NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from Recordati Rare Diseases

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. **British Association of Dermatologists**
   b. **Lymphoma Action**

4. **Expert personal perspectives from:**
   a. Sean Whittaker, Professor of Skin Oncology – clinical expert, nominated by Recordati Rare Diseases
   b. Julia Scarisbrick, Consultant Dermatologist – clinical expert, nominated by British Association of Dermatologists & Recordati Rare Diseases
   c. Stephen Scowcroft – patient expert, nominated by Lymphoma Action

5. **Evidence Review Group report** prepared by Aberdeen HTA Group

6. **Evidence Review Group – factual accuracy check**

7. **Notes on discussions with experts with:**
   a. Sean Whittaker, Professor of Skin Oncology – clinical expert, nominated by Recordati Rare Diseases
   b. Julia Scarisbrick, Consultant Dermatologist – clinical expert, nominated by British Association of Dermatologists & Recordati Rare Diseases

8. **Technical Report**

9. **Technical engagement response** from Recordati Rare Diseases

10. **Evidence Review Group critique of company response to technical engagement** prepared by Aberdeen HTA Group

11. **Evidence Review Group additional information**

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

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Document B

Company evidence submission

January 2020

File name	Version	Contains confidential information	Date
ID1589 Company Evidence Submission Document B_Updated_May 2020 [REDACTED]	Final	Yes	21st May 2020

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Abbreviations

Abbreviation	Definition
1L	First line
AE	Adverse event
AP	Aquaphor (chlormethine ointment)
ATU	Temporary Use Authorisation (Autorisations Temporaires d'Utilisation)
BAD	British Association of Dermatologists
BB	Broadband
BCC	Basal cell carcinomas
BNF	British National Formulary
BSA	Body surface area
CAILS	Composite Assessment of Index Lesion Severity
CBCL	Cutaneous B-cell lymphoma
CCL17	CC chemokine ligand 17
CCR4	CC chemokine receptor 4
CD	Cluster of differentiation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLA	Cutaneous lymphocyte antigen
CLTF	Cutaneous Lymphoma Task Force
COMP	Committee for Orphan Medicinal Products
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
DC	Dendritic cell
DNA	Deoxyribonucleic acid
DSA	Deterministic sensitivity analysis
EADV	European Academy of Dermatology and Venerology
EBRT	External beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
ECP	Extracorporeal photopheresis
EE	Efficacy evaluable
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy: General
FAS	Full analysis set
FDA	Food and Drug Administration
GBP	Great British Pound
G-CSF	Granulocyte-colony stimulating factor
HCP	Healthcare professional
HRQoL	Health-related quality of life
HUI3	Health Utilities Index Mark 3
ICER	Incremental cost-effectiveness ratio
IFN(-α)	Interferon(-α)

IgE	Immunoglobulin E
IQR	Interquartile range
ISCL	International Society for Cutaneous Lymphomas
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LCT	Large cell transformation
LDH	Lactate dehydrogenase
LN	Lymph node
LY	Life year
LYG	Life years gained
MCH	Mechlorethamine
MedDRA	Medical Dictionary for Regulatory Activities
MF-CTCL	Mycosis fungoides-type cutaneous T-cell lymphoma
MIMS	Monthly Index of Medical Specialities
(m)SWAT	(Modified) Severity Weighted Assessment Tool
MTX	Methotrexate
NB-UVA/B	Narrowband ultraviolet A/B
NC	Not calculated
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphomas
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NK	Natural killer
NM	Nitrogen mustard
NR	Not reported
NYU	New York University (study centre)
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PC	Physician's choice
PET	Positron-emission tomography
PFS	Progression-free survival
PG	Propylene glycol
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PUVA	Psoralen-ultraviolet A
QALY	Quality-adjusted life year
QD	Once daily
QoL	Quality of life
RCT	Randomised clinical trial
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SCT	Stem cell transplantation
SD	Standard deviation
SDT	Skin-directed therapy
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
SWAT	Severity Weighted Assessment Tool

TH1	T helper 1 cell
TH2	T helper 2 cell
TNMB	Tumour, nodes, metastasis, blood
ToT	Time on treatment
TSEB	Total skin electron beam
TTO	Time-trade-off
USCLC	United States Cutaneous Lymphoma Consortium
USD	United States dollar
UVB	Ultraviolet B
WTP	Willingness-to-pay

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

B.1.1 *Decision problem*

This submission presents the evidence for the clinical and cost-effectiveness of chlormethine gel within its full marketing authorisation; for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients.

The decision problem addressed within this submission is largely consistent with the NICE final scope for this appraisal as outlined in Table 1; any deviations from the final scope are detailed in Table 1, with accompanying justification.

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-type cutaneous T-cell lymphoma	Adults with mycosis fungoides-type cutaneous T-cell lymphoma	N/A – in line with the final NICE scope
Intervention	Chlormethine gel	Chlormethine gel	N/A – in line with the final NICE scope
Comparator(s)	Skin directed therapies such as photo therapy (PUVA, UVB) and total skin electron beam therapy. In patients for whom the above skin directed therapies are contraindicated: • Established clinical management without chlormethine gel (including systemic therapies such as interferons and retinoids)	Phototherapy (PUVA, UVB) In patients for whom the above skin directed therapies are unsuitable: • Bexarotene • Pegylated IFN-α	TSEB is not considered a comparator to chlormethine gel. Firstly, whilst both treatments are used to target the skin symptoms of MF-CTCL, these therapies may be used to treat patients with notably different degrees of skin involvement in MF-CTCL. Chlormethine gel is anticipated to be used on specific thin patches and plaques, whilst TSEB, as a treatment for the whole body, would more likely be considered for patients with very widespread plaques covering most of the body. Clinical expert opinion supports this,[1] and although it was acknowledged that there may be minor overlap in the patient populations treated with chlormethine gel and TSEB, the introduction of chlormethine gel is not anticipated to displace the majority of TSEB use. Secondly, the use of TSEB is very limited in UK clinical practice, supported by data from the PROCLIPI registry; therefore, it is not considered standard of care.[2] Wording regarding contraindication to phototherapy in the NICE final scope has been updated to 'unsuitable' in the submission decision problem. This is because there are reasons beyond contraindication as to why patients may not receive phototherapy; these include prior receipt of phototherapy (as there is a maximum number of cycles that patients can receive), restricted access geographically, and low levels of lesional coverage for which the risk benefit ratio for phototherapy precludes its use.[3, 4] Although we consider a broader definition of "unsuitable" to be more appropriate to the clinical setting than "contraindicated", it should be noted that the proportion of patients who would not be considered

			suitable for phototherapy and who would receive bexarotene or pegylated IFN-α remains low (approximately 10% of the eligible patient population for chlormethine gel addressed in the submission, based on clinical expert feedback).[1] Finally, it should be noted that the decision problem addressed specifies *pegylated* IFN-α specifically; based on feedback from a UK clinical expert, IFN-α will soon no longer be available in UK clinical practice and the pegylated form will be used in its place.[1, 4]
Outcomes	• Skin symptoms (for example erythema, scaling and pruritus) • Response rates • Duration of response • Adverse effects of treatment • Health-related quality of life Mortality	• Skin symptoms (via CAILS) • Response rates • Duration of response • Adverse effects of treatment • Health-related quality of life Mortality	N/A – in line with the final NICE scope
Subgroups to be considered	None specified	• A cost-effectiveness analysis in the subgroup of patients with early stage MF-CTCL (Stage IA-IIA) only is performed, as this reflects the population of Study 201	N/A

Abbreviations: IFN-α: interferon alpha; MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; N/A: not applicable; NICE: National Institute for Health and Care Excellence; PUVA: psoralen-ultraviolet A; TSEB: total skin electron beam therapy; UK: United Kingdom; UVB: ultraviolet B
Source: NICE Final Scope, ID1589 (2019).[5]

B.1.2 *Description of the technology being appraised*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with the technology, chlormethine gel, for the treatment of adult patients with MF-CTCL is presented in Table 2 below.

Table 2: Technology being appraised

UK approved name and brand name	Chlormethine gel (Ledaga®)
Mechanism of action	The pathophysiology of MF-CTCL is described in detail in Section B.1.3. Briefly, the pathology of MF-CTCL manifests as oval patches or thicker, raised plaques on the skin, formed as a result of the infiltration of malignant T-cells into the skin.[6] SDTs such as chlormethine gel aim to address these skin symptoms (patches and plaques). Chlormethine is a cytotoxic, bifunctional DNA alkylating agent which inhibits rapidly proliferating (i.e. malignant cancer) cells by disrupting DNA replication through various mechanisms such as DNA cross-linking, abnormal base pairing, or nucleic acid depurination.[7, 8] When absorbed into the affected areas of the skin, chlormethine therefore has a cytotoxic (fatal) effect on the malignant T-cells underlying patches and plaques, thus reducing the appearance of the skin lesions.[9]
Marketing authorisation/CE mark status	The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Ledaga® (chlormethine gel), intended for the treatment of mycosis fungoides-type cutaneous T-cell lymphoma on 15th December 2016.[10] The European Commission granted a marketing authorisation valid throughout the European Union for Ledaga® on 3rd March 2017.[11] Ledaga® was designated as an orphan medicinal product by the Committee for Orphan Medicines (COMP) on 22nd May 2012.[10]
Indications and any restriction(s) as described in the Summary of Product Characteristics (SmPC)	The marketing authorisation indication wording for chlormethine gel is as follows:[11] • *"Chlormethine gel is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients"* • Chlormethine gel is contraindicated for patients with hypersensitivity to chlormethine or to any of the excipients listed in section 6.1 of the summary of product characteristics (SmPC)[11] Full details are provided in the SmPC for chlormethine gel, which is included in the reference pack accompanying this submission.[11]
Method of administration and dosage	**Method of administration** Chlormethine gel is a topical therapy for application to the affected areas of the skin. The gel formulation of this product allows patients to apply the treatment at home, which is convenient and reduces the need for regular trips to hospital versus alternative treatment options. Chlormethine gel should be administered as follows:[11] • Patients must wash hands thoroughly with soap and water immediately after handling or applying chlormethine gel • Patients should apply chlormethine gel to affected areas of the skin. In case of chlormethine gel exposure to non-affected areas of the

	skin, patients should wash the exposed area with soap and water • Caregivers must wear disposable nitrile gloves when applying chlormethine gel to patients. Caregivers should remove gloves carefully (turning them inside out during the removal to avoid contact with chlormethine gel) and wash hands thoroughly with soap and water after removal of gloves. If there is accidental skin exposure to chlormethine gel, caregivers must immediately wash exposed areas thoroughly with soap and water for at least 15 minutes. • Remove and wash contaminated clothing • Chlormethine gel should be applied to completely dry skin at least four hours before or 30 minutes after showering or washing. The patient should allow treated areas to dry for five to ten minutes after application before covering with clothing. Occlusive (air- or water-tight) dressings should not be used on areas of the skin where chlormethine gel was applied • Emollients (moisturisers) or other topical products may be applied to the treated areas two hours before or two hours after application of chlormethine gel • Fire, flame, and smoking must be avoided until chlormethine gel has dried **Dosage** • Chlormethine gel (Ledaga®) contains chlormethine at a concentration of 0.016% (w/w) (160 micrograms/gram), equivalent to 0.02% (w/w) chlormethine hydrochloride • A thin film of chlormethine gel should be applied to affected areas of skin once daily o In the case of skin ulceration, blistering, moderately severe or severe dermatitis, chlormethine gel therapy should be discontinued. It may then be introduced with treatment every three days, and if tolerated for at least one week, the dosage may be increased to every-other day, and if tolerated for at least one week this can be increased to daily
Additional tests or investigations	N/A
List price and average cost of a course of treatment	Chlormethine gel is supplied in a tube. Each tube of chlormethine gel is associated with a list price of £1,000.
Patient access scheme (if applicable)	N/A

Abbreviations: CHMP: Committee for Medicinal Products for Human Use; COMP: Committee for Orphan Medicinal Products; DNA: deoxyribonucleic acid; MF-CTCL: mycosis fungoides-type cutaneous T-Cell lymphoma; N/A: not applicable; NHS: National Health Service; PAS: patient access scheme; SDT: skin-directed therapy; SmPC: Summary of Product Characteristics; w/w: weight for weight.

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

Disease overview

- MF-CTCL is a slow-progressing form of CTCL, the pathophysiology of which leads to visible, oval patches and plaques on the skin.[12] These patches and plaques can be painful and itchy, and may progress to form tumours over time[13]
- Although MF-CTCL is the most common subtype of CTCL, CTCL is a rare disease. Thus, MF-CTCL has low incidence in the population[14, 15]
  - In an audit of cases of newly diagnosed CTCL in England between 2009 and 2013, the average number of annual cases was 332. Of these, approximately 55% were MF-CTCL[14]
  - MF-CTCL is more common in males than females (1.5:1 ratio), and is usually diagnosed in older adult patients; the peak age of incidence of CTCL is 50–74 years of age[14]
- MF-CTCL is categorised into disease stages based on the number and type of skin lesions, lymph node or peripheral blood involvement and metastasis. Malignant T-cells are confined to the skin in the early stages of disease, but spread as disease stage advances over time[3, 16, 17]
  - 'Early' stage disease comprises Stages IA, IB and IIA, whilst 'advanced' stage disease comprises Stage IIB–IVB[17, 18]
- The skin symptoms of MF-CTCL are associated with a substantial patient burden, including physical discomfort, sleep disruption, embarrassment, social withdrawal and absenteeism[4, 19-23]

Clinical pathway of care

- The aim of treatment for MF-CTCL is to reduce the visibility and body surface area (BSA) coverage of lesions in order to decrease patient burden from skin symptoms. For patients with advanced disease, delay or prevention of the progression of the underlying disease is also a goal of treatment[3, 24]
- There are two main types of therapy for MF-CTCL: SDTs and systemic therapies
  - SDTs target the skin patches and plaques associated with MF-CTCL, whilst systemic therapies also aim to delay or prevent progression of the underlying cancer[3, 24]
- There are no NICE guidelines informing treatment decisions in UK clinical practice. The primary reference guideline in UK practice is that of the British Association of Dermatologists (BAD),[3] but individual patient and clinician preference forms a substantial part of treatment decision-making[24]
  - Topical chlormethine is the only SDT ranked with level 1+ for evidence in the BAD guidelines. However, no chlormethine formulation is currently available for use in UK clinical practice[3, 25]
  - Despite reference to many treatment options in the BAD guidelines,[3] there are few licensed therapies that have proven clinical efficacy through randomised controlled trials (RCTs) and widespread use in UK clinical practice[3, 24]
  - Expanding the clinician armamentarium to include chlormethine gel would provide patients with a treatment option that was developed specifically for MF-CTCL, is licensed for this indication, and is supported by clinical trial evidence for its efficacy and safety; thereby representing a step change in the management of this condition[3, 25]

B.1.3.1 Disease overview

Non-Hodgkin lymphomas (NHLs) are cancers that develop within the network of vessels in which lymph circulates throughout the body (the lymphatic system) and the glands through which it is

filtered (lymph nodes). In NHL, lymphocytes (B- and T-cells) that circulate within the lymphatic system multiply abnormally and then group together in particular locations in the body, for example in the lymph nodes themselves, or outside of these nodes ('extra-nodally').[26]

Primary cutaneous lymphomas are extra-nodal NHLs that only affect the lymphatic cells in the skin, with no extracutaneous disease at the time of diagnosis.[16] Cutaneous lymphomas can affect either the T-cells (cutaneous T-cell lymphoma [CTCL]) or B-cells (cutaneous B-cell lymphoma [CBCL]). CTCLs are the larger group of primary cutaneous lymphomas, accounting for approximately 75–80% of all cases, and represent the second-most common type of extra-nodal NHL.[16, 27] There are a number of sub-types of CTCL, of which MF-CTCL and Sézary Syndrome (SS; a leukaemic disorder related to MF-CTCL), are the most common. Other, rarer variants of CTCL include cutaneous CD30+ lymphoproliferative disorders, primary cutaneous γ/δ T-cell lymphoma and subcutaneous panniculitis-like T-cell lymphoma.[3]

MF-CTCL specifically is sometimes referred to as a 'low-grade' lymphoma, due to its slow progression in the early stages.[28] The pathophysiology underlying MF-CTCL (described below) leads to visible, oval or ring-like patches and plaques on the skin.[12] These patches and plaques can be painful and itchy, and may progress to form tumours over time. Patches and plaques may be mistaken for other skin conditions such as eczema or psoriasis, sometimes for many years, commonly leading to delayed diagnosis of MF-CTCL.[28, 29]

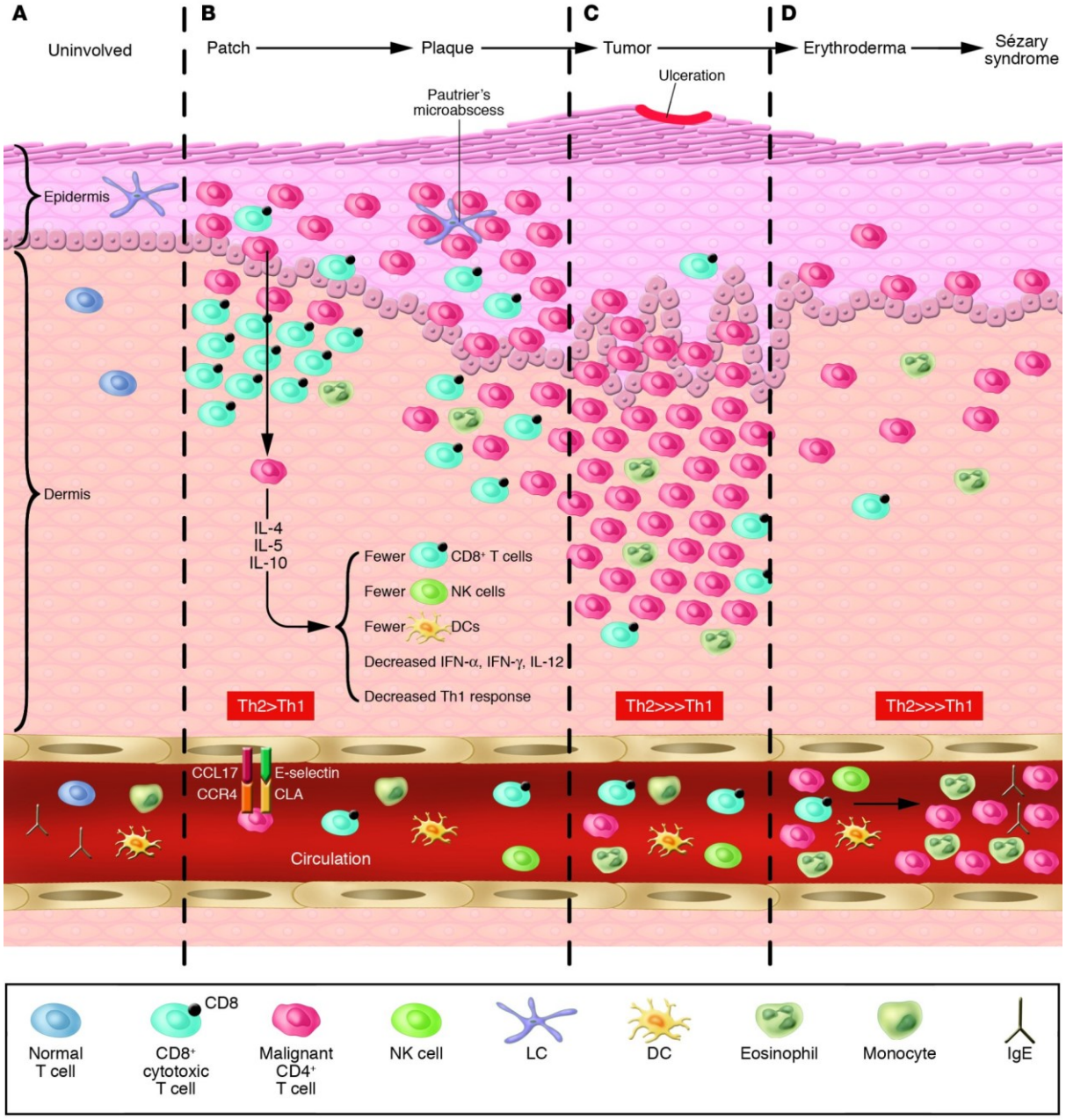
Pathophysiology

T helper cells form a part of the normal adaptive immune system. These cells directly and indirectly influence immune responses to external or internal threats to the body through their ability to influence a wide variety of other immune cells involved in both the innate (short-term) and adaptive (long-term) immune response.[30]

When the skin is subjected to injury, inflammatory responses lead to the activation of naïve T-cells, causing them to mature into effector T-cells or memory T-cells. These mature T-cell types can 'home' to the original site of inflammation (the skin) through expression of cutaneous lymphocyte antigen (CLA), alongside other chemokine receptors and ligands, as shown in Figure 1 (see part [B] below).[6, 27, 31, 32] In MF-CTCL, these skin-homing T-cells become malignant, clonal in nature, and are constitutively activated.[6, 27, 31, 32] Unlike the *normal* skin environment, which is characterised by T-cells circulating around the body and skin-homing T-cells in the dermis (see [A] in Figure 1 below), in the early stages of MF-CTCL ([B]), malignant T-cells accumulate in epidermis and subcutaneous tissue. Interactions between the malignant T-cells and the cutaneous microenvironment lead to the formation of patches and plaques, which can be associated with pruritus (itching) and pain and present a visual symptom of the disease.[6, 31]

With disease progression ([C]) the cytokine production by malignant T-cells changes from a TH1 to a TH2 pattern, which leads to abnormalities in cellular immunity. The malignant T-cell receptor expression profile shifts from those involved in skin homing to those involved in lymphatic homing. The result of this is an increased infiltration of malignant T-cells into the lower dermal layer, and the subsequent development of thicker plaques and tumours on the skin, and even ulceration of these lesions. In the late stages of the disease ([D]), patients may experience erythroderma, where greater than 80% of the BSA is affected by lesions.[6] Large numbers of clonal, malignant T-cells may also be detected in the blood, and there is a systemic loss of T-cell diversity, leading to immunosuppression.[6, 33, 34]

Figure 1: Changes in the skin during MF-CTCL



Abbreviations: CCL17: CC chemokine ligand 17; CCR4: CC chemokine receptor 4; CD: cluster of differentiation; CLA: cutaneous lymphocyte antigen; DC: dendritic cell; IFN: interferon; IgE: immunoglobulin E; IL: interleukin; LC: Langerhans cell; MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; NK: natural killer; TH1: T helper 1 cell; TH2: T helper 2 cell.
Source: Kim *et al.* (2005).[6]

Epidemiology

MF-CTCL is a rare disease, as recognised by the granting by the Committee for Orphan Medicinal Products (COMP) of an orphan designation for chlormethine gel (Ledaga®) on 22nd May 2012.[10]

Epidemiological data on CTCL (and MF-CTCL) for England specifically is available from a Public Health England National Cancer Registration and Analysis Services Short Report on registration of CTCL in England between 2009 and 2013.[14] In this audit of cases of newly diagnosed CTCL,

a total of 1,659 cases were reported across the time period studied, corresponding to an average number of annual diagnosed cases of CTCL in England of 332. In the same audit, it was stated that 920 cases of MF-CTCL diagnosis were recorded between 2009 and 2013, thereby indicating that approximately 55% of CTCL cases diagnosed over this period were MF-CTCL.[14] This would therefore correspond to an estimate of 182 new diagnoses of MF-CTCL on average in England each year. The age-standardised incidence rate of MF-CTCL was reported as 0.42 and 0.29 per 100,000 for males and females, respectively, meaning that MF-CTCL diagnosis was found to be 1.5 times more common in males than females.[14] MF-CTCL is usually diagnosed in older, adult patients but can affect individuals of all ages; the peak age of incidence of CTCL is 50–74 years of age.[14]

There are limited data on the prevalence of MF-CTCL in the UK; however, the disease is incurable and has a low mortality rate. Prevalence would therefore be expected to be higher than incidence. In a survey of clinical experts, healthcare professionals (HCPs) and patients, via online questionnaires and telephone interviews, the prevalence of MF-CTCL was estimated to be 3,515 for England and 4,077 for the UK in total.[35] When considering CTCL prevalence in Europe, this has been estimated as approximately 2.7 in 10,000 population.[36] For MF-CTCL specifically, the 5-year partial prevalence was estimated, based on an incidence rate of 0.52 per 100,000 population, to be 11,735 in EU-28 countries.[10]

Staging and progression

When a patient is diagnosed with MF-CTCL in UK clinical practice, staging of the cancer is assessed using techniques including computed tomography (CT) scan of neck, chest, abdomen and pelvis, and morphological assessment of peripheral blood.[3] The disease is classified using a CTCL-specific modification of the tumour, nodes, metastasis, blood (TNMB) classification system, summarised in Table 3 and Table 4 below.[3, 17, 37] Patients are classified based on the number and type of skin lesions they have (T), lymph node involvement (N), metastasis or visceral organ involvement (M), and peripheral blood involvement (B), resulting in a diagnosis of a disease stage from IA through to IVB.[17] These stages can be grouped as 'early' stage (Stages IA, IB and IIA) and 'advanced' stage (Stage IIB–IVB) disease.[17, 18] The TNMB classification system has been adapted over time for use in diagnosis and management guidelines in Europe and in the UK, with the BAD guidelines being most commonly used to inform clinical practice in England.[3]

Disease presentation and patient prognosis differ by stage of disease and severity of skin lesions. Patients with early stage disease may have a very good prognosis, with 5-year progression free survival (PFS) rates ranging from 75–95% and overall survival (OS) from 78–97%.[3, 38] The likelihood of progression increases with disease stage, and prognosis is poor in advanced stages of disease.[3, 38, 39] In a study by Quaglino *et al.* (2012), patients with Stage IA to Stage IB disease demonstrated a steady, low annual incidence of disease progression to Stage IIB disease of 2.0 and 1.8% respectively, whilst patients with Stage IIA disease had a significantly higher risk of progression to Stage IIB (9.4%) within the first year. Furthermore, this study also supported the notion of poorer prognosis with worsening disease stage. 5- and 10-year OS was reported as 97% and 93%, 91% and 86%, 79% and 72%, and 69% and 51% for Stage IA, Stage IB, Stage IIA and Stage IIB, respectively. Although there were no differences between Stage IIB and Stage III disease in terms of prognosis, Stage IV disease demonstrated an extremely poor prognosis, with a 5-year survival rate of only 24%.[40]

Table 3: Grading for the MF-CTCL modification of the TNMB classification system (from BAD guidelines)

Grade	Tumour (T)	Nodes (N)	Metastasis (M)	Blood (B)
0	-	No clinically abnormal peripheral lymph nodes; biopsy not required	No visceral organ involvement	Absence of significant blood involvement; <5% peripheral blood lymphocytes are atypical (Sézary) cells (a) Clone negative (b) Clone positive
1	Limited patches, papules and/or plaques covering <10% of the skin surface (a) Patch only (b) Plaque ± patch	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2} (a) Clone negative (b) Clone positive	Visceral involvement; must have pathology confirmation and organ involved should be specified	Low blood tumour burden: >5% peripheral blood lymphocytes atypical (Sézary) cells but does not meet the criteria of B_2 (a) Clone negative (b) Clone positive
2	Patches, papules or plaques covering ≥10% of the skin surface (a) Patch only (b) Plaque ± patch	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3 (a) Clone negative (b) Clone positive	-	High blood tumour burden: >1000 Sézary cells per µL with positive clone
3	One or more tumours (≥1 cm diameter)	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 3–4 or NCI LN_4; clone positive or negative	-	-
4	Confluence of erythroderma covering ≥80% BSA	Clinically abnormal peripheral lymph nodes; no histological confirmation	-	-

Abbreviations: BSA: body surface area; LN: lymph node; MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; NCI: National Cancer Institute; TNMB: tumour, nodes, metastasis, blood (classification system).
Source: Gilson *et al.* (2019) (Supplementary Information).[41]

Table 4: Disease staging for MF-CTCL

Stage	Tumour (T)	Nodes (N)	Metastasis (M)	Blood (B)
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1, 2	1, 2	0	0, 1
IIB	3	0–2	0	0, 1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA1	1–4	0–2	0	2
IVA2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

Abbreviations: MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; TNMB: tumour, nodes, metastasis, blood (classification system).
Source: Gilson *et al.* (2019) (Supplementary Information).[41]

Diagnosis and monitoring

Diagnosis of MF-CTCL is performed by a multi-disciplinary team of specialists, including dermatologists, haematologists and oncologists. Multiple skin biopsies may be required to confirm the diagnosis, and T-cell receptor clone analysis of peripheral blood can provide critical prognostic information for confirmation and staging of the disease.[3] Formal diagnosis of MF-CTCL is typically delayed due to the similarity of the skin pathology to benign skin conditions and a lack of MF-CTCL specific diagnostic tests.[42] A registry of UK MF-CTCL patients found that there was a median diagnostic delay of 36 months (interquartile range [IQR] 12–90 months).[29] This can cause inconvenience to patients and lead to delayed treatment with MF-CTCL therapies, with patients often instead being treated with therapies that are not specific to MF-CTCL, such as (cortico)steroids, prior to receiving their diagnosis of MF-CTCL (see Section B.1.3.2).[3, 18, 43]

Monitoring of MF-CTCL involves the assessment of the burden of skin symptoms. There are multiple measures available for this. The Composite Assessment of Index Lesion Severity (CAILS) index is based on assessment of four clinical features (erythema, scaling, plaque elevation and surface area) of individual lesions, whilst the Severity Weighted Assessment Tool (SWAT), or its modification, mSWAT, derives scores by weighting the percentage BSA involvement for patches, plaques and tumours, assigning a numerical value to each of these three aspects (1 for patch, 2 for plaques and 3 for tumours).[3, 15, 18, 43]

SWAT or mSWAT are the most commonly used method for skin scoring, and have been previously used in clinical trials.[43-45] To generate a SWAT score, the severity of skin involvement is classified into three grades based on clinical lesions: 1 for patch disease and erythroderma with mild infiltration; 2 for plaques and erythroderma with moderate infiltration; 3 for cutaneous tumours or ulceration (including fissuring) and erythroderma with tumorous infiltration. The percentage BSA (from 0–100%) affected by each of the three lesion types is measured and severity weighting is then applied by multiplying the BSA for patches by 1, the area for plaques by 2, and the area for tumours or ulcers by 3 to give a total score on a 0–300 scale.[46]

SWAT has subsequently been modified (mSWAT) for use in a number of studies and clinical trials, such as Study 201.[25, 43, 45] When modified, Lund and Brower charts may be used to calculate patient BSA (rather than the grid-point counting previously used), and the weighting of tumours is increased to 4, rather than 3.[44, 47]

Clinicians may also use quality of life assessments, such as the skin-specific Skindex 29 index, to monitor patients through their disease course.[3, 43, 48] By determining the extent of the skin symptoms of MF-CTCL, in addition to consideration of patient and clinician preferences, clinicians are able to work alongside patients to determine the best paradigms to alleviate the skin symptoms of their disease and minimise the risk of adverse events (AEs) and inconvenience that may be associated with current treatment options (see Section B.1.3.2).

Burden of disease

The skin symptoms of MF-CTCL are associated with a substantial patient burden. In studies investigating health related quality of life (HRQoL), patients report a number of physical, functional and psychological impairments, which are present at early stages but may worsen as MF-CTCL progresses.[19-21]

Patients have reported discomfort with itching, skin redness, scaling and pain caused by skin lesions; they also suffer with sleep interruption and fatigue.[20] MF-CTCL patients have also been shown to be more likely to suffer from depression and anxiety than the general population; in one study, patients reported that they felt depressed, frustrated and angry about their disease and were worried about the seriousness of their illness.[19, 20, 23] Clinical expert opinion has also confirmed that patients with particularly visible lesions such as on the hands and face may retract from work or socialising,[4] which has also been reported in the literature, where reports of patient quality of life reveal that CTCL impacts upon patients' ability to meet the needs of their family, interferes with their job (including missing work), limited their normal daily activities, and had a substantial impact on social interactions.[20, 22]

When assessing patients using a skin disease–specific HRQoL instrument (Skindex-29), patient HRQoL is diminished compared to healthy individuals and is comparable to patients with psoriasis when comparing the effects of each disease on patient functioning. When comparing early and late stage patients, HRQoL was shown to decrease with disease stage, with patients with advanced disease experiencing decreased quality of life versus those with early stage disease.[19] Worsening of HRQoL with disease progression is also apparent when considering MF-CTCL using a general oncology HRQoL instrument (Functional Assessment of Cancer Therapy: General [FACT-G]), which may include the impact of both skin symptoms and the underlying disease on patients. Patients with advanced disease have been shown to have lower FACT-G scores both overall and across all domains versus those with early stage disease, indicating lower, patient-reported HRQoL (these differences were statistically significant [$p<0.05$] for all individual scales except social/family wellbeing).[19]

Patients may also require dressings for any lesions which are weeping or infected and, in some cases, these may need to be replaced daily. This, in addition to the need for regular visits to hospital to receive treatment and disease monitoring leads to not only patient burden, but also extensive healthcare resource use.[4]

B.1.3.2 Clinical pathway of care

Aims of treatment

The aim of treatment for MF-CTCL at all stages is to reduce the visibility and BSA coverage of lesions, thereby reducing symptoms related to the patches and plaques of their disease such as pain and discomfort, itching and insomnia, as well as reducing the social and psychological burden associated with visible symptoms.[49] Clinical expert opinion suggest that patients aim to achieve a partial response (PR), or in some cases a complete response (CR), in skin symptoms. In practice, achievement of CR is infrequent due to the stringency of this response criterion and hence PR generally represents the realistic expectation of treatment for clinicians.[4] For patients with advanced disease, treatment may also aim to delay or prevent the progression of the underlying disease.[3, 15, 18] Ultimately, however, patients are not anticipated to achieve remission from the underlying cancer, and therefore treatments are largely not given with the aim of achieving a sustained remission.[4]

Overall, there are two main types of therapy for MF-CTCL that are used in UK clinical practice to achieve these aims: SDTs and systemic therapies. SDTs are used for local treatment of the disease (skin lesions) and are the first choice of treatment in early stage disease, whilst also often being used in combination with systemic therapies in later stage disease.[3] Systemic therapies target disseminated cancer cells and represent an escalation of treatment, as they may be associated with toxicity burden to patients.[4, 50, 51] They are therefore used as either second-line therapy in early stages of disease, or in advanced stages of disease.[3] In clinical practice, topical versus systemic treatments are also selected based on the presentation of the individual patient; in cases where there is a high percentage BSA coverage, such as erythrodermic disease, or where lesions are in locations which are not suitable for SDTs, a systemic therapy may be used.[4]

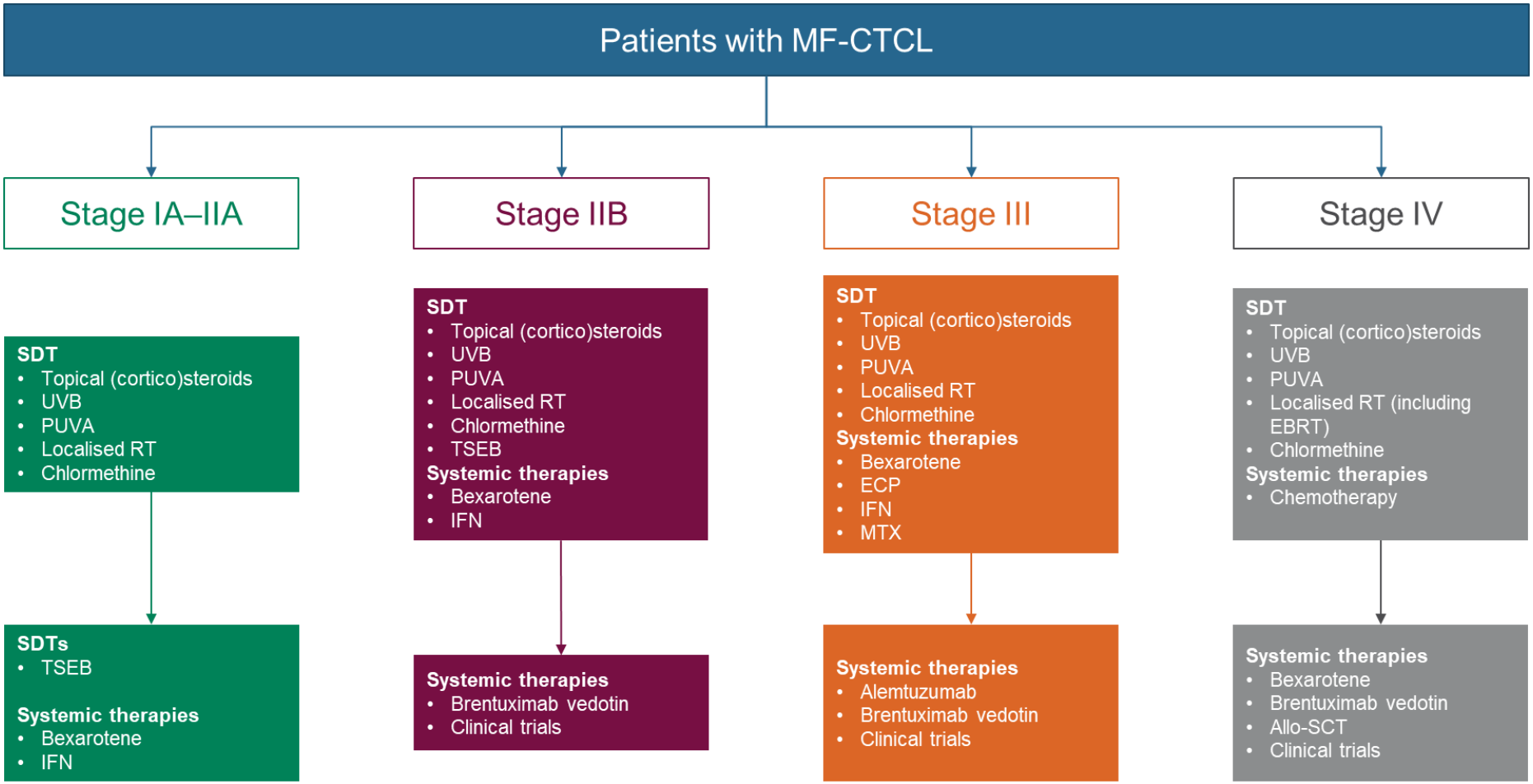
Treatment guidelines

There are currently no NICE guidelines for the management of MF-CTCL; however, clinical guidelines for adults with MF-CTCL of relevance to the UK are available from the European Society for Medical Oncology (ESMO), European Organisation for Research and Treatment of Cancer (EORTC) and the British Association of Dermatologists (BAD).[3, 15, 18] Of these, clinical expert opinion suggests that the UK-specific BAD guidelines are the most commonly used to inform clinical practice in the UK.[4]

The BAD guidelines do not rank treatments in an order of preference; this is consistent with clinical expert feedback, which indicates that patient and physician choice is a key factor in making treatment decisions.[4] Whilst the treatments that patients receive may depend on their disease stage (in addition to patient and clinician preference), this is largely due to the fact that at more advanced disease stages the treatment strategy may need to be escalated to target cancer cell dissemination, rather than only addressing the local disease, and thereby the skin symptoms associated with MF-CTCL.[3] Thus, therapies for addressing skin symptoms (patches and plaques) may be considered as options regardless of disease stage (as evidenced below), though the context of their use may differ by disease stage. In early stages of disease, patients are likely to receive SDTs in isolation at first line, whereas in advanced disease stages patients are more likely to receive SDTs in combination with a systemic treatment.[3, 4, 15]

The treatment recommendations from the BAD guidelines for the treatment of MF-CTCL are presented in Figure 2. Chlormethine gel would be expected to be used as an option at first line in the treatment of the skin symptoms of MF-CTCL. In reference to the treatment pathway outlined in the BAD guidelines, chlormethine gel would therefore be expected to be added as an additional SDT option in the first row of Figure 2, across all disease stages. As such, those treatments that are presented as first line options in the BAD guidelines (i.e. the first row of Figure 2) are most relevant for consideration as clinical comparators and these are therefore discussed in more detail below. Additionally, it should be noted that for a proportion of patients, existing first line SDTs (i.e. phototherapy) may be contraindicated or unsuitable (see decision problem description in Table 1). As per the NICE final scope, and in line with Figure 2, both bexarotene and pegylated IFN-α are considered for patients for whom phototherapy is not suitable or contraindicated (approximately 10% patients with MF-CTCL).[4]

Figure 2: A summary of the treatment options for MF-CTCL (both SDTs and systemic therapies) in UK clinical practice



Abbreviations: allo-SCT: allogeneic stem cell transplantation; EBRT: external beam radiotherapy; ECP: extracorporeal photopheresis; IFN: interferon; MTX: methotrexate; PUVA: psoralen-ultraviolet A; RT: radiotherapy; SDT: skin-directed therapy; TSEB: total skin electron beam therapy; UVB: ultraviolet B.
Source: Adapted from Gilson *et al.* (2019).[3]

SDTs: topical therapies

The BAD guidelines highlight that there have been few RCTs investigating topical therapies for MF-CTCL, and therefore, there is a lack of high-quality evidence evaluating topical therapies.

