2019	
Other drug treatment (antihistamines)									
Hydroxyzine	0%	0.00	50%	4.67	100%	4.67	0.02	BNF 2019	
Gabapentin	0%	0.00	33%	14.00	50%	14.00	0.03	BNF 2019	
Other drug treatment (antidepressants)									
Mirtazapine	0%	0.00	50%	7.00	50%	7.00	0.04	BNF 2019	
Pregabalin	0%	0.00	50%	7.00	50%	7.00	0.10	BNF 2019	
Other drug treatment (antibiotics)									
Flucloxacillin	0%	0.00	100%	4.83	100%	3.22	0.10	BNF 2019	
Aciclovir	0%	0.00	25%	28.00	25%	28.00	0.05	BNF 2019	
Other drug treatment (antibiotics)									
Fusidic acid	0%	0.00	0%	0.00	80%	0.02	4.16	BNF 2019	
Total Cost (per week) (£)	205.89		376.03		797.89				

Appendix 3. Additional information on the HES database requested by the ERG

Table 15. Patient characteristics

		Mycosis fungoides	Sézary disease
Age at first diagnosis (years)	<65	[redacted]	[redacted]
	≥65	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
Sex	Male	[redacted]	[redacted]
Second-line therapies	SACT	[redacted]	[redacted]
	Radiotherapy	[redacted]	[redacted]
	SCT - Allo	[redacted]	[redacted]
	SCT - Other	[redacted]	[redacted]
	Skin - Phototherapy	[redacted]	[redacted]
	Skin - Surgery*	[redacted]	[redacted]

Table 16. Survival results for 2nd line systematic treatment

	Mycosis fungoides				**Sézary disease**			
Time	**Begin**	**Fail**	**Survivor**	**Standard error**	**Begin**	**Fail**	**Survivor**	**Standard error**
1	82	69	0.568974	0.03937	14	12	0.573725	0.094895
2	49	22	0.402329	0.040996	12	2	0.491765	0.097442
3	29	10	0.311738	0.040615	7	2	0.397386	0.099141
4	14	2	0.279698	0.042302	6	0	0.397386	0.099141
5	8	1	0.24862	0.04767	5	0	0.397386	0.099141
6	4	1	0.207184	0.054853	1	3	0.099346	0.089535
7	1	0	0.207184	0.054853	1	0	0.099346	0.089535
8	1	0	0.207184	0.054853	-	-	-	-

Appendix 4. Additional results for the revised base case

Table 17: Discounted disaggregated life -years (LYs)

	Mogamulizumab	Established clinical management	Increment	% increment
Disease control - Current treatment	[redacted]	[redacted]	[redacted]	[redacted]
Disease control - Surveillance	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments/ESC	[redacted]	[redacted]	[redacted]	[redacted]
aSCT DF	[redacted]	[redacted]	[redacted]	[redacted]
aSCT Relapsed	[redacted]	[redacted]	[redacted]	[redacted]
Total	**6.40**	**2.71**	**3.69**	**100%**
Key: aSCT, allogeneic stem cell transplant; DF, disease free; ESC, end stage care.				

Table 18. Discounted disaggregated quality-adjusted life-years (QALYs)

	Mogamulizumab	Established clinical management	Increment	% increment
Disease control - Current treatment	[redacted]	[redacted]	[redacted]	[redacted]
Disease control - Surveillance	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments/ESC	[redacted]	[redacted]	[redacted]	[redacted]
aSCT DF	[redacted]	[redacted]	[redacted]	[redacted]
aSCT Relapsed	[redacted]	[redacted]	[redacted]	[redacted]
Total	**4.60**	**1.78**	**2.83**	**100%**
Key: aSCT, allogeneic stem cell transplant; DF, disease free; ESC, end stage care.				

Table 19. Discounted disaggregated costs [redacted]

	Mogamulizumab	Established clinical management	Increment	% increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs - current treatment	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs - Surveillance	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs - Subsequent treatments	[redacted]	[redacted]	[redacted]	[redacted]
ESC costs – Progressed	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs - non aSCT	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]
aSCT costs and monitoring DF	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs - aSCT	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring aSCT – Relapsed	[redacted]	[redacted]	[redacted]	[redacted]
ESC costs – aSCT	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	£72,736	100%
Key: aSCT, allogeneic stem cell transplant; DF, disease free; ESC, end stage care.				