However, using the available evidence, the BAD guidelines recommend a number of SDTs for use in patients diagnosed with MF-CTCL in Stage IA–IIA who are initiating active therapy, including: topical (cortico)steroids, topical chlormethine, psoralen-ultraviolet A (PUVA), ultraviolet B (UVB) and local radiotherapy.[3]

According to the BAD guidelines, there is little evidence for the efficacy of (cortico)steroids in MF-CTCL. The guidelines acknowledge that topical (cortico)steroids, particularly very potent compounds, are effective for patches and plaques in some early stage (IA/IB) patients, but also state that responses are rarely complete or durable. Importantly, topical (cortico)steroids are also considered to not be 'MF-CTCL-specific' treatments by clinicians and are very frequently prescribed to patients prior to diagnosis of MF-CTCL in order to control the non-specific skin symptoms of inflammation and irritation that patients experience (and which clinicians often confuse with symptoms of other skin conditions, such as eczema and psoriasis). (Cortico)steroids use post-diagnosis is generally as a concomitant therapy to manage the skin toxicities (e.g. pruritus) that may arise from treatments used for MF-CTCL, rather than as a viable alternative to the use of MF-CTCL treatments such as those described below.[46]

Topical chlormethine is the only SDT ranked with level 1+ for evidence in the BAD guidelines, based on the availability of evidence from Study 201, the largest RCT performed in MF-CTCL, that comprises the core evidence base for chlormethine gel presented in this submission (see Section B.2).[3, 25] However, there is not currently a chlormethine formulation available for use in UK clinical practice due to issues associated with previous formulations (water- or oil-based chlormethine) such as compound stability, inconvenience for patients when applying to the skin, and inconvenience for pharmacists when compounded (due to precaution required to avoid toxicity specific to these formulations).[3]

Additional topical therapies (topical bexarotene, imiquimod, 5-fluorouracil [FU] cream and tacrolimus ointment) are also mentioned in the BAD guidelines. Collectively, there are limited data supporting the use of any of these treatments in addressing the skin symptoms of MF-CTCL. Furthermore, none of them are licensed for use in clinical practice in the UK and clinician feedback indicates that their off-label use is sporadic at most and that they do not form part of routine clinical practice in the UK. Topical carmustine is also mentioned in the guidelines; however, data are limited, and it has been suggested to be more extensively absorbed than chlormethine, leading to increased risk of bone marrow suppression.[3]

SDTs: phototherapy

The BAD guidelines state that phototherapy (namely PUVA and UVB) may be considered for patients who do not respond to topical therapies; phototherapy can have high response rates, however, the response is often not durable.[3] Phototherapies are also associated with serious AEs, particularly secondary malignancies, and these limit the number of treatments that patients can receive in a lifetime. This secondary malignancy risk also precludes phototherapy as a maintenance treatment, in addition to being a consideration for patients with low lesion coverage, for whom the risk of secondary malignancy may not be worth any potential benefit of

phototherapy.[3, 4, 52, 53] In addition, approximately 5% of MF-CTCL patients may be contraindicated for phototherapy due to previous melanoma.[4]

PUVA specifically, may also be combined with IFN or bexarotene (systemic therapies) with the aim of improving the duration of response and reducing the cumulative UVA dose.[3]

SDTs: localised radiotherapy

Also, known as 'spot' radiotherapy, localised radiotherapy may be used across disease stages, and is usually used with palliative intent on thick, scaly plaques or tumours or plaques or tumours in places particularly uncomfortable for patients. Clinical expert opinion suggests that localised radiotherapy would not be used in the same presentation as topical chlormethine, as chlormethine would be used primarily for patches and thinner plaques, as opposed to the thicker plaques and tumours, for which localised radiotherapy is the preferred approach. Repeat treatment of the same area is facilitated (using a low-dose), and this approach can also be used on sensitive areas such as the face.[3, 22] Localised, peripheral nodal MF-CTCL and visceral metastases at Stage IVA2/IVB specifically can also be treated with local external beam radiotherapy (EBRT).[4]

SDTs: total skin electron beam therapy

Total skin electron beam (TSEB) therapy is an approach that targets the entire surface of the skin. It is therefore largely reserved for patients with extensive lesions covering most of the body, rather than for treating specific lesions. It may also be used in patients for whom other SDTs are not effective. At more advanced disease stages, TSEB may be combined with chemotherapy, or used prior to allogeneic stem cell transplantation.[3]

TSEB has shown similar efficacy to chlormethine in early stage disease. However, it requires numerous clinical visits as it is delivered in 1-day cycles over five weeks. Moreover, this procedure is only available in the UK in specialist centres and is also associated with significant toxicity including alopecia, erythema and desquamation, fatigue, lower-leg oedema, skin infections and blisters; this results in a high treatment burden to patients, and may lead to patient age being a factor in deciding to commence TSEB (as younger patients may better tolerate the adverse effects).[3, 54]

Systemic biological therapies: interferon (IFN)

According to the BAD guidelines, unless patients fail to respond to SDTs, or are contraindicated, IFN-α should not be used in early stage MF-CTCL as there is no evidence that IFN affects long-terms outcomes (there are no RCTs investigating IFN alone in the treatment of early stage patients with MF-CTCL). In such refractory or contraindicated patients, IFN may be used in combination with PUVA as a treatment option to alleviate the skin symptoms of MF-CTCL. At more advanced stages, there are studies investigating IFN-α in combination with methotrexate, bexarotene or retinoids; however, robust data are lacking, and CRs rare. IFN-α is also associated with certain, serious AEs; namely hypothyroidism, cytopaenias and flu-like symptoms.[51, 55]

Importantly, expert clinical opinion has elucidated that IFN-α will soon no longer be available for use in UK clinical practice. Given the withdrawal of this treatment, it is understood that pegylated IFN-α would be considered as an appropriate alternative.[1, 4]

Systemic biological therapies: retinoids and rexinoids

Of the retinoids and rexinoids mentioned in the BAD guidelines, bexarotene is the treatment most widely used in UK clinical practice. Bexarotene may be used in both early and advanced stages of disease and has demonstrated efficacy and durable responses in a limited number of prospective, open-label studies including early stage patients. This therapy may also be used in combination with PUVA at early stages, although there is no proven benefit of this combination versus PUVA alone.[3]

Bexarotene is associated with hypothyroidism, dyslipidaemia, leukopaenia, increases in creatine kinase, pancreatitis and glucose dysregulation.[50] Therefore, all patients being treated with bexarotene must also receive treatment with thyroxine and phenofibrate, and may also require statins and granulocyte-colony stimulating factor (G-CSF).[50] On this, UK consensus guidelines for bexarotene prescribing and management have been published, providing instructions on monitoring the aforementioned adverse reactions.[50] Considerations such as the aforementioned AE profile of bexarotene and a lack of RCT data for bexarotene alone in the treatment of MF-CTCL contribute to its recommendation as a second-line (rather than first line) treatment for Stage IA–IIA patients in the BAD guidelines, with its recommendation as a first line treatment reserved for patients with Stage IIB disease or later (Figure 2).[3]

Chemotherapy

Systemic chemotherapy is usually reserved for patients with advanced disease, or disease refractory to SDTs or immunobiological therapy, and is given with palliative intent. Although good responses are reported with both single-agent chemotherapy such as methotrexate, as well as combination regimens, overall the results are disappointing when compared with other lymphomas.[3]

Extracorporeal photopheresis

Extracorporeal photopheresis (ECP) is also included in the BAD guidelines, but the evidence base is sparse and in a single randomised trial versus PUVA in early stage MF-CTCL; PUVA was more effective over a 6-month treatment period. There is some evidence supporting the use of ECP for patients with advanced disease (with the highest response rates at Stage III/IVA1), and in combination with other systemic therapies.[3]

Actual treatment utilisation in real-life UK clinical practice

Whilst the BAD guidelines provide a summary of treatment options and recommendations, the therapies referenced in the guidelines do not necessarily all reflect treatments that are actually used in UK clinical practice. Registry data is useful for understanding real-world treatment patterns. Hence, to inform understanding of treatment utilisation on the NHS, data was sought from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study. PROCLIPI is a prospective international registry for patients with CTCL, and was also cited as a source of information on treatment utilisation in the previous NICE appraisal in MF-CTCL (TA577).[56] Recordati Rare Diseases/Helsinn Healthcare SA was granted access to confidential data for the UK, including some aggregate data on patient characteristics and data on treatment by stage at diagnosis, for the purposes of this submission. As these data are confidential, all PROCLIPI inputs have been marked as Academic in Confidence (AiC).'

Data from the PROCLIPI registry on the utilisation of treatments by patient stage at diagnosis are provided in Table 5, expressed as percentage of overall recorded treatment utilisation for patients diagnosed at that stage. Although this data provides the stage that patients receiving a given therapy were diagnosed at, this is expected to correlate closely with the stage at which the specified treatment was administered since the treatments recorded in the analysis are those that were used first-line post-diagnosis or up to six months prior to diagnosis. Therefore, the data in Table 5 would only diverge from representing the stage at which treatments were administered if patients received no treatment whilst in their initial diagnosed stage of disease, progressed, and then received treatment. As this is unlikely, the data available should represent a good proxy for the stage at which treatments are used as first-line therapy in clinical practice. It should be noted that as patients in PROCLIPI may have received more than one of the listed therapies, the percentages do not represent the proportion of patients but rather the proportional contribution of each treatment to overall treatment utilisation for the specified disease stage. As noted above, the use of steroids in MF-CTCL often occurs alongside other therapies in order to manage non-specific skin symptoms of MF-CTCL, or potentially help to manage potential AEs with therapies. Therefore steroids should be viewed as a concomitant medication, rather than a potential comparator to chlormethine gel. As such, it was considered appropriate to reweight the treatment utilisation values presented in Table 5 after removing steroid use (corticosteroids and topical steroids) from the dataset. The reweighted values are provided in Table 6, representing the proportional contribution of each treatment to overall non-steroid treatment utilisation at a given disease stage.

The PROCLIPI data presented below do not indicate where therapies are used as monotherapy or in combination; in advanced stage in particular many therapies would be expected to be used in combination. As such, the data do not provide an explicit picture of the precise context of utilisation of each treatment. However, they do provide a broad overview of the extent to which the potential comparator therapies noted in the BAD guidelines are utilised as first-line therapies (the line of treatment at which chlormethine gel would be used). This demonstrates that phototherapy is the most utilised therapy by a considerable margin for early stage disease (Stage IA–IIA). In contrast, TSEB has very limited utilisation, particularly in early disease stages. Where TSEB is used, it is likely largely for patients with extensive lesions covering most of the body and hence a different type of patient to that for whom chlormethine gel would usually be used. Therefore, TSEB is not considered to be reflective of routine clinical practice for patients who would receive chlormethine gel in practice and hence does not represent a relevant comparator for the purposes of the submission. Bexarotene and IFN are associated with reasonably low levels of utilisation, but are amongst the more utilised therapies (outside of phototherapy), consistent with the role for these therapies as described above.

Table 5: Treatment utilisation data by stage from PROCLIPI

Treatment	Stage at Diagnosis								
	IA	IB	IIA	IIB	IIIA	IIIB	IVA(1)	IVA(2)	IVB
[redacted]	[redacted]								

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BB-UVB: broadband ultraviolet B; ECP: extracorporeal photopheresis; IFN-α: interferon alpha; NB-UVB: narrow band ultraviolet b; NM: nitrogen mustard; PUVA: psoralen-ultraviolet A; RT: radiotherapy; TSEBT: total skin electron beam therapy.
Source: PROCLIPI registry.[2]

Table 6: Treatment utilisation data by stage from PROCLIPI, adjusted for removal of steroid treatments

Treatment	Stage at Diagnosis								
	IA	IB	IIA	IIB	IIIA	IIIB	IVA(1)	IVA(2)	IVB
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BB-UVB: broadband ultraviolet B; ECP: extracorporeal photopheresis; IFN-α: interferon alpha; NB-UVB: narrow band ultraviolet b; NM: nitrogen mustard; PUVA: psoralen-ultraviolet A; RT: radiotherapy; TSEBT: total skin electron beam therapy.
Source: PROCLIPI registry.[2]

Proposed positioning of chlormethine gel

Chlormethine gel has a marketing authorisation for the topical treatment of MF-CTCL in adult patients.[11] Based on clinical expert opinion, chlormethine gel could be used to treat the skin symptoms associated with MF-CTCL irrespective of disease stage, with the exception of patients with erythroderma for whom chlormethine gel may not be appropriate due to the fact that over 80% of the BSA is affected and the skin is often inflamed and therefore, may not tolerate a topical therapy.[4] In early stages of disease, chlormethine gel would be used as a monotherapy. As there is not currently evidence to support the effectiveness of chlormethine gel in delaying or preventing progression of underlying disease, when used in advanced disease stages it is likely that chlormethine gel would be used in combination with systemic therapies that aim to treat the underlying cancer, thereby providing dual treatment of both skin symptoms and underlying disease.

Chlormethine gel would be expected to be used as an option at first line in the treatment of the skin symptoms of MF-CTCL. In reference to the treatment pathway outlined in the BAD guidelines, chlormethine gel would therefore be expected to be added as an additional SDT option in the first row of Figure 2, across all disease stages.

It should be noted, however, that it is not the case that all therapies noted as current first line options in Figure 2 would represent comparators to chlormethine gel. As noted above, treatment is highly individualised, with patient and clinician preference an important factor. Furthermore, the range of treatments presented in the BAD guidelines provide a variety of options for addressing skin symptoms in different contexts: different therapies would be considered as appropriate potential options for different patients depending on the nature of their skin symptoms. Furthermore, as described above and supported by data from the PROCLIPI registry, some treatment options listed in the BAD guidelines are not actually used/have limited usage in UK clinical practice.[3, 4]

A relevant comparator to chlormethine gel is a therapy that:

- is currently used in UK clinical practice; and
- is used to treat the patches and plaques (skin symptoms) associated with MF-CTCL (i.e. not used with the specific intention of delaying or preventing progression of the underlying cancer); and
- would be used for patients who present with a similar degree of skin involvement (i.e. similar level of patch/plaque skin coverage) to that for which chlormethine gel would be considered as an appropriate treatment option

Therefore, within the context of this appraisal, and based on expert clinical opinion and supported by data from the PROCLIPI registry, the most relevant comparator for chlormethine gel is phototherapy (PUVA or UVB).[4] IFN and bexarotene may also represent clinical comparators in a small proportion of patients. A summary of the reasons why other therapies from the BAD guidelines do not represent relevant comparators to chlormethine gel is presented in Table 7. This information has been validated by UK clinical expert opinion.[1, 4]

Table 7: Summary of reasons for exclusion of BAD guideline therapies as comparators

Therapy presented in Figure 2[a]	Reason therapy is not a relevant comparator to chlormethine gel

Topical (cortico)steroids	• Clinical feedback indicates that almost all patients diagnosed with MF-CTCL and hence considered for treatment with chlormethine gel would have already received topical (cortico)steroids for treatment of non-specific symptoms (due to delayed diagnosis of MF-CTCL in practice) • Clinical expert feedback also suggests that (cortico)steroids treat the skin inflammation associated with MF-CTCL, and are not-considered anti-MF-CTCL therapies as they do not have an impact on malignant T-cells • Further, (cortico)steroids are used to manage skin toxicities such as dermatitis and pruritis,[46] and are therefore a concomitant therapy used alongside existing treatments for MF-CTCL (and would be used concomitantly to chlormethine gel). (cortico)steroids use would therefore not be expected to be displaced should chlormethine gel be introduced as a treatment option
Localised radiotherapy (including EBRT)	• Clinical feedback suggests that localised radiotherapy would not be used in the same clinical presentation as topical chlormethine, as localised radiotherapy would be used for thicker plaques and tumours for which topical chlormethine would not be considered
TSEB	• TSEB is largely reserved for patients with extensive lesions covering most of the body or for use in patients for whom other SDTs are not effective. In contrast, chlormethine gel would be used on specific thin patches and plaques • In early disease stages (IA–IIA), the BAD guidelines recommend TSEB as a second-line option, after first line use of other SDTs • Data from the PROCLIPI registry demonstrates that TSEB use in UK clinical practice is very limited (Table 5/Table 6)[2]
Systemic chemotherapy (including methotrexate)	• Reserved for patients with advanced disease or disease refractory to SDTs. Chlormethine gel would either be used prior to systemic chemotherapy (in early disease stages) or in combination with systemic chemotherapy (in advanced disease stages)
ECP	• Clinical expert opinion suggests that ECP is a therapy which is used primarily in patients with erythroderma, the patient population for which chlormethine gel may not be appropriate; thus, chlormethine gel would not replace ECP in UK clinical practice

[a] First line options only are presented in Figure 2 as chlormethine gel is to be considered as a first line option for the treatment of MF-CTCL across disease stages.
Abbreviations: 5-FU: 5-fluorouracil; BAD: British Association of Dermatologists; EBRT: external beam radiotherapy; ECP: extracorporeal photopheresis; IFN: interferon; MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; SDT: skin-directed therapy; TSEB: total skin electron beam therapy.

Addressing the unmet need

The skin symptoms of MF-CTCL are associated with a substantial patient burden, including physical discomfort such as pruritus, sleep disruption, embarrassment, social withdrawal and absenteeism. Thus, this rare condition has a substantial impact on patient quality of life and

psychological wellbeing.[19, 20, 23] Furthermore, there are no NICE recommended treatments or management guidelines for the treatment of the skin lesions of MF-CTCL, and there are also a lack of RCTs for current therapies used to treat this condition.[3] Currently available treatments in the UK such as phototherapy often require patients to attend multiple hospital appointments each week, and are associated with a number of AEs (for example, secondary malignancies).[3, 4] Phototherapy is also incompatible with an active daily life, as patients may be required to cover up for long periods of time to avoid sunlight due to the potential adverse effects of sensitisation with psoralen.[57] These issues may result in not only patient inconvenience and poor quality of life, but healthcare resource use and wider societal costs.[3, 50-53, 58] In addition, systemic therapies such as bexarotene and IFN-α, whilst offering an escalated treatment option for those unsuitable for phototherapy, are also associated with severe AEs, and are not supported by robust evidence bases for the treatment of the skin lesions of MF-CTCL. Specifically, bexarotene treatment can lead to hypothyroidism, dyslipidaemia, leukopaenia, increases in creatine kinase, pancreatitis and glucose dysregulation, whilst IFN-α is also associated with hypothyroidism, in addition to cytopaenias and flu-like symptoms.[50, 51, 55]

Overall, there is a considerable unmet need for licensed treatments supported by robust evidence that specifically target the skin patches and plaques associated with MF-CTCL.

Chlormethine gel was specifically developed for the treatment MF-CTCL and is the only topical therapy recommended in the BAD guidelines with level 1+ for evidence, based on the results of the RCT Study 201; Study 201 represents a robust source of evidence for the demonstrated efficacy of chlormethine gel, whilst there are few RCTs for other SDTs in MF-CTCL.[3, 25] Its gel formulation allows for safe home application, which is beneficial for reducing patient waiting times to initiate treatment, as well as reducing the need to attend regular hospital appointments to receive ongoing treatment. Moreover, chlormethine gel is well-tolerated, with no evidence to suggest an increased risk of secondary malignancies.[3, 25, 59] [3, 25, 59] Clinical evidence suggests that chlormethine gel is not absorbed systemically, which makes it a suitable option for combination therapy with systemic MF-CTCL treatments, or with other concomitant medicines patients may require.[46] Different formulations of chlormethine have been used previously in clinical practice in the UK, further supporting the well-characterised and manageable safety profile of chlormethine and also providing clinical experience in prescription of this compound and its effectiveness in UK clinical practice.[4] However, chlormethine is currently not accessible for UK clinicians, due to issues associated with previous formulations such as compound stability and inconvenience, which chlormethine gel would resolve.[4]

In summary, the introduction of chlormethine gel in the UK would allow patients to access an alternative treatment option with a distinct mechanism of action for treating the skin patches and plaques related to MF-CTCL. Chlormethine gel is supported by a robust evidence base from Study 201, which contrasts with the limited clinical evidence from RCTs for other SDTs. Chlormethine gel is also associated with a distinct safety profile versus the relevant comparators, with no evidence of systemic absorption or an increased risk of secondary non-melanoma skin cancers, as evidenced by Study 201.[25, 46] This option would also be expected to decrease the need for patients to attend regular hospital appointments to receive phototherapy, alleviating the burden of travelling to these on patients' ability to lead active everyday lives, as well as conserving NHS resources.

B.1.4 *Equality considerations*

No equality issues related to the use of chlormethine gel are foreseen.

B.2 Clinical effectiveness

Summary of clinical effectiveness of chlormethine gel

- An SLR identified one RCT demonstrating the efficacy of chlormethine gel in the treatment of MF-CTCL: Study 201.[25, 46]
- Study 201 was a Phase II, multicentre, randomised, observer-blinded, active controlled trial comparing 0.02% chlormethine gel with 0.02% chlormethine compounded ointment in previously treated patients with Stage IA–IIA MF-CTCL
    - 260 patients were enrolled onto the study and were subsequently randomised to receive chlormethine gel (n=130) or chlormethine ointment (n=130)[25, 46]
- Data for two ITT populations are presented within this submission for transparency: ITT including and excluding the New York University (NYU) study centre, respectively, following a protocol violation at this study centre[46]
- The primary efficacy endpoint was a ≥50% improvement (i.e. CR or PR) in a patient's CAILS score versus the Baseline measurement[25]
    - Chlormethine gel demonstrated non-inferiority to chlormethine ointment in both ITT populations for this endpoint
    - The 95% CI of the CAILS score in the EE population was entirely above 1, at 1.301 (95% CI: 1.065–1.609).[25]
      [redacted]
- Non-inferiority of chlormethine gel was also demonstrated with regards to a key secondary endpoint of Study 201: the mSWAT response rate[25]
- The time to a confirmed CAILS response was significantly reduced in the chlormethine gel arm (p<0.012 for ITT including NYU and p<[redacted] for ITT excluding NYU), whilst the duration of response and time to progressive disease were not statistically different between the two treatment arms (p=[redacted] [unadjusted log-rank] and p=[redacted] for the ITT including NYU population, respectively)[25, 46]

Summary of the safety results for chlormethine gel

- The safety profile of chlormethine is well characterised and manageable based on clinical expert experience in UK clinical practice, in addition to robust evidence for the gel formulation specifically from Study 201 and Study 202.[4, 25, 60] Full details of the tolerability of chlormethine in patients with MF-CTCL are presented in Section B.2.10
    - Importantly, in Study 201, there was also no evidence of systemic absorption of chlormethine, indicating that chlormethine gel is a viable and flexible treatment option as part of a combination therapy and there was no evidence to support that chlormethine gel is associated with an increased risk of non-melanoma skin cancers[25, 46]
- In real-world studies, chlormethine gel was also well tolerated; rates of skin-related AEs were seen to be lower than those observed in Study 201, suggesting that these AEs are manageable with concomitant medications (that were not permitted in Study 201) and that their incidence may thus be overestimated in Study 201 compared to what is anticipated for UK clinical practice[25, 61, 62]
- Overall, chlormethine gel has been shown to have a good benefit:risk ratio for the treatment of skin lesions of MF-CTCL[25, 46, 60]

B.2.1 *Identification and selection of relevant studies*

An SLR was conducted to identify relevant clinical evidence for the efficacy and safety of chlormethine gel and relevant comparators for treatment of adult patients with MF-CTCL. The review was conducted and reported in line with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines and full details of the SLR search strategy, study selection process and results are reported in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

The SLR identified one RCT (Study 201) that provided evidence for the efficacy and safety of chlormethine gel in the treatment of adult patients with MF-CTCL at the dose included in the SmPC (0.02% chlormethine).[11] Study 201 was a pivotal Phase II, multicentre, randomised, observer-blinded, active controlled trial comparing 0.02% chlormethine gel with 0.02% chlormethine compounded ointment in patients with Stage IA–IIA MF-CTCL.[25] An overview of Study 201 is provided in Table 8. The context and relevance of the chlormethine ointment comparator selected for the study is that it represents a treatment for which the effectiveness and safety has been well established through numerous studies and historical use in real-world clinical practice (including the UK).[4, 46, 63, 64] Non-gel (i.e. water- or oil-based formulations) of chlormethine were previously used as part of clinical practice and demonstrated effectiveness as an SDT in the treatment of MF-CTCL. These formulations are no longer available for use in UK clinical practice due to issues associated with the formulation such as compound stability, inconvenience for patients when applying to the skin, and inconvenience for pharmacists when compounded; the gel formulation aims to overcome these formulation-based issues.[4]

When considering non-RCTs, two studies that investigated chlormethine gel, in addition to 45 publications on 42 unique studies of other chlormethine formulations were also identified by the SLR; however, as these studies are non-RCTs (i.e. a less robust study design than Study 201) and in the vast majority of cases also correspond to a different formulation (and hence different product), respectively, they were not considered relevant for presentation in this submission. Chlormethine has also been extensively used previously in clinical practice in the UK in either aqueous or ointment based formulations. Thus, the effectiveness (and tolerability profile) of chlormethine as an active compound is well-characterised in the UK setting.[4]

In addition, a Phase II, multicentre, open-label extension trial of Study 201, Study 202, is reported in the submission to provide evidence on the safety profile of chlormethine gel. The aim of Study 202 was to evaluate the safety and efficacy of daily treatment with topical chlormethine gel (0.04%) in patients with Stage I or IIA MF-CTCL who completed 12 months of treatment with either chlormethine gel or chlormethine ointment in Study 201, but did not achieve a CR (i.e. their CAILS score remained greater than 0 at Baseline of Study 202). Study 202 ran concurrently with the 12-month post-treatment follow-up of patients enrolled in Study 201. Efficacy results from Study 202 are not presented in this submission given that patients received an unlicensed dose of chlormethine gel (0.04% chlormethine). This study was not identified in the clinical SLR as it is currently unpublished; however, data are available from the Study 202 clinical study report (CSR) (Recordati Rare Diseases/Helsinn Healthcare SA data on file).[60]

Additional sources of evidence are also presented in this submission to complement Study 201. MIDAS (NCT03380026), is an ongoing split-face, open-label, non-randomised study designed to investigate the incidence and severity of common adverse reactions to chlormethine gel (0.02%)

treatment, particularly contact dermatitis, which had enrolled [redacted] patients as of May 2019. This study is presented in the Adverse Reactions section of this submission (Section B.2.10.3).[65, 66] In addition, real-world evidence on the effectiveness and tolerability of chlormethine gel from PROVe (NCT02296164) and from France during a Temporary Use Authorisation (Autorisations Temporaires d'Utilisation [ATU]) are presented in order to report on the effectiveness and tolerability of chlormethine gel in real-world clinical practice. PROVe is an ongoing open-label, single-arm, multi-centre, US-based, observational study investigating effectiveness and HRQoL in patients treated with chlormethine gel (0.02%).[61, 67] In France, an ATU was granted for the prescription of chlormethine 0.02% gel to [redacted] patients with MF-CTCL from October 2014 to July 2019, meaning that effectiveness data from real-world use of chlormethine gel is available from this French setting.[62] These studies were not identified in the clinical SLR as they were not published in the electronic databases or congresses specified within the scope of the SLR at the time of searching. Information on these studies is available as data on file; published abstracts are also available for the French ATU data and the PROve study.[67, 68]

Table 8: Clinical effectiveness evidence

Study	Study 201 (NCT00168064)		
Study design	Phase II, multicentre, randomised, observer-blind [a], active comparator trial		
Population	Adult patients with Stage IA–IIA MF-CTCL (as confirmed by skin biopsy), previously treated with at least one SDT, who had not been treated with topical chlormethine in the past two years, and who were naïve to topical carmustine therapy.		
Intervention(s)	Chlormethine hydrochloride 0.02% gel, applied once daily for up to 12 months		
Comparator(s)	Chlormethine hydrochloride 0.02% compounded ointment, applied once daily for up to 12 months		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Reported outcomes specified in the decision problem[b]	• CAILS response rate • **mSWAT response rate** • Duration of confirmed CAILS response • **Adverse effects of treatment**		
All other reported outcomes	• Time to progression based on CAILS score • Time to confirmed CAILS response • CAILS response rate by stratum • Extent of cutaneous disease		

[a] This was a single-blinded (Investigator-blinded) rather than a double-blinded trial, as the two formulations of chlormethine differed in appearance, the gel formulation being dispensed in a tube whereas the ointment formulation was dispensed in a jar. [b] Outcomes in bold are used to inform the cost-effectiveness model.
Abbreviations: CAILS: Composite Assessment of Index Lesion Severity; MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; mSWAT: modified Severity Weighted Assessment Tool; SDT: skin-directed therapy
Source: Lessin *et al.* (2013).[25]

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

B.2.3.1 Trial design

Study 201 was a Phase II, multicentre, randomised, observer-blinded, active controlled trial comparing 0.02% chlormethine gel with 0.02% chlormethine compounded ointment in previously treated patients with Stage IA–IIA MF-CTCL.[25, 46]

MF-CTCL patients with persistent or recurrent Stage IA, IB or IIA disease, without history of progression beyond Stage IIA, who had received at least one prior SDT for MF-CTCL were included in the study. Diagnosis was confirmed with a skin biopsy of a representative lesion, obtained in the 90 days prior to study initiation and after a four week treatment washout period of treatments directed at the disease.[25, 46]

A total of 322 patients were assessed for eligibility for Study 201, after which 260 patients were enrolled and subsequently randomised in a 1:1 ratio to receive chlormethine gel (n=130) or chlormethine ointment (n=130). Both treatments were applied once daily to specific lesions, or to the total skin surface, depending on the extent of BSA coverage of the patient. If new lesions appeared in untreated areas, patients were converted from spot treatment to regional or whole-body treatment.

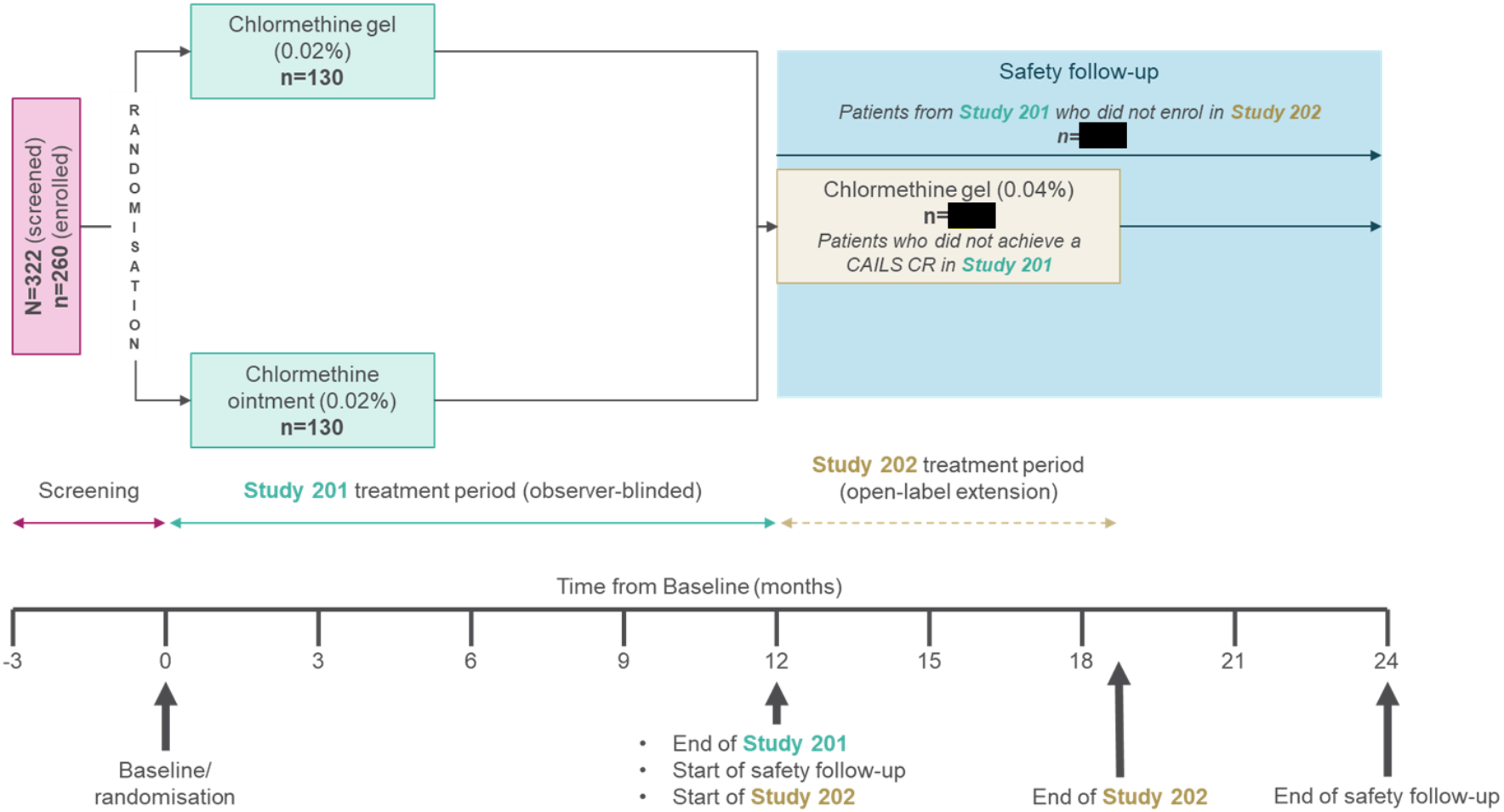
Patients were treated for 12 months unless disease progression, treatment-limiting toxicity, concomitant illness, or other change in health status necessitated discontinuation of study therapy. Patients were also free to withdraw consent for any reason at any time during the trial. Patients were followed off-study for an additional 12 months to assess the potential for the development of secondary non-melanoma skin cancers, in particular squamous cell carcinomas (SCCs). This follow-up was deemed necessary as these secondary malignancies have been reported in the literature as a potential toxicity associated with topical chlormethine and other SDTs such as PUVA and electron beam radiation used in the treatment of MF-CTCL.[7, 46]

During this 12-month follow-up period, patients who had not achieved a CR based on CAILS with either the chlormethine gel or chlormethine ointment (0.02%) could enrol in Study 202: an open label, 7-month trial investigating chlormethine gel (0.04%).[25, 46] Patients who did not enrol onto Study 202 from the chlormethine gel 0.02% arm (n=[redacted]) or chlormethine ointment arm (n=[redacted]) were able to begin any other therapy for MF-CTCL within the follow-up period, as deemed medically necessary by the principal Investigator.[69]

A total of [redacted] patients who received chlormethine gel (0.02%) during Study 201 were not followed beyond the conclusion of Study 201. Of the [redacted] patients who received chlormethine gel (0.02%) and were followed during the follow-up period, [redacted] withdrew early from the study, [redacted] did not enter Study 202, [redacted] entered Study 202 and received chlormethine gel (0.04%), and [redacted] entered Study 202 and did not receive chlormethine gel (0.04%). [redacted] of the [redacted] patients who received chlormethine ointment (0.02%) during Study 201 were not followed-up. Of the [redacted] patients who received chlormethine ointment (0.02%) and were followed during the follow-up period, [redacted] withdrew early from the study, [redacted] did not enter Study 202, [redacted] entered Study 202 and received chlormethine (0.04%) gel, and [redacted] entered Study 202 and did not receive chlormethine gel (0.04%).[70]

A schematic for the Study 201 and Study 202 trial design is presented in Figure 3.

Figure 3: Study 201 trial design



Abbreviations: CAILS: Composite Assessment of Index Lesion Severity; CR: complete response.
Source: Adapted from the Study 201 and Study 202 CSRs.[46, 60, 69]

The primary endpoint of Study 201 was the CAILS response rate (either a complete or partial response), defined as a ≥50% improvement from the Baseline CAILS score.

The secondary endpoints were:

- mSWAT response rate, defined as a ≥50% improvement from the Baseline mSWAT score
- Time to confirmed CAILS response
- Duration of confirmed CAILS response
- Time to progression based on CAILS score
- Extent of cutaneous disease, measured as change in the percentage of total BSA involvement

A summary of the definitions for the above endpoints is presented in Table 9 below.

Table 9: Outcome definitions in Study 201

Outcome	Definition
CAILS or mSWAT response categories	
Confirmed response	Any response which had a duration of ≥28 days
CR	No evidence of disease; 100% improvement from Baseline score (score of 0), confirmed at the next visit ≥28 days later
PR	Partial but incomplete clearance of disease (evidence of disease remains); ≥50% improvement from Baseline score, confirmed at the next visit ≥28 days later
SD	Disease has not changed from Baseline score; <50% improvement or <25% increase from Baseline
PD	Disease has worsened since Baseline; ≥25% increase from Baseline score
(CAILS/mSWAT) response rate	Proportion of patients with ≥50% improvement (CR+PR) from the Baseline score, confirmed at the next visit ≥28 days later
Other CAILS/mSWAT endpoints	
Duration of confirmed CAILS response	Time from the first appearance of confirmed response (CR or PR) to the first assessment where the response was no longer apparent (i.e. when SD or PD was subsequently documented)
Time to progression based on CAILS score	Time from Baseline to PD
Time to confirmed CAILS response	Time from Baseline to the first confirmed CAILS response (CR or PR)
Extent of cutaneous disease	Change from Baseline in the total percentage of the BSA component of the mSWAT score calculation

Abbreviations: CAILS: Composite Assessment of Index Lesion Severity; CR: complete response; mSWAT: modified Severity Weighted Assessment Tool; PD: progressive disease; PR: partial response; SD: stable disease
Source: Study 201 CSR (2011);[46] Lessin *et al.* (2013).[25]

B.2.3.2 Trial methodology

A summary of the methodology and trial design of Study 201 is presented in Table 10.[25, 46, 71] Further details of the methodology of Study 201, including the full eligibility criteria are reported in Appendix L.

Table 10: Summary of Study 201 methodology

Trial name	Study 201 (NCT00168064)
Location	13 sites in the United States
Trial design	Phase II, multicentre, randomised, active comparator, observer-blind, study
Eligibility criteria for participants	**Key inclusion criteria** • Diagnosis of IA, IB or IIA MF-CTCL confirmed by skin biopsy ○ Patients with histologic variants, folliculotropic/syringotropic MF-CTCL and LCT were eligible • Treated previously with at least one SDT for MF-CTCL **Key exclusion criteria** • Newly diagnosed MF-CTCL with no prior therapy • Prior treatment with topical chlormethine within the last two years or topical carmustine at any point previously • Use of topical or systemic therapies, including corticosteroids, for MF-CTCL within four weeks of entry in the study • Diagnosis of Stage IIB–IV MF-CTCL • History of a higher T score than T2 or a higher N score than N1 • Patients who had radiation therapy within one year of study start • Pregnant or nursing females, or males and females of childbearing potential not using an effective means of contraception • Serious known concurrent medical illness or infection, which could potentially present a safety risk and/or prevent compliance with the requirements of the treatment program A full list of inclusion and exclusion criteria is presented in Appendix L.
Settings and locations where the data were collected	• The study was carried out at 13 medical and/or cancer centres in the United States • The study was conducted according to applicable State and Federal regulations and International Conference on Harmonisation Good Clinical Practice guidelines
Intervention (n=130) and comparator (n=130)	• A total of 260 patients were randomised in a 1:1 ratio to receive either 0.02% chlormethine gel (n=130), or 0.02% chlormethine ointment (n=130) • Following the screening visit, eligible patients were stratified into two groups by MF-CTCL stage (IA versus IB, IIA) then randomised separately within each stratum at each centre in blocks of ten • Patients in both arms received treatment for up to 12 months or until death, unacceptable toxicity or withdrawal of consent
Method of study drug administration	• Patients applied a thin film of topical chlormethine once daily for 12 months to each lesion (generally Stage IA) or to the whole body (generally Stage IB, IIA or severity of new lesions developing after treatment initiation met criteria for progressive disease [≥25% worsening]) • Patients were instructed to wear disposable gloves and/or wash their hands after applying chlormethine. If someone helped to apply chlormethine, they were also instructed to wear disposable gloves. If the medicine got on the skin of other people, they were instructed to wash with soap and water • Patients were instructed not to cover the lesion with clothing for 5–10 minutes after administration and not to wash off the chlormethine for a minimum of four hours

Permitted and disallowed concomitant medication	• During the trial, other therapies to treat MF-CTCL were prohibited • Topical steroids (up to 1%) were permitted, but only on non-MF-CTCL lesions[a] • Non-topical steroids (eye drops, nasal sprays, inhalers, injections and oral steroids) were permitted for concurrent or pre-existing medical conditions
Primary outcomes	• CAILS response rate (including CAILS response by stratum)
Secondary and exploratory outcomes	**Secondary outcomes** • mSWAT response rate • Time to confirmed CAILS response • Duration of confirmed CAILS response • Time to progression based on CAILS score • Extent of cutaneous disease • AEs
Pre-planned subgroups	The following subgroups were explored for CAILS response:[b] • Sex (Male, Female) • Race (Caucasian, African American, Other) • Age (<18, 18–64, 65–74, ≥65) • MF-CTCL Stage (Stage IA, Stage IB/IIA)
Discontinuation of study treatment and premature patient withdrawal	Patients were treated on this trial for 12 months unless they experienced disease progression, treatment-limiting toxicity, concomitant illness, or other change in health status necessitated discontinuation of study therapy. Patients were also free to withdraw consent for any reason at any time during the trial. Specifically, criteria for terminating study therapy included: • Grade 3 or 4 local dermal irritation that did not improve to Grade 2 or lower within 2 weeks for Grade 3 and 4 weeks for Grade 4 • Positive patch test and Grade 3 or 4 dermal irritation • Concurrent illness which prevented further treatment with topical chlormethine or required protocol-prohibited therapy • General or specific changes in the patient's condition, including progressive disease, which in the judgment of the Investigator rendered the patient unacceptable for further study treatment, or was in the patient's best interest • Non-compliance for ≥28 days • Patient decision to withdraw It should be noted that because the appearance of new lesions is common with initiation of topical chlormethine treatment, Investigator discretion and patient's best interest determined if a patient was withdrawn when progressive disease was documented.
Duration of study and follow-up	• The first patient was enrolled on 8th May 2006, and the last patient completed treatment on 8th July 2010 • The study comprised a pre-study visit (screening), a Baseline (Day 1) visit, and visits at Months 1, 2, 3, 4, 5, 6, 8, 10, and 12 • Additional safety data, to assess the occurrence of SCC were captured in an extended 12-month follow-up • Data presented within this submission are from the 1st June 2011 data cut-off at which time [redacted] patients had completed the 12-month safety follow-up

	• The Study 201 safety follow-up was completed on the 4th August 2011 for non-melanoma skin cancers

[a] With the following two exceptions, topical steroid use was confined to non-index lesions as allowed in the protocol. 1. One patient in the chlormethine ointment arm used topical steroids on one of two index lesions being followed. As there was an index lesion treated with only topical chlormethine, this patient was included in the ITT and EE data sets (see Section B.2.4 for a definition of these analysis sets). 2. One patient in the chlormethine gel arm was treated with prednisone due to a treatment-limiting toxicity that led to withdrawal from the study. This patient was excluded from the EE analyses. [b] Note that Study 201 was not powered for subgroup analyses.
Abbreviations: AE: adverse event; CAILS: Composite Assessment of Index Lesion Severity; EE: efficacy evaluable; ITT: intention-to-treat; LCT: large cell transformation; MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; N: nodes; SDT: skin-directed therapy; T: tumour
Source: Study 201 CSR (2011);[46] Lessin *et al.* (2013);[25] ClinicalTrials.gov;[71, 72] Interim addendum to Study 201 CSR (2011).[72]

B.2.3.3 Baseline characteristics

The study populations presented within this submission include the intention-to-treat (ITT) population and the ITT population excluding a centre where there was a protocol violation (ITT excluding NYU). These patient populations are described in detail in Section B.2.4 (Table 12).

Baseline characteristics were generally well-balanced across the two arms, and for all study populations. In the ITT population, including the NYU patients as assigned and treated, there were more patients with Stage IA disease in the chlormethine gel arm, though the difference was not statistically significant (p=[redacted]).[46] This is primarily due to the non-random assignment of patients at NYU. When these patients are excluded, as in the ITT excluding NYU dataset, [redacted] of the patients on the chlormethine gel arm and [redacted] of the patients on the compounded ointment arm had Stage IA disease.[46]

Baseline demographics, disease characteristics and a summary of prior therapies of the patients included in the ITT population and the ITT population excluding NYU population are summarised in Table 11.[25, 46]

Table 11: Baseline characteristics (ITT including NYU and ITT excluding NYU)

Characteristic	ITT including NYU		ITT excluding NYU	
	Chlormethine gel (n=130)	Chlormethine ointment (n=130)	Chlormethine gel ([redacted])	Chlormethine ointment ([redacted])
Gender, n (%)				
Male	77 (59.2)	77 (59.2)	[redacted]	[redacted]
Female	53 (40.8)	53 (40.8)	[redacted]	[redacted]
Race, n (%)				
Caucasian	97 (74.6)	96 (73.8)	[redacted]	[redacted]
Afro-American	16 (12.3)	19 (14.6)	[redacted]	[redacted]
Other	17 (13.1)	15 (11.5)	[redacted]	[redacted]
Age, n (%)				
<65 years	93 (71.5)	87 (66.9)	[redacted]	[redacted]
≥65 years	37 (28.5)	43 (33.1)	[redacted]	[redacted]
Time from initial diagnosis, n (%)				
<6 months	[redacted]	[redacted]	[redacted]	[redacted]
6 months–1 year	[redacted]	[redacted]	[redacted]	[redacted]

1–2 years	[redacted]	[redacted]	[redacted]	[redacted]
≥2 years	[redacted]	[redacted]	[redacted]	[redacted]
Prior therapies, n (%)				
Topical corticosteroids	112 (86.1)	113 (86.9)	[redacted]	[redacted]
Phototherapy	50 (38.5)	53 (40.8)	[redacted]	[redacted]
Bexarotene (topical and oral)	23 (17.7)	23 (17.7)	[redacted]	[redacted]
Topical chlormethine	16 (12.3)	13 (10.0)	[redacted]	[redacted]
IFNs	3 (2.3)	5 (3.8)	[redacted]	[redacted]
Methotrexate	3 (2.3)	3 (2.3)	[redacted]	[redacted]
Radiation (local and total skin)	3 (2.3)	2 (1.5)	[redacted]	[redacted]
Other[a]	14 (10.8)	34 (26.2)	[redacted]	[redacted]
MF-CTCL stage, n (%)				
Stratum 1: Stage IA	76 (58.5)	65 (50.0)	[redacted]	[redacted]
Stratum 2	54 (41.5)	65 (50.0)	[redacted]	[redacted]
Stage IB	52 (40.0)	63 (48.5)	[redacted]	[redacted]
Stage IIA	2 (1.5)	2 (1.5)	[redacted]	[redacted]
Baseline CAILS score				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mSWAT score				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline percentage BSA				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]

[a] 'Other' includes primarily emollients, anti-bacterials, anti-fungals, and retinoids other than bexarotene.
Abbreviations: BSA: body surface area; CAILs: Composite Assessment of Index Lesion Severity; IFN: interferon; ITT: intention-to-treat; MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; mSWAT: modified Severity Weighted Assessment Tool; NYU: New York University; SD: standard deviation.
Source: Study 201 CSR (2011);[46] Lessin *et al*. (2013).[25]

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

As described in Section B.2.3.1, 260 patients were initially enrolled in Study 201. However, the study coordinator at the NYU study centre did not follow the correct randomisation process, as patients should have been stratified into two groups by their MF-CTCL stage (Stage IA versus IB–IIA) and then randomised to the gel or ointment formulation. However, at NYU, Stage IA patients were assigned to the chlormethine gel arm, and Stage IB/IIA were assigned to the chlormethine ointment arm, leading to a protocol violation. Thus, when conducting analysis of the

results of Study 201, two ITT populations were utilised; the full ITT population and an ITT population excluding the NYU study centre.

Definitions and details of these ITT populations, in addition to the efficacy evaluable (EE) and safety sets are presented in Table 12 below.

Table 12: Trial populations used for the analysis of outcomes in Study 201

Analysis set	Definition
ITT population including NYU (N=260) Chlormethine gel (n=130) Chlormethine ointment (n=130)	• All patients enrolled in Study 201 • This includes data from NYU patients ([redacted]) based on the treatment assigned and received ([redacted] chlormethine gel; [redacted] chlormethine ointment) and is consistent with the way that NYU patients were evaluated for safety outcomes
ITT population excluding NYU (N=[redacted]) Chlormethine gel ([redacted]) Chlormethine ointment ([redacted])	• All patients randomised as per the trial protocol for Study 201 • This excludes the NYU patients as they were not randomised in accordance with the protocol • The aim of this data set is to address the potential bias resulting from patients with less severe disease (Stage IA) being assigned to the chlormethine gel formulation and the consequent unblinding of the Investigator
Safety set (N=255) Chlormethine gel (n=128) Chlormethine ointment (n=127)	• Patients who received at least one application of study drug

EE set (N=185)
Chlormethine gel (n=90)
Chlormethine ointment (n=95)
	• Patients with no major protocol violations or who did not withdraw from the study prior to the 6-month timepoint
	  ○ Protocol violation:
	  ▪ NYU patients (not randomised in accordance with the protocol)
	  ○ Reasons for withdrawal:
	  ▪ Withdrawal due to skin toxicity
	  ▪ Never received drug
	  ▪ Lack of efficacy
	  ▪ Concurrent illness
	  ▪ Withdrew consent
	  ▪ Subject's best interest
	  ▪ Non-compliance/lost to follow-up
	  ▪ Other

Abbreviations: EE: efficacy evaluable; ITT: intention-to-treat; NYU: New York University.
Source: Study 201 CSR (2011);[46] Lessin *et al.* (2013).[25]

The statistical analyses used to calculate the primary endpoint (≥50% improvement in the Baseline CAILS score), alongside sample size calculations and methods for handling missing data, are presented in Table 13 below.

Table 13: Statistical methods for the primary analysis of Study 201

Trial name	Study 201
Hypothesis objective	• The primary objective of this two-arm study was to evaluate the efficacy of topical application of chlormethine in a gel formulation compared to an ointment formulation in subjects with Stage IA–IIA MF with respect to CAILS response • This trial was designed as a non-inferiority study; the primary non-inferiority hypothesis test was the comparison of H_0 versus H_A where H_0 and H_A are given by: ○ H_0: p1/p2 ≤0.75; H_A: p1/p2 >0.75 ○ where p1 = proportion of chlormethine gel patients with CAILS overall response at 12 months and p2 = proportion of chlormethine ointment patients with CAILS overall response at 12 months
Statistical analysis	• All statistical tests of the primary endpoint were two-sided with a significance level of 0.05 and CIs were based on two-sided 95% confidence limits • It was determined that the chlormethine gel formulation would be considered non-inferior to the ointment formulation if the lower limit of the 95% confidence interval around the ratio of response rates (based on ≥50% improvement in the Baseline CAILS score which was confirmed at the next visit at least four weeks later) of the gel formulation to the ointment formulation was >0.75 • The CAILS response rates for the two treatment arms were compared using a Fisher's Exact Test; Cochran-Mantel-Haenszel tests were also performed to indicate whether or not differences existed between the two treatment groups after controlling for strata (Stage IA versus IB/IIA) • Although switching from non-inferiority to superiority was not pre-specified in the trial protocol, a post-hoc analysis approach highlighted that if the inferior limit of the 95% CIs of the CAILS score for the EE population was ≥0.75 and entirely above 1, this would have been consistent with superiority of the gel formulation versus the ointment at a p<0.05 in terms of CAILS responses only in the EE
Sample size, power calculation	• The sample size was estimated based on the EE patient population, i.e. patients who completed at least 6 months of study therapy and had no major protocol violations • Due to the recognised side effect of dermatitis with topical chlormethine, the sample size calculation assumed that up to 25% of patients might not be able to complete six months of study therapy as prescribed in the protocol • Thus, to provide at least 80% power to demonstrate non-inferiority, it was calculated that approximately

	180 subjects would be required in the EE patient population and therefore, 240–250 patients should be randomised onto the protocol (ITT)
Data management, patient withdrawals	• For the primary endpoint, any patient randomised or treated who did not achieve a documented CR or PR was counted as a non-responder for the ITT populations. Similarly, for the EE population, any patient included in the data set who did not achieve a CR or PR was considered a non-responder • In the Kaplan-Meier curves, subjects who never had an 'event' were censored as of their last available CAILS score • Subjects with no Baseline CAILS score ([redacted] patients who never received study drug [[redacted] in the chlormethine gel arm and [redacted] in the chlormethine ointment arm]) were excluded from the analysis • Subjects with only a Baseline CAILS score, i.e. no post-Baseline assessment (seven patients [six chlormethine gel patients and one chlormethine ointment patient]), were censored at time 0

Abbreviations: CAILS: Composite Assessment of Index Lesion Severity; CI: confidence interval; EE: efficacy evaluable; ITT: intention-to-treat; MF: mycosis fungoides.
Source: Study 201 CSR (2011);[46] Study 201 Statistical Analysis Plan (2008);[73] Recordati Rare Diseases and Helsinn Healthcare SA, data on file.[74]

B.2.4.1 Participant flow in the relevant randomised controlled trials

In Study 201, the first patient was enrolled on the 8th May 2006 and the last patient completed treatment on 8th July 2010. The data cut-off for efficacy and safety analysis was 1st June 2011; patients were followed from the study completion date for an additional 12 months to assess the incidence of squamous cell carcinomas.[46]

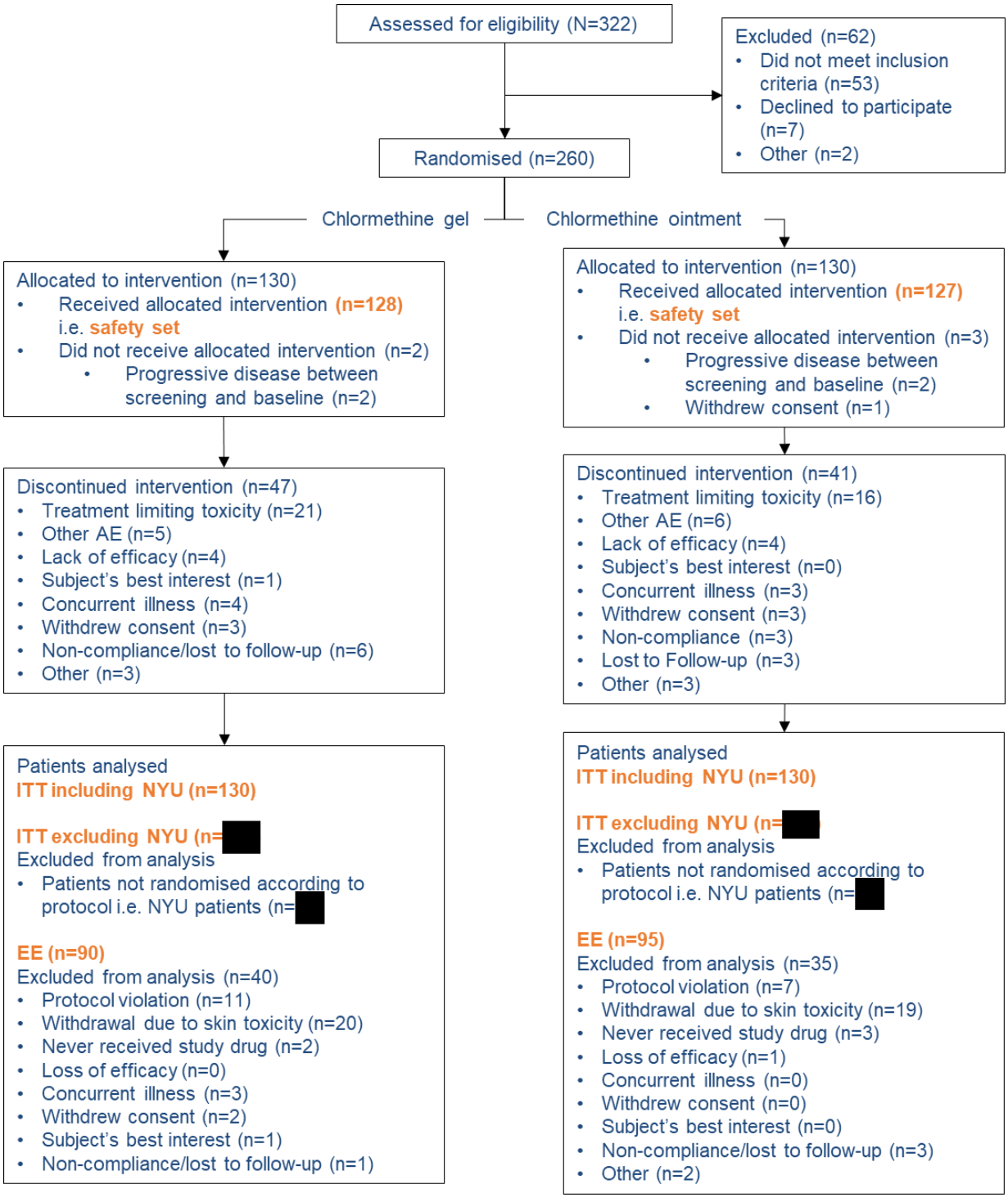
From the first date of first enrolment, 322 patients were assessed for eligibility for Study 201. Of these, 260 patients were then stratified into two groups by their MF-CTCL stage: Stage IA versus IB–IIA, and then randomised between the two treatment arms (chlormethine gel or chlormethine ointment) in a ratio of 1:1. A total of five patients (two patients assigned to chlormethine gel and three patients assigned to chlormethine ointment) did not receive their allocated intervention (four due to disease progression between screening and Baseline and one due to withdrawal of consent).[25, 46]

Up to the data cut-off presented within this submission (1st June 2011), 47 patients in the chlormethine gel arm and 41 patients in the chlormethine ointment arm had discontinued their assigned intervention. However, efficacy data for the full ITT population (both ITT including and ITT excluding NYU) are presented within the submission. Note that the ITT excluding NYU further excludes patients who were not randomised according to the trial protocol i.e. those at the NYU study centre (n=[redacted]; [redacted] patients assigned to chlormethine gel and [redacted] assigned to chlormethine ointment).[25, 46]

Results are presented for both ITT populations (including and excluding NYU) in order to transparently report the results of all patients randomised to receive either chlormethine gel or chlormethine ointment, rather than only those who had no major protocol violations and were on study for at least 6 months (the EE analysis set). Safety data are presented for all patients who received at least one application of study drug (n=128 for chlormethine gel and n=127 for chlormethine ointment).[25]

Full details of the participant flow (CONSORT diagram) for Study 201 are presented in Figure 4 below.

Figure 4: Participant flow (CONSORT diagram) in Study 201



Abbreviations: AE: adverse event; EE: efficacy evaluable; ITT: intention-to-treat; NYU: New York University.
Source: Adapted from Lessin *et al.* (2013)[25] and Study 201 CSR (2011).[46]

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

A quality assessment was performed for the RCTs identified and extracted through the SLR as being relevant to this submission. A summary of the quality assessment for Study 201 is summarised in Table 14.

Table 14: Quality assessment of Study 201

Trial name	Study 201
Was randomisation carried out appropriately?	Yes – Randomisation was done separately at each site by site pharmacists or study coordinators not involved in patient assessment, who were not blinded to treatment in order to maintain blinding of the Investigators; eligible patients were stratified into two groups by MF-CTCL stage (IA [Strata 1] versus IB/IIA [Strata 2]) then randomised separately within each stratum at each centre in blocks of ten to treatment with chlormethine gel or chlormethine ointment. Prior to the start of the study, the unblinded study coordinator received two boxes of envelopes, one for Strata 1 and one for Strata 2 and each envelope had a randomisation number. After the patient was staged by the investigator, the unblinded study coordinator selected the top envelope from the appropriated stratum. There was a protocol violation at the NYU study site, where the pharmacist assigned chlormethine gel to all patients with Stage IA disease and chlormethine ointment to Stage IB/IIA patients. However, this violation is transparently reported in the CSR, and outcomes from Study 201 are analysed for the ITT including and excluding NYU to address this.
Was the concealment of treatment allocation adequate?	Yes – see above.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – Patients, clinical personnel at Yaupon Therapeutics, Inc., the investigators, and any other individuals involved with patient assessments were blinded to the assigned treatment.
Were the outcome assessors blind to treatment allocation?	Yes – see above.
Were the groups similar at the outset of the study in terms of prognostic factors	Yes – In the ITT population, including the NYU patients as assigned and treated, there were more patients with Stage IA disease in the chlormethine gel arm, though the difference was not statistically significant (p=[redacted]) (primarily due to the non-random assignment of patients at NYU). The two treatment arms were well matched with respect to other demographics and baseline characteristics.
Were there any unexpected imbalances in drop-outs between groups?	No – There were no differences in drop-outs between the two treatment arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – All outcomes appear to have been reported.

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 – Given the protocol violation at the NYU study centre, results for both the full ITT (including NYU) and the ITT excluding NYU are presented. The ITT including NYU evaluated all patients enrolled in Study 201 based on the treatment assigned and received. The ITT excluding NYU evaluated all patients randomised as per the study protocol. For quantitative and qualitative parameters, the number of patients with missing data was reported if applicable. In the calculation of percentages for a qualitative variable, patients with missing data were not considered, unless otherwise specified. For qualitative measurements, no imputation of missing data was performed, unless otherwise specified. For the safety analyses, missing data or assessments were not estimated or imputed; all calculations were based on non-missing data.
Details of study funding	Study 201 was supported in part by an FDA Orphan Product Development grant (R01FD003017) (Dr. Lessin) and by Cepartis Therapeutics, Inc., Malvern, PA.

Abbreviations: CSR: clinical study report; FDA: Food and Drug Administration; ITT: intention-to-treat; MF-CTCL: mycosis fungoides type T-cell lymphoma; NYU: New York University.
Source: Study 201 CSR (2011).[46]

Full details of the quality assessment are reported in Appendix D.

B.2.6 *Clinical effectiveness results of the relevant trials*

Summary of Clinical Effectiveness

- The primary efficacy endpoint was a ≥50% improvement (i.e. CR or PR) in a patient's CAILS score versus the Baseline measurement[25]
  - Chlormethine gel demonstrated non-inferiority to chlormethine ointment in both ITT populations[25]
  - In the ITT including NYU population, the confirmed CAILS response rate for chlormethine gel was 58.5%, and for chlormethine ointment was 47.7%.[25] In the ITT excluding NYU population, the confirmed CAILS response rate was [redacted] in the chlormethine gel arm and [redacted] in the chlormethine ointment arm[46]
- A key secondary endpoint of Study 201 was the mSWAT response rate[25]
  - In the ITT including NYU population, response rates were non-inferior in the chlormethine gel arm (46.9%) compared to the chlormethine ointment arm (46.2%) (response rate ratio 1.02 [95% CI: 0.783–1.321])[25]
  - Chlormethine gel also demonstrated non-inferiority in the ITT excluding NYU population (response rate ratio [redacted] [95% CI: [redacted]]), with response rates of [redacted] and [redacted] for the chlormethine gel and chlormethine ointment arms, respectively[46]
- The time to a confirmed CAILS response was significantly reduced in the chlormethine gel arm, with Kaplan-Meier analysis predicting that a 50% response rate would occur 16 weeks sooner in the chlormethine gel arm compared to the chlormethine ointment arm in the both the ITT population including NYU ($p<0.012$) and excluding NYU ($p<$[redacted]).[25, 46]
- Duration of response and time to progressive disease were not statistically different between the two treatment arms
  - In the ITT including NYU population at Week 40, [redacted] and [redacted] patients in the chlormethine gel and chlormethine ointment arm sustained a response, respectively, and in the ITT excluding NYU population, [redacted] and [redacted] patients in the chlormethine gel and chlormethine ointment arm sustained a response, respectively[46]
  - In the ITT including NYU population approximately [redacted] of patients in both arms never experienced progression (≥25% increase in CAILS score) during the study (Kaplan-Meier analysis of the two treatment arms: p=[redacted]). Similarly, in the ITT excluding NYU population at Week 52, [redacted] and [redacted] patients in the chlormethine gel and chlormethine ointment arms did not experience progression[46]
- The evidence for clinical efficacy of chlormethine gel from Study 201 is supported by evidence of real-world effectiveness from two studies (a French ATU report and PROVe).
  - French ATU data revealed that [redacted] patients achieved an overall response (OR), defined as PR, "nearly CR" or CR, following treatment with chlormethine gel. In total, [redacted] patients achieved a favourable response, defined as OR or SD (SD was defined as <50% reduction from baseline score).[75] It should be noted that the French ATU study was an early access programme and therefore there was no specification of the type of response measure physicians should use; this represents a limitation of the presented data
  - PROVe provides evidence that [redacted] of early stage (Stage IA and IB) patients treated with chlormethine gel achieved ≥50% reduction in baseline BSA percentage coverage of lesions over 12 months (the peak response rate of [redacted] was achieved at 18 months), with this clinical response found to be associated with statistically significant improvements in HRQoL by Skindex-29 ($p<0.001$)[61]

As described above in B.2.4, clinical efficacy results from Study 201 are presented for both ITT populations (including and excluding NYU) in order to transparently report the results for all patients randomised to receive either chlormethine gel or chlormethine ointment; both including and excluding NYU populations are presented because of the potential for bias introduced by the protocol violation at NYU. As the EE analysis set only included those who had no major protocol violations and were on study for at least six months (with the aim of demonstrating the efficacy of topical chlormethine in a population for which this treatment is tolerable), it represents a selected population and hence is not presented in full in this submission. Full data for the EE population are presented in the Study 201 CSR.[46] A post-hoc analysis of the CAILS outcome in which the non-inferiority hypothesis that was pre-defined in the protocol was switched to one assessing superiority; this was done for the EE population and hence for this analysis the results from the EE population are presented in the submission.[46, 74]

B.2.6.1 Primary endpoint: CAILS response rate

The primary efficacy endpoint in Study 201 was a ≥50% improvement (i.e. CR or PR) in a patient's CAILS score versus Baseline measurement. Response was measured at each study visit up to 12 months of treatment; a confirmed response was defined as CR or PR and a patient was considered to be a responder if the response was maintained for at least two consecutive visits (or at least 28 days). The CAILS score is obtained by adding a severity score for each of the following symptoms for up to five index lesions: erythema, scaling, plaque elevation and surface area (with severity scored from 0–8 for erythema and scaling, from 0–3 for plaque elevation and 0–9 for surface area). In Study 201, up to five representative index lesions were identified at Baseline, based on the physician's choice, and were assessed throughout the study in all patients. Patients' responses were categorised according to the definitions presented in Table 9 at each follow-up timepoint. Patients were labelled as having a response of 'unevaluable' if they had no Baseline CAILS assessment, or if they had no post-Baseline CAILS assessment.[46]

In the ITT including NYU population, the confirmed response rate (CR+PR) was higher for chlormethine gel versus chlormethine ointment, with response rates of 58.5% and 47.7%, respectively, although this was not statistically significant (p=[redacted], stratified by MF-CTCL Stage [IA versus IB/IIA]). The ratio of these response rates was 1.226 (95% CI: 0.974–1.552). As the lower limit of the 95% CI was ≥0.75, these data confirmed that the chlormethine gel formulation was non-inferior to the compounded ointment formulation. In the ITT excluding NYU population, the confirmed response rate was [redacted] in the chlormethine gel arm and [redacted] in the chlormethine ointment arm. The ratio of the response rates was [redacted] (95% CI: [redacted]), also meeting the protocol defined criterion for non-inferiority. Thus, the results for both ITT populations consistently demonstrate that chlormethine gel is non-inferior to chlormethine ointment in terms of CAILS response rates.

CAILS response rates for the ITT including NYU and ITT excluding NYU populations are summarised in Table 15.[25, 46]

Table 15: Summary of CAILS response in the ITT and ITT excluding NYU populations

CAILS response, n (%)	ITT including NYU		ITT excluding NYU	
	Chlormethine gel (n=130)	Chlormethine ointment (n=130)	Chlormethine gel ([redacted])	Chlormethine ointment ([redacted])
Response	**76 (58.5)**	**62 (47.7)**	[redacted]	[redacted]

CR	18 (13.8)	15 (11.5)	[redacted]	[redacted]
PR	58 (44.6)	47 (36.2)	[redacted]	[redacted]
Non-response	**54 (41.5)**	**68 (52.3)**	[redacted]	[redacted]
SD	42 (32.3)	61 (46.9)	[redacted]	[redacted]
PD	5 (3.8)	3 (2.3)	[redacted]	[redacted]
Unevaluable[a]	7 (5.4)	4 (3.1)	[redacted]	[redacted]

If patients did not achieve a response, their last CAILS score was compared with the Baseline value.
[a] Includes patients with no Baseline CAILS assessment or no post-Baseline CAILS assessment. For the ITT including NYU population for the primary endpoint, five patients never received study drug and six patients were withdrawn without any post-Baseline assessment (one for non-compliance and five due to treatment-limiting toxicity).
Abbreviations: CAILS: Composite Assessment of Index Lesion Severity; CR: complete response; ITT: intention-to-treat; NYU: New York University; PD: progressive disease; PR: partial response.
Source: Lessin *et al.* (2013);[25] Study 201 CSR (2011).[46]

CAILS response rates by stratum

In the ITT including NYU population, subset analysis by strata revealed relative balance between stratum 1 (Stage IA; n=141) and stratum 2 (Stages IB/IIA; n=119). The CAILS response rate was 59.2% for chlormethine gel versus 40.0% for chlormethine ointment for stratum 1 (ratio of response rates = 1.48 [95% CI: 1.05–2.14]).[25] Stratum 2 subjects achieved a 57.4% response rate for chlormethine gel versus 55.4% for chlormethine ointment (ratio of response rates = 1.04 [95% CI: 0.75–1.43]).[25]

For the ITT population excluding NYU, strata were also well balanced when considering CAILS response rates. For stratum 1 (n=[redacted]), the response rate for chlormethine gel was [redacted] and for chlormethine ointment was [redacted].[46] For stratum 2 (n=[redacted]), the response rates for chlormethine gel and chlormethine ointment were [redacted] and [redacted], respectively.[46]

Categorisation of CAILS response by stratum in Study 201 for both ITT populations is summarised in Table 16.

Table 16: Categorisation of CAILS response by stratum in Study 201 (ITT including NYU and ITT excluding NYU)

CAILS response, n (%)	ITT including NYU				ITT excluding NYU			
	Chlormethine gel		Chlormethine ointment		Chlormethine gel		Chlormethine ointment	
	Stage IA (n=76)	Stage IB/IIA (n=54)	Stage IA (N=65)	Stage IB/IIA (N=65)	Stage IA (N=65)	Stage IB/IIA (N=54)	Stage IA (N=64)	Stage IB/IIA (N=59)
Response	45 (59.2)	31 (57.4)	26 (40.0)	36 (55.4)	[redacted]	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	31 (40.8)	23 (42.6)	39 (60.0)	29 (44.6)	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unevaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Baseline CAILS assessment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No post-Baseline CAILS assessment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAILS: Composite Assessment of Index Lesion Severity; CR: complete response; ITT: intention-to-treat; NYU: New York University; PD: progressive disease; PR: partial response; SD: stable disease.
Source: Lessin *et al.* (2013);[25] Study 201 CSR (2011).[46]

B.2.6.2 Secondary Endpoints: mSWAT response rate

A key secondary outcome in Study 201 was the mSWAT response rate (CR+PR), measured at each study visit up to 12 months of treatment, with confirmed responses maintained until the next visit at least 28 days later. The mSWAT score (on a scale of 0–300) is obtained by classifying each lesion on a patient into one of three categories: patch, plaque and tumour. The BSA covered by that lesion is then multiplied by 1, 2 or 4 for a patch, plaque or tumour, respectively to weight the score based on lesion severity.[43, 46]

In the ITT including NYU population, the mSWAT response rate was 46.9% and 46.2% for chlormethine gel and ointment, respectively (response rate ratio 1.017 [95% CI: 0.783–1.321]) and this difference in response rates was not statistically significant (p=[redacted], X^2=[redacted]).[25, 46] In the chlormethine gel arm, a total of [redacted] patients ([redacted]) achieved a CR and [redacted] patients ([redacted]) achieved a PR. In the chlormethine ointment arm, [redacted] patients ([redacted]) and [redacted] patients ([redacted]) achieved a CR and PR, respectively.[46]

For the ITT excluding NYU population, the mSWAT response rate was [redacted] and [redacted] for the chlormethine gel and chlormethine ointment arms, respectively. The response rate ratio was [redacted] (95% CI: [redacted]), and again, there was no statistically significant difference between the treatment arms (p=[redacted], X^2=[redacted]), which is consistent with the ITT including NYU population. In the chlormethine gel arm, a total of [redacted] patients ([redacted]) achieved a CR and [redacted] patients ([redacted]) achieved a PR.[46] In the chlormethine ointment arm, [redacted] patients ([redacted]) and [redacted] patients ([redacted]) achieved a CR and PR, respectively.[46]

Based on the above, whether response is assessed by improvement in the CAILS score or SWAT score (and in either ITT population), the data demonstrate that chlormethine gel meets the protocol criterion for non-inferiority versus chlormethine ointment.[25, 46]

The mSWAT response rates for the ITT including NYU and ITT excluding NYU populations are presented in Table 17.

Table 17: mSWAT response rates Study 201 (ITT including NYU and ITT excluding NYU)

mSWAT response, n (%)	ITT including NYU		ITT excluding NYU	
	Chlormethine gel (n=130)	Chlormethine ointment (n=130)	Chlormethine gel ([redacted])	Chlormethine ointment ([redacted])
Response	**61 (46.9)**	**60 (46.2)**	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Unevaluable	[redacted]	[redacted]	[redacted]	[redacted]
No Baseline mSWAT assessment	[redacted]	[redacted]	[redacted]	[redacted]

No post-Baseline mSWAT assessment	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CR: complete response; ITT: intention-to-treat; mSWAT: modified Severity Weighted Assessment Tool; NYU: New York University; PD: progressive disease; PR: partial response; SD: stable disease.
Source: Lessin *et al.* (2013);[25] Study 201 CSR (2011).[46]

B.2.6.3 Secondary Endpoints: Time to confirmed CAILS response

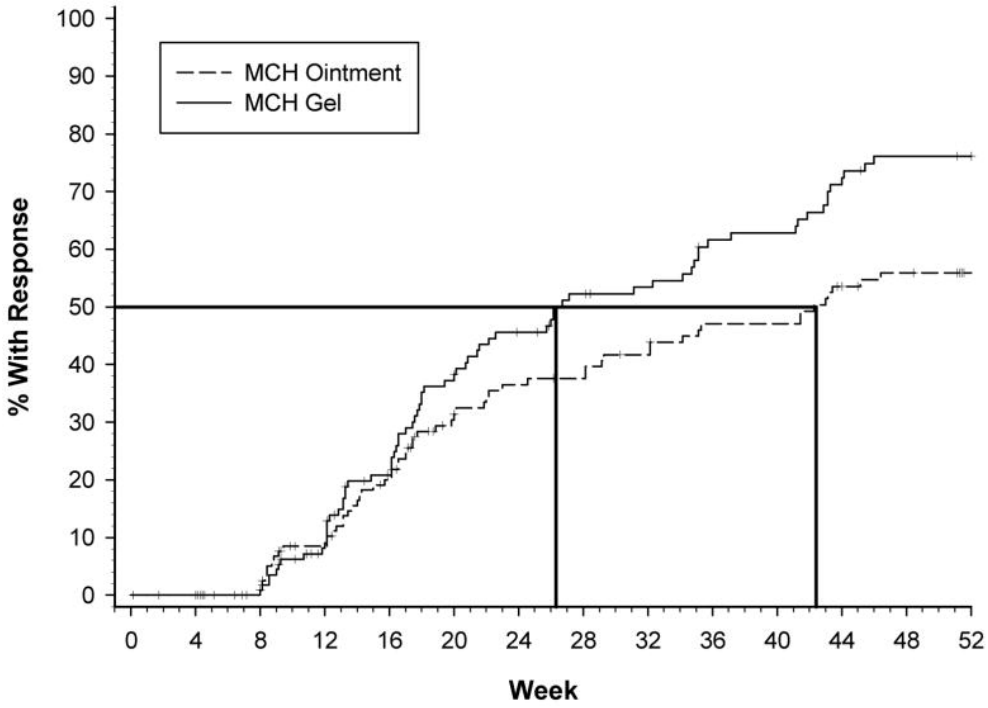
In Study 201, time to CAILS response was defined as the time from Baseline to the first confirmed CAILS response (CR or PR).[46]

Patients with no Baseline CAILS assessment ([redacted] patients [redacted] in the chlormethine gel arm and [redacted] in the chlormethine ointment arm]) who never received study drug were excluded from this analysis. Patients with a Baseline, but no post-Baseline CAILS assessment ([redacted] patients [redacted] patients in the chlormethine gel arm and [redacted] patient in the chlormethine ointment arm] were censored at time 0).[46]

In the ITT including NYU population, approximately 46% of patients treated with gel achieved a confirmed response at 24 weeks and 76% achieved a confirmed response at 52 weeks.[25] Of patients treated with ointment approximately 37% achieved a confirmed response at 24 weeks and approximately 56% achieved a confirmed response at 52 weeks. Kaplan-Meier analysis revealed that the estimated time to a 50% response rate was 26 weeks (95% CI: 20.71–35.14) in the chlormethine gel arm and 42 weeks (95% CI: 29.14–53.00) in the chlormethine ointment arm, indicating a statistically significant difference between the treatment arms ($p<0.012$).[25] Therefore, patients in the chlormethine gel arm attained a 50% response rate approximately 16 weeks sooner than the ointment and had a higher response rate than patients treated with chlormethine ointment beginning at approximately 16 weeks through 52 weeks of treatment. The Kaplan-Meier curve for time to response in the ITT including NYU population from Study 201 is presented in Figure 5.[25]

The results for the ITT excluding NYU population were similar, with Kaplan-Meier analysis demonstrating an estimated 50% response rate at [redacted] in the chlormethine gel arm (n=[redacted]), while this was estimated at [redacted] for the compounded ointment arm (n=[redacted]). Again there was a statistically significant reduction in the time to CAILS response (p<[redacted]).[46] The Kaplan-Meier curve for time to response in the ITT excluding NYU population from Study 201 is presented in Figure 6.

Figure 5: Kaplan-Meier curve of time to CAILS response in Study 201 (ITT including NYU population)



Abbreviations: CAILS: Composite Assessment of Index Lesion Severity; ITT: intention-to-treat; MCH: mechlorethamine; NYU: New York University.
Source: Lessin *et al.* (2013).[25]

Figure 6: Kaplan-Meier curve of time to CAILS response in Study 201 (ITT excluding NYU population)

[redacted]

Abbreviations: AP: Aquaphor (chlormethine ointment); CAILS: Composite Assessment of Index Lesion Severity; ITT: intention-to-treat; NM: nitrogen mustard; NYU: New York University; PG: propylene glycol (chlormethine gel).
Source: Study 201 CSR (2011).[46]

B.2.6.4 Secondary Endpoints: Duration of confirmed CAILS response

Duration of CAILS response was defined as the time from the first appearance of confirmed response (CR or PR) to the first assessment where SD or progressive disease was documented. This endpoint was analysed in patients who achieved a response (76 patients in the chlormethine gel arm and 62 patients in the chlormethine ointment arm for the ITT including NYU population).[25]

In the ITT including NYU population, 65/76 (85.6%) patients in the chlormethine gel arm and 51/62 (82.2%) patients in the chlormethine ointment arm maintained their response to the end of the trial (12 months) and were censored as of their last visit; thus, [redacted] patients lost a response designation during the trial ([redacted] patients on each arm). [redacted] patients in the chlormethine gel arm and [redacted] patients in the chlormethine ointment arm lost the response designation and then achieved a second response prior to completing the trial.[25, 46]

Based on Kaplan-Meier analysis, there was no statistically significant difference between the two treatment arms with respect to duration of response (p=[redacted] unadjusted log-rank; p=[redacted] stratified log-rank) and it was estimated that at least [redacted] of responses would be maintained for 10 months or greater. At Week 24, [redacted] of patients in the chlormethine gel arm and [redacted] of patients in the chlormethine ointment arm sustained a response.[46] At Week 40, [redacted] and [redacted] patients in the chlormethine gel and chlormethine ointment arm sustained a response, respectively.[46]

Comparable results for the comparison of treatment arms for the duration of first confirmed response were obtained for the ITT excluding NYU population. At [redacted], [redacted] of patients in the chlormethine gel arm and [redacted] of patients in the chlormethine ointment arm sustained a response. At [redacted], [redacted] and [redacted] patients in the chlormethine gel and chlormethine ointment arm sustained a response, respectively.[46]

The Kaplan-Meier curve for the duration of confirmed CAILS response is presented in Figure 7 for the ITT including NYU population and in Figure 8 for the ITT excluding NYU population.

Figure 7: Kaplan-Meier curve of duration of confirmed CAILS response in Study 201 (ITT including NYU population)

Abbreviations: AP: Aquaphor (chlormethine ointment); CAILS: Composite Assessment of Index Lesion Severity; ITT: intention-to-treat; NM: nitrogen mustard; NYU: New York University; PG: propylene glycol (chlormethine gel).
Source: Study 201 CSR (2011).[46]

Figure 8: Kaplan-Meier curve of duration of confirmed CAILS response in Study 201 (ITT excluding NYU)

Abbreviations: AP: Aquaphor (chlormethine ointment); CAILS: Composite Assessment of Index Lesion Severity; ITT: intention-to-treat; NM: nitrogen mustard; NYU: New York University; PG: propylene glycol (chlormethine gel).
Source: Study 201 CSR (2011).[46]

B.2.6.5 Secondary Endpoints: Time to progression based on CAILS score

Time to progression based on CAILS score was defined as the time from Baseline to progressive disease (≥25% increase from Baseline CAILS score) in Study 201. Patients who had no Baseline and no post-Baseline CAILS assessments were not included in the analysis.

In the ITT including NYU population, 15 patients (11.5%) randomised to the chlormethine gel arm and ten (7.7%) patients randomised to the chlormethine ointment arm had a ≥25% increase from Baseline CAILS score (i.e. progressive disease) at some time during the study.[25] However, the majority of patients remained on treatment. Seven of the patients on the chlormethine gel arm who stayed on treatment subsequently achieved a CR.[25] Only [redacted] patients ([redacted] in the gel arm; [redacted] in the compounded ointment arm) met this criterion for disease progression at the time of their last visit. At Week 24, [redacted] patients in the chlormethine gel arm and [redacted] patients in the chlormethine ointment arm did not have progressive disease and at Week 52, [redacted] and [redacted] patients in the chlormethine gel and chlormethine ointment arms did not have progressive disease, respectively.[46] Comparison of Kaplan-Meier curves for time to progression in the two treatment arms showed no statistical difference (p=[redacted]); approximately [redacted] of patients in both arms never experienced ≥25% increase in CAILS score (i.e. progressive disease) during the study.[46]

For the ITT excluding NYU, at Week 24, [redacted] patients in the chlormethine gel arm and [redacted] patients in the chlormethine ointment arm did not have progressive disease and at Week 52, [redacted] and [redacted] patients in the chlormethine gel and chlormethine ointment arms did not have progressive disease, respectively.[46]

The Kaplan-Meier curve for time to progression based on CAILS score is presented in Figure 9 for the ITT including NYU population and in Figure 10 for the ITT excluding NYU population.

Figure 9: Time to progression based on CAILS score from Study 201 (ITT including NYU)

Abbreviations: AP: Aquaphor (chlormethine ointment); CAILS: Composite Assessment of Index Lesion Severity; ITT: intention-to-treat; NM: nitrogen mustard; NYU: New York University; PG: propylene glycol (chlormethine gel).