Table 20: Base-case results (discounted) [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Established clinical management	[redacted]	2.71	1.78					
Mogamulizumab	[redacted]	6.40	4.60	£95,577	3.69	2.83	£33,819	£33,819
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

Figure 5. Cost-effectiveness plane [redacted]

Figure 6. Cost-effectiveness acceptability curves (CEACs) [redacted]

Figure 7. Tornado diagram [redacted]

NICE National Institute for Health and Care Excellence

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Deadline for comments: **5pm** on **Friday 5 June 2020**

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Royal College of Pathologists, British Association Dermatology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[redacted]

Questions for engagement

Issue 1: Population	
1. In clinical practice, is mogamulizumab likely to be used for people with severe disease (defined as stage ≥IIB for MF and all patients with SS) after 1 prior treatment and after disease progression with brentuximab or if it is inappropriate (see section 1.2 of technical report on the treatment pathway)? a. Is this subgroup a clinically relevant population for the NHS in England? b. Are trial results from the subgroup with severe disease in MAVORIC generalisable to the NHS in England (see table 2 in technical report for baseline characteristics)?	**Brentuximab is only lisenced for CD30+ CTCL, mogamulizumab if for MF or SS CD30 – or CD30 + , 1 prior systemic,** **It is also an important treatment for IB/IIA MF refractory to skin directed therapy, and advanced stages IIB-IVB.** a Yes b Yes

Issue 2: Comparator	
2. What treatments are currently used in the NHS in England for people with severe disease after brentuximab vedotin or if it is not appropriate? a. What proportion of patients would have each treatment (see table 4 in technical report)? b. Is vorinostat likely to be clinically comparable to standard care in the NHS in England?	**After BV or if BV not appropriate we would be forced to go to chemotherapy which is not very effective and has short duration of action plus has immunosuppressive effects and high risk of infection in this group** a All chemo b Vorinostat is not available in Europe so not possible to comment
3. Would you expect symptoms to be controlled after current treatment is stopped? If so, approximately how long would symptom control last until further treatment is needed?	**Progression free survival was 7.7 months is MAVORIC so implies that symptom relief is approximately at least this long**
Issue 3a: Cross-over adjustment	
4. Which cross-over adjustment method provides the most clinically plausible OS estimates for the standard care arm to represent people with severe disease in the NHS in England (see figure 4 in technical report)? a. Is a large drop in survival at around 6 months clinically plausible for this subgroup with severe disease?	**Yes they were heavily pre-treated MF/SS patients**
Issue 3b: Extrapolation of overall survival	

5. In current clinical practice, what is the average survival time for people eligible for second-line treatment? a. approximately what proportion of people would you expect to survive at 5 and 10 years? b. What is the average survival for people with severe disease in the NHS?	This is stage dependant – taken form diagnosis Median time from diagnosis to death in IVA2 / IVB is just 12 months Stage IIB-IVA1 is median around 3-5 years Stage IB/IIA variable 5-10 yrs in those requiring systemic therapy
6. In current clinical practice, what is the average survival time for people eligible for third-line treatment? a. approximately what proportion of people would you expect to survive at 5 and 10 years? b. What is the average survival for people with severe disease in the NHS?	Can be extrapolated from above if you imagine each treatment given between 4- 12 months?
7. Is the company or ERG extrapolation of OS most clinically plausible (see figures 5 and 6 and table 6 in the technical report)?	Yes but I would add that the patients with IB/IIA refractory to skin directed therapy requiring systemics have a much worse outcome 5-10 years
Issue 4: Allogenic stem cell transplant (aSCT)	

8. At what point in the treatment pathway are patients likely to have an allogeneic SCT (aSCT)? Would eligibility for aSCT be based on fixed time points or depend on a patient's response to treatment? a. Approximately what proportion of people who are eligible for second or third-line treatment are likely to have an aSCT?	Only a small number are eligible for transplants <10% of advanced patients, most would have historically had a high number of prior treatments but we are transplanting earlier now after 1-2 systemics if there is a good response Evaluation of haematopoietic stem cell transplantation in patients diagnosed with cutaneous T-cell lymphoma at a tertiary care centre: should we avoid chemotherapy in conditioning regimes? Ritchie S, Qureshi I, Molloy K, Yoo J, Shah F, Stevens A, Irwin C, Chaganti S, Scarisbrick JJ. Br J Dermatol. 2020 Mar;182(3):807-809
9. In your clinical opinion, is treatment with mogamulizumab likely to impact on a patient's eligibility for aSCT?	It may help bridge them to transplant
Issue 5: Stopping rule for mogamulizumab	
10. In your clinical opinion, would a 2-year stopping rule for mogamulizumab be appropriate?	For the majority of patients but there are always the odd exception that does very well for longer
Issue 6: Utility values	