Source: Study 201 CSR (2011).[46]

Figure 10: Time to progression of cutaneous disease based on CAILS score from Study 201 (ITT excluding NYU)

Abbreviations: AP: Aquaphor (chlormethine ointment); CAILS: Composite Assessment of Index Lesion Severity; ITT: intention-to-treat; NM: nitrogen mustard; NYU: New York University; PG: propylene glycol (chlormethine gel).
Source: Study 201 CSR (2011).[46]

B.2.6.6 Secondary Endpoints: Extent of cutaneous disease

The total percentage of BSA component of the mSWAT score calculation was used as a measure of the overall extent of cutaneous disease. To assess non-inferiority with respect to percentage BSA, in a manner consistent with CAILS and SWAT scores, response was defined as ≥50% improvement from Baseline in percentage BSA that is confirmed at the next visit ≥28 days later.

The changes in BSA coverage were not statistically significant between treatment arms, p< for ITT including NYU and p< for ITT excluding NYU. For the ITT population including NYU, the ratio of response rate was (95% CI:), and for the ITT population excluding NYU, the ratio of response rate was (95% CI:), both meeting the protocol defined criterion for non-inferiority.[46]

Percentage BSA response rates for the ITT population including and excluding NYU are presented below in Table 18.

Table 18: percentage BSA response rates Study 201 (ITT including NYU and ITT excluding NYU)

	ITT including NYU		ITT excluding NYU	
	Chlormethine gel (n=130)	Chlormethine ointment (n=130)	Chlormethine gel ( )	Chlormethine ointment ( )

Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Non-responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSA: body surface area; ITT: intention-to-treat; NYU: New York University
Source: Study 201 CSR (2011).[46]

B.2.6.7 Post-hoc analyses

Superiority of CAILS response in the EE population in Study 201

As pre-specified in the protocol, Study 201 was initially designed to assess the non-inferiority, rather than superiority, of chlormethine gel versus chlormethine ointment with the measurement of the proportion of patients with a ≥50% improvement (i.e. CR or PR) in a patient's CAILS score compared to Baseline as the primary efficacy endpoint. However, a post-hoc analysis of the results of Study 201 (data cut-off 1st June 2011) was conducted in which the assessment of non-inferiority with regards to CAILS response rate was switched to superiority.

Both ITT and EE data sets met the criteria for non-inferiority for both the primary and secondary endpoints. The non-inferiority of chlormethine gel to the ointment formulation was demonstrated as the lower bound of the 95% CI around the ratio of response rates (gel to ointment) was greater than the non-inferiority threshold (≥0.75). The 95% CI of the CAILS score in the EE population not only exceeded the non-inferiority threshold (≥0.75) but was entirely above 1, at 1.301 (95% CI: 1.065–1.609).[25]

[redacted].[74]

By-time post-hoc analysis of CAILS and mSWAT in Study 201

A further post-hoc analysis was carried out to evaluate the efficacy of chlormethine gel using a by-time approach, to identify any possible trends in treatment response (via CAILS and mSWAT), which was assessed monthly between 1–6 months and bi-monthly between 7–12 months, over the course of one year. This analysis only included patients who had data available at each assessment timepoint, and patients who withdrew due to lack of efficacy or progressive disease were counted as non-responders to prevent selection bias.[76, 77]

Clinically relevant response rates (CAILS: 8.5% [n=118]; mSWAT 5.9% [n=119]) occurred from Month 1. Peak response rates for CAILS was 78.9% (visit 8; n=90) and the peak mSWAT response rate was 60.7% (final visit; n=90). These results demonstrate that response rates increased over time in Study 201, and that maximum response to treatment typically occurs in the 8–10-month timeframe.[74, 76]

The results of the traditional overall response rates (ORRs) from the pre-specified analyses from Study 201, in addition to this by-time analysis for clinical response evaluation, demonstrate the substantial proportion of patients who achieve clinical response with chlormethine gel and provide useful data in support of continuation of chlormethine gel to enable reaching of maximum response.[76, 77]

B.2.6.8 Efficacy of chlormethine gel in the real-world setting

Clinical expert opinion has suggested that in clinical practice, chlormethine gel may be a valuable option in patients with advanced disease stage, who were not recruited into Study 201 but are covered by the marketing authorisation for chlormethine gel.[4] It is also likely that in clinical practice, corticosteroids may be used concomitantly with chlormethine gel, as steroids can be used to treat symptoms that may arise from SDTs, such as pruritis and dermatitis, but are not considered to be anti-MF-CTCL therapies. Furthermore, evidence from clinical practice can be used to complement data from Study 201 in informing the effectiveness and safety profile of chlormethine gel outside of the clinical trial setting.

A number of real-world evidence sources were identified that provide evidence corresponding to the use of chlormethine gel in a real-world setting.

The French ATU report

In France in 2014, a Temporary Use Authorisation (ATU) was granted for the prescription of chlormethine 0.02% gel to patients with MF-CTCL. Chlormethine gel was subsequently prescribed to [redacted] patients in France from October 2014 until July 2019, of which [redacted] received at least one treatment with chlormethine gel.[62, 75] Patient baseline characteristics and demographics, effectiveness and safety results are presented below (Table 19).[62, 75]

Early access program (EAP) design and methodology

Initially, only patients with early stage MF-CTCL could be awarded an ATU for one, two, three or six months, after which response was measured and treatment could be continued on another ATU; up to August 2016, chlormethine gel was prescribed according to the criteria set out in Study 201, to only include patients with Stage IA–IIA disease; the nominative cohort. However, in August 2016, the prescription criteria were expanded to allow for treatment of patients regardless of disease stage; forming the ATU cohort.[75]

Patient demographics and baseline characteristics

In total, [redacted] patients were included in the nominative and ATU cohorts overall; [redacted] were included in the nominative cohort only, [redacted] were included in the ATU cohort only and [redacted] were included in the nominative cohort and then moved into the ATU cohort. Overall, there were [redacted] patients in the nominative cohort and [redacted] patients in the ATU cohort.[62]

Of the [redacted] patients, [redacted] did not initiate treatment with chlormethine gel, therefore the total number of patients exposed to chlormethine gel was [redacted].[62, 75] Overall, [redacted] patients from the nominative ATU and [redacted] patients from the cohort ATU presented with early-stage MF-CTCL (Stage IA–IIA).[62] In the nominative cohort, [redacted] patients had received prior therapy for MF-CTCL and in the ATU cohort, [redacted] patients [redacted] for which data on prior therapies were available had received prior treatment for MF-CTCL ([redacted] of patients in this cohort had received prior phototherapy).[75] When considering all [redacted] patients overall, the median age was [redacted] years (range: [redacted]), with [redacted] and [redacted] patients female and male, respectively.[62]

Patient demographics and baseline characteristics of all the patients included in the study are summarised in Table 19 below.

The usage of concomitant treatments with chlormethine gel was permitted; [redacted] of patients from the ATU cohort used chlormethine gel in combination with other treatments, with topical corticosteroids being the most prescribed concomitant treatment ([redacted] patients), as displayed in Table 20.[62]

Table 19: Patient baseline characteristics from the nominative and ATU cohorts of the French ATU Study

Characteristic	Overall patients (N=876)	
Age, median (range), years	[redacted]	
Gender, n (%)		
Male	[redacted]	
Female	[redacted]	
Diagnosis and disease stage	**Nominative cohort (n=[redacted])**	**ATU cohort (n=[redacted])**
IA	[redacted]	[redacted]
IB	[redacted]	[redacted]
IIA	[redacted]	[redacted]
IIB	[redacted]	[redacted]
III	[redacted]	[redacted]
IV or Sézary Syndrome	[redacted]	[redacted]
Other	[redacted]	-
Missing or unknown[a]	[redacted]	[redacted]

[a] Information on disease stage at diagnosis was not provided in the patient forms for these patients.
Abbreviations: ATU: temporary use authorisation.
Source: Bagot *et al.* EADV Oral Presentation (2019).[62]

Table 20: Treatment duration and concomitant therapies in the ATU cohort from the French ATU Study

Concomitant treatments	ATU cohort ([redacted])
Median duration of treatment, months	[redacted]
Chlormethine prescribed as, %	
Monotherapy	[redacted]
Combination therapy	[redacted]
Chlormethine in combination, %	
Corticosteroids	[redacted]
Methotrexate	[redacted]
Bexarotene	[redacted]

Abbreviations: ATU: temporary use authorisation.
Source: Bagot *et al.* EADV Oral Presentation (2019).[62]

Response rates in the French ATU Study

Overall, there were efficacy data available for [redacted] patients who had returned at least one follow-up form (follow-up was not mandatory in the context of the ATU). Of these, [redacted] patients achieved OR, defined as PR, “nearly CR” or CR, following treatment with chlormethine gel. In

total, [redacted] patients achieved a favourable response, defined as OR or SD (SD was defined as <50% reduction from baseline score).[62] Whilst the majority of these patients ([redacted]) were Stage IA/IB, responses were also observed in advanced stage patients, with [redacted] of the [redacted] patients with advanced disease experiencing a favourable response of OR or SD.[62]

The response to treatment of patients with at least one follow-up form in the French ATU Study is displayed in Table 21.

Table 21: Treatment response rates in patients with at least one follow-up form, French ATU Study

Response	Patients with ≥1 follow-up form ([redacted])
OR	[redacted]
CR, n (%)	[redacted]
"Nearly CR", n (%)	[redacted]
PR, n (%)	[redacted]
SD, n (%)	[redacted]
PD, n (%)	[redacted]
Unspecified, n (%)	[redacted]

Abbreviations: ATU: temporary use authorisation; CR: complete response; OR: overall response; PD: progressive disease; PR: partial response; SD: stable disease.
Source: French ATU Report (2019).[75]

Given that the French ATU was an early access program rather than a clinical trial, there was no obligation for clinicians to report the response measure used to evaluate their patients. Therefore, use of the response measure for the response rates reported above is unknown (meaning the extent to which CAILS or mSWAT was used is also unknown). In addition, there are some limitations of data collected as part of the ATU in France in terms of missing follow-up for some patients (follow-up was not mandatory in the context of the ATU).

Despite these limitations, the effectiveness data collected support the clinical effectiveness findings from Study 201 in the real-world setting.[62]

PROVe (NCT02296164)

PROVe was a prospective, observational, US-based study assessing outcomes, AEs, treatment patterns, and QoL in patients diagnosed with MF-CTCL and actively using topical chlormethine gel during standard-of-care visits.[61, 67, 78] PROVe enrolled 298 adult patients at [redacted] US university-affiliated and community hospitals. The first patient was enrolled in March 2015 and the last patient completed the study in October 2018. All patients completed a 2-year follow-up, regardless of whether or not chlormethine gel was discontinued.[61]

The aims of the PROVe trial were to assess clinical characteristics, treatment patterns, response assessment patterns and healthcare utilisation in MF-CTCL, safety of chlormethine gel (including dermatitis) and patient reported outcomes focusing on HRQoL in MF-CTCL.[61]

Preliminary data analysis (as of September 2019) are presented in the submission, which include the patient demographics and baseline characteristics, 12-month response rates measured by

the extent of cutaneous disease, and the peak response determined by a by-time analysis (from one to 24 months), where patients who withdrew due to lack of efficacy or disease progression were deemed non-responders.[61] HRQoL of patients as measured by the emotions, symptoms and functioning domains of Skindex-29 and the number of AEs and the AEs affecting ≥3% of patients are also reported (see Section B.2.10 for safety data).[61, 67]

Patients and baseline characteristics

In the PROVe patient population the majority of patients ([redacted]) were male and the mean (±SD) age of patients was [redacted] years.[61] The majority of patients had either Stage IA ([redacted]) or Stage IB ([redacted]) disease; a relatively large proportion of patients had unknown or missing disease stage ([redacted]).[61] Patient demographics and baseline characteristics from PROVe are presented in Table 22.

Table 22: Demographics and baseline characteristics from the PROVe trial

Characteristic	PROVe (N=298)
Age, mean (SD), years	[redacted]
Female	[redacted]
Male	[redacted]
Duration of MF-CTCL, mean (SD), years	[redacted]
Time since MF-CTCL diagnosis to enrolment, mean (SD), months	[redacted]
TNMB classification, n (%)	
IA	[redacted]
IB	[redacted]
IIA	[redacted]
IIB	[redacted]
III–IV	[redacted]
Missing/unknown	[redacted]

Abbreviations: MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; SD: standard deviation; TNMB: tumour, nodes, metastasis, blood (classification system).
Source: Kim *et al.* Oral Presentation (2019).[61]

Response by percentage BSA coverage

In the PROVe study, a response was defined as a ≥50% reduction in pre-enrolment baseline BSA percentage coverage of lesions.[61]

In Stage IA and IB patients at 12 months, [redacted] had responded to treatment with chlormethine gel; using a by-time approach, the peak response rate of [redacted] was achieved at 18 months. In the whole (Stage IA–IV) evaluable patient population at 12 months, the response rate was [redacted] ([redacted]).[61, 67]

Clinical response by percentage BSA reduction was associated with statistically significant improvement in HRQoL in patients with Stage IA and IB disease, measured by three domains of Skindex-29, emotions ($p<0.001$), symptoms ($p<0.001$) and functioning ($p<0.001$). In the whole study population over the 12-month period, weighted mean Skindex-29 scores were lower in responders (26.4, 26.8 and 13.2) versus non-responders (37.1, 34.8 and 22.8) for the same three domains, respectively. Over the 24-month period, Skindex-29 scores were also lower in responders versus non-responders (26.4, 25.6 and 14.0 versus 35.7, 35.6 and 22.6) for

emotions, symptoms and functioning, respectively.[67] All scores were statistically significantly improved (p<0.001) in responders versus non-responders.[67]

Response rates by percentage BSA coverage for patients in the PROVe study with Stage IA and IB MF-CTCL are displayed in Table 23.

Table 23: Skindex-29 scores from the PROVe study

Skindex-29 domain	Responder, mean Skindex-29 score		Non-responder, mean Skindex-29 score		p-value[a]
	12 months (n=[redacted])	24 months (n=[redacted])	12 months (n=[redacted])	24 months (n=[redacted])	
Emotions	26.4	26.4	37.1	35.7	<0.001
Symptoms	26.8	25.6	34.8	35.6	<0.001
Functioning	13.2	14.0	22.8	22.6	<0.001

[a] p-value for responders versus non-responders for both 12 and 24 months.
Source: Kim *et al*. Abstract (2019);[67] Recordati Rare Diseases/Helsinn Healthcare SA data on file.[74]
Overall, in the PROVe study, chlormethine gel demonstrated similar efficacy as was reported in Study 201, with similar response rates as measured by percentage BSA coverage being reported. Furthermore, HRQoL was shown to be improved in responders versus non-responders.[25, 61, 67]

B.2.7 *Subgroup analysis*

As discussed in Table 10 above, response rates based on the CAILS score were calculated for the following subgroups: sex (Male, Female), race (Caucasian, African American, Other), age (<18, 18–64, 65–74, ≥65) and the stratification variable, MF-CTCL stage (Stage IA, Stage IB/IIA). In the ITT including NYU population, the results were consistent among subgroups, demonstrating the robustness of the CAILS response data from Study 201. For the stratification variable, MF-CTCL Stage at Baseline, both strata were consistent for non-inferiority. Furthermore, similar results were also found for the ITT excluding NYU population.[46]

The results of this subgroup analysis are presented in Table 24 and Table 25 below for the ITT including NYU and ITT excluding NYU populations, respectively.

Table 24: Subgroup analysis of CAILS response rate from Study 201 (ITT including NYU)

CAILS Response	Chlormethine gel (n=130)	Chlormethine ointment (n=130)	Ratio of response rates	95% CI for ratio of response rates
Age, n/N (%)				
<18	[redacted]	[redacted]	[redacted]	[redacted]
18–64	[redacted]	[redacted]	[redacted]	[redacted]
65–74	[redacted]	[redacted]	[redacted]	[redacted]
≥75	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n/N (%)				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Race, n/N (%)				
Caucasian	[redacted]	[redacted]	[redacted]	[redacted]
African-American	[redacted]	[redacted]	[redacted]	[redacted]

Other	[redacted]	[redacted]	[redacted]	[redacted]
MF-CTCL stage at Baseline, n/N (%)				
IA	[redacted]	[redacted]	[redacted]	[redacted]
IB, IIA	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAILS: Composite Assessment of Index Lesion Severity; CI: confidence interval; ITT: intention-to-treat; MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; NC: not calculated; NYU: New York University.
Source: Study 201 CSR (2011).[46]

Table 25: Subgroup analysis of CAILS response rate from Study 201 (ITT excluding NYU)

CAILS Response	Chlormethine gel ([redacted])	Chlormethine ointment ([redacted])	Ratio of response rates	95% CI for ratio of response rates
Age, n/N (%)				
<18	[redacted]	[redacted]	[redacted]	[redacted]
18–64	[redacted]	[redacted]	[redacted]	[redacted]
65–74	[redacted]	[redacted]	[redacted]	[redacted]
≥75	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n/N (%)				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Race, n/N (%)				
Caucasian	[redacted]	[redacted]	[redacted]	[redacted]
African-American	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
MF-CTCL stage at Baseline, n/N (%)				
IA	[redacted]	[redacted]	[redacted]	[redacted]
IB, IIA	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAILS: Composite Assessment of Index Lesion Severity; CI: confidence interval; ITT: intention-to-treat; MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; NYU: New York University.
Source: Study 201 CSR (2011).[46]

B.2.8 *Meta-analysis*

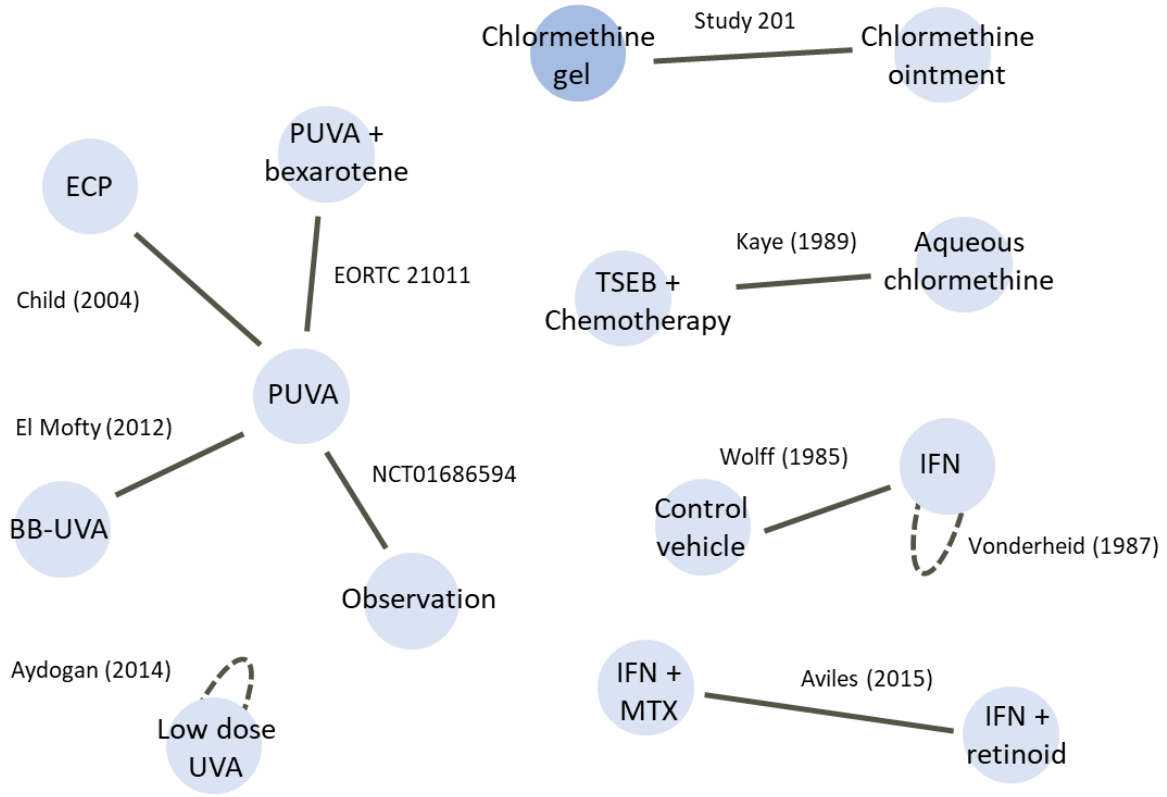
The SLR identified only one RCT of chlormethine gel (Study 201) relevant to the decision problem; therefore, a meta-analysis was not conducted as part of this appraisal.

B.2.9 *Indirect and mixed treatment comparisons*

The feasibility of conducting an indirect treatment comparison (ITC) on the basis of the ten RCTs (Study 201 and nine comparator studies) identified by the SLR was performed. The connectivity of the identified studies is presented in Figure 11. In summary, no connected network could be formed between Study 201 and any comparator studies via a common comparator. The only potential connected network that could be formed was between chlormethine gel and TSEB + chemotherapy, via an assumption that chlormethine ointment and aqueous chlormethine can be considered sufficiently similar to be pooled into a single node. However, TSEB + chemotherapy does not represent a relevant comparator for the decision problem. In addition to the lack of connectivity, heterogeneity was identified across included studies which may introduce bias into

any ITC, and hence undermine the robustness of any comparison, had a connected network been viable. These elements of heterogeneity are discussed in more detail in Appendix D.

Figure 11: Network of evidence



Abbreviations: BB-UVA: broadband ultraviolet A; ECP: extracorporeal photopheresis; IFN: interferon; MTX: methotrexate; PUVA: psoralen-ultraviolet A; TSEB: total skin electron beam.
Notes: solid lines represent two-arm studies; dashed lines represent data arising from a single cohort. References for studies included in the figure are available in Appendix D.

More recently, alternative methods have been proposed in the absence of a connected network, including population-adjusted indirect comparisons.[79] Population-adjusted methods (e.g. matching-adjusted indirect comparisons [MAIC]) may be explored where individual patient data (IPD) are available for an index study (i.e. Study 201) with only aggregate-level comparator data arising from one or more comparator studies. These methods may also be utilised for single-arm studies or to compare interventions which do no connect via a common comparator (e.g. no connected network), and these methods may be seen as an improvement to conducting a naïve comparison. Unanchored comparisons are severely limited; strong assumptions are required, for example, that all prognostic factors and treatment-effect modifiers are included in any matching procedure, and that there are no unmeasured confounders. This assumption is nearly always impossible to meet. Additionally, whilst population-adjusted ITC approaches (e.g. MAIC) may go some way to address observed heterogeneity in the evidence base, particularly with regard to imbalances in study populations, no adjustment can be made for inconsistencies in outcome definitions or treatment regimens. Moreover, if there is little overlap in patient populations, this may substantially reduce the effective sample size (ESS) of any MAIC analysis. Furthermore, unanchored comparisons only allow estimation of absolute effects. Taken together, there are many challenges to an unanchored comparison yielding robust estimates of the treatment effect; as such, it should only be explored following careful consideration of these factors, and not

simply as the default option where connected networks cannot be formed. Conducting unanchored ITC where it is not appropriate runs the risk of providing biased or misleading estimations of treatment effectiveness. Nevertheless, given the lack of a connected network, the feasibility of conducting an unanchored ITC was considered.

When considering the potential for the use of unanchored indirect treatment comparisons, there is no longer a requirement for the evidence base to be formed solely from RCTs; non-RCTs, such as single-arm prospective or retrospective studies are also relevant sources of evidence to consider. For a study to be considered for an unanchored ITC, relevant considerations are: whether there is sufficient reporting of information regarding any potential prognostic factors or treatment effect modifiers; the extent of population characteristics which need to be adjusted for (i.e. level of similarity of patient populations in important prognostic factors or treatment effect modifiers), which has implications for retention of effective sample size in the index study; consistency of outcome definitions and quality of the study (i.e. does the study provide a robust estimation of the treatment effect it aimed to measure). These factors can be considered for non-RCTs as well as the relevant study arm(s) from RCTs. The clinical SLR did not include non-RCTs for comparator therapies in the eligibility criteria, meaning that it did not provide a systematic appraisal of the non-RCT evidence base for clinical comparator therapies. Due to time constraints, it was not feasible to conduct a separate SLR for non-RCTs of clinical comparators. Therefore, in order to try to identify the non-RCT evidence base for comparators as thoroughly as possible in the absence of a formal SLR, the evidence base (RCT and non-RCT) for the clinical comparators addressed in the decision problem as appraised in the BAD guidelines was considered.[3] Full details of the methodology of this review are provided in Appendix D.

All studies of comparator therapies (phototherapy, IFN or bexarotene) identified either by the clinical SLR or by the review of evidence cited in the BAD guidelines were reviewed to determine whether the study may allow a robust and reliable unanchored ITC with Study 201. Factors considered included comparability of populations, sample size, study quality, generalisability of the study to the current (modern) treatment setting and comparability of outcome measures with Study 201. The full results of this assessment are presented in Appendix D.

The studies cited in the BAD guidelines were frequently historical in nature, low quality design (e.g. retrospective studies or case series) or associated with notable differences in population and/or outcomes definitions versus Study 201. Therefore, in the majority of cases the studies were not considered a robust or reliable source of evidence for informing estimates of relative effectiveness with chlormethine gel.

For IFN and bexarotene, only three studies and one study, respectively, were cited in the BAD guidelines;[80-83] three RCTs of IFN and no RCTs of bexarotene had additionally been identified by the clinical SLR.[84-86] For the reasons outlined in Appendix D, none of these were considered appropriate for conducting an unanchored ITC, or even informing a naïve indirect comparison with Study 201. This conclusion is coherent with the summaries of the evidence for IFN and bexarotene in the BAD guidelines in general.[3] For IFN, the BAD guidelines class the available evidence base as level 2-: “case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal [studies with a level of evidence ‘-‘ should not be used as a basis for making a recommendation]”. For bexarotene, the level of evidence is considered less susceptible to bias or confounding, but is still only graded as a level 2 (albeit 2+).[3]

For phototherapy, the majority of studies were judged to be of poor quality, particularly in relation to the factors such as their historical nature, small sample size, study design (e.g. retrospective studies) and limited reporting of patient characteristics; this conclusion is coherent with the overall rating of evidence for phototherapy in the BAD guidelines (ranging from 2- to 2+).[3] Further, there were notable issues of comparability with Study 201, in particular around response outcome definition. As such, it was not considered that any identified studies of phototherapy could be used to inform a robust formal unanchored ITC with chlormethine gel. However, whilst acknowledging the considerable limitations inherent in any naïve indirect comparison, in addition to specific concerns over phototherapy study quality and comparability to Study 201, it was considered that a small number of studies of phototherapy could potentially be considered to inform an estimate for phototherapy efficacy as a naïve comparison to chlormethine gel. Given that phototherapy represents the main comparator to chlormethine gel in the submission, it was considered that such a comparison should at least be presented, despite the considerable caveats and limitations surrounding any interpretation.

Seven phototherapy studies were considered to have better robustness and comparability to Study 201 and were taken forwards to inform an estimate for phototherapy efficacy.[87-93] These studies, and their reported CR and PR rates for phototherapy, are summarised in Table 26. It should be noted that in only one case (NCT01686594) was the measurement tool used to define response directly comparable to Study 201 (mSWAT).[93] However, it was considered that where CR is defined on the basis of complete (i.e. 100%) clearance/resolution of skin symptoms (as is the case in all seven studies), the use of different measurement tools may be less of a concern for comparability and CR rates could therefore be considered. This was on the basis of an assumption that 'complete' resolution is arguably more definitive as a definition and hence less likely to differ depending on the measurement tool used than a level of response with a more complicated or nuanced definition. This assumption around CR was considered appropriate in light of the paucity of available data. In contrast, this assumption was considered less appropriate for PR, for which the definitions are arguably more sensitive to measurement tool, and often more variable in terms of the clinical outcomes considered to meet the definition. As such, only three of the seven studies (Pavlotsky *et al.* 2006; EORTC 21011; NCT01686594) were considered to have used definitions of PR that could be considered in any way comparable to that used in Study 201: these were the studies where PR was defined solely by a >50% reduction in skin symptoms (by some measure of skin symptoms).[87, 91, 93] For the Pavlotsky *et al.* 2006 and EORTC 21011 studies, this remains a strong assumption as the scoring system used to derive percentage change was not the mSWAT.[87, 91]

Based on this assessment of the seven studies contributing CR rate estimates and three studies contributing PR estimates, a weighted average (weighted based on study sample size) estimate of CR and PR with phototherapy was derived: this gave a CR rate of 73% and a PR rate of 21%. The weighted average approach was considered most appropriate, because no single study could be clearly identified as the most robust or appropriate to consider as "representative" of phototherapy efficacy.

The results of this assessment therefore find an overall response rate of 94% for phototherapy. This is not inconsistent with the range of response rates for phototherapy summarised in the BAD guidelines summary of evidence, though it is at the more optimistic end of the range presented and the issues with the quality of the evidence for phototherapy mean that this estimate should be taken as highly uncertain.

[redacted]

[redacted]

- [redacted]
- [redacted]

This supports that the average estimate derived from the assessment of the seven phototherapy studies may represent an optimistic assessment of phototherapy efficacy.

With regards to inferring relative effectiveness of phototherapy and chlormethine gel, any comparison is open to such considerable bias as a result of differences in study design, study quality, recruited population and/or outcome measure definitions, that the relative CR and PR rates from Study 201 and from the assessment of phototherapy efficacy from the seven studies described above should be seen purely as exploratory and for the purpose of providing a “base case” input to the cost-effectiveness model in the absence of being able to derive any robust relative effectiveness estimates from the available evidence base for phototherapy.

Table 26: Summary of phototherapy efficacy from studies identified as most appropriate to inform naïve indirect comparison

Study	Sample size	Definition of response	CR rate	PR rate	Notes on PR rate
Pavlotsky *et al.* (2006)[87]	111	CR = complete clinical clearance PR = >50% clearance	79% (weighted average across Stage IA and IB)	7%	PR definition considered more comparable as defined by a >50% reduction (though not CAILS or mSWAT)
Herrmann *et al.* (1995)[88]	74	CR = total clinical and histologic clearing for a minimum of 4 weeks PR = Minimum of 50% reduction in the size of measurable lesions, or clinical clearance but continuation of atypical cells on histologic examination or more than 5% Sézary cells in peripheral blood	66%	Not comparable	PR definition considered insufficiently comparable to Study 201 even for naïve comparison due to additional criteria around atypical cells
Oguz *et al.* (2003)[89]	58 (early stage patients)	CR = unclear, but likely complete clearance PR = definition not provided	98%	Not comparable	PR definition considered insufficiently comparable to Study 201 as definition of PR not provided
Anadolu *et al.* (2005)[90]	92 (early stage treated with PUVA)	CR = no clinical or dermopathologic evidence of disease PR = >50% decrease in skin involvement with no new lesions or an improvement resulting in a lower stage	80%	Not comparable	PR definition considered insufficiently comparable to Study 201 due to additional criteria around improvement resulting in a lower stage
EORTC 21011 (Whittaker *et al.* [2012])[91]	45	CR = complete resolution of all clinically apparent cutaneous disease for at least 4 weeks PR = >50% reduction of cutaneous disease burden based on tumour burden index score compared with baseline score and sustained for at least 4 weeks	22%	49%	PR definition considered more comparable as defined by a >50% reduction (though not CAILS or mSWAT)
El Mofty *et al.* (2012)[92]	30	CR = complete clinical and histopathological clearance PR = not measured	77% (weighted average across PUVA and BB-UVA)	Not reported	N/A

NCT01686594[93]	27	CR = mSWAT score reduced to zero PR = mSWAT score reduction of more than 50%	70% (over initial 12-24 week period)	30% (over initial 12-24 week period)	mSWAT measure used so definition is comparable to Study 201
Overall range			**22–98%**	**7–49%**	
Weighted average			**73%**	**21%**	

Abbreviations: BB-UVA: broadband ultraviolet A; CAILS: Composite Assessment of Index Lesion Severity; CR: complete response; mSWAT: modified Severity Weighted Assessment Tool; N/A: not applicable; PR: partial response; PUVA: psoralen-ultraviolet A.

B.2.9.1 Uncertainties in the indirect and mixed treatment comparisons

No sufficiently robust formal ITC, either via a connected network using conventional methods or via population-adjusted methods for conducting unanchored ITC, could be performed. Full discussion of this is provided in Appendix D.

The derived estimate of phototherapy efficacy can therefore only be compared naively to that for chlormethine gel. Such naïve comparison is associated with considerable uncertainty. Firstly, the estimate for phototherapy efficacy is a pooled estimate from across a number of studies that report in some cases quite disparate estimates of efficacy. The pooling of these studies is based on weighting by sample size only, without adjustment for any differences between phototherapy studies. Therefore, the estimates for phototherapy efficacy are subject to uncertainty.

Comparing these estimates with those for chlormethine gel from Study 201 in a naïve comparison is then associated with further uncertainty. Naïve comparison does not adjust for any differences in study characteristics (e.g. population) that may be prognostic factors or treatment effect modifiers. Whilst efforts were made to try to select the phototherapy studies that had the best comparability to Study 201 in order to mitigate this, the naïve comparison should nevertheless be treated as associated with considerable uncertainty.

B.2.10 *Adverse reactions*

Summary of safety analysis from Study 201 and Study 202

Study 201

- A total of 128 patients received at least one topical application of chlormethine gel during Study 201 and were analysed as part of the safety set, with a median exposure of [redacted] weeks (range: [redacted]). In the chlormethine ointment arm (safety set; n=127) the median exposure was [redacted] weeks (range: [redacted])[25, 46]
- The most commonly reported AEs regardless of study drug relationship were skin and subcutaneous disorders, which were reported in [redacted] of patients treated with chlormethine gel, and [redacted] of patients treated with chlormethine ointment[46]
    - Of these, the most commonly reported was skin irritation, which was reported in 32 (25.0%) of patients in the chlormethine gel and 18 (14.2%) in the chlormethine ointment arm (p=0.040).[25] There were very few Grade 4 (severe) skin AEs reported with either chlormethine gel ([redacted]) or chlormethine ointment ([redacted])[46]
    - Twenty-six patients (20.3%) treated with chlormethine gel and 22 (17.3%) patients treated with chlormethine ointment discontinued treatment due to a drug-related AE associated with skin toxicity (p=0.631)[25]
- Serious adverse events (SAEs) were reported in [redacted] patients in the chlormethine gel arm and [redacted] patients in the chlormethine ointment arm (p=[redacted]); none of the SAEs reported were considered to be related to study drug[25, 46]
    - [redacted] death occurred in the chlormethine gel arm, but this was not considered to be related to the study drug[46]
- Patients were assessed for non-melanoma skin cancers during the 12-month study and for an additional 12-month follow-up[25]

    - Three patients in the chlormethine gel arm and eight in the chlormethine ointment arm were diagnosed with 20 non-melanoma skin cancers. The majority of these occurred outside of areas treated with topical chlormethine (14/20); none were considered to be due to treatment with topical chlormethine[25]
    - There is no evidence to support that chlormethine gel is associated with an increased risk of non-melanoma skin cancers[46]
- There was also no evidence of systemic absorption of chlormethine, indicating that chlormethine gel is a viable and flexible treatment option as part of a combination therapy[25]

Study 202

- Study 202 investigated chlormethine gel 0.04% in patients who completed 12 months of treatment with either chlormethine gel or chlormethine ointment in Study 201 but did not achieve a CR[76]
    - Safety data are generally consistent between Study 201 and 202 and indicate a well-characterised safety profile for chlormethine gel[25, 46, 60]
- Safety was assessed in the full analysis set (FAS) for Study 202; i.e. all patients who were enrolled and received any amount of study drug (n=98)[94]
- Patients were treated with chlormethine gel for a median duration of [redacted] weeks (range: [redacted]); [redacted] patients received >24 weeks of treatment[60]
- Consistent with Study 201, the most frequently reported AEs were skin and subcutaneous tissue disorders, which occurred in [redacted] patients[60]
    - The most frequently reported AEs were skin irritation in [redacted] patients, erythema in [redacted] patients, and pruritus in [redacted] patients[60]
    - Most skin-related AEs were Grade 1 [redacted] or [redacted]; Grade 3 skin AEs occurred in [redacted] patients, and Grade 4 skin AEs occurred in only [redacted] patient[60]
    - A total of [redacted] patients withdrew from study drug treatment due to skin-related AEs[60]
- SEAs occurred in [redacted], none of which were considered to be related to the study drug; no deaths were reported in Study 202[60, 94]
- Non-melanoma skin cancers were also monitored throughout Study 202; [redacted] non-melanoma skin cancer was reported 80 days after completing treatment with chlormethine gel (0.04%), however, this was not in a treated area and was considered to be unrelated to the study drug[70]

MIDAS

- As of May 2019, [redacted] patients were enrolled in the investigator-initiated MIDAS study, where two different therapies were administered concurrently to the same patients but on different lesions[65]
    - Chlormethine gel (once nightly) (0.02%)
    - Chlormethine gel (once nightly) (0.02%) and triamcinolone ointment once daily
- [redacted] patients experienced a severe cutaneous reaction; [redacted] were allergic contact dermatitis and only [redacted] was irritant contact dermatitis[65]
- Only [redacted] patients were not able to continue treatment with chlormethine gel[65]
- [redacted] patients analysed had reactions to various allergens other than chlormethine, indicating that they may have an allergic phenotype that predisposes them to allergic cutaneous reactions to common allergens (unrelated to chlormethine gel)[65]

Safety of chlormethine in the real-world setting

- **French ATU Study:**
  - Safety was assessed in the [redacted] patients who initiated treatment with chlormethine gel from October 2014 onwards in the French ATU Study[75]
  - [redacted] patients experienced AEs; there were [redacted] drug-related AEs and [redacted] were not related to chlormethine[62]
  - AEs of special interest included skin and subcutaneous tissue disorders; since the beginning of the ATU [redacted] cases of cutaneous AEs were reported, including only [redacted] serious cases[75]
  - AEs which were reported in >5% of the population were contact dermatitis ([redacted]), skin irritation ([redacted]) and erythema ([redacted])[62]
- **PROVe:**
  - Of the 298 adult patients enrolled in the PROVe study, AEs occurred in 125 ([redacted]) patients[61]
  - All AEs which affected ≥3% patients were skin related AEs, in line with both Study 201/202 and the French ATU data
  - The most common AE reported was dermatitis ([redacted]), followed by pruritis ([redacted]) and skin irritation ([redacted])[61]
- These studies show that in the real-world setting, the incidence of skin related AEs (the AEs most commonly reported in Study 201 and 202), may be lower than suggested in the clinical trial setting
- This demonstrates that the AE profile of chlormethine gel is manageable in clinical practice compared to in Study 201 where prescription of concomitant therapies for skin symptoms was not permitted.[25, 60-62, 67, 75]

B.2.10.1 Study 201

The secondary objective of Study 201 was to evaluate the tolerability and safety of topical chlormethine gel and chlormethine ointment in patients with Stage IA–IIA MF-CTCL. As described previously (Table 12), the safety population included all patients who received at least one application of study drug. Therefore, 128 patients in the chlormethine gel arm and 127 patients in the chlormethine ointment arm were included in the safety analysis.

The safety of all patients enrolled in this study was monitored throughout the study. A physical exam and AE reporting was part of each clinic visit (monthly for the first six months and every two months for the last six months). Severity of AEs and relationship to study medication were assessed by the Investigator, with severity graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3. Safety was assessed by comparison of the two treatment arms with respect to the incidence of all treatment-emergent AEs, SAEs, treatment-limiting toxicities, deaths and laboratory abnormalities. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 8.1).

Patients were checked for dermatitis at each clinic visit during the 12-month treatment period. In the case of Grade 3 or 4 dermatitis, patients were patch tested. If this test was positive, study therapy was discontinued. The occurrence of skin cancer was also assessed at each clinic visit during the 12-month treatment period and for an additional 12 months after completing protocol therapy. Thus, all safety data presented within this submission is from the 12-month study, with

the exception of data concerning skin cancers, for which a 24-month observation period was undertaken.[25]

Treatment duration, treatment suspensions and reductions in dosing frequency

Duration of exposure

In Study 201, the duration of exposure was calculated as the date of last application of chlormethine indicated on the case report form, minus the date that study drug was initiated. If the date of last application was missing, the date of last clinic visit was used.

Overall, there was no difference in extent of exposure between the two treatment arms (p=[redacted]). The median duration of exposure was [redacted] and [redacted] weeks in the chlormethine gel and chlormethine ointment arms, respectively. A summary of the duration of exposure data for the safety set in Study 201 is presented in Table 27 below.

Table 27: Duration of exposure in Study 201 (safety set)

Exposure, weeks[a]	Chlormethine gel (n=128)	Chlormethine ointment (n=127)
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
IQR (Q1–Q3)	[redacted]	[redacted]
Range (min–max)	[redacted]	[redacted]
By range of weeks, n (%)		
0	[redacted]	[redacted]
>0–4	[redacted]	[redacted]
>4–8	[redacted]	[redacted]
>8–12	[redacted]	[redacted]
>12–16	[redacted]	[redacted]
>16–20	[redacted]	[redacted]
>20–24	[redacted]	[redacted]
>24–28	[redacted]	[redacted]
>28–32	[redacted]	[redacted]
>32–36	[redacted]	[redacted]
>36–40	[redacted]	[redacted]
>40–44	[redacted]	[redacted]
>44–48	[redacted]	[redacted]
>48	[redacted]	[redacted]

[a] The duration of exposure was from the date of study treatment first dispensed to date of last study treatment.
Abbreviations: IQR: interquartile range; SD: standard deviation.
Source: Study 201 CSR (2011).[46]

Treatment suspensions and reductions in dosing frequency

The majority of patients on both arms were able to tolerate daily application of topical chlormethine. [redacted] patients ([redacted]) in the chlormethine gel arm compared to [redacted] patients ([redacted]) in the ointment arm had a least one reduction in the frequency of dosing, whilst [redacted] patients ([redacted]) in the gel arm compared to [redacted] patients ([redacted]) on the ointment arm had their study medication temporarily suspended at least once during the trial. These differences were

statistically significant, with p values of p=[redacted] and p=[redacted], respectively.[46] However, the number of patients who discontinued for a treatment-limiting toxicity or other drug-related skin AE were similar between the two treatment arms: 26 patients treated with chlormethine gel (20.3%) and 22 patients treated with chlormethine ointment (17.3%) discontinued treatment due to a drug-related AE associated with skin toxicity (p=0.631).[25] A total of 21/26 of these drug-related AEs leading to withdrawal in the chlormethine gel arm and 16/22 in the chlormethine ointment arm met the protocol defined definition of treatment-limiting toxicity.[25]

The criteria for reducing the frequency, temporarily suspending dosing or discontinuing study medication are presented in Table 28 below.

A summary of the proportions of patients experiencing temporary treatment suspensions and/or reductions in dosing frequency is presented in Table 29 below.

Table 28: Treatment adjustments for toxicity in Study 201

Type and degree of toxicity[a]	Treatment adjustment required
Local dermal irritation	
Grade 0, 1, 2	• No action required; observation and treatment continued
Grade 3	• Treatment frequency was reduced or suspended for up to two weeks • If irritation improved to Grade 2 or lower, and treatment was restarted, treatment frequency was increased every week as tolerated. Patients were patch tested no sooner than one week off treatment • Positive patch test associated with Grade 3 reactions; treatment was discontinued and patient withdrawn
Grade 4	• Treatment was discontinued until irritation improved to Grade 2 or lower (this had to occur within four weeks); treatment was then be restarted at <QD for at least one week before increasing frequency, as tolerated • Treatment was not be restarted if Grade 4 toxicity occurred at <QD • Positive patch test associated with Grade 4 reactions; treatment was discontinued and patient withdrawn
Systemic toxicity	• If a systemic AE occurred that was thought to be possibly or more related to the study drug administration and possibly treatment-limiting, the Principal Investigator was notified immediately

[a] Toxicities were graded as per the NCI criteria.
Abbreviations: AE: adverse event; NCI: National Cancer Institute; QD: once daily.
Source: Study 201 CSR (2011).[46]

Table 29: Temporary treatment suspensions and reductions in dosing frequency in Study 201 (safety set)

	Chlormethine gel (n=128)	Chlormethine ointment (n=127)
Reductions in dosing frequency		
None	[redacted]	[redacted]
Any	[redacted]	[redacted]

One reduction in dosing frequency	[redacted]	[redacted]
Two reductions in dosing frequency	[redacted]	[redacted]
Three or more reductions in dosing frequency	[redacted]	[redacted]
Temporary suspensions		
None	[redacted]	[redacted]
Any	[redacted]	[redacted]
One temporary suspension	[redacted]	[redacted]
Two temporary suspensions	[redacted]	[redacted]
Three or more temporary suspensions	[redacted]	[redacted]
Permanent suspension due to drug-related treatment-limiting toxicity or other skin toxicity[a]		
None	[redacted]	[redacted]
Any	26 (20.3)	22 (17.3)
No prior temporary suspension	[redacted]	[redacted]
Any prior temporary suspension	[redacted]	[redacted]

[a] Twenty-six patients treated with chlormethine gel (20.3%) and 22 patients treated with chlormethine ointment (17.3%) discontinued treatment due to a drug-related AE associated with skin toxicity (i.e. a treatment-limiting toxicity or other drug-related skin AE). Treatment-limiting toxicity was defined in the protocol as Grade 3 or 4 skin toxicity with a positive patch test or skin toxicity that does not resolve to ≤Grade 2 within 2 or 4 weeks, respectively.
Abbreviations: AE: adverse event.
Source: Study 201 CSR (2011);[46] Lessin *et al.* (2013).[25]

Safety analysis in Study 201

Summary of AEs

In total, [redacted] patients treated with the chlormethine gel formulation and [redacted] patients treated with chlormethine ointment reported at least one AE during Study 201 (12-month follow-up), with [redacted] and [redacted] patients experiencing at least one AE that led to discontinuation of the study drug in the chlormethine gel and chlormethine ointment arms, respectively.[46] At least one AE that was considered to be possibly, probably, or definitely related to study drug was reported by 61.7% of the patients in the chlormethine gel arm and 50.4% of patients in the chlormethine ointment arm.[25]

SAEs were reported for [redacted] patients in the chlormethine gel arm and [redacted] patients in the chlormethine ointment arm. However, none of the SAEs reported during this trial were considered to be possibly, probably or definitely related to study drug. There was [redacted] death in the chlormethine gel arm (reported as not related to study drug), and [redacted] deaths in the chlormethine ointment arm during the 12 months of the trial.[46]

A summary of AEs, drug-related AEs, SAEs and deaths for the safety population of Study 201 is presented in Table 30 below.

Table 30: Summary of AEs in Study 201 (safety population)

AEs, n (%)	Chlormethine gel (n=128)	Chlormethine ointment (n=127)	p-value[a]
AEs	[redacted]	[redacted]	[redacted]
Drug-related AEs[b]	79 (61.7)	64 (50.4)	[redacted]
SAEs[c]	[redacted]	[redacted]	[redacted]
Discontinuation due to AEs[d]	[redacted]	[redacted]	[redacted]
Discontinuation due to drug-related AEs[d]	[redacted]	[redacted]	[redacted]
Deaths[e]	[redacted]	[redacted]	-

[a] Fisher's exact test. [b] AEs with relation to drug of 'Yes, related', 'Probably related', 'Possibly related' or where such a relationship was not specified. [c] No SAEs were considered possibly, probably or definitely related to study drug. [d] Subjects were categorised as 'Discontinued' if the course of action following an AE included 'Study Discontinuation'. Three patients, two on the chlormethine gel arm and one on the chlormethine ointment arm met this criterion. The reasons for withdrawal checked on the CRF were categorised as follows: 1. "Other": need for prohibited chemotherapy (Xeloda) for recurrence of metastatic squamous cell carcinoma originating on the scalp (untreated area); the AE was recurrent SCC, not related to study drug. 2. "Lack of Efficacy": the AE listed with action discontinued was "skin pain" which was "probably related" to study drug. 3. "Withdrew Consent": the AE was itching on lesion (severe) probably related to study drug. [e] This was reported as an SAE not related to study drug.
Abbreviations: AE: adverse event; CRF: case report form; SAE: serious adverse event; SCC: squamous cell carcinoma.
Source: Study 201 CSR (2011);[46] Lessin *et al.* (2013).[25]

AEs by preferred term regardless of study drug relationship

As mentioned above, [redacted] of the patients treated with the chlormethine gel formulation and [redacted] of the patients treated with chlormethine ointment formulation reported at least one AE during Study 201.

The vast majority of AEs in both arms were skin-related, characterised mainly as local dermatitis (skin irritation). Skin irritation occurred in 32 patients (25.0%) and 18 patients (14.2%) in the chlormethine gel and chlormethine ointment formulations, respectively (p=0.040). However, the protocol guidelines for reducing dose frequency and temporary suspending treatment for dermatitis were effective in ameliorating this side effect in a portion of patients as only 20.3% of patients in the chlormethine gel arm and 17.3% of patients in the chlormethine ointment arm withdrew due to treatment-limiting toxicity or drug-related AE associated with skin toxicity (p=0.631). Dermatitis typically occurs within the first few months of treatment, can be readily detected by both the patient and the physician and thus managed accordingly. In addition, it should be noted that corticosteroids, which are used in clinical practice to manage emerging dermatitis associated with topical chlormethine and MF-CTCL, could not be applied to lesions in this trial to avoid confounding the effect of chlormethine. Thus, the withdrawal of [redacted] and [redacted] patients from the chlormethine gel and chlormethine ointment arms for treatment-limiting skin toxicity prior to Month 6 is not unexpected and is likely an overestimation of the impact of skin toxicities in UK clinical practice.[25, 46]

Further research is also planned to investigate particular patients that may benefit from the use of concomitant topical corticosteroids to manage dermatitis (the REACH study). This study aims to determine the aetiology of skin reactions with chlormethine gel (irritant vs allergic contact dermatitis) and to compare efficacy in those developing a skin reaction and with those not. REACH also aims to test if reduced frequency of application and/or use of topical steroids increases tolerability of chlormethine gel without loss of efficacy in those with a skin drug reaction

unable to tolerate chlormethine gel.

[redacted]

There were no statistically significant differences in overall incidence of AEs or any other subcategory between the gel and ointment arms.[25]

A summary of AEs occurring in ≥5% of patients in either arm from Study 201 is presented in Table 31 below.

Table 31: AEs occurring in ≥5% patients regardless of study drug relationship in either arm from Study 201 (safety set)

AEs, n (%)	Chlormethine gel (n=128)	Chlormethine ointment (n=127)	p-value[a]
Any AE	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	-
Skin irritation	32 (25.0)	18 (14.2)	0.040
Pruritis	25 (19.5)	20 (15.7)	-
Erythema	22 (17.2)	18 (14.2)	
Dermatitis contact	19 (14.8)	19 (15.0)	-
Skin hyperpigmentation	7 (5.5)	9 (7.1)	-
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	-
Upper respiratory tract infection	11 (8.6)	10 (7.9)	-
Infections and infestations	[redacted]	[redacted]	-
Folliculitis	7 (5.5)	5 (3.9)	-

[a] Fisher's exact test.
Abbreviations: AE: adverse event.
Source: Study 201 CSR (2011);[46] Lessin *et al.* (2013).[25]

AEs by preferred term suspected to be drug-related

A summary of drug-related AEs from Study 201 is presented in Table 16 in Appendix F.

Overall, the most common drug-related AEs were skin and subcutaneous disorders, specifically skin irritation, pruritis and contact dermatitis, which occurred in [redacted] and [redacted], [redacted] and [redacted], and [redacted] and [redacted] patients in the chlormethine gel and chlormethine ointment arms, respectively.[46]

Severity of drug-related skin and subcutaneous AEs

As mentioned previously, skin toxicities were the primary AE reported in Study 201, with [redacted] and [redacted] patients in the chlormethine gel and chlormethine ointment arms experiencing skin and subcutaneous tissue disorders regardless of study drug relationship, and [redacted] and [redacted] patients experiencing drug-related skin and subcutaneous tissue disorders.

The severity of skin toxicities in Study 201 is presented in Table 32 below.

Table 32: Severity of drug-related skin and subcutaneous AEs in Study 201 (safety set)

Severity[a]	Chlormethine gel (n=128), n (%)	Chlormethine ointment (n=127), n (%)
Grade 0 (none)	[redacted]	[redacted]
Grade 1 (mild)	[redacted]	[redacted]
Grade 2 (moderate)	[redacted]	[redacted]
Grade 3 (moderately severe)	[redacted]	[redacted]
Grade 4 (severe)	[redacted]	[redacted]

[a] The maximum intensity recorded was used to categorise AEs.
Abbreviations: AE: adverse event.
Source: Study 201 CSR (2011).[46]

Deaths

Over the 12-month follow-up for Study 201 (data cut-off 1st June 2011), [redacted] in the chlormethine gel arm died from widely disseminated metastatic colorectal cancer after <2 months on treatment. However, [redacted] was not considered by the Investigator to be possibly, probably, or definitely related to chlormethine gel. There were [redacted] deaths in the chlormethine ointment arm.[46]

SAEs regardless of study drug relationship

A total of [redacted] patients ([redacted] and [redacted] in the chlormethine gel and chlormethine ointment arms, respectively) experienced an SAE during Study 201. None of the SAEs were considered by the Investigator to be possibly, probably or definitely related to the study drugs and there was no difference between the two treatment arms with respect to the incidence of SAEs (p=[redacted]; p=[redacted] when the death from metastatic colorectal cancer is included).[25, 46]

A summary of SAEs regardless of study drug relationship from Study 201 is presented in Table 33 below.

Table 33: SAEs regardless of study drug relationship from Study 201 (safety set)

AEs, n (%)	Chlormethine gel (n=128), n (%)	Chlormethine ointment (n=127), n (%)
Any SAE	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Coronary artery occlusion	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Asthma	[redacted]	[redacted]
Lung disorder	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Gastrointestinal infection	[redacted]	[redacted]

AEs, n (%)	Chlormethine gel (n=128), n (%)	Chlormethine ointment (n=127), n (%)
Haemorrhoids	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
General disorders	[redacted]	[redacted]
Chest discomfort	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]
Staphylococcal infection	[redacted]	[redacted]
Neoplasms malignant	[redacted]	[redacted]
Neuroendocrine carcinoma of the skin	[redacted]	[redacted]
Thyroid gland cancer	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Global amnesia	[redacted]	[redacted]
Vascular disorders[b]	[redacted]	[redacted]
Aortic aneurysm	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Peripheral vascular disorder	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Biliary colic	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]
Menorrhagia	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]
Parathyroidectomy	[redacted]	[redacted]

[a] An SAE was submitted for [redacted] due to hospitalisation for an appendectomy. Laboratory data showed Grade 1 anaemia and Grade 2 thrombocytopenia when hospitalised.
[b] One patient experienced both an aortic aneurysm and peripheral vascular disease; therefore, whilst three vascular disorder SAEs were reported, only two patients experienced these SAEs.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: Study 201 CSR (2011).[46]

Skin (non-melanoma) malignancies

Development of secondary non-melanoma skin cancers was monitored throughout the 12-month trial and an additional 12-month follow-up period.[25]

During the 24-month observation period, 11 patients (three patients in the chlormethine gel arm and eight in the chlormethine ointment arm [4.3%]) were diagnosed with 20 non-melanoma skin

cancers. [redacted] of these patients developed non-melanoma skin cancer during treatment and [redacted] additional patients developed non-melanoma skin cancer during the 1-year follow-up period. [redacted] of these patients were treated only with chlormethine gel (0.02%), [redacted] were treated only with chlormethine ointment (0.02%), and [redacted] patient was treated with chlormethine ointment (0.02%) followed by seven months treatment with chlormethine gel (0.04%) in Study 202.

The non-melanoma skin cancers included nine SCCs of the skin, ten basal cell carcinomas (BCCs) and one Merkel cell carcinoma. In all of these cases, the skin cancers cannot be attributed specifically to the application of topical chlormethine as they occurred in untreated areas, in patients with a history of skin cancers, or in patients who had been previously treated with therapies for MF-CTCL recognised to increase the risk of skin cancer.[25, 46, 70] Specifically, the majority of skin cancers (14/20) occurred in untreated areas of the skin, on sun exposed areas and in patients with a prior history of skin cancers or who had received prior SDTs, including phototherapy, for the treatment of MF-CTCL. One of nine SCCs, five of ten BCCs and no Merkel cell carcinomas occurred in treated areas.[25]

Overall, these data do not support an obvious association between the development of secondary non-melanoma skin cancers and the daily application of topical chlormethine (0.02%).[25, 46]

B.2.10.2 Study 202

The secondary objective of Study 202 (a study which investigated chlormethine gel in patients who completed 12 months of treatment [with either chlormethine gel or chlormethine ointment] in Study 201 but did not achieve a CR), was to assess the tolerability and safety of topical application of chlormethine gel (0.04%) in patients with Stage I or IIA MF. Given that Study 202 involved patients receiving an unlicensed (higher) dose of chlormethine gel, only supportive safety data, rather than safety and efficacy data, are presented within this submission. Full results from Study 202 are presented in the Study 202 CSR.[60]

The safety of all patients enrolled in Study 202 was assessed at each visit during treatment throughout the 7-month study i.e. at Months 2, 4, 6, and a final assessment at Month 7, with the Month 12 assessments for Study 201 serving as the baseline assessment for this extension study. Severity of AEs and relationship to study medication were assessed by the Investigator, with severity graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 9.0).[60]

Safety data are presented for the FAS, which was comprised of all patients who were enrolled and received any amount of study drug in Study 202 (n=[redacted]).[60]

Treatment duration and treatment suspensions

Duration of exposure

In Study 202, patients were treated with chlormethine gel for a median duration of [redacted]. [redacted] of patients received at least six months of treatment with chlormethine gel (0.04%). A total of [redacted] patients received >24 weeks of treatment.[60]

A summary of the duration of exposure data for the safety set in Study 202 is presented in Table 34 below.

Table 34: Duration of exposure in Study 202 (FAS)

Exposure, weeks[a]	Chlormethine gel (0.04%) (n=[redacted])
n	[redacted]
Mean (SD)	[redacted]
Median	[redacted]
IQR (Q1–Q3)	[redacted]
Range (min–max)	[redacted]
By range of weeks, n (%)	
>0–8	[redacted]
>8–16	[redacted]
>16–24	[redacted]
>24–32	[redacted]
>32	[redacted]
Missing	[redacted]

[a] The duration of exposure was from the date of study treatment first dispensed to date of last study treatment.
[b] Two patients were dispensed study medication, but the duration of treatment could not be calculated.
Abbreviations: FAS: full analysis set; IQR: interquartile range; SD: standard deviation.
Source: Study 202 CSR (2012).[60]

Treatment suspensions and dose reductions

In Study 202, reductions in dosing frequency or temporary suspension of treatment could occur as a result of Grade 3 or greater skin AEs (local dermal irritation). Few patients required dose reductions; [redacted] patients required a reduction in dosing frequency and [redacted] patients required a temporary suspension of dosing.[60]

A summary of the proportions of patients experiencing temporary treatment suspensions and/or dose reductions is presented in Table 35 below.

Table 35: Temporary treatment suspensions and dose reductions in Study 202 (FAS)

	Chlormethine gel (0.04%) (n=[redacted])
Dose reductions	
None	[redacted]
Any	[redacted]
One dose reduction	[redacted]
Two dose reductions	[redacted]
Three or more dose reductions	[redacted]
Temporary suspensions	
None	[redacted]
Any	[redacted]
One temporary suspension	[redacted]

Two temporary suspensions	[redacted]
Three or more temporary suspensions	[redacted]

Abbreviations: FAS: full analysis set.
Source: Study 202 CSR (2012).[60]

Discontinuations

In Study 202, [redacted] patients withdrew from study drug treatment due to AEs. All [redacted] withdrawals were due to skin and subcutaneous tissue disorders; [redacted] patients experienced treatment-limiting skin toxicity requiring discontinuation from the study, as defined in the protocol and [redacted] additional patients were discontinued due to skin AEs, [redacted] with pruritus and [redacted] with erythema.[60]

Safety analysis in Study 202

Summary of AEs

Seventy-one ([redacted]) patients reported a total of [redacted] AEs during Study 202, with [redacted] patients experiencing drug-related AEs. Drug-related AEs were primarily skin and subcutaneous disorders (consistent with the safety profile identified in Study 201), and these were reported by [redacted] patients. Skin and subcutaneous disorders were principally characterised as skin irritation ([redacted]), erythema ([redacted]), and pruritis ([redacted]).[60]

There were [redacted] deaths during the study or within 30 days of stopping chlormethine gel (0.04%). [redacted] developed a basal cell carcinoma 80 days after completion of Study 202, but it was in an untreated area and was not considered to be related to chlormethine gel (0.04%). [redacted] patients experienced SAEs, but [redacted] were considered to be related to study medication.[60]

A summary of AEs, drug-related AEs, SAEs and deaths for the safety population of Study 201 is presented in Table 36 below.

Table 36: Summary of AEs in Study 202 (FAS)

AEs, n (%)	Chlormethine gel (0.04%) (n=[redacted])
AEs	[redacted]
Drug-related AEs[a]	[redacted]
SAEs[b]	[redacted]
Discontinuation due to AEs	[redacted]
Deaths	[redacted]

[a] AEs with relation to drug of 'Yes, related', 'Probably related', 'Possibly related' or where such a relationship was not specified. [b] No SAEs were considered possibly, probably or definitely related to study drug.
Abbreviations: AE: adverse event; FAS: full analysis set; SAE: serious adverse event.
Source: Study 202 CSR (2012).[60]

AEs by preferred term regardless of study drug relationship

A total of [redacted] patients reported at least one AE during the study. The most frequently reported AEs were skin and subcutaneous tissue disorders, which occurred in [redacted] patients. The most frequently reported AEs were skin irritation in [redacted] patients, erythema in [redacted] patients, and pruritus in [redacted] patients.[60]

The proportion of patients with at least one AE in Study 202 with chlormethine gel (0.04%) was higher among patients who were previously treated with chlormethine ointment (0.02%) in Study 201 ([redacted]) compared with those who were treated with chlormethine gel (0.02%) in Study 201 ([redacted]). Similarly, the proportion of patients with skin-related AEs in Study 202 was higher among patients who were previously treated with chlormethine ointment in Study 201 (0.02%) versus those previously treated with chlormethine gel (0.02%) ([redacted] versus [redacted], respectively).

Most of the skin and subcutaneous tissue disorder AEs were Grade 1 or 2. Grade 1 skin AEs occurred in [redacted] patients, Grade 2 skin AEs occurred in [redacted] patients, Grade 3 skin AEs occurred in [redacted] patients, and Grade 4 skin AEs occurred in only [redacted] patient. This patient had bleeding from scratching a severe skin irritation with blisters on Day 4 of treatment. Treatment was suspended for [redacted], after which the patient reinitiated treatment at a reduced dosing frequency and completed the study.

A summary of AEs occurring in ≥5% of patients in Study 202 is presented in Table 37 below.

Table 37: AEs occurring in ≥5% patients regardless of study drug relationship in Study 202 (FAS)

AEs, n (%)	Treatment group in Study 201		Study 202 FAS
	Chlormethine gel (0.02%) (n=[redacted])	Chlormethine ointment (0.02%) (n=[redacted])	Chlormethine gel (0.04%) (n=[redacted])
Any AE	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Skin irritation	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]
Pruritis	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; FAS: full analysis set.
Source: Study 202 CSR (2012).[60]

AEs by preferred term suspected to be drug-related

A summary of drug-related AEs from Study 202 is presented in Table 17 in Appendix F.

Overall, as in Study 201, the most common drug-related AEs were skin and subcutaneous disorders, specifically skin irritation, erythema and pruritis, which occurred in [redacted], [redacted] and [redacted] patients, respectively. [redacted] in the incidence of drug-related skin AEs with chlormethine gel (0.04%) was apparent based on the formulation of topical chlormethine (0.02%) received in Study 201.[60]

Deaths

In Study 202, there were [redacted] deaths during the study or within 30 days of stopping chlormethine gel (0.04%).[60]

SAEs regardless of study drug relationship

[redacted] patients experienced at least one SAE in Study 202; [redacted] were considered to be related to study medication and [redacted] individual SAE occurred in more than one patient.[60]

A summary of SAEs regardless of study drug relationship from Study 202 is presented in Table 38 below.

Table 38: SAEs regardless of study drug relationship from Study 202 (FAS)

AEs, n (%)	Chlormethine gel (0.04%) (n=[redacted])
Any SAE	[redacted]
Cardiac disorders	[redacted]
Aortic valve stenosis	[redacted]
Supraventricular tachycardia	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]
Arthritis	[redacted]
Hip fracture	[redacted]
General disorders	[redacted]
Non-cardiac chest pain	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]
Lung cancer metastatic	[redacted]
Reproductive system and breast disorders	[redacted]
Prostatitis	[redacted]

Abbreviations: AE: adverse event; FAS: full analysis set; SAE: serious adverse event.
Source: Study 202 CSR (2012).[60]

Skin (non-melanoma) malignancies

As in Study 201, patients in Study 202 were closely monitored for the development of non-melanoma skin cancer (SCC or BCC) during and following treatment with topical chlormethine. [redacted] patients developed a non-melanoma skin cancer while participating in Study 202. [redacted], who had been treated with chlormethine ointment (0.02%) during Study 201, developed a BCC on the left shoulder during the 1-year follow-up period for Study 201, [redacted] days after completing treatment with chlormethine gel (0.04%). However, [redacted] in an untreated area and not considered related to study drug treatment by the Investigator.[60]

B.2.10.3 MIDAS

MIDAS (NCT03380026) is an ongoing split-face, open-label, non-randomised study designed to investigate the incidence and severity of common adverse reactions to chlormethine gel (0.02%) treatment, particularly contact dermatitis.[65] The MIDAS study is investigator-initiated.

Trial design and methodology

MIDAS recruited adult patients with histologically confirmed Stage IA or IB MF-CTCL. Patients were excluded if they had received topical chlormethine within the last six months or any SDT treatment within the last two weeks on lesions to be evaluated during the trial. They were also excluded if they had received any systemic therapy within the last three weeks prior to initiation of treatment.[65] Patients' pre-determined representative patches or plaques were treated at home with either topical chlormethine gel (0.02%) once nightly, or topical chlormethine gel (0.02%) once nightly and triamcinolone ointment (0.1%) once daily, for four months.[65]

The primary endpoint was the incidence of dermatitis and the secondary endpoint was the nature of contact dermatitis: irritant contact dermatitis or allergic contact dermatitis. Patients' reactions were classified as mild-moderate or severe reactions; a mild-moderate reaction was defined as not interfering with treatment, and without signs of a severe reaction. A severe reaction was defined as blistering, vesiculation, erosions and pain or itch leading to treatment interruption. In addition, patients who developed a severe reaction were patch tested for irritant versus allergic contact dermatitis.[65]

Results

As of September 2019, [redacted] patients were enrolled in the study; there were [redacted] male and [redacted] female patients, with a mean age of [redacted]. [redacted] of these patients experienced a severe cutaneous reaction, with an average time to reaction development of [redacted]. The majority of cutaneous reactions were allergic rather than irritant; of the [redacted] patients with a reaction, [redacted] reactions were allergic contact dermatitis and only [redacted] was irritant contact dermatitis, and only [redacted] patients were not able to continue treatment with chlormethine gel. [redacted] of the [redacted] patients who were evaluated for contact allergy were also evaluated for other contributing allergens; [redacted] of these patients also had reactions to various other allergens.[65]

Based on these preliminary results, treating patients with chlormethine gel may be associated with improved tolerance when compared to the aqueous formulation of chlormethine ([redacted] patients from a historical control group developed allergic contact dermatitis versus [redacted] in this cohort). Furthermore, given that the majority of reactions were allergic rather than irritant, the majority of patients could restart chlormethine treatment. MIDAS also revealed that certain patients may have an allergic-type phenotype that predisposes them to allergic cutaneous reactions to common allergens (unrelated to chlormethine treatment), although only a small number of patients were assessed.[65]

B.2.10.4 Adverse events in the real-world setting

Additional AE data were collected as part of the real-world evidence studies which have taken place in the US (PROVe) and France (ATU). In both of these studies, patients were permitted to use other concomitant therapies and symptomatic treatments such as corticosteroids, in line with the expected usage of chlormethine gel in UK clinical practice.[61, 67, 75]

French ATU Study

Of the [redacted] patients who initiated treatment with chlormethine gel from October 2014 onwards, [redacted] patients discontinued treatment, of which [redacted] were temporary and [redacted] were permanent discontinuations. The main reasons for discontinuation were the incidence of AEs [redacted] and complete or partial response ([redacted]).[75]

Since beginning of the ATU, [redacted] treatment-related AEs and [redacted] AEs not linked to treatment with chlormethine, have been reported in [redacted] patients. Of the [redacted] treatment-related cases, [redacted] were severe ([redacted] led to the death of the patient) and [redacted] were considered as non-severe. AEs of special interest included skin and subcutaneous tissue disorders; since the beginning of the ATU [redacted] cases of cutaneous AEs were reported, including [redacted] serious cases.[75]

AEs which were reported in >5% of the population were contact dermatitis ([redacted]), skin irritation ([redacted]) and erythema ([redacted]);[62] the incidence of these three AEs were therefore lower in the real-world setting than in Study 201 (contact dermatitis [14.8%], skin irritation [25.0%] and erythema [17.2%]) and lower than skin irritation ([redacted]) and erythema ([redacted]) in Study 202.[25, 60, 62, 75]

PROVe

The overall number of AEs and AEs which occurred in ≥3% of patients were recorded in the PROVe trial. AEs occurred in [redacted] patients. All AEs which affected ≥3% patients were skin related AEs, in line with both Study 201/202 and the French ATU data; the most common AE reported was [redacted], followed by [redacted] and [redacted]. The rates of development of skin symptoms was lower in PROVe than in Study 201 (contact dermatitis [14.8%], skin irritation [25.0%] and pruritis [19.5%] for the chlormethine gel arm) and Study 202 (skin irritation [redacted] and pruritis [redacted] in the FAS), demonstrating that the AE profile of chlormethine gel is manageable in clinical practice compared to in Study 201 where prescription of concomitant therapies for skin symptoms was not permitted.[25, 61, 67]

AEs reported in the PROVe study are presented in Table 39.

Table 39: Overall AEs and AEs occurring in ≥3% of patients in the PROVe trial

AEs	PROVe (N=298)
Overall, n (%)	[redacted]
AEs occurring in ≥3% of patients, n (%)	
Dermatitis	[redacted]
Erythema	[redacted]
Pruritus	[redacted]
Rash	[redacted]
Skin burning sensation	[redacted]
Skin irritation	[redacted]

Abbreviations: AE: adverse event.
Source: Kim *et al.* Oral Presentation (2019).[61]

B.2.11 *Ongoing studies*

The MIDAS trial is anticipated to finish in Q1/Q2 2020. This is an investigator-initiated study and therefore Recordati Rare Diseases/Helsinn do not have direct control over data and timings.

As mentioned in Section B.2.10.1, the protocol for the REACH study [redacted]

B.2.12 *Innovation*

As initially discussed in Section B.1.3.2, the skin symptoms of MF-CTCL are associated with a substantial burden for patients, spanning not only the pain and physical discomfort associated with their patches and plaques, but also social embarrassment and withdrawal, and economic implications from absenteeism due to the need for regular medical appointments to receive treatment.[19, 20, 23] There are also are also severe AEs and inconveniences associated with

current treatment options, with secondary malignancies associated with phototherapy being a particular concern, in addition to the fact that patients may be required to go for long periods without sunlight exposure in order to reduce to potential negative effects of psoralen (one treatment given as part of phototherapy).[3, 4, 57] Systemic treatments such as bexarotene and IFN-α are also associated with severe AEs such as hypothyroidism, dyslipidaemia, leukopaenia, increases in creatine kinase, pancreatitis and glucose dysregulation (bexarotene), and hypothyroidism, cytopaenias and flu-like symptoms.[50, 51, 55] All of these factors contribute to a decrement in patient quality of life for those with this condition, yet there are limited treatment options that specifically target the cancerous cells underlying the skin symptoms of this disease.[3, 19, 20]

There is a clear unmet need for a convenient treatment option that can specifically target and alleviate the skin symptoms of MF-CTCL in a tolerable manner. Despite this, there are currently no NICE guidelines for the treatment of this condition, and there is a distinct lack of licensed therapies for this indication specifically, as well as a lack of robust evidence supporting therapies currently used in this setting.[3] Thus, chlormethine gel represents a step-change in the management of MF-CTCL. This formulation of a compound that has a history of efficacious use in clinical practice in previous formulations can be applied at home and is the only topical therapy recommended in the BAD guidelines with level 1+ evidence following the results of the RCT, Study 201.[3, 25] Given that chlormethine has been used in alternative formulations in UK clinical practice before, this compound has both a well-characterised effectiveness and safety profile, with UK clinicians experienced in its prescription; the gel formulation allows for improvements in the stability of the compound, whilst maintaining efficacy, and allows patients to avoid having to spend extensive amounts of time travelling to and from hospital for alternative treatments such as phototherapy.[4, 25] Whilst secondary malignancies have been associated with phototherapy and are a concern for both patients and their clinicians, there is no evidence to support that chlormethine gel increases the risk of secondary malignancies such as non-melanoma skin cancer.[3, 25, 46]

Furthermore, as the gel formulation is not absorbed systemically, chlormethine gel is a viable and flexible treatment option as part of a combination therapy. Combination therapy is a particularly common treatment paradigm in more advanced disease stages; the broad licence of chlormethine gel combined with its lack of systematic absorption hence allows it to be used in the treatment of patients across all disease stages of MF-CTCL.[46]

As an innovative therapy, chlormethine gel has the potential to provide an efficacious treatment with a distinct mechanism of action for the skin symptoms of MF-CTCL supported by a robust evidence base. In addition, there is no evidence of additional risk of secondary malignancies, and the gel formulation provides substantial improvements in convenience versus the relevant comparators, given the opportunity for home application. Chlormethine gel thus provides an important treatment option to reduce the burden of this disease on both patients and their caregivers, in a condition with a high unmet need.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Principal findings from the clinical evidence base

Study 201 is the largest RCT to be carried out to investigate the efficacy and safety of an SDT in adults with Stage IA–IIA MF-CTCL; 260 patients with Stage IA–IIA MF-CTCL were enrolled onto

the study and 128 patients received treatment with chlormethine gel for up to 12 months.[25] During Study 201, chlormethine gel was shown to be non-inferior to a compounded ointment formulation of chlormethine in a number of clinically relevant outcomes, including ≥50% reduction in CAILS and SWAT scores for skin lesions.

In Study 201, chlormethine gel met the pre-defined criteria for non-inferiority for both the primary and key secondary endpoints (CAILS and mSWAT response rates, respectively) in both ITT populations. In the ITT including NYU population, the confirmed CAILS response rate (proportion of patients achieving a ≥50% improvement in CAILS for a duration of at least 28 days) for chlormethine gel was 58.5%, and for chlormethine ointment was 47.7% (ratio of response rates: 1.226; 95% CI: 0.974–1.552). In the ITT excluding NYU population, the confirmed CAILS response rate was [redacted] in the chlormethine gel arm and [redacted] in the chlormethine ointment arm (ratio of response rates: [redacted]; 95% CI: [redacted]).[25, 46] [redacted].[74] For the mSWAT, in the ITT including NYU population, the response rate was 46.9% in the chlormethine gel arm compared to 46.2% in the chlormethine ointment arm (ratio of response rates: 1.017; 95% CI: 0.783–1.321).[46] In the ITT excluding NYU population, the response rates were [redacted] and [redacted] for the chlormethine gel and chlormethine ointment arms, respectively (ratio of response rates: [redacted]).[25, 46] Response rates have also been confirmed in the real-world setting, where responses have also been demonstrated in advanced stage patients. Therefore, the efficacy demonstrated in Study 201, has already been shown to translate to real-world effectiveness.[61, 62, 67, 75]

In those patients who responded, the time to response was significantly lower with chlormethine gel compared to the compounded ointment formulation, with a 50% response rate predicted to occur 16 weeks sooner with the gel formulation in both the ITT including NYU ($p<0.012$) and excluding NYU ($p<$[redacted]) populations.[25, 46] Responses were also shown to be durable in the majority of patients. At Week 40, [redacted] and [redacted] patients in the chlormethine gel and chlormethine ointment arm sustained a response, respectively in the ITT including NYU population. In the ITT excluding NYU population, [redacted] and [redacted] patients in the chlormethine gel and chlormethine ointment arm sustained a response, respectively.[46] At [redacted], in both ITT populations, [redacted] of patients treated with chlormethine gel did not have progressive disease.[25, 46]

With regards to the safety analysis assessing chlormethine in Study 201, the majority of patients completed the 12-month duration of Study 201, with 20.3% of patients in the chlormethine gel arm and 17.3% in the chlormethine ointment arm withdrawing due to treatment-limiting-toxicity or skin AEs.[25] The median duration of exposure was [redacted] weeks for chlormethine gel and [redacted] weeks for chlormethine ointment.[46] Skin irritation was the most common AE and was reported by 25.0% of patients in the chlormethine gel arm compared to 14.2% in the chlormethine ointment arm ($p=0.04$).[25] The skin toxicities associated with topical chlormethine were in-line with the anticipated tolerability profile, and it was noted that topical corticosteroids, which may be applied to treat dermatitis in clinical practice, were not permitted in Study 201; it is therefore expected that the impact of skin related toxicity in Study 201 is likely an overestimate compared to UK clinical practice, with real-world data suggesting this is the case.[25, 46] The safety profile of topical chlormethine from Study 201 was consistent in Study 202, where patients were treated with 0.04% chlormethine gel for an median duration of exposure of [redacted] weeks. Skin irritation was the most common AE ([redacted]), and was higher in patients who had previously received chlormethine

ointment during Study 201 ([redacted]) compared to those who previously received chlormethine gel ([redacted]).[60] In both Study 201 and Study 202, patients were monitored for non-melanoma skin cancers, in both trials no non-melanoma skin cancers were deemed to be related to the study drug, leading to the conclusion that there was no evidence from either trial to support that topical chlormethine is associated with an increased risk of non-melanoma skin cancer.[8, 25, 46, 60] Furthermore, the safety profile of chlormethine gel has been shown to be improved in the real-world setting, where concomitant therapies (such as corticosteroids), which were not allowed in Study 201 due to the risk of confounding the results, were permitted to manage AEs; thus, safety data from Study 201 may overestimate the burden of AEs versus clinical practice in the UK should chlormethine gel become available.[25, 61, 62, 65, 67, 75]

B.2.13.2 Strengths and limitations of the clinical evidence base

Strengths

Study 201 is an RCT with a large patient population for a rare disease

Study 201 was a Phase II RCT and is the largest to be performed in adults with Stage IA–IIA MF-CTCL, providing a robust clinical evidence base for a disease where there is a paucity of evidence for therapies in the form of RCTs; indeed, topical chlormethine is the only SDT to have been ranked with level 1+ for evidence in the BAD guidelines, with this rating being assigned on the basis of the evidence provided by Study 201.[3, 25, 46] Study 201 was an active comparator trial in which chlormethine gel demonstrated non-inferior efficacy to a therapy which has previously been used in UK clinical practice across a number clinically relevant outcomes.[25] The patient population included in Study 201 is also large, at 260 patients in the full ITT; this is particularly pertinent considering the rare nature of MF-CTCL, with only approximately 332 diagnosed cases estimated in England on average each year (see Section B.1.3.1).[14, 25]

Clinically relevant and internationally recommended study endpoints used

The primary endpoint in study was a ≥50% improvement (i.e. CR or PR) in a patient's CAILS score versus the Baseline measurement, where CAILS response is a measure of the severity of five specified (index) skin lesions over time.[43] CAILS is particularly useful for measuring response to targeted therapy given its focus on specific lesions such as those which cause patients significant pain, discomfort or embarrassment. Therefore a ≥50% reduction in these lesions would result in a significant benefit to these patients, and clinical expert opinion sought in the context of this submission has suggested that improvements of 25–50% in lesion severity would represent a clinically relevant response.[4] In addition, mSWAT response, including the assessment of the extent of cutaneous disease, was also measured as a key secondary endpoint in Study 201.[25, 46] Whilst the CAILS response looks to measure index lesions, mSWAT considers all of a patient's lesions (and their severity) in determining the total score. mSWAT score has been shown to correlate with patient HRQoL, with increased skin involvement associated with decreased HRQoL.[95] Therefore, it follows that reducing the BSA coverage of lesions in addition to the severity of individual lesions will improve patients HRQoL, particularly for patients with widespread lesions.[4, 95] This makes mSWAT a highly relevant outcome for determining patient benefit.[19, 20] Both mSWAT and CAILS are recommended by the International Society for Cutaneous Lymphomas (ISCL), United States Cutaneous Lymphoma Consortium (USCLC) and EORTC consensus guidelines for clinical endpoints and response criteria in MF-CTCL and Sézary Syndrome, and are commonly used to assess skin symptoms in trials investigating treatments for cutaneous lymphomas. By evaluating data from each of these

measures, a comprehensive view of the effects of chlormethine on patients' skin lesions can be determined.[43, 96-98]

In addition, as MF-CTCL is a relapsing disease and clinical expert opinion suggests that a key aim of treatment in the UK is to control disease symptoms (such as skin lesions), the duration of skin response, and the time taken for this response to emerge are also key outcomes to measure when considering how to maximise the time at which a patient's skin symptoms are controlled.[4, 61, 62, 67, 75]

AE profile versus comparators

In Study 201 and Study 202 the safety of chlormethine gel (0.02% and 0.04%, respectively) was assessed. This included a 12-month follow-up period with particular attention to non-melanoma skin cancers, which was an important addition endpoint considering the known risks of developing secondary malignancies with existing therapies for MF-CTCL.[3, 25] Importantly, from the results of both Study 201 and Study 202, there were no non-melanoma skin cancers that were directly attributable to topical chlormethine; there is therefore, no evidence to indicate that topical chlormethine increases the risk of developing non-melanoma skin cancer, in contrast to phototherapy, where skin cancer risk limits the number of courses patients can receive and also leads to contraindication for patients with a history of prior skin cancers.[25, 60]

Also, as mentioned above in Section B.2.13.1, the safety of chlormethine gel has been evaluated in the real-world setting (in the US and France), with favourable results compared to those of Study 201, where concomitant medications were not permitted to manage AEs. This supports that in real-world UK clinical practice chlormethine gel is anticipated to be tolerable and have a manageable AE profile.[25, 61, 62]

Limitations

Study 201 only included patients with Stage IA–IIA disease

The patients enrolled onto Study 201 all had Stage IA–IIA MF-CTCL, and therefore, there is no direct evidence from this trial to support the use of chlormethine gel in patients with more advanced disease (a patient group that is also within the marketing authorisation of chlormethine gel).[11, 25] However, clinical expert feedback suggests that chlormethine gel, should it be available for use in UK clinical practice, would be used in patients irrespective of disease stage, and there would be no reason to suggest a lack of efficacy in the advanced patient population.[4] A small number of advanced stage patients have received treatment with chlormethine gel in the real-world setting, with responses to this treatment demonstrated (see Section B.2.6.8). In addition, chlormethine gel treats the skin symptoms of MF-CTCL, which are present in patients with both early and later stage disease (by TNMB definition advanced patients may have the same skin [T] burden as patients in early stage disease [see Table 4]; i.e. skin burden is not the defining differentiator between a classification of early and advanced stage disease), thus the same unmet need for a convenient, tolerable and approved treatment that specifically targets MF-CTCL exists for patients with advanced disease. Furthermore, data from Study 201 support the notion that topical chlormethine is not systemically absorbed, which means that it may be used as part of a combination therapy, which are particularly important in advanced patients, who may require treatments aiming to target the skin symptoms of MF-CTCL, but may also require systemic therapies that can work to alleviate the burden of disseminated cancer cells.[25, 46] The broad licence for chlormethine gel also supports its use in patients across all disease stages.[11]

Study 201 is a US-based RCT

Study 201 was a multicentre trial with a robust design, however, all study centres were in the US. Thus, no UK-specific patients were included.[25, 46] However, the study population from Study 201 is expected to be largely generalisable to the UK MF-CTCL population in the UK, and therefore there are not expected to be differences in population characteristics that would impact on the efficacy and safety profile of chlormethine gel demonstrated in Study 201 when used in UK clinical practice.