11. In your clinical opinion, is a patient's health-related quality of life generally stable while on treatment?	No it should improve with effective drugs and this is very important as treatments not curative and generally resulting in partial responses We saw this improvement with MAVORIC
12. Compared with other cancers, do you think MF and SS has a similar impact on carers?	No there is a huge burden on carers – quality of life is effected for all Patients have painful, itchy, disfiguring lesions, often involving hands/ feet so affecting function and fear of cancer diagnosis with no widely available cure 'It's a traumatic illness, traumatic to witness': a qualitative study of the experiences of bereaved family caregivers of patients with cutaneous T-cell lymphoma. Orlowska D, Selman LE, Beynon T, Radcliffe E, Whittaker S, Child F, Harding R. Br J Dermatol. 2018 Oct;179(4):882-888. doi: 10.1111/bjd.16447. Epub 2018 Jun 19.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Takeda UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Population	
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Issue 2: Comparator	
2. What treatments are currently used in the NHS in England for people with severe disease after brentuximab vedotin or if it is not appropriate? a. What proportion of patients would have each treatment (see table 4 in technical report)? b. Is vorinostat likely to be clinically comparable to standard care in the NHS in England?	a. The UKCLG treatment guidelines[1] state that for stage IIB and higher, third-line options after brentuximab vedotin include chemotherapy, total skin electron beam therapy, reduced intensity allogenic stem cell transplantation (if patients are eligible) and enrolment into clinical trials. We have no comment regarding what proportion of patients would have each treatment. b. Vorinostat is not approved by the EMA because the applicant company Merck Sharp & Dohme withdrew the application in February 2009, at Day 206 of the procedure.[2] At the time of the withdrawal, the CHMP's view was that a benefit of vorinostat had not been sufficiently demonstrated and any benefits did not outweigh the identified risks. We are not aware of any data comparing vorinostat to the standard of care in the NHS in England. References: [1] https://www.bad.org.uk/shared/get-file.ashx?id=6265&itemtype=document [2] https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-withdrawal-marketing-application-vorinostat-msd_en.pdf
3. Would you expect symptoms to be controlled after current treatment is stopped? If so, approximately how long would symptom control last until further treatment is needed?	No comment
Issue 3a: Cross-over adjustment	
4. Which cross-over adjustment method provides the most clinically plausible OS estimates for the standard care arm to represent people with severe disease in the NHS in England (see figure 4 in technical report)? a. Is a large drop in survival at around 6 months clinically plausible for this subgroup with severe disease?	a. No comment

Issue 3b: Extrapolation of overall survival	
5. In current clinical practice, what is the average survival time for people eligible for second-line treatment? a. approximately what proportion of people would you expect to survive at 5 and 10 years? b. What is the average survival for people with severe disease in the NHS?	Two UK studies have been reported for survival rates: • 5-year OS rate was 47% for stage IIB, and 18% for stage IV; median survival time was 4.7 years and 1.4 years, respectively [3] • 5-year survival rates for stages IIB and IVB were 57% and 39%, respectively. In patients with advanced-stage MF/SS, reported median survival times ranged from 2.4 to 5.2 years, despite treatment [4] References: [3] Agar NS et al. J Clin Oncol. 2010;28(31):4730-4739 [4] Scarisbrick J et al. J Clin Oncol. 2015;33(32):3766-3773
6. In current clinical practice, what is the average survival time for people eligible for third-line treatment? a. approximately what proportion of people would you expect to survive at 5 and 10 years? b. What is the average survival for people with severe disease in the NHS?	a. No comment b. No comment
7. Is the company or ERG extrapolation of OS most clinically plausible (see figures 5 and 6 and table 6 in the technical report)?	No comment
Issue 4: Allogenic stem cell transplant (aSCT)	

8. At what point in the treatment pathway are patients likely to have an allogeneic SCT (aSCT)? Would eligibility for aSCT be based on fixed time points or depend on a patient's response to treatment? a. Approximately what proportion of people who are eligible for second or third-line treatment are likely to have an aSCT?	UKCLG guidelines state: Reduced-intensity allogeneic (RIC) HSCT should be considered for selected groups of patients with advanced MF/SS to consolidate treatment responses. Maximal benefit from RIC-HSCT is observed when it is performed before patients develop highly refractory disease and when there is low disease bulk at the time of transplantation. No specific timepoint is recommended but instead transplantation is based on patient eligibility and response to treatment (complete response or very good partial responses required).
9. In your clinical opinion, is treatment with mogamulizumab likely to impact on a patient's eligibility for aSCT?	No comment
Issue 5: Stopping rule for mogamulizumab	
10. In your clinical opinion, would a 2-year stopping rule for mogamulizumab be appropriate?	No comment
Issue 6: Utility values	
11. In your clinical opinion, is a patient's health-related quality of life generally stable while on treatment?	No comment
12. Compared with other cancers, do you think MF and SS has a similar impact on carers?	No comment