Moreover, UK clinicians do have experience of prescribing chlormethine (albeit in different formulations), and are therefore aware of its efficacy and tolerability profile when treating the skin symptoms of MF-CTCL.[4] On this, the gel formulation has been shown in Study 201 to maintain the existing and established efficacy and safety profile of alternative chlormethine formulations (such as chlormethine ointment), yet would provide improvements in terms of compound stability and a convenient method of application when compared to these previous formulations should it be available in UK clinical practice.[4, 25]

Comparison of chlormethine gel to chlormethine ointment

A limitation of the evidence base provided by Study 201 is the comparator in the trial (chlormethine ointment), which is neither a relevant clinical comparator in UK clinical practice nor placebo (meaning the potential for a placebo effect to be contributing to observed results for chlormethine gel cannot be understood from Study 201). However, discussion of the relative efficacy of chlormethine gel and chlormethine ointment is of relevance given that numerous studies and historical use in clinical practice (including in the UK) means that the clinical activity and effectiveness of chlormethine ointment is well established. There is an extensive body of literature documenting the clinical efficacy and safety of topical chlormethine in an Aquaphor formulation at a concentration of 0.01–0.02%, and it was for this reason that the pivotal trial for chlormethine gel (Study 201) was designed as a non-inferiority trial comparing the chlormethine gel formulation to an Aquaphor chlormethine formulation that was being used in clinical practice in the US.[46]

Study 201 only recruited patients who had been treated previously with at least one skin-directed therapy for MF-CTCL

Whilst patients in Study 201 had received at least one prior therapy for MF-CTCL, and approximately 40% of these patients had received prior phototherapy, a subgroup analysis for CAILS or mSWAT score based on the receipt of prior phototherapy or not was not possible given data constraints; data on all prior therapies received was not fully available for all patients, and some patients had received multiple and overlapping prior therapies (as treatment is so patient-specific) for which the effects on efficacy would not be able to be disentangled.[74] However, clinical expert opinion supports the notion that prior receipt of phototherapy would not be likely to influence the efficacy of chlormethine gel.[1] Therefore, the results of Study 201 in terms of the efficacy of chlormethine gel are anticipated to be generalisable to the anticipated patient population in the UK, irrespective of prior treatment with phototherapy.

Protocol violation at the NYU study centre

As described in Section B.2.4, there was a protocol violation at the NYU study centre whereby patients were incorrectly randomised. At this centre, Stage IA patients were assigned to chlormethine gel arm, and Stage IB/IIA were assigned to the chlormethine ointment arm rather

than the coordinator stratifying patients based on disease stage and then conducting randomisation to each arm. Therefore, the full ITT population (including NYU) does include patients who were not randomly assigned to a treatment arm, which could introduce potential bias in the results. However, results for both the ITT including and excluding NYU populations are available and transparently presented throughout this submission and are also consistent with each other. This subsequently supports that the protocol violation did not have a substantial impact upon the outcomes measured in Study 201.[46]

Study 201 did not collect quality of life outcomes

Study 201 did not collect any measures of health-related quality of life, meaning this study is unable to provide evidence for the impact of efficacious chlormethine gel treatment on patient quality of life. As a result of this, Study 201 is unable to provide HRQoL data for use either directly or indirectly in informing utilities for the cost-effectiveness model; this limitation and the resultant approach to utility generation is discussed in Section B.3.4.

In addition, as discussed in Section B.2.6.8, real-world data from the PROVe trial does provide some evidence for the effects of treatment with chlormethine gel (albeit mostly in combination with concomitant therapies) on patient HRQoL; in this study, clinical response by percentage BSA reduction was associated with statistically significant improvement in HRQoL in patients with Stage IA and IB disease, measured by three domains of Skindex-29, emotions ($p<0.001$), symptoms ($p<0.001$) and functioning ($p<0.001$).[67]

B.3 Cost effectiveness

Summary of the cost-effectiveness analysis

Base case cost-effectiveness results

- Base case deterministic results show that chlormethine gel is associated with lower QALYs (-0.16) and cost savings (-£7,000) versus phototherapy, resulting in an incremental cost-effectiveness ratio (ICER) of £44,915, representing a south-west ICER interpretable as the ICER for phototherapy versus chlormethine gel
- As this ICER is above the conventional NICE cost-effectiveness thresholds, this indicates that chlormethine is a cost-effective use of NHS resources
- Subgroup analysis of the early stage population produced a similar conclusion, with an ICER for phototherapy versus chlormethine gel of £57,389

Sensitivity analyses

- Probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) were conducted to assess the impact of parameter and structural uncertainty on model results
- The mean probabilistic ICER was estimated to be £42,477 per QALY gained for phototherapy versus chlormethine gel, with a 62.40% probability of chlormethine gel being a cost-effective treatment option at the £20,000/QALY gained threshold
- Of parameters explored in deterministic sensitivity analysis (DSA), treatment cost for subsequent therapies received on entry to the Progressed from 1L health state, mean BSA and treatment cost of chlormethine gel were found to be the most influential parameters on the ICER
- Scenario analyses were conducted to explore key areas of uncertainty within the model, including estimates of phototherapy efficacy, chlormethine gel dosing and subsequent therapy costs. Results of these scenario analysis generally produced conclusions regarding cost-effectiveness consistent with the base case

Summary

- Uncertainty in relative effectiveness estimates for chlormethine gel and phototherapy poses challenges to robust cost-effectiveness, with the nature of utility data available representing the main other limitation with the analysis.
- However, the economic analysis finds chlormethine gel to represent a cost-effective treatment compared to phototherapy, with this finding robust to exploration of model uncertainty.

B.3.1 *Published cost-effectiveness studies*

A single SLR was performed to identify relevant published economic evaluations, studies reporting utility values, and studies reporting cost and resource use data in CTCL. Searches were performed in July 2019 and full details of the SLR search strategy, study selection process and results are reported in Appendix G.

A total of four publications, representing four unique economic evaluations were identified. A summary of these studies is presented in Table 40 below, with further details presented in Appendix G. However, no evaluations of chlormethine gel in patients with MF-CTCL across all disease stages were identified. Three studies were from a US perspective (including Xia *et al.* [2019]) and therefore, were not considered relevant to decision-making in the UK; the fourth

study was from a UK perspective (from NICE TA577) but considered advanced stage patients only. Therefore, a *de novo* cost-effectiveness model was constructed to inform this appraisal.

The models from TA577 and Xia *et al.* (2019) were assessed prior to commencing *de novo* model development. While the model described in Xia *et al.* (2019) was published from a US perspective, aspects of the model were still deemed relevant to this appraisal (more so than the other two US economic evaluations) given the treatments considered by the model (SDTs) and the model structure spanning early and advanced disease stages. TA577 was assessed as the only prior NICE appraisal identified as being of relevance, though the different treatment context (advanced stage disease) of that appraisal limited its usefulness for informing the *de novo* model. The similarity of these published models to the *de novo* model in terms of key features of the economic analysis, and the reasoning as to why these models were ultimately not considered relevant to adapt to the current submission, is discussed in Section B.3.2.2.[56, 99]

Table 40: Summary of the cost-effectiveness studies identified in the economic SLR

<table>
<tr><th>Study</th><th>Country (Year)</th><th>Summary of model</th><th>Patient population (average age in years)</th><th>QALYs (intervention, comparator)</th><th>Costs (currency) (intervention, comparator)</th><th>ICER (per QALY gained)</th></tr>
<tr>
<td>Geskin et al.[100]</td>
<td>US; payer perspective (2018)</td>
<td>

Decision-analytic model to compare systemic bexarotene, denileukin diftitox, IFN-α, methotrexate, pralatrexate, romidepsin, vorinostat, and ECP treatment of CTCL
Overall response rate was used as the primary effectiveness measure and was defined as the proportion of patients achieving complete or partial response.
Efficacy rates were obtained from published trials (where at least 70% of enrolled patients had advanced CTCL) and evidence summaries of each intervention
AEs of treatments that were deemed most likely to result in additional resource consumption were modelled, including hyperthyroidism, hypertriglyceridemia and hypercholesteremia for bexarotene, derived from trials used for efficacy rates
Costs were obtained from wholesale acquisition cost pricing files and Medicare reimbursement rates
A probabilistic design was used, including variable distributions for effectiveness rates, frequency of AEs, dosing, and costs
A first and second-order Monte Carlo simulation was conducted to ascertain tendency of treatment success and costs of each regimen
ICERs were determined relative to the lowest-cost option
Probabilistic sensitivity analyses were performed
A 6-month time horizon was used
No discounting was applied due to the short time horizon

</td>
<td>Patients with advanced-stage CTCL</td>
<td colspan="3">
<u>Base case results from Monte Carlo simulation with first and second-order sampling</u>
<table>
<tr><th>Treatment</th><th>Mean (SD) cost, USD</th><th>Mean (SD) effect</th></tr>
<tr><td>Bexarotene</td><td>239,424 (178,881)</td><td>0.51 (0.05)</td></tr>
<tr><td>Denileukin diftitox</td><td>40,107 (18,598)</td><td>0.38 (0.04)</td></tr>
<tr><td>ECP</td><td>40,985 (45,633)</td><td>0.64 (0.03)</td></tr>
<tr><td>IFN-α</td><td>32,174 (27,582)</td><td>0.53 (0.04)</td></tr>
<tr><td>Methotrexate</td><td>436 (284)</td><td>0.45 (0.05)</td></tr>
<tr><td>Pralatrexate</td><td>81,527 (49,068)</td><td>0.43 (0.10)</td></tr>
<tr><td>Romidepsin</td><td>134,980 (6,703)</td><td>0.35 (0.04)</td></tr>
<tr><td>Vorinostat</td><td>65,958 (40,637)</td><td>0.29 (0.05)</td></tr>
</table>
<u>Cost-effectiveness results</u>
<table>
<tr><th>Treatment</th><th>Cost, USD</th><th>Incremental cost, USD</th><th>Effect</th><th>Incremental effect</th><th>ICER</th></tr>
<tr><td>Methotrexate</td><td>436</td><td>-</td><td>0.45</td><td>-</td><td>Reference</td></tr>
<tr><td>IFN-α</td><td>32,174</td><td>31,738</td><td>0.53</td><td>0.08</td><td>396,725</td></tr>
<tr><td>ECP</td><td>40,985</td><td>40,549</td><td>0.64</td><td>0.19</td><td>213,416</td></tr>
<tr><td>Denileukin diftitox</td><td>40,107</td><td>39,671</td><td>0.38</td><td>-0.07</td><td>Dominated</td></tr>
<tr><td>Vorinostat</td><td>65,958</td><td>65,522</td><td>0.30</td><td>-0.15</td><td>Dominated</td></tr>
<tr><td>Pralatrexate</td><td>81,527</td><td>81,091</td><td>0.45</td><td>0.01</td><td>5,068,188</td></tr>
<tr><td>Romidepsin</td><td>134,980</td><td>134,544</td><td>0.35</td><td>-0.09</td><td>Dominated</td></tr>
<tr><td>Bexarotene</td><td>239,424</td><td>238,988</td><td>0.51</td><td>0.06</td><td>3,983,133</td></tr>
</table>
</td>
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</table>

<table>
<tr>
<td>NICE TA577[56]</td>
<td>UK; NHS perspective (2017)</td>
<td>

Cost-effectiveness analysis of brentuximab vedotin versus PC (bexarotene, methotrexate and IFN-α) using a partitioned-survival model
Patients enter the model in pre-progression health state, where they receive treatment with either brentuximab vedotin or PC; on disease progression, patients will transition to either the alloSCT health state if eligible for this treatment, or to the non-SCT health state if ineligible
Clinical data (OS and PFS) and health benefits (EQ-5D-3L and Skindex-29) were sourced from the ALCANZA study; for the alloSCT health state, clinical data were taken from Palanicawandar et al. 2017, a study of real-world evidence collected at Hammersmith Hospital, UK
Unit costs associated with treatment acquisition were taken from eMIT were appropriate, and otherwise taken from MIMS
The cost associated with brentuximab vedotin was subject to a PAS, reducing the unit cost from £2,500 per 50 mg vial; the post-PAS discount was redacted. Results were presented including and excluding the PAS for brentuximab vedotin
A weekly cycle length was implemented, and results were presented over a lifetime time horizon of 45 years
Costs and QALYs were discounted annually at 3.5%
Cost year was 2016/2017
If necessary, other costs were adjusted to 2016/2017 prices using inflation indices published by the PSSRU
Probabilistic and deterministic sensitivity analyses were conducted
An addendum of updated evidence was also submitted post-submission, the results of which are also presented; this addendum updated the allo-SCT health state of the economic model with a new dataset, derived from Morris et al. 2018, which featured a longer follow-up and larger dataset versus Palanicawandar et al. 2017

</td>
<td>Patients with advanced CTCL, defined as MF-CTCL Stage IIB and above, Sézary syndrome, and all pcALCL patients</td>
<td>
Original Submission
Base case results of the economic model including PAS
<table>
<tr><th>Intervention</th><th>Total LYs</th><th>Incremental LYs</th><th>Cost per QALY</th><th>Net monetary benefit*</th></tr>
<tr><td>PC</td><td>7.23</td><td>-</td><td>-</td><td></td></tr>
<tr><td>Brentuximab vedotin</td><td>8.43</td><td>1.20</td><td>Dominates</td><td>GBP 134,218</td></tr>
</table>
*Assuming a willingness to pay threshold of GBP 30,000 per QALY

Other outcomes of the model, including costs and QALYs, were redacted. Base case results of the economic model excluding the PAS discount (excluding LYs gained, which were unchanged from the results including PAS, above) were redacted.

Evidence Addendum
Updated base case results using Morris et al. 2018
<table>
<tr><th>Intervention</th><th>Total LYs</th><th>Incremental LYs</th><th>Cost per QALY</th><th>Net monetary benefit*</th></tr>
<tr><td>PC</td><td>7.36</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Brentuximab vedotin</td><td>8.93</td><td>1.58</td><td>Dominates</td><td>GBP 153,693</td></tr>
</table>
*Assuming a willingness to pay threshold of GBP 30,000 per QALY

As in the original submission, other outcomes of the model, including costs and QALYs, were redacted.
</td>
</tr>
</table>

<table>
<tr>
<td>Semenov et al.[101]</td>
<td>US, societal perspective (2019)</td>
<td>

Economic model (design NR) to calculate total individual QALYs lost across CTCL patients recruited as part of a cross-sectional study, by compounding the yearly adjusted health utility loss (measured using HUI3) associated with CTCL across a given individual's remaining life expectancy according to disease stage
A USD 50,000/QALY willingness-to-pay threshold was used to calculate the overall economic burden of CTCL
The economic burden associated with QALY loss from the cross-sectional cohort was generalised to the overall susceptible US population using estimated CTCL prevalence and US census data
An annual health utility decrement of 0.13 was used, based on the CTCL coefficient derived from the adjusted generalised linear model of overall HUI3 score from the patients within the cohort
Costs and benefits were discounted by 3% annually
Time horizon and cycle length N
Deterministic sensitivity analyses were undertaken

</td>
<td>The cross-sectional sample consisted of 67 patients with CTCL (mean age: 65; SD: 12.8; range: 24–90)</td>
<td>
<u>Summary of QALYs lost and the financial burden of CTCL</u>
<table>
<tr><th></th><th>Value</th></tr>
<tr><td>Average QALYs lost</td><td>1.478</td></tr>
<tr><td>Population QALYs lost</td><td>57,286</td></tr>
<tr><td>Individual burden, USD</td><td>73,889</td></tr>
<tr><td>Societal burden (billions), USD</td><td>2.86</td></tr>
</table>
</td>
</tr>
<tr>
<td>Xia et al.[99]</td>
<td>US; societal perspective (2019)</td>
<td>

Cost-effectiveness analysis of each initial treatment option for Stage IA MF-CTCL: topical bexarotene, topical nitrogen mustard, topical corticosteroids, local radiation, NB-UVB, and PUVA using a state-transition model to represent the decision process
As patients progressed to subsequent stages of MF-CTCL (Stages IB, IIA, IIB, III and IV) they underwent escalated treatment options: PUVA (Stage IB), NB-UVB (Stage IB), oral bexarotene (Stage IB), methotrexate (Stage IB/IIA/IIB), vorinostat (Stage IB-IV), romedepsin (Stage IIB-IV), pralatrexate (Stage IIB-IV), total skin electron beam therapy (Stage IB-III), extracorporeal photophoresis (Stage III/IV), pentostatin (Stage IV), brentuximab (Stage IV), alemtuzumab (Stage IV), and stem cell transplantation (Stage IV).
The cost and efficacy of escalated therapy were calculated as an average of the cost and efficacy of the applicable treatment options.

</td>
<td>Patients with Stage IA MF-CTCL (aged 59 years)</td>
<td>
<u>Aggregate health benefits and cost by treatment option for Stage IA MF-CTCL</u>
<table>
<tr><th>Treatment</th><th>Cost (95% CI), USD</th><th>Effectiveness (95% CI), LYs</th><th>ICER</th></tr>
<tr><td>Local radiation</td><td>225,399 (1742–2,030,372)</td><td>15.40 (2.53–23.03)</td><td>Reference</td></tr>
<tr><td>NB-UVB</td><td>344,728 (8365–2,742,049)</td><td>15.17 (2.29–23.19)</td><td>Dominated</td></tr>
<tr><td>PUVA</td><td>371,741 (5291–2,652,559)</td><td>15.07 (2.29–22.95)</td><td>Dominated</td></tr>
<tr><td>Topical corticosteroids</td><td>469,354 (4167–3,055,679)</td><td>14.65 (2.06–22.95)</td><td>Dominated</td></tr>
<tr><td>Topical nitrogen mustard</td><td>951,662 (60,374–3,484,453)</td><td>14.29 (2.06–22.87)</td><td>Dominated</td></tr>
<tr><td>Topical bexarotene</td><td>11,892,496 (1,543,984–25,006,532)</td><td>13.55 (1.82–22.54)</td><td>Dominated</td></tr>
</table>
</td>
</tr>
</table>

		• Health benefits (rates and time to complete remission and relapse) for each treatment were taken from RCTs where available and/or weighted analyses of retrospective cohort studies; with the exception of studies where information was available for Stage I disease only, Stage IA MF-CTCL specific rates were taken • When more than one CR rate or relapse rate for each therapy was available, a Comprehensive Meta Analysis software was used to combine information for an overall response rate and relapse rate • Natural history (overall survival and progression) of MF-CTCL were taken from a recent large cohort study • LYs were used as the measure of health benefit • Costs included medications (wholesale acquisition cost), office visits/ hospitalisations, laboratory monitoring, related procedures for a treatment duration of 3 months (obtained from the 2016 Medicare National Median Physician Reimbursement Schedule and 2017 Clinical Diagnostic Laboratory Fee Schedule midpoint fees), work missed (US Department of Labor July 2017 national average hourly wage), and transportation costs • 3-month cycles were used with a 40-year time horizon • Costs and benefits were discounted annually at 3% • Deterministic and probabilistic sensitivity analyses were performed		

Abbreviations: AE: adverse event; allo-SCT: allogeneic stem cell transplantation; CI: confidence interval; CR: complete response; CTCL: cutaneous T-cell lymphoma; ECP: extracorporeal photopheresis; eMIT: electronic market information tool; EQ-5D-3L: EuroQol-Five Dimensions-Three Levels; GBP: Great British Pound; HUI3: Health Utilities Index Mark 3; ICER: incremental cost-effectiveness ratio; IFN-α: interferon alpha; LY: life year; MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; MIMS: Monthly Index of Medical Specialities database of prescription and generic drugs; NB-UVB: narrowband ultraviolet light type B; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; non-SCT: non-stem cell transplant; NR: not reported; OS: overall survival; PAS: patient access scheme; PC: physician's choice; pcALCL: primary cutaneous anaplastic large cell lymphoma; PFS: progression-free survival; PSSRU: Personal Social Services Research Unit; PUVA: psoralen-ultraviolet A; QALY: quality-adjusted life year; QoL: quality of life; PAS: patient access scheme; RCT: randomised controlled trial; SD: standard deviation; SLR: systematic literature review; USD: United States dollar.

B.3.2 *Economic analysis*

As mentioned in Section B.3.1 above, a *de novo* cost-effectiveness model was constructed for the economic analysis. The methodology of this model is described in the following sections.

B.3.2.1 Patient population

The patient population for the model was adult patients with MF-CTCL. This is in line with the final scope from NICE,[5] the licensed indication for chlormethine gel, and the decision problem addressed within this submission.[11]

The patient population in the pivotal trial supporting the use of chlormethine gel in adult patients (Study 201) is narrower than the full licensed indication, as only Stage IA–IIA MF-CTCL patients were evaluated. However, clinical expert opinion, clinical guidelines and the licence support the use of chlormethine gel in patients irrespective of disease stage.[3, 4, 11] Thus, the economic model evaluates both early (Stage IA–IIA) and advanced (Stage IIB–IV) stage MF-CTCL patients. However, given data constraints in informing efficacy for the advanced population specifically (see Section B.2.13.2), modelling of advanced stage disease required an assumption that the efficacy of the modelled interventions in treating the skin symptoms of MF-CTCL would not differ based on a patients' disease stage, but is instead dependent on their skin burden. Study 201 patients were therefore categorised into either Low or High Skin Burden (see Section B.2.3.2), and the efficacy observed in Study 201 for Low and High Skin Burden patients, respectively, with early stage disease (the Study 201 population only included early stage patients) was assumed to translate to patients with Low or High Skin Burden, respectively, in advanced disease stages. Subgroup analyses are also presented for the early stage and advanced stage populations separately (see Section B.3.9).

B.3.2.2 Model structure

A *de novo* health economic model was constructed in Microsoft Excel to evaluate the cost-effectiveness of chlormethine gel versus the relevant comparator (phototherapy) in adult patients with MF-CTCL (see Figure 12).

The cost-effectiveness model was a state transition (Markov) cohort model evaluating patients across all disease stages of MF-CTCL. The model defined three staging 'categories' based on clinically accepted definitions of early (Stage IA–IIA) and late (Stage IIB–IV) stage disease, as well as further separation according to clinical expert opinion into categories within which patient treatments, monitoring and prognosis would be expected to be similar:[4]

- Stage IA
- Stage IB/IIA
- Stage IIB–IV

Patients in Stage IA or Stage IB/IIA (which together comprise 'early stage' disease) were assumed to receive active treatment for skin lesions only (i.e. chlormethine gel or the relevant comparator), whilst patients in Stage IIB–IV (advanced stage) were assumed to receive active treatment for disseminated cancer i.e. systemic therapies (bexarotene, ECP [UVADEX], gemcitabine, methotrexate or pegylated IFN-α) in addition to their treatment for skin lesions. The systemic treatments for advanced disease were included as a basket of treatments weighted

based on data from the PROCLIPI registry (see Section B.1.3.2).[2] It should be noted that chlormethine gel is an SDT aimed at treating the skin symptoms of the disease and is not a systemic treatment for disseminated cancer. Therefore, whilst the model captured the use of active systemic treatments for advanced stage disease, this was in order to reflect the background context in which chlormethine gel and relevant comparators would be used in advanced stage disease. Differential treatment effects between chlormethine gel and its relevant comparators, and the impact of these treatment effects on costs and quality of life, were modelled at the level of impact on skin symptoms only – no differential treatment effects between chlormethine gel and comparators were applied with regards to treatment of underlying systemic disease. This reflects the fact that in advanced stages of disease chlormethine gel would be used for its impact on skin symptoms rather than systemic disease, and would therefore be used in combination with systemic therapies.

Upon entering the model, patients were defined as either Low or High Skin Burden within each disease stage category. The Low/High distinction was based on the percentage BSA affected: Low = <10% BSA; High = 10–80% BSA. Patients with >80% BSA would be classed as erythrodermic and are excluded from the model based on clinical feedback which indicates that erythrodermic patients would not be considered for treatment with chlormethine gel.[4, 102] Skin burden category at model entry by disease stage was based on the TNMB classification system, according to which Stage IA patients have <10% BSA affected (and hence were assumed to have Low Skin Burden at model entry), Stage IB patients have at least 10% BSA affected, and patients in Stage IIA–IV can have either <10% or at least 10% BSA affected. Based on data from PROCLIPI, the majority of Stage IIA patients ([redacted]) have at least 10% BSA affected, and therefore Stage IB/IIA patients were all assumed to have High Skin Burden at model entry given that this reflects the skin burden of all Stage IB and a majority of Stage IIA patients.[2] Patients in Stage IIB–IV were assumed to consist of a combination of patients with Low Skin Burden and patients with High Skin Burden ([redacted] low, [redacted] high based on data from the PROCLIPI registry).[2] These skin burden category assumptions were validated by clinical expert opinion.[4] This categorisation enabled treatment efficacy for advanced stage patients to be modelled depending on whether they have a Low Skin Burden (efficacy assumed equivalent to that for Stage IA patients) or High Skin Burden (efficacy assumed equivalent to that for Stage IB–IIA patients). In the absence of efficacy data for advanced stage disease, this approach allowed treatment impact on skin burden in advanced stage disease to be modelled in a manner that better accounted for the distribution of initial skin burden in advanced stage disease. Without these skin burden categorisations, modelling of efficacy in advanced stage disease would have had to simply assume that efficacy observed across early stage patients as a whole translated directly to advanced stage patients as a whole. This would ignore the differing distributions of skin burden across early and advanced stage disease and the impact this may have on treatment effectiveness.

Patients in the Low or High Skin Burden health states within each disease stage category were modelled to experience degrees of response to treatment, including remission (either CR, resulting in transition to No Skin Burden, or PR, resulting in transition to Reduced Skin Burden), relapse of skin lesions (i.e. progressive disease, resulting in transition to Progressed from 1L) or no change (i.e. SD, resulting in patients remaining in Low/High Skin Burden). Responses of CR, PR, progressive disease and SD are aligned to the response categories from Study 201 based on the mSWAT index (see Section B.3.3.2) – to avoid confusion, it should be noted that an outcome of progressive disease on the mSWAT measure corresponds to a progression of skin symptoms (i.e. relapse of skin lesions) and should not be confused as progression of disease

stage. The model transitions resulting from these various responses to treatment are presented in Figure 12. mSWAT was selected as the outcome measure of response despite CAILS being the primary endpoint of Study 201 because mSWAT is the only response measure for which a relationship to quality of life has been reported in the literature.[95] mSWAT was therefore considered a more appropriate outcome measure for reflecting changes in skin burden and their consequent impact on patient quality of life.

No patients were classified as having progressive disease within the first 6 months of the model. This was based on the fact that in Study 201, patients were only categorised as having progressive disease at the end of the trial period (or last known follow-up); the time frame of 6 months was based on clinical expert opinion that a patient experiencing a sufficient worsening of skin symptoms would not be classed as having progressed, and therefore moved onto a new treatment, until this timepoint after initiating treatment.

The level of treatment response influenced the continuation or not of treatment (intervention or comparator) as follows:

- CR (transition to No Skin Burden) → discontinuation of treatment (i.e. positive discontinuation)
- PR (transition to Reduced Skin Burden) → remain on the same treatment
- Progressive disease (transition to Progressed from 1L) → change treatment (move to subsequent treatment). Subsequent treatment was modelled as a bundle of skin-lesion treatments that accounted for some patients discontinuing treatment altogether and others commencing one of a number of potential new treatments [see Section B.2.3.2 for detailed description])
- SD (remain in Low/High Skin Burden) → remain on the same treatment
- Death (transition to Death)

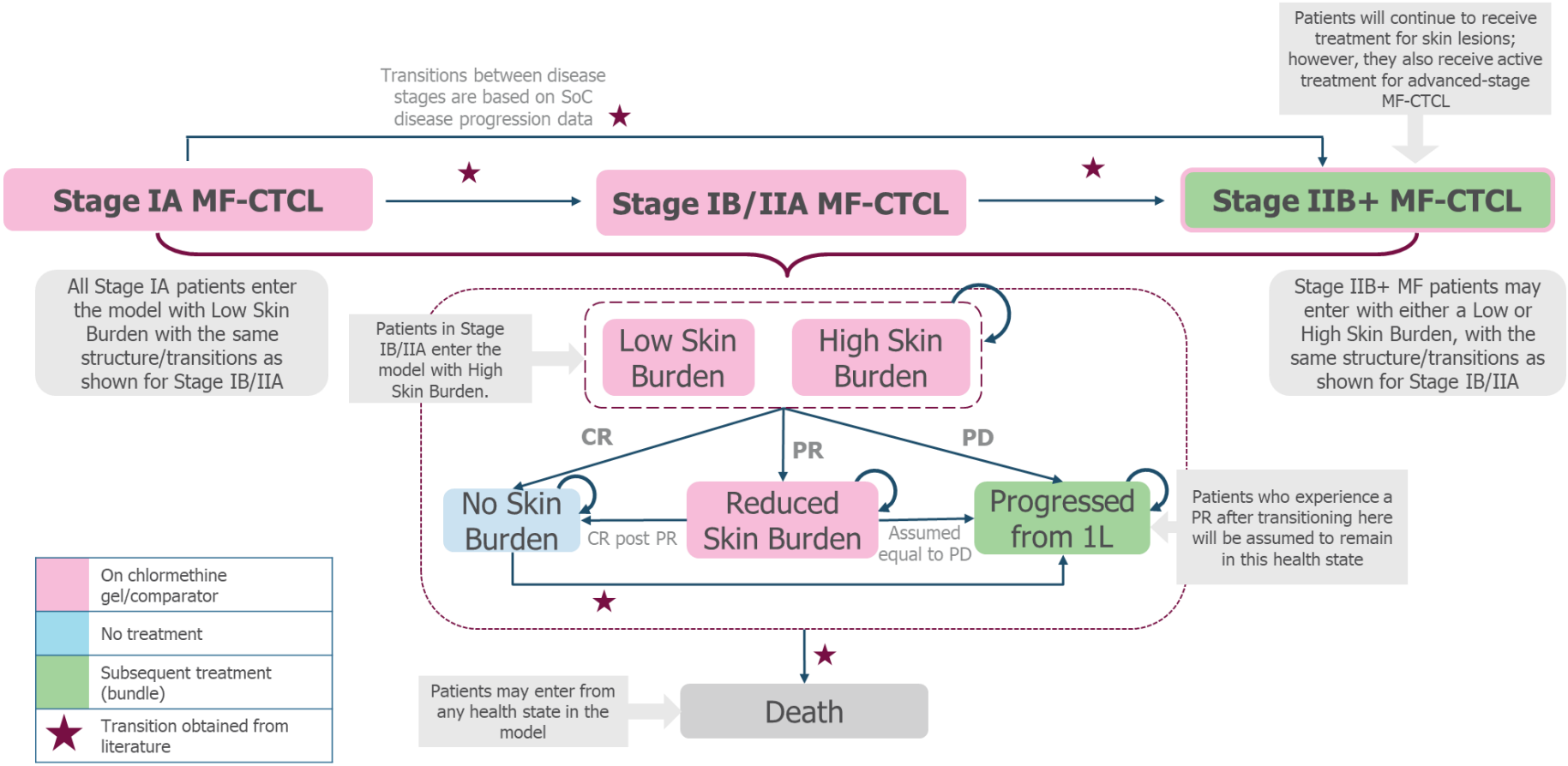
Patients continued to transition between these subsequent health states throughout the model time horizon as per the possible transitions indicated in Figure 12. Patients who transitioned to Progressed from 1L remained in this health state until Death. The Progressed from 1L health state represented a simplification of skin symptom progression/improvement and subsequent treatments; patients were assumed to receive either bexarotene or pegylated IFN-α in a 50:50 split. This was based on clinical expert opinion that patients would receive either bexarotene or pegylated IFN-α following phototherapy, and was assumed to also be appropriate for patients receiving chlormethine gel given that both bexarotene and pegylated IFN-α are second line treatment options following first-line SDTs (including chlormethine) in the BAD guidelines (for Stage IA–IIA patients).[2] Patients in the Progressed from 1L health state were assigned the weighted costs of bexarotene and pegylated IFN-α and the utility associated with patients defined as having progressive disease in Study 201 (see Section B.3.4 for the description of how utilities were applied in the model). A scenario analysis was explored that set the costs of subsequent treatments to zero, in order to explore the extent to which the assumed subsequent treatment costs impact on cost-effectiveness results.

Over the model time horizon, patients could progress through disease stages but not regress. This assumption was based on clinical expert input that patients would not be considered to achieve regressed disease stage, even if their skin symptoms improved.[4] Furthermore, it was assumed that if a patient progressed in disease stage whilst in an initial skin burden health state (Low Skin Burden or High Skin Burden), their initial severity of skin burden did not necessarily

change as a result of the disease stage progression (for example, if a patient in Stage IA [and therefore Low Skin Burden] progressed to Stage IIB–IV, their skin burden was not assumed to change to High Skin Burden by default). Patients transitioning to a more advanced disease stage from an initial Low Skin Burden or High Skin Burden health state were instead assumed to move into the 'Progressed from 1L' health state within the more advanced disease stage. This assumption was applied because the transition probabilities applied to the initial health states were reflective of initial treatment with therapy, and it was therefore not considered appropriate to reapply these transition probabilities to patients who were not new to a given skin burden state (and indeed may have spent significant time in that skin burden state prior to disease stage progression). It should be noted that the relative timescales of treatment response versus disease progression mean that by the time patients' disease stage progresses, very few patients are modelled to still be in the initial skin burden health state. Therefore, in practice this assumption affects only a small number of patients in the model. Patients who experienced disease stage progression whilst in other (non-initial) skin burden health states were assumed to transition to the Progressed from 1L health state in their new disease stage category upon transition, as it's likely from the disease stage classification that a progression in terms of disease stage would be associated with a worsening of skin burden (as per Table 3 and Table 4). This assumption is unlikely to have a notable impact on the model, as the timescales of response/response duration are much shorter than those of disease stage progression.

Finally, patients could transition to the Death health state from any other health state and from any disease stage. The likelihood of this transition was dependent on disease stage and independent of skin burden; the likelihood of entering the Death health state was equally likely from any Skin Burden health state.

Figure 12: Model structure



Abbreviations: 1L: first line; CR: complete response; MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; PD: progressive disease; PR: partial response; SoC: standard of care.

Features of the economic analysis

Full details of the clinical efficacy sources for chlormethine gel and the relevant comparator are provided in Section B.3.3.2. Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. The costs considered within the model included treatment acquisition costs, associated administration costs, AE costs and monitoring and resource use costs. Effectiveness measures included life years (LYs) and QALYs. The incremental cost-effectiveness ratio (ICER) of chlormethine gel versus phototherapy was evaluated in terms of the incremental cost per QALY gained.

The analysis was conducted from the perspective of the UK NHS and Personal Social Services (PSS) in England over a lifetime time horizon. A lifetime time horizon was used as MF-CTCL is characterised by slow disease progression, meaning a lifetime time horizon will allow all relevant differences between treatment arms to be captured, as per the NICE reference case.[103] Time horizon was explored in scenario analyses. A monthly cycle length was considered in the base case to align with the assessment timepoints utilised in Study 201, and both costs and effectiveness estimates were discounted at 3.5% annually.

The key features of the economic analysis and the associated justifications are presented in Table 41 below. No previous NICE appraisals have been conducted evaluating patients with MF-CTCL specifically for both early and advanced stage patients (or indeed early stage patients alone). TA577 evaluated brentuximab vedotin for the treatment of CTCL and has therefore been compared to, but it should be noted that this model considered advanced stage patients only. In addition, the key features of this economic analysis have also been compared to a model from the US perspective by Xia *et al.* (2019), which evaluated various monotherapies [topical corticosteroids, topical nitrogen mustard, topical bexarotene, PUVA, narrowband UVB and local radiation] for the treatment of Stage IA MF-CTCL and was considered the most relevant of the SLR-identified studies in terms of a reference for prior modelling approaches to determine impact of SDTs on skin symptoms.[56, 99]

As mentioned in Section B.3.1, these models were reviewed prior to *de novo* model development; ultimately, whilst there are similarities in some of the approaches taken in the current model compared to both TA577 and Xia *et al.* (2019), a *de novo* approach was preferred in order to best utilise the clinical data from Study 201, to assess patients across all stages of MF-CTCL, and to group disease stages (rather than modelling each stage separately as per Xia *et al.* [2019]) into categories with similar resource use, response to treatment, survival prognosis and quality of life, in line with clinical expert opinion.[4, 56, 99]

Table 41: Features of the economic analysis

	Previous models		Current appraisal	
Factor	**TA577[a]**	**Xia *et al.* (2019)[b]**	**Chosen values**	**Justification**
Time horizon	Lifetime (45 years)	Lifetime (40 years)	Lifetime (46 years)	As stipulated in the NICE reference case; MF-CTCL is characterised by slow disease progression, meaning a lifetime time horizon will allow all relevant differences between treatment arms to be captured.[103]
Model structure	Partition survival model	State transition (Monte Carlo first order microsimulation) model	State transition (Markov) cohort model	Based on the large number of health states for both disease stages and skin burden (enabling the model to capture the progression and regression of skin burden that patients with MF experience), a state transition (Markov) cohort model was considered the best approach to utilise the available data. A partitioned survival model structure is more appropriate for evaluations of systemic treatments for advanced stage disease that aim to delay or prevent outcomes relating to disease progression or death (time-to-event outcomes). As chlormethine gel is aimed at treating the skin lesions and not the underlying trajectory of disease stage progression or death, a partitioned survival model would not be appropriate.
Cycle length	1 week	3 months	1 month	Safety and efficacy data in Study 201 were collected monthly for 6 months, and then bimonthly.
Perspective	Healthcare payer perspective – NHS and PSS	Restricted societal perspective (US)	Healthcare payer perspective – NHS and PSS	As stipulated in the NICE reference case.[103]
Discount rate for costs and QALYs	3.5%	3.0%	3.5%	As stipulated in the NICE reference case.[103]
Clinical parameters	• Clinical parameters (OS, PFS and ToT)	• Treatment-specific transition probabilities	• mSWAT response rates were derived	As chlormethine gel is aimed at treating the skin lesions and not the underlying trajectory of disease stage progression or death, the relevant clinical

	were derived from the ALCANZA trial • Progression data were based on ISCL, USCLC and CLTF of the EORTC Consensus guidelines • OS was assumed equal to the comparator (i.e. no survival benefit of intervention was modelled), due to high patient cross-over in ALCANZA	were derived from the literature for each comparator, for remission (Stage IA to No MF) and relapse (No MF to Stage IA MF) • Transition probabilities between later disease stages (Stage IB+) and to death (from any disease stage) were derived from Quaglino *et al.* 2012 (non-treatment specific)[40] • Patients could only progress sequentially through disease stages, and cannot regress through disease stages	from Study 201 • Transitions between disease stages (treatment independent) were derived from disease progression data for standard of care from Wernham *et al.* (2015)[104] • Transitions from No Skin Burden to Progressed from 1L (treatment independent) were derived from Whittaker *et al.* (2012)[91] • Transitions to the Death health state (disease stage specific) were derived from Agar *et al.* (2010)[38]	parameters for capturing relative treatment effect are those based on skin response (mSWAT). Disease stage progression data was modelled to be independent of treatment, hence the use of the Wernham *et al.* (2015).[104]
Subsequent treatments	• Subsequent treatments were modelled as a basket in terms of costs and efficacy (toxic single or multi-agent chemotherapy, TSEB) • Patients were also modelled to receive end-stage care, after active treatments	• Subsequent treatments were modelled as a disease stage-specific basket in terms of costs and efficacy (PUVA, oral bexarotene, methotrexate, vorinostat, romedepsin, pralatrexate, TSEB, ECP, pnteostatin,	• For the Progressed from 1L health state – a combination of therapies, calculated as a weighted average based on market share; the same bundle for all disease stages	The bundle of Progressed from 1L treatments enables the variety of subsequent treatments that are used in clinical practice to be captured, without explicitly modelling separate lines of treatment. Given the number of potential subsequent treatment options that might be used, the highly patient-specific nature of the choice of subsequent treatment and the general low quality of efficacy data for treatments, explicit modelling of lines of treatments is not feasible.

	were exhausted	brentuximab, alemtuzumab and SCT)		
Source of utilities	• EQ-5D and Skindex-29 were collected in ALCANZA • In absence of a mapping algorithm from Skindex-29 to EQ-5D, a regression model was included as the base case	• No utility measure was included (overall life expectancy was used as a measure of health benefit)	• Vignette study conducted to inform the cost-effectiveness model	A SLR (Section B.3.4.3) identified no relevant utility values to reflect different Skin Burden health states. The pivotal trial, Study 201, did not collect HRQoL data, EQ-5D data or any other utility data directly. Therefore, a vignette study was used to generate utility values for the model.
Source of costs	• NHS Reference Costs • PSSRU • BNF/eMIT/MIMS	• Medicare National Median Physician Reimbursement Schedule • Clinical Diagnostic Laboratory Fee Schedule • Wholesale acquisition cost (for treatments)	• NHS Reference Costs • BNF/eMIT	NHS Reference Costs, the BNF and eMIT are standard sources of UK-relevant costs and were used where possible. Where costs were not reported in these sources, cost inputs were sourced from appropriate literature.

[a] Note that whilst TA577 has been noted as a 'Previous appraisal' here, this appraisal was for patients with advanced stage MF-CTCL only (defined as MF Stage IIB and above, stable disease, and all pcALCL patients) and patients had received at least one prior systemic treatment (e.g. bexarotene, IFN-α, methotrexate) but not chemotherapy. Therefore, the patient population does not fully align with the current *de novo* model.[56]

[b] Xia *et al.* (2019) has been used to guide *de novo* model development as it evaluated various monotherapies [topical corticosteroids, topical nitrogen mustard, topical bexarotene, PUVA, narrowband UVB and local radiation] for the treatment of Stage IA MF-CTCL and was considered the most relevant of the SLR-identified studies in terms of a reference for prior modelling approaches to determine impact of SDTs on skin symptoms. However, this model is from the US perspective and would not allow full utilisation of the clinical data from Study 201, in addition to precluding the ability to group disease stages into categories (Stage IA, Stage IB/IIA and Stage IIB–IV) with similar resource use, response to treatment, survival prognosis and quality of life, in line with clinical expert opinion.[4, 99]

Abbreviations: 1L: first line; BNF: British National Formulary; CLTF: Cutaneous Lymphoma Task Force; ECP: extracorporeal photopheresis; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: EuroQol-Five Dimensions; IFN: interferon; ISCL: International Society for Cutaneous Lymphomas; MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; MIMS: Monthly Index of Medical Specialities database of prescription and generic drugs; mSWAT: modified Severity Weighted Assessment Tool; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; pcALCL: primary cutaneous anaplastic large cell lymphoma; PFS: progression-free survival; PUVA: psoralen-ultraviolet A; SCT: stem cell transplantation; SLR: systematic literature review; ToT: time on treatment; TSEB: total skin electron beam therapy; USCLC: United States Cutaneous Lymphoma Consortium.

B.3.2.3 Intervention technology and comparators

Intervention: chlormethine gel

The intervention of interest was topical chlormethine gel (0.02%). Within the economic model, chlormethine gel was assumed to be applied once daily as per the SmPC.[11] The dose of chlormethine gel was assumed to be differ by disease stage, based on patients' skin burden. In the absence of data to inform the difference in dose by disease stage, it was first assumed that the dose would be proportional to the average baseline BSA % at each stage (IA and IB/IIA), given that chlormethine gel is a topical treatment, whilst preserving the median daily dose of 1.80 g received across all patients in Study 201 as stated in the SmPC.[11] This led to an estimate of 0.73 g daily, or 4.5 tubes (each containing a 60 g dose of chlormethine gel) per year, for patients in Stage IA (and therefore also those in Stage IIB–IV with Low Skin Burden). However, this estimate is below the minimum annual consumption of six tubes for Stage IA patients based on clinical expert opinion, which indicated that six tubes would be required per year due to the 2-month expiry date of the tubes. Patients in Stage IA (and those in Stage IIB–IV with Low Skin Burden) were therefore instead assumed to use the minimum of six tubes per year, equivalent to a daily dose of 0.99 g. The dose for patients in Stage IB/IIA and those in Stage IIB–IV with High Skin Burden was then calculated such that the overall weighted average daily dose for all patients was equal to the median daily dose of 1.80 g received in Study 201, leading to a daily dose of 2.93 g for these patients. An alternative scenario in which all patients were assumed to receive an equal dose of 1.80 g daily was also explored (see Section B.3.8.3).

Comparators

Phototherapy

The phototherapy comparator in the model was assumed to comprise a proportion of patients ([redacted]) receiving PUVA and a proportion of patients ([redacted]) receiving UVB, with the proportional split based on data from the PROCLIPI registry (across all disease stages).[2] These were not considered as separate comparators given the generally low quality of evidence generally available to model phototherapy efficacy, which precluded robustly modelling any differential efficacy of PUVA and UVB. The BAD guidelines support that an assumption of equivalent efficacy of PUVA and UVB is reasonable, stating "There have been no prospective RCTs of narrowband UVB, but a retrospective case series showed it to be as effective as PUVA for treatment of early-stage disease, with no difference in time to relapse".[3] However, the treatment acquisition and administration costs associated with UVB and PUVA individually were taken into account and weighted accordingly in order to represent each of these interventions within the data constraints.

PUVA

PUVA comprises of patients receiving oral psoralen followed by treatment with UVA, and was assumed to be administered three times weekly for a maximum of 13 weeks in line with the BAD guidelines.[3, 91 91]

UVB

UVB was assumed to be provided two and a half times weekly, for a maximum of 13 weeks in line with the BAD guidelines (two to three times weekly).[3]

Pegylated IFN-α and bexarotene

As described in the decision problem table (Table 1) and discussed in B.1.3.2, pegylated IFN-α and bexarotene represent relevant clinical comparators to chlormethine gel for the proportion of patients for whom phototherapy is not suitable. However, as noted in Section B.2.9 the evidence base for these therapies is limited. Based on results of a clinical SLR of RCTs and a review of all non-RCT evidence cited in the BAD guidelines, there are no published studies of IFN or bexarotene that provide data that would allow a comparison to chlormethine gel for the cost-effectiveness model. As such, whilst we acknowledge that pegylated IFN-α and bexarotene represent relevant clinical comparators, it is not possible to include these therapies as comparators for the purpose of relative effectiveness assessment or cost-effectiveness analysis. These comparators are therefore not included in the model presented here. It should be noted that it is anticipated that only a minority of patients who would be considered for treatment with chlormethine gel would currently receive pegylated IFN-α or bexarotene in UK clinical practice (~10% based on expert clinical feedback),[4] with the rest receiving an SDT as represented by the phototherapy comparator.

Subsequent therapies

As mentioned in Section B.3.2.2 above, once patients transitioned into the Progressed from 1L health state, they were assumed to receive either bexarotene or pegylated IFN-α in a 50:50 split. The therapy use in early stage disease specifically was considered the most relevant as the aim was to understand therapy usage for treatment of skin lesions rather than underlying disease – use of therapies for underlying disease in advanced stages was captured separately as background treatment for advanced stage disease [see below]). This bundle was the same irrespective of disease stage, with weighting according to data from the PROCLIPI registry on the most common SDTs prescribed in UK clinical practice.[2] The patient numbers for chlormethine gel were assumed to be those reported for topical nitrogen mustard, in the absence of data for chlormethine gel specifically. The proportion of patients receiving each treatment, as well as the associated dosing regimens are presented in Table 42 below.

Given that phototherapy has a maximum duration of 13 weeks in the model (in line with the BAD guidelines) and clinical expert feedback, patients who finished their course and were in the initial health state (Low or High Skin Burden) or in Reduced Skin Burden were then assumed to receive either bexarotene or pegylated IFN-α in a 50:50 split.[3]

Background treatment for advanced disease stages

Patients with advanced disease (Stage IIB–IV) would not be treated solely with SDTs such as chlormethine gel or phototherapy as they would also receive systemic therapies that aim to treat the underlying disease. The specific combinations of therapies that would be used in advanced stage disease are many, varied and highly specific to the individual patient taking into account patient preferences, treatment history and specific disease context. As such, it is not feasible to model specific combinations of SDTs and systemic therapies for advanced stage disease within the context of this model that is focused on assessing treatment benefit on the skin symptoms of MF-CTCL. As such, within the model patients in advanced stage disease were assumed to receive systemic treatment for disseminated disease in addition to their skin lesion treatments, and this systemic treatment was modelled as a bundle of treatments including bexarotene, ECP, gemcitabine and methotrexate, weighted according to data from the PROCLIPI registry on the most common treatments prescribed among advanced stage MF-CTCL patients in UK clinical

practice.[2] The proportion of patients receiving each treatment, as well as the associated dosing regimens are presented in Table 42 below.

Table 42: Dosing regimens and proportions patients receiving subsequent therapies in the cost-effectiveness model

Treatment	Dosing regimen	Proportion patients within bundle of interventions	
		Progressed from 1L	Advanced disease
Bexarotene	300 mg/m^2 daily	50%	[redacted]
ECP	Two consecutive days every four weeks; UVADEX treatment volume × 0.017 (mL) per ECP session	-	[redacted]
Gemcitabine	1000 mg/m^2 three days every 28 days	-	[redacted]
Methotrexate	23.44 mg weekly	-	[redacted]
Pegylated IFN-α	1.5 µg/kg weekly	50%	[redacted]

Abbreviations: 1L: first line; ECP: extracorporeal photopheresis; IFN-α: interferon alpha.
Source: PROCLIPI registry;[2] Recordati Rare Diseases/Helsinn Healthcare SA data on file.[1]

B.3.3 *Clinical parameters and variables*

B.3.3.1 Baseline characteristics

The baseline characteristics for the modelled cohort are provided in Table 43, based on data from Study 201 and the PROCLIPI registry.[2, 25] Where patient characteristic data were available from the PROCLIPI registry these were preferentially used over Study 201, as they reflected average characteristics for a population across all disease stages (in contrast, Study 201 recruited only early stage patients). Where data were not available from the PROCLIPI registry (age, gender), data from Study 201 were used. In the subgroup analysis of the early stage population only, all available patient characteristics were similarly taken from PROCLIPI where available and Study 201 where PROCLIPI data were not available. Neither mean BSA nor mean weight were available from Study 201 or the PROCLIPI registry, and were therefore based on data from the NHS Health Survey for England 2017: Adult Health, with the mean BSA approximated from the reported mean height and weight using the du Bois formula.[105]

Table 43: Patient characteristics in the cost-effectiveness model

Model parameter	Value	Source
Age, mean (SD)	[redacted]	Study 201 CSR; Pooled data across treatment arms
Proportion female	[redacted]	
Mean BSA, m^2	1.91	NHS Health Survey for England 2017: Adult Health, approximated from height and weight using du Bois formula[105]
Mean weight, kg	79.96	NHS Health Survey for England 2017: Adult Health[105]

Disease stage			
Stage IA	[redacted]		PROCLIPI registry[2]
Stage IB/IIA	[redacted]		PROCLIPI registry[2]
Stage IIB–IV	[redacted]		PROCLIPI registry[2]
Skin burden	**<10% BSA**	**10–80% BSA**	
Stage IA	100%	-	As per the TNMB classification system, all Stage IA patients have <10% BSA affected[3]
Stage IB/IIA	-	100%[a]	As per the TNMB classification system, all Stage IB patients have >10% BSA affected. Based on PROCLIPI [redacted] Stage IIA patients similarly have >10% BSA[2, 3]
Stage IIB–IV	[redacted]	[redacted]	PROCLIPI registry[2]
Baseline mSWAT score, mean (SD)			
Stage IA	[redacted]		PROCLIPI registry[2] (SDs calculated from Study 201)[46]
Stage IB/IIA	[redacted]		
Stage IIB–IV (Low Skin Burden)	[redacted]		
Stage IIB–IV (High Skin Burden)	[redacted]		

[a] As described in Section B.3.2.2, whilst Stage IIA–IV patients can have either <10% or at least 10% BSA affected, based on data from PROCLIPI, [redacted] have at least 10% BSA affected, and therefore Stage IB/IIA patients were all assumed to have High Skin Burden at model entry given that this reflects the skin burden of all Stage IB (who have High Skin Burden by definition) and a majority of Stage IIA patients.
Abbreviations: BSA: body surface area; mSWAT: modified Severity Weighted Assessment Tool; SD: standard deviation; TNMB: tumour, nodes, metastasis, blood (classification system).

B.3.3.2 Derivation of transition probabilities

As described in Section B.3.2.2, the cost-effectiveness model considered patients moving between disease stages, but also between health states of varying degrees of skin burden of their MF-CTCL within those disease stages (see Figure 12).

Transitions between disease stages (PFS transition probabilities)

The probability of patients progressing from an earlier to a more advanced disease stage e.g. Stage IA to Stage IB/IIA, or Stage IA to Stage IIB–IV was treatment independent, and derived from Wernham *et al.* (2015), a database study investigating disease progression in 86 patients with early MF-CTCL.[104] This study was identified by a clinical expert, and was the only study identified with sufficient granularity of progression data (i.e. including data on proportion of patients progressing, as well as what disease stage the patient progressed to).[1]

Specifically, data on the time to progression for Stage IA and Stage IB/IIA patients, in addition to data for the proportion of patients progressing to Stage IB/IIA and to Stage IIB–IV from either Stage IA or Stage IB/IIA were used to calculate the transition probabilities required (Table 44 and Table 45), assuming an exponential distribution (i.e. constant with respect to time).

Table 44: Progression data from Wernham *et al.* (2015)

	Mean time to progression, months	Total number of patients	No progression	Progression to Stage IB/IIA	Progression to Stage IIB–IV
Stage IA	85	38	24	9	5
Stage IB/IIA	55	48	35	-	13

Source: Wernham *et al.* (2015).[104]

A summary of the transition probabilities for transitions between disease stages is presented in Table 45 below.

Table 45: Transition probabilities between MF-CTCL disease stages

Initial disease stage	End disease stage		
	Stage IA	Stage IB/IIA	Stage IIB–IV
Stage IA	0.9969	0.0028	0.0004
Stage IB/IIA	-	0.9951	0.0049
Stage IIB–IV	-	-	1.0000

Abbreviations: MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma.

Transitions within disease stages

The transition probabilities for transitions between different degrees of skin burden within each disease stage were derived as described below. In the absence of data for advanced stage patients, transition probabilities for advanced stage patients with Low Skin Burden (<10%) were assumed equal to those for Stage IA (as all Stage IA patients similarly have Low Skin Burden) and advanced stage patients with High Skin Burden (>10%) were assumed equal to those for IB/IIA (as all Stage IB/IIA patients are assumed to have High Skin Burden). This assumption was considered reasonable given that the model structure splits advanced stage patients into those with Low or High Skin Burden to match to either Stage IA or Stage IB/IIA, respectively, on the basis of similar skin symptoms and therefore similar expected efficacy.

Transitions from Low/High Skin Burden

Transitions from Low/High Skin Burden to No Skin Burden, Reduced Skin Burden and Progressed from 1L for chlormethine gel were derived from mSWAT response rates from Study 201, in line with the response definitions provided in the Study 201 CSR:[46]

- **Transition to No Skin Burden** – calculated based on the number of patients who achieved a confirmed CR (excluding any patients who previously achieved a confirmed PR), and the time at which this first occurred from baseline (baseline was the first day the drug was dispensed). A confirmed response was the date of the evaluation at least 28 days after the first assessment of CR i.e. second consecutive CR
- **Transition to Reduced Skin Burden** – calculated based on the number of patients who achieved a confirmed PR, and time at which this occurred from baseline (baseline was the first day the drug was dispensed). Confirmed response was the date of the evaluation at least 28 days after the first assessment of PR i.e. second consecutive PR

- **Transition to Progressed from 1L** – calculated based on the number of patients with progressive disease by end of trial follow-up (12 months). A patient was considered to have progressive disease if they never achieved a confirmed response [confirmed PR or CR] and their last recorded mSWAT score was ≥25% above baseline). The initial timepoint at which patients were considered to be assessed for treatment discontinuation based on skin progression was six months, based on clinical expert opinion that clinicians would treat for at least six months before discontinuing therapy on the basis of lack of efficacy[4]

As described in Section B.2.9, it was not possible to perform a network meta-analysis or unanchored ITC in order to derive adjusted estimates of the relative effectiveness of phototherapy and chlormethine gel. A number of studies of phototherapy were identified as being more appropriate for naïve comparison to the results of Study 201 for chlormethine gel, though such naïve comparison remained subject to considerable limitations with regards to comparability of study populations and outcome measures and study quality. Furthermore, estimates of the efficacy of phototherapy in terms of response rates were seen to vary quite considerably across the identified studies. Therefore, there remains considerable uncertainty regarding the estimates for response rates with phototherapy.

In order to model phototherapy efficacy, estimates of CR, PR, progressive disease and stable disease (SD) were required to calculate the proportions of patients who 'Transition to No Skin Burden', 'Transition to Reduced Skin Burden', 'Transition to Progressed from 1L' or remain in their initial skin burden state, respectively. Based on the identified phototherapy studies reported in Section B.2.9 (Table 26), a number of alternative approaches were explored for deriving these estimates:

1. **Base case:** CR and PR derived as a weighted average (weighted by sample size) of the CR and PR rates from all studies summarised in Table 26. In the absence of consistent reporting of rates of progressive disease and SD across these studies, it was assumed that the remainder of patients not achieving CR or PR were split equally between progressive disease and SD. This is consistent with the EORTC 21011 study, in which an equal proportion of patients were classified as having SD and having progressive disease.[91]
2. **Scenario analysis:** Two of the studies summarised in Table 26 (Oguz *et al.* 2003; Anadolu *et al.* 2005)[89, 90] did not provide any information on the duration of phototherapy treatment over which responses were achieved (i.e. no time to response information). This is a concern for modelling the effectiveness of phototherapy, as it is not possible to determine how long phototherapy was received for before a response was confirmed, and therefore how generalisable the efficacy observed in these studies is to the effectiveness of 13 weeks of phototherapy treatment as modelled for this submission. This is in contrast to the other studies in Table 26, for which an average time to response could be calculated (all lying between 9 and 25 weeks). Therefore, a scenario was conducted in which CR and PR were derived as a weighted average (weighted by sample size) of the CR and PR rates from all studies summarised in Table 26 *with the exception of Oguz et al. 2003 and Anadolu et al. 2005.*[89, 90] As per the base case, it was assumed that the remainder of patients not achieving CR or PR were split equally between progressive disease and SD.
3. **Scenario analysis:** The only study of those summarised in Table 26 that used the same outcome measure for determination of response rates as Study 201 (mSWAT) was NCT01686594.[93] This study is associated with a small sample size (only 27 patients) and therefore the reported estimates are susceptible to sampling uncertainty and should be

treated with caution. Furthermore, the combined estimates of complete and partial response in this study might be reasonably considered to be optimistic from the perspective of phototherapy efficacy: the study reports an overall response rate (CR+PR) of 100%, which is evidently a maximum possible estimate of overall response rate, and is notably higher than the response rates summarised in Table 7 of the BAD guidelines for phototherapy.[3] Nevertheless, as this is the only identified study that used the mSWAT outcome measure, an 'optimistic phototherapy effectiveness' scenario was conducted using the direct CR and PR estimates from this study.

4. **Scenario analysis:** Given the range of estimated response rates to phototherapy that are reported across the identified literature, it was also considered appropriate to explore a scenario that is more pessimistic with regards to the estimated effectiveness of phototherapy. The EORTC 21011 study (Whittaker *et al.* 2012) was identified by the clinical SLR of RCTs and provided CR, PR, SD and progressive disease outcomes, as well as time to response data.[91] The median number of weeks of PUVA received was 12 and a median of 27.5 sessions were required to achieve CR; this is relatively well aligned to the modelled administration of phototherapy in the cost-effectiveness model of two-and-a-half (UVB) or three (PUVA) times weekly for 13 weeks. The CR rate observed in this study was markedly lower than for the other studies summarised in Table 26, and the rates from this study were therefore used directly to provide a 'pessimistic phototherapy effectiveness' scenario to explore the uncertainty in phototherapy effectiveness (although it should be noted that the overall response rate of phototherapy in this scenario of 71% was not overly dissimilar to the overall response rates summarised in Table 7 of the BAD guidelines, perhaps suggesting that this scenario may not be overly pessimistic).[3] In interpreting this scenario it should be noted that whilst the definitions of CR and PR in EORTC 21011 were relatively well aligned to those of Study 201 (i.e. effectively complete clearance for CR, and a >50% reduction in score from baseline for PR), the measurement tools used were different (mSWAT for Study 201, compared to Tumour Burden Index for EORTC 21011).[91] Therefore, the comparability of the response rates from the two studies must be treated with caution.

Time to response

Time to response was also required in order to be able to derive the transition probabilities between health states. For chlormethine gel, mean time to response was calculated for each response type (CR, PR and CR following initial PR) based on patient-level data from Study 201.

For phototherapy, a weighted average time to response (weighted by number of responders) was calculated from all studies reporting time to response data. The value obtained, of 13.8 weeks, was closely aligned to the duration of phototherapy assumed in the model (13 weeks), and hence 13 weeks was taken to be the time to response for relevant phototherapy state transitions (it was considered appropriate to assume that response would be achieved whilst on treatment, rather than following completion of the treatment course).

Other transitions

Transition from Reduced Skin Burden to No Skin Burden

For chlormethine gel, this transition probability was derived from patients who had a confirmed PR, and then subsequently a confirmed CR from Study 201. The mean time to this response was calculated as the time of confirmed CR minus time of confirmed PR.

In the absence of relevant reported data for phototherapy on probability of CR following PR, this transition probability was assumed equal to that for chlormethine gel.

Transition from Reduced Skin Burden to Progressed from 1L

In the absence of data for this transition from Study 201, this transition probability for chlormethine gel was assumed to be the same as the transition to Progressed from 1L from the Low/High Skin Burden health states respectively, based on expert clinical opinion.[1] The reason these data were not available from Study 201 was due to the fact that, by the definition of the progressive disease outcome in Study 201, patients with progressive disease could not have had a previous confirmed CR or PR. This is a conservative assumption with regards to relapse rates as it would be expected that patients who had previously had a PR would be less likely to relapse compared to those who have never had a PR.

The same assumption was correspondingly made for phototherapy, again due to a lack of relevant data, i.e. this transition probability for phototherapy was assumed to be the same as the transition to Progressed from 1L from the Low/High Skin Burden health states respectively.

Transition from No Skin Burden to Progressed from 1L

The transition from No Skin Burden to Progressed from 1L was treatment independent, as patients are no longer receiving treatment in this health state (this assumption was validated by clinical expert opinion).[1] This transition was calculated based on a source derived from the literature. Data from Study 201 could not be utilised due to the fact that, by definition of the trial outcome, patients with progressive disease in Study 201 could not have had a previous confirmed CR i.e. patients could not go from having No Skin Burden to progressive disease. Therefore, data from Whittaker *et al.* (2012), an RCT of PUVA alone versus PUVA plus bexarotene in IB/IIA MF-CTCL patients was used to inform this transition in the model (data from both treatment arms was used due to the treatment-independent nature of this transition [see above] and to therefore maximise sample size.[91] The probability was calculated using relapse post-CR data pooled across treatment arms and across all early stage patients. In the absence of Stage IA patients specifically in this trial, a simplifying and conservative assumption that Stage IA patients would be equally likely to relapse from CR than Stage IB/IIA patients was made.

Summary of within stage transition probabilities

Summaries of the transition probabilities utilised in the cost-effectiveness model are presented in Table 46, Table 47, Table 48 and Table 49 below for Stage IA and Stage IB/IIA patients treated with chlormethine gel and phototherapy, respectively. Note that, as discussed previously, the probabilities for Stage IA and Stage IB/IIA were assumed to also apply for advanced stage (Stage IIB–IV) patients with Low and High Skin Burden, respectively, in the absence of data for this advanced population.

Stage IA

Table 46: Transition probabilities for Stage IA patients (and advanced patients with Low Skin Burden) receiving chlormethine gel in the cost-effectiveness model

Initial health state	End health state			
	Low Skin Burden	No Skin Burden	Reduced Skin Burden	Progressed from 1L

Low Skin Burden	[redacted]	[redacted]	[redacted]	[redacted]
No Skin Burden	-	[redacted]	-	[redacted]
Reduced Skin Burden	-	[redacted]	[redacted]	[redacted]

Table 47: Transition probabilities for Stage IA patients receiving phototherapy in the cost-effectiveness model

Initial health state	End health state			
	Low Skin Burden	**No Skin Burden**	**Reduced Skin Burden**	**Progressed from 1L**
Low Skin Burden	0.559	0.356	0.075	0.010
No Skin Burden	-	0.873	-	0.127
Reduced Skin Burden	-	0.017	0.973	0.010

Stage IB/IIA

Table 48: Transition probabilities for Stage IB/IIA patients (and advanced patients with High Skin Burden) receiving chlormethine gel in the cost-effectiveness model

Initial health state	End health state			
	High Skin Burden	**No Skin Burden**	**Reduced Skin Burden**	**Progressed from 1L**
High Skin Burden	[redacted]	[redacted]	[redacted]	[redacted]
No Skin Burden	-	[redacted]	-	[redacted]
Reduced Skin Burden	-	[redacted]	[redacted]	[redacted]

Table 49: Transition probabilities for Stage IB/IIA patients receiving phototherapy in the cost-effectiveness model

Initial health state	End health state			
	High Skin Burden	**No Skin Burden**	**Reduced Skin Burden**	**Progressed from 1L**
High Skin Burden	0.566	0.356	0.075	0.003
No Skin Burden	-	0.873	-	0.127
Reduced Skin Burden	-	0.020	0.978	0.003

Transition to Death

Within the cost-effectiveness model, patients could transition to the Death health state from any other health state within any disease stage. Transition probabilities were treatment independent and were based on disease stage only (i.e. independent of skin burden). Therefore, the likelihood of entering the Death health state was equally likely from any Skin Burden health state.

Median survival by disease stage data from Agar *et al.* (2010) and patient number estimates on the number of patients at each disease stage in UK clinical practice from the PROCLIPI registry (see Table 50), were used to derive weighted median survival in months for patients at each disease stage (i.e. weighted averages for IB/IIA and IIB–IV).[2] This was subsequently used to derive transition probabilities for use in the model, assuming an exponential distribution.[38]

Table 50: Median survival by disease stage in the cost-effectiveness model

Clinical stage	N	Median survival (years)	Weighted median survival (years)	Weighted median survival (months)
Stage IA	[redacted]	35.50	[redacted]	[redacted]
Stage IB/IIA				
IB	[redacted]	21.50	[redacted]	[redacted]
IIA	[redacted]	15.80		
Stage IIB–IV				
IIB	[redacted]	4.70	[redacted]	[redacted]
IIIA	[redacted]	4.70		
IIIB	[redacted]	3.40		
IVA1	[redacted]	3.80		
IVA2	[redacted]	2.10		
IVB	[redacted]	1.40		

Source: Agar *et al.* (2010);[38] PROCLIPI registry.[2]

A summary of the transition probabilities to the Death health state is presented in Table 51 below.

Table 51: Transition probabilities to the Death health state in the cost-effectiveness model

	Transition probability
Stage IA to Death	0.0016
Stage IB/IIA to Death	0.0028
Stage IIB–IV to Death	0.0147

B.3.3.3 Mortality

In addition to transition probabilities to the Death health state to account for disease-specific mortality, baseline general population mortality from the Office of National Statistics for England and Wales for 2016–2018 (by single year of age and by gender) was applied.[106] A built-in constraint was applied to ensure that the modelled (i.e. disease-specific) mortality did not drop below that of the general population mortality at any time point.

B.3.3.4 Adverse events

AEs at Grade 3 or greater that occurred in at least 5% of patients for chlormethine gel or the comparator (phototherapy) were included in the cost-effectiveness model, as it was considered that these AEs would be the ones associated with a substantial cost and/or quality of life burden.

The frequency of AEs for chlormethine gel was derived from the safety set from Study 201 (data cut off 1st June 2011) and for phototherapy from Whittaker *et al.* (2012) (Table 52). As discussed in Section B.2.9, a robust indirect comparison between chlormethine gel and phototherapy was not possible for any outcomes, and therefore, it was not possible to inform the proportion patients experiencing AEs in the cost-effectiveness model using such methods. As such, naïve frequencies of AEs as reported in the respective sources were applied.

The Whittaker *et al.* (2012) study did not report any AEs of Grade 3 or Grade 4 severity occurring in ≥5% of patients treated with PUVA monotherapy, and therefore no AEs were assumed for phototherapy in the model. Although phototherapy is not associated with significant AEs directly associated with its use in the short-term, the use of phototherapy is not without risk of SAEs. An increased risk of secondary malignancies (i.e. melanoma) has been associated with the use of phototherapy where exposure is too high or the number of repeat courses is too great. This is highlighted in the BAD guidelines, which state with regards to the link between phototherapy and secondary malignancies:

- "Repeated courses may be considered but the increased risk of skin cancer (including melanoma) limits the number of phototherapy courses in a lifetime"
- [in relation to a retrospective study of long-term outcomes following complete remission from PUVA monotherapy, in which maintenance PUVA was given to almost all responding patients] "A total of 30% of patients showed chronic photodamage and secondary skin cancers"
- "For PUVA, an increased risk has been identified for patients receiving more than 250 treatments and/or >2000 J cm^{-2}. Based on the data available, the cumulative lifetime PUVA exposure should be limited (1200 J cm^{-2} and/or 250 sessions). For maintenance PUVA, the risks may outweigh the benefits…"

As a result of these risks, clinical expert feedback indicates that, in line with the BAD guidelines, use of phototherapy in UK clinical practice is limited to a treatment course of 13 weeks for a course of phototherapy. The cost-effectiveness model presented here models a maximum of 13 weeks of treatment of phototherapy in alignment with this; in acknowledgement that this restriction to treatment duration recommendation applies to mitigate the risk of secondary malignancies with phototherapy, the model therefore assumes no occurrence of secondary malignancies with phototherapy. However, were phototherapy to be assumed to be used for longer periods (e.g. with maintenance phototherapy following response), then the potential inclusion of secondary malignancies in the model would need to be considered.

Table 52: Frequency of AEs in the cost-effectiveness model

AE, n (%)	Chlormethine gel	Phototherapy
Dermatitis contact	[redacted]	0.00%
Erythema	[redacted]	0.00%
Skin irritation	[redacted]	0.00%

Abbreviations: AE: adverse event.
Source: Study 201 CSR appendix (2011) for chlormethine gel; Whittaker *et al.* (2012) for PUVA.[107]

B.3.4 *Measurement and valuation of health effects*

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

As HRQoL data were not collected in Study 201 and no relevant utilities for health states based on skin burden were identified by a SLR (see Section B.3.4.3), a vignette study was conducted to derive utility values associated with the health states included within the economic model (see Section B.3.4.3 below).

B.3.4.2 Mapping

As HRQoL data were not collected in Study 201, considerations of mapping from trial HRQoL data to a utility measure were not relevant.

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

HRQoL outcomes, including generic measures (e.g. SF-36 and EQ-5D) and disease-specific measures (e.g. Skindex-29) were included in the eligibility criteria for the clinical SLR. However, no studies were identified which collected HRQoL data of relevance to the submission. Targeted literature reviews of internal materials also revealed no further relevant HRQoL data.

A single SLR was also performed to identify relevant published economic evaluations, studies reporting utility values, and studies reporting cost and resource use data in CTCL. Searches were performed in July 2019 and full details of the SLR search strategy and study selection process are reported in Appendix G. The results for HRQoL (utility) studies identified are provided in Appendix H.

A total of 11 publications reporting on four unique studies with health state utility data met the eligibility criteria and were included in the SLR. However, none of these were considered appropriate for use within the cost-effectiveness model presented as part of the submission, as they were either not consistent with the NICE reference case e.g. use of the Health Utilities Index instead of EQ-5D or not relevant to the decision problem.

Unfortunately, the collection of EQ-5D utility values through self-reporting from patients was not feasible due to limitations in access to patients and ethical considerations within the submission timeframe. As such, alignment with the NICE reference case was therefore limited, and a *de novo* approach was required in order to generate the health state utility values required for the cost-effectiveness analysis.[108]

De novo utility (vignette) study

A utility study was conducted by Recordati Rare Diseases/Helsinn Healthcare SA, whereby a series of patient descriptions, referred to here as vignettes, were developed to describe a range of different health states relevant to the cost-effectiveness model. HRQoL data were then obtained through an indirect elicitation method using proxy-reporting via clinicians using the EQ-5D questionnaire.

Twelve distinct vignettes were prepared describing typical patients in different disease stages with varying levels of skin burden, covering the range of health states used in the cost-effectiveness model. A list of these vignettes is presented in Appendix H. Each vignette was

developed based on the advice of both a clinical expert, experienced in the treatment of MF-CTCL patients in the UK, and an independent expert in HRQoL data collection. A patient representative validated the vignettes as being reflective of disease states that might be experienced by patients. The inclusion of the following pieces of information within each vignette was based on expert opinion: disease stage (Stage IA, Stage IB/IIA and Stage IIB–IV); mSWAT range, the clinically validated measure of skin burden used to define response in Study 201 and subsequently in the cost-effectiveness model; Eastern Cooperative Oncology Group (ECOG) score, a simple measure of functional status; and age (at diagnosis).

The vignettes were distributed to respondents alongside the proxy version 2 of the EQ-5D-5L questionnaire (prepared in the online software SurveyMonkey and validated by EuroQoL prior to use). Based on each of the descriptions given in the vignettes, the respondents were asked to rate how they thought a patient would rate their own HRQoL, if the patient were to be asked.

The responses to the EQ-5D-5L questionnaire were then converted to utility values using the UK value set. EQ-5D-3L utility values were then derived using the crosswalk methodology developed by van Hout *et al.* (2012), providing values for the specific mSWAT ranges within each disease stage given in the vignettes.[109]

To determine utility values for each initial health state in the model, baseline mean mSWAT scores were calculated by disease stage from the PROCLIPI registry (SDs were calculated from Study 201 due to the lack of relevant data from the PROCLIPI registry) (as shown in Table 53). mSWAT score were then assigned to the corresponding initial health states – Low Skin Burden in Stage IA, High Skin Burden in Stage IB/IIA and Low or High Skin Burden in Stage IIB–IV (based on % BSA, as described in Section B.3.2.2). A normal distribution was assigned around the mean mSWAT score and associated SD for each initial health state. The mSWAT ranges used in the vignettes were then combined with the normal distribution curves to determine the proportion of patients within each mSWAT range at each disease stage. Using the utility value assigned to each mSWAT range from the vignettes, a weighted average utility for each initial health state was calculated.

Table 53: Base case baseline mSWAT scores from the PROCLIPI registry by disease stage

Disease Stage	mSWAT mean (SD[a])
Stage IA	[redacted]
Stage IB/IIA	[redacted]
Stage IIB–IV (<10% BSA)	[redacted]
Stage IIB–IV (>10% BSA)	[redacted]

[a] SDs were calculated from Study 201.
Abbreviations: BSA: body surface area; mSWAT: modified Severity Weighted Assessment Tool; SD: standard deviation.
Source: PROCLIPI registry;[2] Study 201 CSR (2011).[46]

To capture the utility values associated with the Reduced Skin Burden health state and the Progressed from 1L health state in each disease stage, an analysis of the mean change from baseline in mSWAT scores for partial responders and those with progressive disease from Study 201 was conducted (Table 54). These percentage changes were used to calculate a new mean mSWAT score for the Reduced Skin Burden and Progressed from 1L health states, respectively. A normal distribution was reapplied based on the new mean mSWAT scores, shifting the curves as illustrated in Figure 13. As previously, the mSWAT ranges from the vignettes were combined

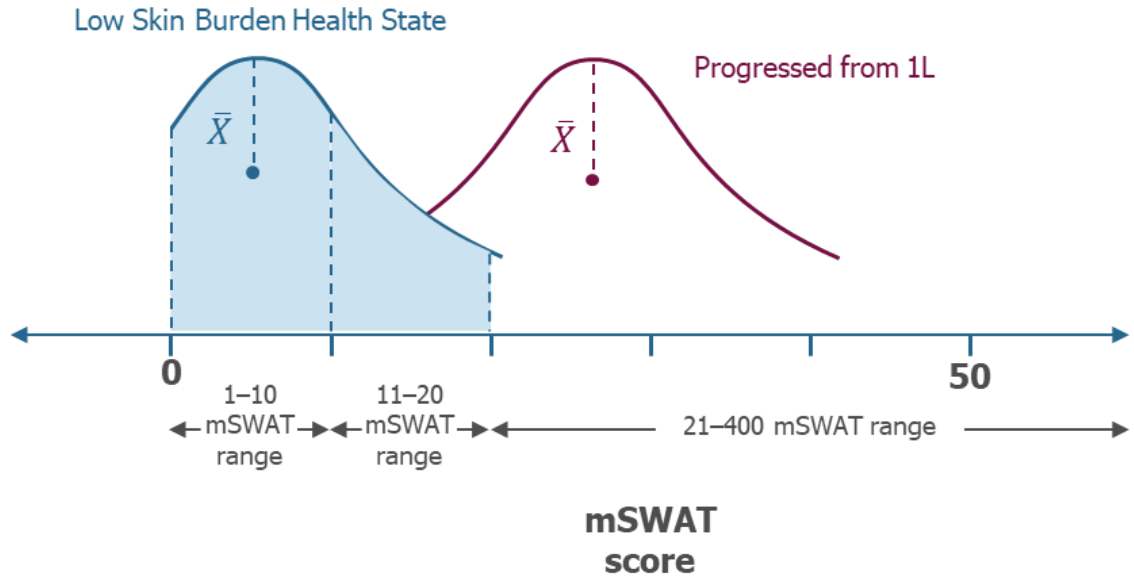
with the (shifted) normal distribution to determine the new proportion of patients within each mSWAT range in each health state (Reduced Skin Burden and Progressed from 1L) and at each disease stage. Weighted average utilities were then recalculated for the shifted curves to provide values for the Reduced Skin Burden health state and the Progressed from 1L health states (by disease stage). Due to the lack of data available from Study 201 on advanced disease stage patients, the mean change in mSWAT for Low Skin Burden (<10% BSA affected; Stage IA) and High Skin Burden (>10% BSA affected; Stage IB/IIA) patients were respectively applied to the advanced disease stage patients (Stage IIB–IV) for Low Skin Burden and High Skin Burden. Patients in the No Skin Burden health state were assumed to have an mSWAT score of 0, and therefore received the corresponding utility value from the vignettes (by disease stage).

Table 54: Mean change from baseline in mSWAT score from Study 201 for patients with PR and progressive disease

Disease Stage	Mean percentage change in mSWAT	
	Partial responders (Reduced Skin Burden)	Progressive disease (Progressed from 1L)
Stage IA	[redacted]	[redacted]
Stage IB/IIA	[redacted]	[redacted]
Stage IIB–IV (<10%)	[redacted]	[redacted]
Stage IIB–IV (>10%)	[redacted]	[redacted]

Abbreviations: 1L: first line; BSA: body surface area; mSWAT: modified Severity Weighted Assessment Tool; SD: standard deviation.
Source: Study 201 CSR (2011).[46]

Figure 13: Illustration of baseline and shifted mSWAT normal distributions for Stage IA



Abbreviations: 1L: first line; mSWAT: modified Severity Weighted Assessment Tool; $\bar{X}$: mean mSWAT score.

Results from the de novo utility (vignette study)

A summary of the utility values derived from the study are presented in Table 55 below.

Table 55: Summary of utility values derived from the *de novo* utility study and used to inform the cost-effectiveness analysis

Health state	Mean value	Standard error	Median value	Minimum value	Maximum value
Stage IA					
Vignette 1 mSWAT score of 0, ECOG score of 0, aged 55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignette 2 mSWAT score of <10, ECOG score of 0, aged 55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignette 3 mSWAT score of 10–20, ECOG score of 0, aged 55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignette 4 mSWAT score of >20, ECOG score of 0, aged 55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IB/IIA					
Vignette 5 mSWAT score of 0, ECOG score of 0, aged 61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignette 6 mSWAT score of <15, ECOG score of 0, aged 61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignette 7 mSWAT score of 15–60, ECOG score of 0, aged 61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignette 8 mSWAT score of >60, ECOG score of 0, aged 61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IIB+					
Vignette 9 mSWAT score of 0, ECOG score of 0, aged 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignette 10 mSWAT score of <35, ECOG score of 0, aged 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignette 11 mSWAT score of 35–65, ECOG score of 0, aged 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignette 12 mSWAT score of >65, ECOG score of 0, aged 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG: Eastern Cooperative Oncology Group; mSWAT: modified Severity Weighted Assessment Tool.

Methodological considerations

As with any study, a number of factors must be considered in terms of its design and associated implications. As MF-CTCL is a rare disease, there are few clinicians in the UK with clinical experience of treating this condition. As such, the leading clinician network for cutaneous lymphoma was contacted in order to engage the maximum number of UK clinicians with experience of MF-CTCL, who could be enrolled in the utility study. As a result of this collaboration, a total of seven clinicians recruited from centres across the UK were enrolled and

completed the study. This was considered to be a substantial proportion of eligible clinicians by the leading clinician network, however does remain a small sample size. To account for the complexities of MF-CTCL being a dermatological and oncological disease, it was also ensured that clinicians across both specialties were enrolled. The opinions of the respondents were therefore considered to be representative of current clinical opinion in the disease area, representing a sufficient coverage level in terms of clinical experience and geography.

As the EQ-5D is a generic rather than disease-specific measure of HRQoL, it may be considered insensitive to changes in HRQoL of patients with MF-CTCL, and indeed, this was highlighted during the appraisal TA577 (brentuximab vedotin for treating CD30-positive CTCL).[56]. As such, an expert in the field of utility collection was consulted on the most appropriate solution to this problem for the purposes of this appraisal. It was agreed with this expert that the EQ-5D-5L version of the questionnaire should be used over the EQ-5D-3L to maximise sensitivity to changes in HRQoL, whilst aligning as closely as possible with the NICE reference case, due to subsequent crosswalk of values to the EQ-5D-3L for use in the cost-effectiveness model.

To account for the respondents' potential lack of experience in responding to EQ-5D questionnaires, an introductory exercise was incorporated into the online questionnaire presenting respondents with the self-complete version of ED-5D-5L questionnaire, to which they were able to respond based on their own health, before they moved on to the proxy response questions. This was to help the respondents familiarise themselves with the structure of the questionnaire and improve the reliability of their responses. As described above, the respondents then completed the proxy 2 version of the EQ-5D-5L questionnaire for each vignette, which were presented to each respondent in a randomised order to minimise bias associated with presentation of vignettes ordered by increasing disease severity.

The possibility of measuring the uncertainty in the respondents' responses was also explored through requesting upper and lower percentiles to their estimations. However, due to the need to limit respondent burden, this information was ultimately not collected. Furthermore, as a result of the small sample size of respondents, one clinician who responded to the questionnaire, was also involved in the validation of the vignettes. However, the potential effect of this was accounted for in an exploratory analysis which excluded the responses from this particular clinician (see Appendix H). There may also be other elements of the condition that could affect quality of life (e.g. the areas of a patient's body that are affected by symptoms) that were not captured within the vignettes and therefore cannot be accounted for; which presents an additional limitation of the study.