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable

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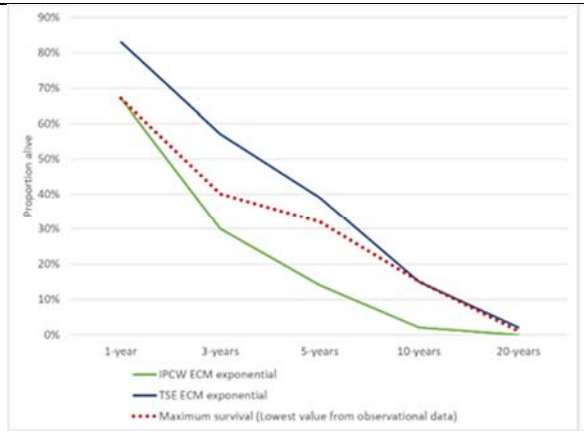
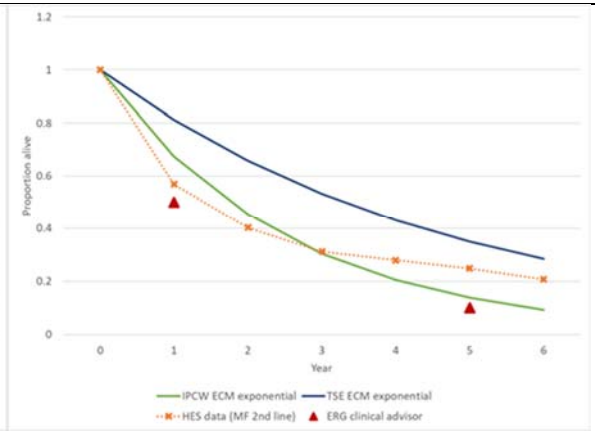
the NHS in England (see table 2 in technical report for baseline characteristics)?		
Issue 2: Comparator		
2. What treatments are currently used in the NHS in England for people with severe disease after brentuximab vedotin or if it is not appropriate? a. What proportion of patients would have each treatment (see table 4 in technical report)? b. Is vorinostat likely to be clinically comparable to standard care in the NHS in England?	In response to NICE, ERG and NHS England, and after additional clinical validation Kyowa Kirin has revised the base case comparator and length of comparator treatment. Using bexarotene as the main comparator and the appropriate length of treatment, resulted in an approximate £5,000/QALY decrease in the ICER. Scenario analyses looking at [redacted] methotrexate use and [redacted] pegylated interferon use resulted in minor changes. Please see section II of the **additional analyses submitted with this response** for more details. Vorinostat is considered a reasonable proxy for standard of care currently used in the NHS according to the clinical experts, as well as evidence in the literature. The approval of bexarotene, a key comparator for this submission, was based on a Phase II study of 193 cutaneous T-cell lymphoma patients; of these patients 93 had advanced stage disease refractory to prior systemic therapy (Eisai 2006). The efficacy data in this study showed an **overall response rate** in the skin of 31%; this is similar to the ORR of 29.7% seen in the skin compartment in the vorinostat arm of the MAVORIC study. The use of vorinostat as a proxy for standard of care is further supported when considering the progression-free survival curves for vorinostat from the MAVORIC study and the physician's choice arm (i.e. methotrexate or bexarotene) from the ALCANZA study (Prince 2017). Progression-free survival curves from the intention-to-treat population of these studies overlap thus confirming clinicians' comments that vorinostat should be considered a proxy for English standard of care.	**ERG comment:** As discussed in section 3.3 of the ERG report, there is some uncertainty regarding the use of vorinostat as a proxy for "established clinical management without mogamulizumab". This affects interpretation of cost effectiveness results, as highlighted in the ERG report (e.g.

	For further details, please see section B.2.9 of the Manufacturer Submission.	section 7.4) and the ERG addendum.
3. Would you expect symptoms to be controlled after current treatment is stopped? If so, approximately how long would symptom control last until further treatment is needed?	Due to its mechanism of action (see MS Section Error! Reference source not found.), patients can experience benefit from mogamulizumab after stopping treatment and after progression. This can be seen in the analyses of the treatment-free period in the MAVORIC trial using time to next treatment (see MS Section Error! Reference source not found.). Clinical experts suggested that, time to next treatment is more aligned with symptom control, thus time to next treatment acts as a good proxy for the length of symptom control: "Progression as defined in the MAVORIC trial: • Can indicate changes in quality of life • However not sensitive enough, e.g. patients' quality of life can deteriorate prior to progression requiring treatment change, or after progression • Treatment change is a better proxy for quality of life" (9th September 2019) "Treatment-free period reflects the higher response rates, but also better response (longer and better quality of response), so you can do 'watch and wait'. Time to next treatment thus reflects the rate, quality and durability of response and is clinically important. […] Progression-free survival is technical. A minimal disease occurrence, such as a small rash can trigger it. This results in a situation, where the patient might have progressed, but is still doing ok. Time to next treatment is clinically more meaningful.[…] Quality of life is influenced mostly by response and duration of response, thus time to next treatment is a good proxy. Resource use depends on time to next treatment, and what that next treatment is based on response" (3rd October 2019) "Clinical benefit usually comes from symptom alleviation and increased life expectancy. Treatment discontinuation is not really a good predictor, as it depends why the patient	**ERG comment:** As highlighted in sections 4.2.5.1 and 4.2.5.4 of the ERG report, assessment of progression is associated with some uncertainty and there were potential problems in the reporting of this outcome.

	stops the treatment. It could be due to progressive disease but could be due to complete response. Time until next treatment is a good predictor." (14th October 2019).	
Issue 3a: Cross-over adjustment		
4. Which cross-over adjustment method provides the most clinically plausible OS estimates for the standard care arm to represent people with severe disease in the NHS in England (see figure 4 in technical report)? a. Is a large drop in survival at around 6 months clinically plausible for this subgroup with severe disease?	While statistically both inverse probability of censoring weighted (IPCW) and two-stage estimation (TSE) methods are potential options, both the external validation against observational data from the UK Hospital Episode Statistics (HES) and published data from Kim 2003, Talpur 2012 and Agar 2010 support the use of IPCW adjustment for crossover adjustment. Additionally, the shorter predicted survival with the TSE method on subsequent treatments after mogamulizumab compared to on subsequent treatments after the comparator, and the lower life-years for the advanced population despite the better results from the MAVORIC trial compared to the intention-to-treat population are clinically implausible. Survival estimates with IPCW/TSE from 2+ line of treatment are compared below to published observational data from diagnosis for a better patient population (time measures from diagnosis as opposed to from start of 2nd line treatment, lower proportion of SS patients, lower proportion of more advanced patients, and less heavily pre-treated) and UK HES data from 2nd line treatment. Survival estimates with IPCW are below the maximum threshold of the observational data and in line with the HES database findings, while results with the TSE are likely to overestimate the survival.	**ERG comment:** The ERG agrees with the company that both IPCW and TSE methods are potential options for cross-over adjustment. However, which cross-over adjustment to choose remains uncertain. Please refer to the ERG addendum for a detailed response to the company's newly submitted evidence.





For further details please see the **additional analyses attached**, the Manufacturer Submission section B.3.3.1 and the Clarification answers.

Issue 3b: Extrapolation of overall survival

5. In current clinical practice, what is the average survival time for people eligible for second-line treatment?
   a. approximately what proportion of people would you expect to survive at 5 and 10 years?
   b. What is the average survival for people with severe disease

For the proportion of patients surviving at the different timepoints from the UK Hospital Episode Statistics (HES) database and from the MAVORIC trial using inverse probability of censoring weighted (IPCW) and two-stage estimation (TSE) adjustment are presented below:

Crossover adjustment	Source (comparison to MAVORIC patients)	1-year	3-years	5-years
-	HES database (MF patients, staging not available, 2nd line)	57%	31%	25%
IPCW	For Established Clinical Management arm from model	67%	30%	14%
TSE	For Established Clinical	83%	57%	39%

ERG comment: Please refer to the ERG addendum for a detailed response to the company's newly submitted evidence.

in the NHS?		Management arm from model			

Median survival from the UK Hospital Episode Statistics (HES) database and from the MAVORIC trial using IPCW/TSE adjustment are presented below:

Median survival from:	Source	Median survival	Comments
From the start of 2nd line systemic treatment	HES database	1.3 years	Weighted by the distribution of MF/SS in MAVORIC trial*
From the start of 2nd+ line systematic treatment	For Established Clinical Management arm from model with IPCW	1.8 years	-
	For Established Clinical Management arm from model with TSE	3.4 years	-

In both cases the results with the IPCW adjustment are aligned with the UK HES data, while the TSE adjustment is likely to overestimate survival.

6. In current clinical practice, what is the average survival time for people eligible for third-line treatment? a. approximately what proportion of people would you expect to survive at 5 and 10 years? b. What is the average	Kyowa Kirin is not aware of any published data for survival for patients eligible for third line treatment. The UK Hospital Episode Statistics Database has limited number of patients in third line treatment (95 in mycosis fungoides and 17 in Sézary disease between 1st October 2010 and 31st March 2019). The median survival was 1.1 years for mycosis fungoides and 1.0 year for Sézary disease. However, it would not be clinically appropriate to have mogamulizumab placed as 3rd+ line therapy (that is, much later lines of therapy than license). This is because the disease modifying benefits of mogamulizumab would not be realised clinically if used 3rd+ line for these patients.	**ERG comment:** Uncertainty remains about the population that mogamulizumab will be used in (the ERG clinical advisor considered it third-line) and what the survival gain is in

survival for people with severe disease in the NHS?		this population. The company's model estimates a mean of 3.10 LYs (with ECM, undiscounted, company's base-case) or 4.91 LYs (with ECM, undiscounted, ERG base-case).
7. Is the company or ERG extrapolation of OS most clinically plausible (see figures 5 and 6 and table 6 in the technical report)?	The exponential and the lognormal extrapolations are very close with a high uncertainty. In the mogamulizumab arm, Akaike and Bayesian Information Criteria for all distributions are very close ([redacted] respectively). However, using visual inspection, lognormal distribution (which with log-logistic distribution has the second lowest Akaike and Bayesian Information Criteria) fits better than the exponential curve (with slightly lower Akaike Information Criterion ([redacted]) and Bayesian Information Criterion ([redacted]) at the first half of the curve, where more data are available. Additionally, the evidence shows a potentially disease modifying effect for mogamulizumab, which would result in a longer tail, as opposed to Established Clinical Management (vorinostat) arm. (Please see additional analyses for more details on the disease modifying effect of mogamulizumab.)	**ERG comment:** Please refer to the ERG addendum for a detailed response to the company's newly submitted evidence.
Issue 4: Allogenic stem cell transplant (aSCT)		
8. At what point in the treatment pathway are patients likely to have an allogeneic SCT	In the MAVORIC trial, [redacted] of patients randomised to mogamulizumab and [redacted] of vorinostat patients have received allogenic stem cell transplant. While allogenic stem cell transplant was only allowed after subsequent treatment in the MAVORIC trial design, in clinical	ERG comment: The ERG notes that, according to

<table>
<tr>
<td>(aSCT)? Would eligibility for aSCT be based on fixed time points or depend on a patient's response to treatment?
a. Approximately what proportion of people who are eligible for second or third-line treatment are likely to have an aSCT?</td>
<td>practice app. [redacted] of patients would be receiving it after current treatment according to the clinical experts. This was exactly in line with the findings from the HES database, which showed [redacted] of MF/SS patients receiving allogenic stem cell transplant after second-line treatment.
<table>
<tr><th>Timing and comparator</th><th>UK expert opinion (mean of 3 experts)</th><th>UK HES database</th><th>MAVORIC trial</th></tr>
<tr><td>Immediately after mogamulizumab</td><td>[redacted]</td><td>NA</td><td>NA</td></tr>
<tr><td>After subsequent treatment to mogamulizumab</td><td>[redacted]</td><td>NA</td><td>[redacted]</td></tr>
<tr><td>Immediately after current clinical practice</td><td>[redacted]</td><td>[redacted]</td><td>NA</td></tr>
<tr><td>After subsequent treatment to current clinical practice</td><td>[redacted]</td><td>No data available</td><td>[redacted]</td></tr>
</table>
</td>
<td>UK expert opinion presented by the company, the proportion of aSCT is higher in the mogamulizumab group compared to current clinical practice.
Please refer to the ERG addendum for a detailed response to the company's newly submitted evidence.</td>
</tr>
<tr>
<td>9. In your clinical opinion, is treatment with mogamulizumab likely to impact on a patient's eligibility for aSCT?</td>
<td>The ERG mentioned safety concerns regarding allogenic stem cell transplant after mogamulizumab. However, these safety concerns are for a limited time. As the Summary of Product Characteristics states, "higher risk of transplant complications has been reported if mogamulizumab is given within a short time frame (approximately 50 days) before HSCT." Consequently a 7-week washout period was used in the model. This is in line with the NICE Overview of discussions with key stakeholders about technical aspects of the case: "have experience using mogamulizumab as a bridge to stem cell transplant in a few patients and it doesn't impact eligibility although need to wait 8 weeks before all HSCT to reduce impact on GvHD".</td>
<td>ERG comment: No further comments.</td>
</tr>
<tr>
<td colspan="3">Issue 5: Stopping rule for mogamulizumab</td>
</tr>
</table>

10. In your clinical opinion, would a 2-year stopping rule for mogamulizumab be appropriate?	According to expert opinion**: "**based on proportions of patients in MAVORIC post 24 months (approximately 14% of patients would be still receiving mogamulizumab in the advanced population and 10% in the ITT population) that stopping therapy at 24 months would still provide clinical benefit to the vast majority of patients receiving mogamulizumab**"**..	**ERG comment:** A discussion of this can be found in the ERG report Section 5.2.9.
Issue 6: Utility values		
11. In your clinical opinion, is a patient's health-related quality of life generally stable while on treatment?	While there is uncertainty, the MAVORIC trial shows an increase in utilities while on treatment (see graph below). However due to the uncertainty, Kyowa Kirin revised the base case to include stable health state utilities.	**ERG comment:** No further comment.

		
12. Compared with other cancers, do you think MF and SS has a similar impact on carers?	Both the published literature and the expert interviews indicated greater burden on carers than in other indications. This is in line with the conclusions from NICE TA577. The vignette study conducted by Kyowa Kirin also showed, that not only caregiver utilities are low but they are significantly lower in 3rd line treatment vs. 2nd line treatment: EQ-5D	**ERG comment:** A discussion of this can be found in section 5.2.8 of the ERG report.

	values: 0.366 (95% CI: 0.322-0.411) vs. 0.559 (95% CI: 0.511-0.607) respectively. While there are discussions around the correct implementation of carer utilities, Kyowa Kirin has used a conservative approach that avoided the pitfalls listed by ERG. The model included carer utilities as decrements only for the disease control health state and assumed not to affect any of the subsequent health states, thereby potentially underestimating the effect of carer burden. Please see Manufacturer Submission Section B.3.4 for further details on published studies, expert opinion, the vignette study, and the implementation of the results from the vignette study.	

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Mogamulizumab for treating mycosis fungoides or Sézary syndrome cutaneous T-cell lymphoma

ADDENDUM

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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None.

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[redacted]

Response to technical engagement

The company submitted additional analyses and evidence in response to technical engagement. This includes responses to all issues highlighted during technical engagement and a revised model file with additional analyses. The company presented a new base-case, which includes these notable changes, compared with their previous base-case:

- Bexarotene used as the only comparator
- Comparator treatment duration extended
- New patient access scheme (PAS; [redacted]

The company did not incorporate the Evidence Review Group's (ERG's) amendments in their model file – in fact, the company's model is not based on the amendments the ERG has made, but instead is based upon their re-submission in response to the clarification letter. The company's revised base-case therefore does not include any of the ERG's amendments. Also, the company's results using the above changes could not be exactly replicated. The company's revised incremental cost effectiveness ratio (ICER) was £25,724 per quality-adjusted life year (QALY) gained whilst the ERG's reproduction of the same analysis resulted in an ICER of £25,711 per QALY gained. Therefore, the ERG used the adapted model by the ERG (which was based on the company's resubmission in response to the clarification letter) to replicate the company's new analyses.

Cross-over adjustment

External validation

The company have provided a new analysis of external data, from the Hospital Episode Statistics (HES) database, to validate survival as predicted using the different cross-over adjustment methods and distributions used for extrapolating overall survival. Given the large uncertainty about overall survival (OS), this is definitely appreciated. The company argue that these HES data are much closer to the target population as they include only patients on second-line systemic treatment. In Figure 3, the company show 6-year survival on established clinical management (ECM) predicted using their economic model with different assumptions (inverse probability of censoring weighting (IPCW) and two-stage estimation (TSE) method for cross-over) and the HES data for the mycosis fungoides (MF) second line population. The ERG clinical advisor is also cited in this Figure but this is incorrect: all references to the ERG clinical advisor are only in the ERG report where no mention is made of the quote supposedly attributed to her. Instead, the quote should have been attributed to a clinical advisor for the National Institute for Health and Care Excellence (NICE). Comparing HES data with modelled data, IPCW first over-estimates survival and from year 3 starts to under-estimate survival, whilst the TSE method over-estimates survival over the whole time span and might under-estimate survival in later years given that the lines appear set to cross. Also, there is still a discrepancy between the populations: those eligible for third-line, rather than those on second-line treatment.

Both cross-over adjustment methods appear to be sub-optimal in predicting survival in the United Kingdom (UK) second-line population that receives largely ECM. This may be an artefact of several factors, including differences in the population, the influence of the parametric distributions chosen to extrapolate survival (please see ERG report section 5.2.6 for a discussion of the size of impact of this issue alone), and most importantly, the comparator used to inform the model, which is of course vorinostat and not available in the UK setting.

In conclusion, despite the company's efforts in providing external validation, uncertainty about OS in this population remains substantial. Based on this, it is not possible to choose one cross-over adjustment method over the other. Therefore, results of both methods should be taken into account.

Clinical plausibility

The company states that the IPCW method reflects better than the TSE method any post-progression effects that mogamulizumab may have, i.e. survival estimates on subsequent treatments longer for comparator than for mogamulizumab with the TSE method which is even more pronounced with the choice of the exponential distribution as opposed to the company's base-case log-normal distribution. There is currently no direct evidence for this claim, as attested by statements by clinical experts to support this longer-term effect that mogamulizumab may have, who also refer to a "hypothesis" and "anecdotal evidence". The company's MAVORIC post-hoc analysis does appear to support the hypothesis that mogamulizumab may be disease-modifying: time to next treatment after subsequent treatments was found to be longer in the mogamulizumab arm than in the vorinostat arm. However, uncertainty remains about the disease-modifying nature of mogamulizumab. Furthermore, questions remain whether the IPCW method really produces more clinically plausible estimates: for example, the ERG considers it questionable that the main survival benefit of mogamulizumab would be accrued on subsequent treatments, where a patient can gain [redacted] years compared to when treated with mogamulizumab instead of vorinostat, than on current treatment (i.e. mogamulizumab or vorinostat), where a patient can gain only [redacted] years when treated with mogamulizumab instead of vorinostat (Table 3 in company's TE Additional analyses document). As above, the ERG considers that both results using the IPCW and TSE methods are highly questionable.

Comparator

The company have tried to improve their estimates of comparator costs by 1) using only bexarotene as the comparator (and scenarios with methotrexate and peg interferon) and 2) by adapting the length of treatment to be more in line with UK length of treatment (for bexarotene).

The company provide support for 1), citing an expert survey and National Health Service (NHS) England statements indicating that interferon is not available and methotrexate is uncertain to be used at all in this population. The ERG considers that using a single comparator may be an over-simplification of the non-standardised treatment landscape in these patients (especially for patients with Sézary syndrome (SS), as the company acknowledged). Given the large uncertainty around ECM, the ERG considers that this scenario should be explored.

As for 2), whilst it appears justified to adjust length of treatment to UK data where available, there are some concerns about this adjustment. Firstly, the source of the data is not provided by the company (48 weeks mean treatment duration for bexarotene). Secondly, both adjustments 1) and 2) mean that comparator effectiveness and costs in the model refer to completely different treatments, around which there is a lot of uncertainty.

In conclusion, the ERG considers these adjustments to be valuable for scenario analysis but its base-case remains unchanged. However, the main concern remains that the comparator used for modelling comparator clinical effectiveness (vorinostat) is not available in the UK and it therefore remains very difficult to assess the relative effectiveness of mogamulizumab in the UK setting.

Allogenic stem cell transplant (aSCT)

Concerns remain about how the company implemented the possibility of patients receiving aSCT after current treatment in their model when their treatment effectiveness evidence used in the model

precludes patients from receiving this. This means that in their "no aSCT" pathway, treatment effectiveness and patient response to treatment is likely over-estimated. The company have attempted to address this issue in a new scenario, where patients who would have been eligible for aSCT in the trial were down-weighted. As expected, the ICER increases, by less than £1,000 per QALY gained. The ERG considers that this approach was methodologically questionable. Hence, the ERG keeps its base-case unchanged, but is aware of the caveat that excluding the option of aSCT after current treatment does not reflect clinical practice.

End of life

In the original company submission (CS), the company did not include any statement regarding mogamulizumab meeting the end of life criteria defined by NICE.

NICE end of life considerations apply when two criteria are satisfied:

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months; and
2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, compared to current NHS treatment.

Criterion 1:

Table 10 of the "additional analyses response" submitted by the company during technical engagement shows life expectancy for the advanced population (base-case) as well as two scenario analyses, including the intention-to-treat (ITT) population of the MAVORIC trial. In this population, life expectancy for both, median survival for ECM arm (29.7 months) as well as mean undiscounted life-years for ECM arm (49.0 months), are above the relevant threshold. Furthermore, modelled life expectancy when treated with standard care (ECM) is 3.10 life years (LYs; mean undiscounted, company's base-case) or 4.91 LYs (mean undiscounted, ERG base-case).

Overall, criterion 1 of NICE end of life considerations is not met.

Criterion 2:

OS results are summarised in Table 4.14 of the ERG report. As discussed before (e.g. section 3.3 of the ERG report), there is some uncertainty regarding the use of vorinostat as a proxy for *"established clinical management without mogamulizumab"*.

Overall, it is unclear whether criterion 2 of NICE end of life considerations is met.

ERG analyses

- ERG base-case with new PAS
- ERG base-case with new PAS with IPCW method
- ERG base-case with new PAS 30% IPCW / 70% TSE (10,000 simulations)
- ERG base-case with settings of company's revised base-case (the company's "BIM scenario"; used for their budget impact (BIM) analysis)

Table 1. ERG analyses with company's new cPAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case with new PAS (deterministic)					
Mogamulizumab	[redacted]	3.63	£80,201	0.85	£94,250

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ECM	[redacted]	2.78			
ERG base-case with new PAS (probabilistic, 10,000 simulations)					
Mogamulizumab	[redacted]	3.65	£79,323	0.85	£93,615
ECM	[redacted]	2.81			
ERG base-case with new PAS with IPCW method (deterministic)					
Mogamulizumab	[redacted]	3.63	£98,872	2.04	£48,533
ECM	[redacted]	1.60			
ERG base-case with new PAS 30% IPCW / 70% TSE (probabilistic, 10,000 simulations)					
Mogamulizumab	[redacted]	3.65	£84,863	1.20	£70,529
ECM	[redacted]	2.45			
ERG base-case with settings of company's revised base-case (deterministic BIM scenario)					
Mogamulizumab	[redacted]	3.63	£60,989	0.85	£71,672
ECM	[redacted]	2.78			

BIM = budget impact; cPAS = confidential Patient Access Scheme; ECM = established clinical management; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IPCW = inverse probability of censoring weighting; PAS = Patient Access Scheme; QALY = quality-adjusted life year; TSE = two-stage estimation

Conclusions

The company have provided further data and analyses, which is much appreciated. Due to the limitations around the comparator, relative treatment effectiveness being based upon a comparison that is not relevant to the UK setting and a trial in which treatment switching was possible, uncertainty remains high. Relative treatment effectiveness in the UK setting remains very difficult to assess and this is exacerbated by uncertainty about the choice of cross-over adjustment, which cannot be resolved.