B.3.4.4 Adverse reactions

Inputs for disutilities were included for patients experiencing AEs within the cost-effectiveness model as it was assumed that such disutilities would not be captured by the vignette approach, as the utility vignette descriptions were treatment independent and did not refer to any adverse events.

The disutility for contact dermatitis, erythema and skin irritation was assumed to be 0.003 based on the disutility for rash reported in Nafees *et al.* (2008).[110] This value was used in the NICE appraisal for brentuximab vedotin in CTCL (TA577) for the disutility associated with skin/subcutaneous tissue disorders (based on a targeted literature review of previous NICE submission in lymphoma indications) and was therefore considered an appropriate value in the

absence of disutilities for the specific AEs included for patients with MF-CTCL.[56] These disutilities were adjusted by the relevant per-cycle rate to give the AE disutility per cycle.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Health state utility values

Health state utility values required for the cost-effectiveness analysis were derived from the *de novo* vignette study, as per the methodology outlined in Section B.3.4.3.

AE disutilities

Disutilities relating to AEs were included as per the approach outlined in Section B.3.4.4 above.

Age-related utility decrements

The model considered additional age-related utility decrements (10-year decrements) as the population became older over the modelled time horizon. The decrements were calculated based on Janssen *et al.* (2014), which described the health utilities of healthy populations by different age groups using the EQ-5D index population norms based on the UK time-trade-off (TTO) value sets.[111]

A summary of the utility values included in the cost-effectiveness model is presented in Table 56 below.

Table 56: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% CI[a]	Reference in submission	Justification
Vignette 1	[redacted]	N/A	Section B.3.4.3	Derived from the *de novo* healthcare resource use survey
Vignette 2	[redacted]	N/A		
Vignette 3	[redacted]	N/A		
Vignette 4	[redacted]	N/A		
Vignette 5	[redacted]	N/A		
Vignette 6	[redacted]	N/A		
Vignette 7	[redacted]	N/A		
Vignette 8	[redacted]	N/A		
Vignette 9	[redacted]	N/A		
Vignette 10	[redacted]	N/A		
Vignette 11	[redacted]	N/A		
Vignette 12	[redacted]	N/A		
Contact dermatitis	-0.003	N/A	Section B.3.4.4	Assumed to be the same as the disutility applied
Erythema	-0.003	N/A		

Skin irritation	-0.003	N/A		for skin/ subcutaneous tissue disorders in TA577 (which was based on a disutility for rash reported in Nafees *et al.* (2008)[110]
General population age-adjustment (55–64)	0.810	N/A	Section B.3.4.5	Assumed the same values as those in Janssen *et al*. (2014) (EQ-5D index population norms for England using TTO)[111]
General population age-adjustment (65–74)	0.773	N/A	Section B.3.4.5	
General population age-adjustment (75+)	0.703	N/A	Section B.3.4.5	

[a]95% CI were not available for the utility values, and standard errors were instead used to generate values for the DSA and PSA.
Abbreviations: N/A: not applicable; CI: confidence interval; HS: health state.

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

A single SLR was performed to identify relevant published economic evaluations, studies reporting utility values, and studies reporting cost and resource use data in CTCL. Searches were performed in July 2019 and full details of the SLR search strategy and study selection process are reported in Appendix G. The results for cost and healthcare resource use studies identified is provided in Appendix I.

A total of 11 publications reporting on 11 unique studies with cost and resource use data met the eligibility criteria and were included in the SLR. However, no extractions were carried out for non-quantitative cost and resource use data, or for cost and resource use data specifically and solely associated with a non-comparator intervention. As such, a total of four publications reporting on four studies were extracted. However, no suitable UK-based studies reporting outcomes for the non-drug healthcare resource use associated with treatment of patients with MF-CTCL were identified.

The *de novo* economic analysis was conducted from the NHS and PSS perspective and therefore included only costs that would be incurred by the NHS and PSS. Appropriate sources of unit costs, such as NHS reference costs 2017–18, the British National Formulary (BNF) and the electronic Marketing Information Tool (eMIT) were used for cost inputs in the model.[112-114] Resource use for MF-CTCL patients was evaluated based on the results of a healthcare

resource use study (see Section B.3.5.1 below), in the absence of a suitable UK-based study reporting outcomes for the non-drug healthcare resource use associated with MF-CTCL.

Overall, only direct medical costs were considered in the economic model from the NHS and PSS perspective and these are described in more detail below. In the absence of any additional sources of evidence, assumptions were made for cost/resource inputs included in the model where necessary and were validated through discussions with clinical experts. The impact on caregivers, whether they be formal caregivers or informal caregivers (e.g. family members) is not considered in the analysis.

B.3.5.1 Intervention and comparators' costs and resource use

Treatment acquisition costs

Intervention: chlormethine gel

As described in Section B.3.2.3 above, within the economic model, 0.99 g chlormethine gel was assumed to be applied daily to patients in Stage IA and those in Stage IIB–IV with Low Skin Burden, and 2.93 g chlormethine gel applied once daily to patients in Stage IB/IIA and those in Stage IIB–IV with High Skin Burden, leading to a weighted average dose across Stages IA–IIA of 1.80 g as per the median dose received by patients in Study 201 (and referenced accordingly in the SmPC for chlormethine gel).[11] The cost per tube (pack) of chlormethine gel (60.0 g) was £1,000, based on Recordati Rare Diseases/Helsinn Healthcare SA data on file.

Comparator: Phototherapy

PUVA

As described in Section B.3.2.3 above, PUVA comprises of patients receiving oral psoralen followed by treatment with UVA, and was assumed to be administered three times weekly for a maximum of 13 weeks in line with the BAD guidelines.[3, 91]

UVB

As described in Section B.3.2.3 above, UVB was assumed to be provided two and a half times weekly, for a maximum of 13 weeks in line with the BAD guidelines (two to three times weekly).[3]

The cost of phototherapy (£294.20) was derived from Fonia *et al.* (2010) and inflated to the current cost year from 2010. Fonia *et al.* has been used in several NICE technology appraisals for psoriasis as the source of phototherapy costs (TA475, TA511, TA575 and TA442).[115] This cost was assumed to include the cost of psoralen and the administration of the phototherapy procedure itself. As phototherapy is administered from a device rather than purchased as a consumable product in the manner of a drug the cost of phototherapy is included as an "administration cost" rather than a "drug cost" in the cost-effectiveness model. This is a difference of nomenclature only and has no impact on results, as acquisition and administration costs are applied together in the model. The cost from Fonia *et al.* (2010) was for phototherapy in general, rather than either of PUVA or UVB specifically; therefore, the cost from this source was used for both PUVA and UVB in the model in the absence of more granular cost data.[115]

Subsequent treatments

As described in Section B.3.2.3 above, once patients transitioned into the Progressed from 1L health state, or patients who finished their 13-week course of phototherapy and were in the initial health state (Low or High Skin Burden) or Reduced Skin Burden, were assumed to receive either bexarotene (300 mg/m^2 daily) or pegylated IFN-α (1.5 μg/kg weekly) in a 50:50 ratio, based on clinical expert opinion, and irrespective of disease stage.

The costs of bexarotene and pegylated IFN-α were derived from the BNF (2019): £937.50 per pack (100 × 75.0 mg) for bexarotene and £76.50 per pack (1 × 180.0 μg) for pegylated IFN-α. It was assumed that there would be no vial sharing of pegylated IFN-α.

Background treatments for advanced disease stages

As described in Section B.3.2.3 above, within the model patients in advanced stage disease were assumed to receive systemic treatment for disseminated disease in addition to their skin lesion treatments, and this systemic treatment was modelled as a bundle of treatments including bexarotene (300 mg/m^2 daily), ECP (two consecutive days every four weeks; UVADEX treatment volume × 0.017 [mL] per ECP session), gemcitabine (1000 mg/m^2 three days every 28 days), methotrexate (23.44 mg weekly) and pegylated IFN-α (1.5 μg/kg weekly).

The costs for bexarotene, gemcitabine and pegylated IFN-α were derived from the BNF and for both gemcitabine and pegylated IFN-α, it was assumed that there was no vial sharing. The cost for methotrexate was derived from the eMIT.

A summary of the drug costs included within the cost-effectiveness model is presented in Table 57 below.

Table 57: Drug costs included within the cost-effectiveness model

Treatment	Unit size	Units per pack	Cost per pack	Dose per administration	Dose frequency per month	Drug cost per month	Source
Chlormethine gel (Low Skin Burden)	60.00 g	1	£1,000.00	0.99 g	30.44	£500.00	Recordati Rare Diseases/Helsinn Healthcare SA data on file
Chlormethine gel (High Skin Burden)	60.00 g	1	£1,000.00	2.93 g	30.44	£1,486.91	
Bexarotene	75.00 mg	100	£937.50	574.09 mg	30.44	£1,997.46	BNF
Gemcitabine	2000.00 mg	1	£26.86	1913.64 mg	3.26	£87.59	BNF (assumes no vial sharing)
Methotrexate	2.50 mg	100	£4.37	23.44 mg	4.35	£1.78	eMIT
Pegylated IFN-α	180.00 µg	1	£76.50	119.94 µg	4.35	£332.64	BNF (assumes no vial sharing)

Note that the costs for phototherapy and ECP are included in the administration costs of the cost-effectiveness model.
Abbreviations: BNF: British National Formulary; eMIT: Drugs and pharmaceutical electronic market information tool; IFN-α: interferon alpha.

Administration costs

No administration costs were associated with chlormethine gel due to the method of administration (topical gel). As described above, the cost for phototherapy from Fonia *et al.* (2010; inflated to the current cost year) was assumed to capture drug costs and administration costs.[115]

In terms of subsequent therapies or those for the background treatment of advanced disease, there were also no administration costs assumed to be associated with bexarotene, methotrexate, or pegylated IFN-α, given the oral, oral and assumed self-injected methods of administration, respectively. Omitting administration costs for oral drugs is in line with the ERGs preferred base case for TA577.[56] The administration cost for ECP was derived by summing the phototherapy cost from Fonia *et al.* (2010) and the cost for leucopheresis from the NHS reference costs 2017–2018 (SA43Z), whilst the administration cost for gemcitabine was also derived from the NHS reference costs 2017–2018 (SB12Z Outpatient Deliver Simple Parenteral Chemotherapy at First Attendance).[112, 115]

A summary of the drug costs included within the cost-effectiveness model is presented in Table 58 below.

Table 58: Administration costs included within the cost-effectiveness model

Treatment	Administrations per Month	Cost per Administration	Administration Cost per Month	Source
PUVA	13.04	£294.20	£3,837.73	Fonia *et al.* (2010)[115]
UVB	10.87	£294.20	£3,198.11	
ECP	2.17	£756.32	£1,644.32	NHS reference costs 2017–2018 (SA43Z – Leucopheresis) and Fonia *et al.* (2010)[112, 115]
Gemcitabine	3.26	£247.74	£807.92	NHS reference costs 2017–2018 (SB12Z – Outpatient Deliver Simple Parenteral Chemotherapy at First Attendance)[112]

Abbreviations: ECP: extracorporeal photopheresis; NHS: National Health Service; PUVA: psoralen-ultraviolet A; UVB: ultraviolet B.

Total treatment costs

A summary of the total treatment costs per month for chlormethine gel and phototherapy, treatments received in the Progressed from 1L health state (i.e. bexarotene and pegylated IFN-α) and for the bundle of treatments for advanced disease is presented in Table 59 below.

Table 59: Total treatment costs in the cost-effectiveness model

Treatment	Total treatment cost per month
Chlormethine gel (Low Skin Burden)	£500.00

Chlormethine gel (High Skin Burden)	£1,486.91
Phototherapy	£3,458.52
Progressed from 1L	£1,258.44
Bundle of treatments for advanced disease	£1,123.73

Abbreviations: 1L: first line.

De novo healthcare resource use study

As no suitable UK-based studies reporting outcomes for the non-drug healthcare resource use associated with treatment of patients with MF-CTCL were identified in the economic SLR, further targeted literature searches of internal materials and analysis of the PROCLIPI registry were conducted, which confirmed that this information was not available from other sources.

Therefore, a *de novo* healthcare resource use study was conducted, in order to estimate the average healthcare resource use associated with patients with MF-CTCL in each disease stage. For this healthcare resource use study, a questionnaire was developed which listed resources such as: consultations, monitoring investigations and tests, radiotherapy treatment, and wound dressings. The resource types which were included in this questionnaire were validated as relevant for patients with MF-CTCL by a leading UK-based clinical expert. The questionnaire was structured to collect estimates of the magnitude (i.e. the percentage of patients in each disease stage utilising each resource item) and the frequency of resource use (on a per week or per year basis). The values collected were then adjusted for use in the cost-effectiveness model (i.e. to reflect the 1-month cycle length).

The survey was distributed in an electronic format to UK-based clinicians (n=7) with first-hand experience in treating the MF-CTCL patient population. The clinicians that participated in this healthcare resource use study were the same clinicians that also participated in the utility study (see Section B.3.4.3) and responses were collected and analysed to provide mean resource use values that were used to calculate cost-effectiveness model inputs for the costs associated with use of these resources in Stage IA–IIA MF-CTCL and Stage IIB–IVB MF-CTCL.

HCP consultations and appointments

Patients at differing stages of disease may have different needs with respect to the types of consultations and appointments that they require, and this would be associated with different levels of resource use and cost.

The monthly mean resource use associated with HCP consultations and appointments, as determined in the clinician questionnaire, is presented in Table 60. For this resource, patients from Stage IA and Stage IB/IIA were grouped together. The decision to group these two stages was based on clinical expert opinion that HCP consultations and appointment resource use would not differ substantially between these early disease stage patient groups.[1]

Table 60: HCP consultation and appointment inputs for the cost-effectiveness model

Consultation/appointment type	Mean proportion of patients, % (range)	Mean frequency per month (range)	Average cost per patient per month
Early stage MF-CTCL (Stage IA–IIA) – outpatient appointments			

Oncologist	[redacted]	[redacted]	[redacted]
Consultant oncologist	[redacted]	[redacted]	[redacted]
Clinical nurse	[redacted]	[redacted]	[redacted]
Psychologist	[redacted]	[redacted]	[redacted]
Dermatologist	[redacted]	[redacted]	[redacted]
Early stage MF-CTCL (Stage IA–IIA) – inpatient appointments			
Dermatology day centre or oncology ward	[redacted]	[redacted]	[redacted]
Early stage MF-CTCL (Stage IA–IIA) – home visits			
District nurse	[redacted]	[redacted]	[redacted]
Macmillan nurse	[redacted]	[redacted]	[redacted]
Palliative care support team	[redacted]	[redacted]	[redacted]
Late stage MF-CTCL (Stage IIB–IVB) – outpatient appointments			
Oncologist	[redacted]	[redacted]	[redacted]
Consultant oncologist	[redacted]	[redacted]	[redacted]
Clinical nurse	[redacted]	[redacted]	[redacted]
Psychologist	[redacted]	[redacted]	[redacted]
Dermatologist	[redacted]	[redacted]	[redacted]
Late stage MF-CTCL (Stage IIB–IVB) – inpatient appointments			
Dermatology day centre or oncology ward	[redacted]	[redacted]	[redacted]
Late stage MF-CTCL (Stage IIB–IVB) – home visits			
District nurse	[redacted]	[redacted]	[redacted]
Macmillan nurse	[redacted]	[redacted]	[redacted]
Palliative care support team	[redacted]	[redacted]	[redacted]

[a] Costs associated with consultations and appointments are determined by the 2017/18 NHS reference costs.[112]
Abbreviations: MF-CTCL: mycosis fungoides- cutaneous T-cell lymphoma.

Investigations and tests

Patients in different stages of disease were also expected to have differing requirements with regards to clinical investigations and tests that may be received in order to monitor their health and the status of their disease. The types of investigations and tests relevant for MF-CTCL patients which were included in the clinician questionnaire were validated by clinical expert opinion.

The monthly mean resource use associated with HCP consultations and appointments, as determined in the clinician questionnaire, is presented in Table 61. For this resource, patients from Stage IA and Stage IB/IIA were grouped together. The decision to group these two stages was based on clinical expert opinion that resource use associated with clinical investigations and tests would not differ substantially between these early disease stage patient groups.[1]

Table 61: Clinical investigation/test inputs for the cost effectiveness model

Investigation/test type	Mean proportion of patients, % (range)	Mean frequency per month (range)	Average cost per patient per month[a]

Early stage MF-CTCL (Stage IA–IIA)			
Complete blood count	[redacted]	[redacted]	[redacted]
Liver function test	[redacted]	[redacted]	[redacted]
Urea and electrolytes test	[redacted]	[redacted]	[redacted]
LDH	[redacted]	[redacted]	[redacted]
CT scan	[redacted]	[redacted]	[redacted]
PET scan[b]	[redacted]	[redacted]	[redacted]
Flow cytometry	[redacted]	[redacted]	[redacted]
Late stage MF-CTCL (Stage IIB–IVB)			
Complete blood count	[redacted]	[redacted]	[redacted]
Liver function test	[redacted]	[redacted]	[redacted]
Urea and electrolytes test	[redacted]	[redacted]	[redacted]
LDH	[redacted]	[redacted]	[redacted]
CT scan	[redacted]	[redacted]	[redacted]
PET scan[b]	[redacted]	[redacted]	[redacted]
Flow cytometry	[redacted]	[redacted]	[redacted]

[a] Costs associated with clinical investigations and tests were determined using the 2017/18 NHS reference costs.[112] [b] According to responses collected in the survey PET scans are administered to MF-CTCL patients most commonly in the outpatient setting and therefore the NHS reference costs associated with this have been used (RN07A).
Abbreviations: CT: computed tomography; LDH: lactate dehydrogenase; MF-CTCL: mycosis fungoides-cutaneous T-cell lymphoma; PET: positron-emission tomography.

Radiotherapy treatment

Localised radiotherapy may be used to treat plaques or tumours in MF-CTCL patients, predominantly as a palliative approach.[3] A question was included in the clinician questionnaire to seek clinical expert opinion on how radiotherapeutic treatment differs between the disease stages in the model.

The monthly mean resource use associated with radiotherapy, as determined in the clinician questionnaire, is presented in Table 62. For this resource, patients from Stage IA and Stage IB/IIA were grouped together. The decision to group these two stages was based on clinical expert opinion that resource use associated with radiotherapy would not differ substantially between these two groups.[1]

Table 62: Radiotherapy inputs for the cost effectiveness model[a]

MF-CTCL disease stage	Mean proportion of patients receiving radiotherapy, % (range)	Mean frequency per month (range)	Mean number of fractions per dose (range)	Average cost per patient per month[b]
Early stage MF-CTCL (Stage IA–IIA)	[redacted]	[redacted]	[redacted]	[redacted]
Late stage MF-CTCL (Stage IIB–IVB)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Survey responses on radiotherapy use were based on n=6 responses as one clinician surveyed did not respond to this question. [b] Costs associated with radiotherapy treatment are determined by the 2017/18 NHS reference costs.[112]
Abbreviations: MF-CTCL: mycosis fungoides-cutaneous T-cell lymphoma.

A summary of the cost per cycle for appointments, tests and investigations (i.e. including HCP consultations and appointments, investigations and tests and radiotherapy treatment) by stage from the cost-effectiveness model is presented in Table 63 below.

Table 63: Cost per cycle for appointments, tests and investigations by stage in the cost-effectiveness model

MF-CTCL disease stage	Monitoring cost per cycle
Stage IA	[redacted]
Stage IB/IIA	[redacted]
Stage IIB+	[redacted]

Abbreviations: MF-CTCL: mycosis fungoides-cutaneous T-cell lymphoma.

Wound dressing

Patients with MF-CTCL may require wound dressings for their skin related symptoms. Clinical expert opinion on the use of dressings of various sizes as well as the frequency at which dressings are changed was obtained in the clinician questionnaire, to inform the average level of resource associated with wound dressings for patients at each stage of disease in the model.[1] The cost associated with these dressings was calculated by taking the average cost of the appropriately sized Mepitel, Mepilex, and Allevyn dressings from the BNF database.

The monthly mean resource use associated with wound dressings is presented in Table 64.

Table 64: Wound dressing inputs for the cost-effectiveness model

MF-CTCL disease stage	Mean small[a] dressings required per change (range)	Mean medium[b] dressings required per change (range)	Mean large[c] dressings required per change (range)	Mean dressing changes per month (range)	Average cost[d] of dressings per month
Stage IA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IB/IIA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IIB-IVB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] 5–10 x 5–10 cm. [b] 10–20 x 10–20 cm. [c] 20+ x 20+ cm. [d] Costs associated with dressings were calculated using an average cost for appropriately sized Mepitel, Mepilex and Allevyn dressings, the cost of these dressings was obtained from the BNF.[114]
Abbreviations: MF-CTCL: mycosis fungoides- cutaneous T-cell lymphoma.

Limitations

This study does have some limitations; as MF-CTCL is a rare disease, there are few clinicians in the UK with clinical experience of MF-CTCL. As such, the leading clinician network for cutaneous lymphoma was contacted in order to engage the maximum number of UK clinicians with experience of MF-CTCL who could be enrolled into the healthcare resource study. As a result of this collaboration, a total of seven clinicians recruited from centres across the UK were enrolled

and completed the study. This was considered to be a substantial proportion of eligible clinicians by the leading clinician network. To account for the complexities of MF-CTCL being a dermatological and oncological disease, it was also ensured that clinicians across both specialties were enrolled. The opinions of the respondents are therefore considered to be representative of current clinical opinion in the disease area, representing a sufficient coverage level in terms of clinical experience and geography.

B.3.5.2 Adverse reaction unit costs and resource use

AEs at Grade 3 or greater that occurred in ≥5% of patients for chlormethine gel or the comparator (phototherapy) were included in the cost-effectiveness model, as it was considered that these AEs would be the ones associated with a substantial cost and/or quality of life burden.

A summary of AEs included in the cost-effectiveness model (contact dermatitis, erythema and skin irritation) is presented in Table 52.

To address these AEs, it was assumed that patients were treated with corticosteroids ([redacted], based on most common corticosteroid from Study 201 CSR) for 2–3 weeks, with the cost of hydrocortisone cream derived from the eMIT (2019).[113] A summary of the costs associated with treating AEs in the cost-effectiveness model is presented in Table 65 below, where the cost per duration relates to a 2–3 week course of corticosteroids.

The total cost per cycle for AEs for chlormethine gel and phototherapy, respectively presented in Table 66 below.

Table 65: Treatment acquisition costs for treating AEs in the cost-effectiveness model

AE	Cost per duration	Source
Dermatitis contact	£0.81	eMIT[113]
Erythema	£0.81	
Skin irritation	£0.81	

Abbreviations: AE: adverse event; eMIT: Drugs and pharmaceutical electronic market information tool.

Table 66: Cost per cycle of AEs in the cost-effectiveness model

AE, n (%)	Cost per cycle
Chlormethine gel	£0.18
Phototherapy	£0.00

Abbreviations: AE: adverse event.

B.3.5.3 Miscellaneous unit costs and resource use

End-of-life care costs

In addition to the treatment acquisition and administration, monitoring and resource use and treatment of AEs, end-of-life care costs were applied for one cycle to the proportion of patients who transitioned to the death health state. This cost (£286 per week) was based on a study by Round *et al.* (2015), aligned with the approach taken in TA577.[56, 116] The cost is a generic end-of-life cost for oncology, derived from a weighted mean of the direct and indirect end-of-life costs associated with treatment for lung, breast, colorectal and prostate cancer patients in England and Wales.[116]

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

B.3.6.1 Summary of base-case analysis inputs

A summary of the base case inputs is provided in Table 67.

Table 67: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: SD (distribution)	Reference to section in submission
Mean age	[redacted]	[redacted] (not included in sensitivity analysis)	Section B.3.3.1
Sex (% female)	[redacted]	[redacted] (Beta)[a]	
Mean BSA (m^2)	1.91	0.383 (Normal)[a]	
Mean weight (kg)	79.96	15.99 (Normal)[a]	
Baseline disease distribution, <10% BSA, Stage IIB+	[redacted]	[redacted] (Beta)[a]	
Time point for progression (months)	6.0	1.2 (Normal)[a]	Section B.3.2.2
Treatment duration, maximum no. cycles (months), phototherapy	2.99	0.598 (Gamma)[a]	Section B.3.2.3
Treatment cost per month, chlormethine gel (low skin burden)	£500.00	£100.00 (Gamma)[a]	Section B.3.5.1
Treatment cost per month, chlormethine gel (high skin burden)	£1,486.91	£297.38 (Gamma)[a]	
Treatment cost per month, bexarotene	£2,184.24	£436.85 (Gamma)[a]	
Treatment cost per month, pegylated IFN-α	£332.64	£66.53 (Gamma)[a]	
Treatment cost per month, phototherapy	£3,458.52	£691.70 (Gamma)[a]	
Treatment cost per month, progression from 1L	£1,258.44	£251.69 (Gamma)[a]	
Treatment cost per month, advanced stage treatment	£1,123.73	£224.75 (Gamma)[a]	
Health state utility, Stage IA, mSWAT range: 0	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	Section B.3.4.3

Health state utility, Stage IA, mSWAT range: 1-10	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	
Health state utility, Stage IA, mSWAT range: 11-20	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	
Health state utility, Stage IA, mSWAT range: >20	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	
Health state utility, Stage IB/IIA, mSWAT range: 0	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	
Health state utility, Stage IB/IIA, mSWAT range: 1-15	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	
Health state utility, Stage IB/IIA, mSWAT range: 16-60	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	
Health state utility, Stage IB/IIA, mSWAT range: >60	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	
Health state utility, Stage IIB+, mSWAT range: 0	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	
Health state utility, Stage IIB+, mSWAT range: 1-35	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	
Health state utility, Stage IIB+, mSWAT range: 36-65	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	
Health state utility, Stage IIB+, mSWAT range: >65	[redacted]	[redacted] (ordered variable, as per method in Ren *et al.* [2018])[117]	
AE disutility per cycle, chlormethine gel	0.007	0.001 (Gamma)[a]	Section B.3.4.4
AE disutility per cycle, phototherapy	0.000	0.000 (Gamma)[a]	
Stage IA monitoring and resource use cost per cycle, appointments/tests and investigations	[redacted]	[redacted] (Gamma)[a]	Section B.3.5.1

Stage IB/IIA monitoring and resource use cost per cycle, appointments/tests and investigations	[redacted]	[redacted] (Gamma)[a]	
Stage IIB+ monitoring and resource use cost per cycle, appointments/tests and investigations	[redacted]	[redacted] (Gamma)[a]	
Stage IA monitoring and resource use, skin-burden specific costs per cycle	[redacted]	[redacted] (Gamma)[a]	
Stage IB/IIA monitoring and resource use, skin-burden specific costs per cycle	[redacted]	[redacted] (Gamma)[a]	
Stage IIB+ monitoring and resource use, skin-burden specific costs per cycle	[redacted]	[redacted] (Gamma)[a]	
End-of-life care cost	£1,144.00	£228.80 (Gamma)[a]	Section B.3.5.3
AE cost, chlormethine gel	£0.18	£0.04 (Gamma)[a]	Section B.3.5.2
AE cost, phototherapy	£0.00	£0.00 (Gamma)[a]	
Stage IA monthly mortality probability	0.0016	0.0003 (Beta)[a]	Section B.3.3.3
Stage IB/IIA monthly mortality probability	0.0028	0.0006 (Beta)[a]	
Stage IIB+ monthly mortality probability	0.0147	0.0029 (Beta)[a]	
Baseline disease distribution, Stage IA	[redacted]	N/A, dependent variable (Dirichlet)	Section B.3.3.1
Baseline disease distribution, Stage IB/IIA	[redacted]	N/A, dependent variable (Dirichlet)	
Baseline disease distribution, Stage IIB+	[redacted]	N/A, dependent variable (Dirichlet)	
Transition probabilities between disease stages	N/A	N/A, dependent variable (Dirichlet)	Section B.3.3.2
Skin burden transition probabilities, Stage IA (low skin burden), chlormethine gel	N/A	N/A, dependent variable (Dirichlet)	
Skin burden transition probabilities, Stage IB/IIA (high skin	N/A	N/A, dependent variable (Dirichlet)	

burden), chlormethine gel			
Skin burden transition probabilities, Stage IIB+ (low skin burden), chlormethine gel	N/A	N/A, dependent variable (Dirichlet)	
Skin burden transition probabilities, Stage IIB+ (high skin burden), chlormethine gel	N/A	N/A, dependent variable (Dirichlet)	
Skin burden transition probabilities, Stage IA (low skin burden), phototherapy	N/A	N/A, dependent variable (Dirichlet)	
Skin burden transition probabilities, stage IB/IIA (high skin burden), phototherapy	N/A	N/A, dependent variable (Dirichlet)	
Skin burden transition probabilities, Stage IIB+ (low skin burden), phototherapy	N/A	N/A, dependent variable (Dirichlet)	
Skin burden transition probabilities, Stage IIB+ (high skin burden), phototherapy	N/A	N/A, dependent variable (Dirichlet)	

[a] Standard deviation assumed to be 20% of the mean value
Abbreviations: 1L: first line; AE: adverse event; BSA: body surface area; CI: confidence interval; IFN-α: interferon-α; kg: kilogram; mSWAT: modified Severity Weighted Assessment Tool; N/A: not applicable; SD: standard deviation.

B.3.6.2 Assumptions

A summary of key model assumptions and their justification is provided in Table 68.

Table 68: Summary of key model assumptions

Model assumption	Justification
Effectiveness of modelled therapies (chlormethine gel, phototherapy) is independent of disease stage (i.e. efficacy observed in early stage populations is assumed to translate to advanced stage populations with the same skin burden)	SDTs aim to treat local disease (i.e. skin patches and plaques) rather than targeting cancer cell dissemination. In relation to the TNMB staging system, SDTs therefore impact the tumour stage but evidence for their impact on dissemination of the cancer beyond the skin is limited. As per the TNMB disease stage definitions (Table 4), patients in advanced stage disease can have the same tumour rating (i.e. same level of patch, papule or plaque coverage) as patients in early stage disease. For such advanced patients for whom level of local skin disease is the same as for an early stage patient, it is reasonable to assume that efficacy of SDTs in treating these local skin symptoms in early stage disease would be generalisable to treating equivalent skin symptoms in advanced stage disease.
Effectiveness of phototherapy is the same regardless of whether patients have Low or	Evidence for modelling the effectiveness of phototherapy was limited to a small number of studies for which reported data was limited. Data was available for CR and PR rates, but no studies

High Skin Burden, with the exception of probability of achieving CR post PR which is assumed the same as chlormethine gel (and therefore differs between Low and High Skin Burden)	reported these results stratified by skin burden. Therefore, as a simplifying assumption, CR and PR rates for phototherapy were assumed to be independent of level of Skin Burden. As data for probability of CR post PR were not available for phototherapy, it was necessary to assume the same probabilities as for chlormethine gel.
Patients who achieve CR are assumed to stop treatment for as long as they remain in the 'No Skin Burden' health state	Clinical expert feedback supported that patients who achieve a CR would not be expected to continue treatment.[4]
Patients are assumed to not be classed as having progressive disease within the first 6 months of the model	Based on clinical expert opinion, clinicians would wait for 6 months after initiating a new treatment before moving a patient to a new treatment if their skin symptoms had worsened sufficiently.
Patients who experience skin symptom progression (either initially or via a loss of an initial response) and enter the 'Progressed from 1L' health state are assumed to terminate their first-line treatment and move to receive subsequent therapy (a 50%/50% mix of IFN-α and bexarotene)	Patients who have experienced progression of skin symptoms on their first-line treatment would not continue to receive this treatment. As their disease remains uncontrolled, clinicians would move to a second-line treatment. As per the BAD guidelines and clinical expert feedback, clinicians would most likely escalate treatment to a systemic therapy (IFN-α or bexarotene).
Subsequent therapies received by patients would be a 50%/50% mix of IFN-α and bexarotene	Clinical expert feedback indicated that equal proportions of patients whose skin symptoms progress on their first-line therapy would be escalated to IFN-α and bexarotene.[1]
Disease stage progression (i.e. progression through stages IA, IB, IIA, etc.) is independent of modelled treatments and unidirectional	SDTs aim to treat local disease (i.e. skin patches and plaques) rather than targeting cancer cell dissemination. The evidence base for SDTs is therefore focused on outcomes relating to skin response rather than impact on disease stage progression. Study 201 did not evaluate the impact of chlormethine gel on disease stage progression. Whilst further research may elucidate a role for treatment of skin symptoms in delaying or preventing progression of the underlying cancer to more advanced disease stages, there is currently a lack of evidence to support such benefits. Clinical expert feedback indicated that patients would not in practice be considered to have achieved regressed disease stage even if their skin symptoms improved.[4]
Patients experiencing disease stage progression (i.e. progression through stages IA, IB, IIA, etc.) can be modelled as having experienced progression in their skin symptoms (i.e. move to the 'Progressed from 1L' health state)	For patients who are in an initial High Skin Burden or Low Skin Burden health state when they experience progression in disease stage (e.g. from Stage IA to Stage IB), it was necessary to make an assumption as to which skin burden health state they should enter in the new, more advanced disease stage. It was considered inappropriate to place such patients in an initial skin burden (High or Low) health state in their new disease stage because the transition probabilities applied to the initial health states are reflective of initial treatment. Reapplying these transition probabilities to patients who were not new to a given skin burden state (and indeed may have spent significant time in that skin burden state prior to disease stage progression) was therefore considered inappropriate. Therefore, it was assumed

	that patients would move to the 'Progressed from 1L health state' in their new disease stage. It should be noted that the relative timescales of treatment response versus disease progression mean that by the time patients' disease stage progresses, very few patients are modelled to still be in the initial skin burden health state. Therefore, in practice this assumption affects only a small number of patients in the model.
Duration of CR is the same for chlormethine gel and phototherapy	In the absence of robust comparative data on duration of CR it was considered appropriate to assume the same duration of CR. However, it should be noted that BAD guidelines note that 'duration of response is often limited' with phototherapy, meaning that this assumption may be conservative with respect to the cost-effectiveness of chlormethine gel.[3]
Probability of obtaining CR following PR is the same for chlormethine gel and phototherapy	In the absence of relevant reported data for phototherapy on probability of CR following PR, this transition probability was assumed equal to that for chlormethine gel.
Probability of loss of PR is the same as probability of experiencing skin symptom progression upon in initial treatment	This assumption was made in the absence of data from Study 201 with which to estimate the transition probability from Reduced Skin Burden to Progressed from 1L. This assumption was validated by clinical expert opinion.[1] This is a conservative assumption with respect to relapse rates as it would be expected that patients who previously had a PR would be less likely to relapse compared to those who never had a PR.
Probability of progression and SD for phototherapy is equal	The majority of the identified phototherapy studies reported data only for CR and PR and not for SD of progressive disease. In the absence of consistent reporting of rates of progressive and SD it was considered pragmatic to assume that the proportion of patients not achieving CR or PR would be split equally between stable and progressive disease. This is consistent with evidence from one of the studies (EORTC 21011 [Whittaker *et al. 2012*]) [91] that reported equal rates of SD and progressive disease.
All Stage IB/IIA patients were assumed to have High Skin Burden at model entry	By the TNMB classification system definitions, all Stage IB patients have High Skin Burden (i.e. ≥10% BSA). Stage IIA patients may have Low or High Skin Burden by the TNMB classification system, but based on data from PROCLIPI, the majority of Stage IIA patients ([redacted]) have at least 10% BSA affected.
Dose of chlormethine gel differs by disease stage, based on patient skin burden	As chlormethine gel is applied topically to skin lesions, it is considered clinically realistic to assume that patients with higher BSA would use a higher dose of chlormethine gel each administration.
Phototherapy can be modelled as a single intervention with regards to effectiveness (i.e. PUVA and UVB have the same effectiveness)	The clinical SLR identified no RCTs comparing the relative efficacy of PUVA and UVB. The nature of the studies identified for phototherapy precludes a meaningful comparison of the relative efficacy of PUVA and UVB. The BAD guidelines do not provide a discussion on the relative efficacy of PUVA and UVB, noting only that a retrospective case series of narrow band UVB show it to be as effective as PUVA for treatment of early stage disease.[3]
Patients would receive phototherapy for a maximum of 13 weeks, and time to response to phototherapy is equal to this maximum treatment duration	BAD guidelines cite PUVA and narrow band UVB regimens as being 12–14 weeks. Clinical expert opinion confirmed that in clinical practice phototherapy would be limited to a treatment course of 13 weeks in order to limit phototherapy exposure to avoid the risk of secondary malignancies.

Phototherapy does not carry risk of secondary malignancies when treatment is restricted to a single course of 13 weeks	Given the cost-effectiveness model assumes a restricted treatment course of phototherapy (13 weeks) would be used in clinical practice to avoid the risk of secondary malignancies, it was considered appropriate to therefore assume no risk of secondary malignancies with phototherapy when modelled in this manner.
No vial sharing of pegylated IFN-α or gemcitabine	Simplifying assumption given that these therapies were included only as subsequent therapies/background systemic therapies
The cost of phototherapy in psoriasis is an appropriate proxy for the cost of phototherapy in MF-CTCL	No sources for an MF-CTCL-specific cost of phototherapy were identified. The cost of phototherapy in psoriasis from Fonia *et al.* (2010) has been used in several NICE technology appraisals in psoriasis (TA475, TA511, TA575 and TA442).[115]
Disutility for contact dermatitis assumed equal to disutility for rash	The disutility for rash reported in Nafees *et al.* (2008) was used in the NICE appraisal for brentuximab vedotin in CTCL (TA577) for the disutility associated with skin/subcutaneous tissue disorders.[110]

Abbreviations: 1L: first line; BAD: British Association of Dermatologists; BSA: body surface area; CR: complete response; CTCL: cutaneous T-cell lymphoma; IFN-α: interferon-alpha; MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; NICE: National Institute for Health and Care Excellence; PR: partial response; PUVA: psoralen-ultraviolet A; RCT: randomised controlled trial; SD: stable disease; SDT: skin-directed therapy; SLR: systematic literature review; TNMB: Tumour, nodes, metastasis, blood; UVB: ultraviolet B.

B.3.7 *Base case results*

B.3.7.1 Base case incremental cost-effectiveness analysis results

In the base case analysis, chlormethine gel and phototherapy were associated with total QALYs of 6.42 and 6.57, respectively. Phototherapy was associated with an incremental cost of £7,000 versus chlormethine gel. Therefore, the base case ICER for chlormethine gel was a south-west ICER of £44,915, which should be interpreted as the ICER for phototherapy versus chlormethine gel (see Table 69).

Table 69: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Chlormethine gel	£239,125	9.96	6.42	-	-	-	-
Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,000	0.00	-0.16	£44,915

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

The results of the PSA (1,000 iterations) are presented in Table 70. The incremental probabilistic results and ICER (that take into account the combined uncertainty across model parameters) are similar to those estimated in the base case analysis, confirming the robustness of the base case analysis.

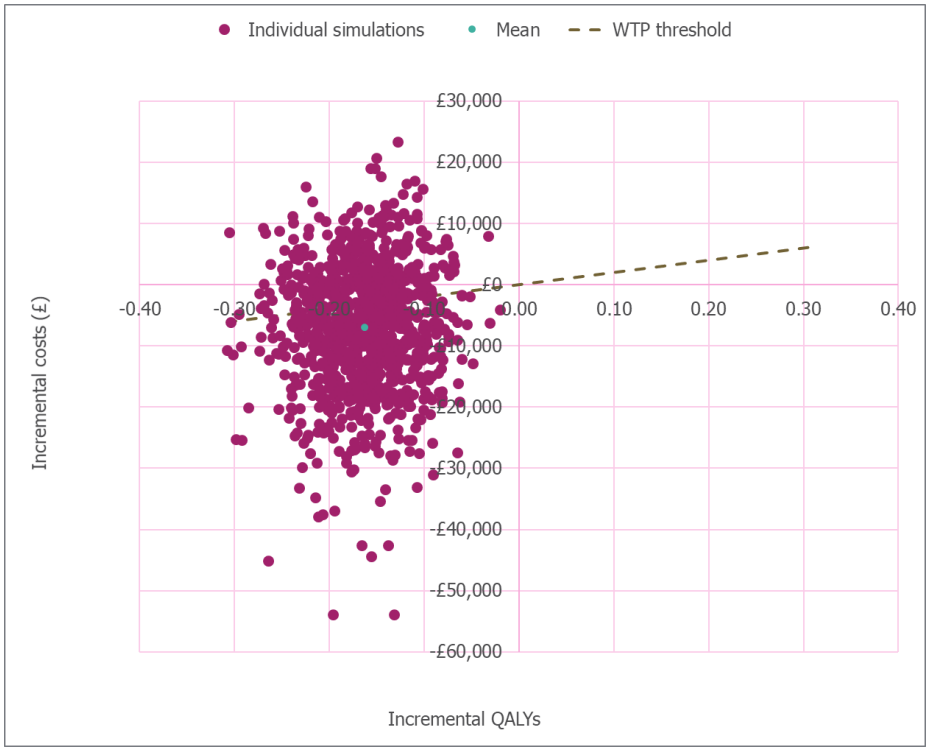
Table 70: Base case results (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Chlormethine gel	£241,136	6.54	-	-	-
Phototherapy (PUVA/UVB)	£248,055	6.70	-£6,920	-0.16	£42,477

Abbreviations: ICER: incremental cost-effectiveness ratio; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

A scatter plot showing the incremental costs and QALYs for chlormethine gel versus phototherapy (PUVA/UVB) is presented in Figure 14. Assuming a willingness-to-pay threshold of £20,000 per QALY gained, the probability of chlormethine gel being the most cost-effective treatment option was 62.40%.

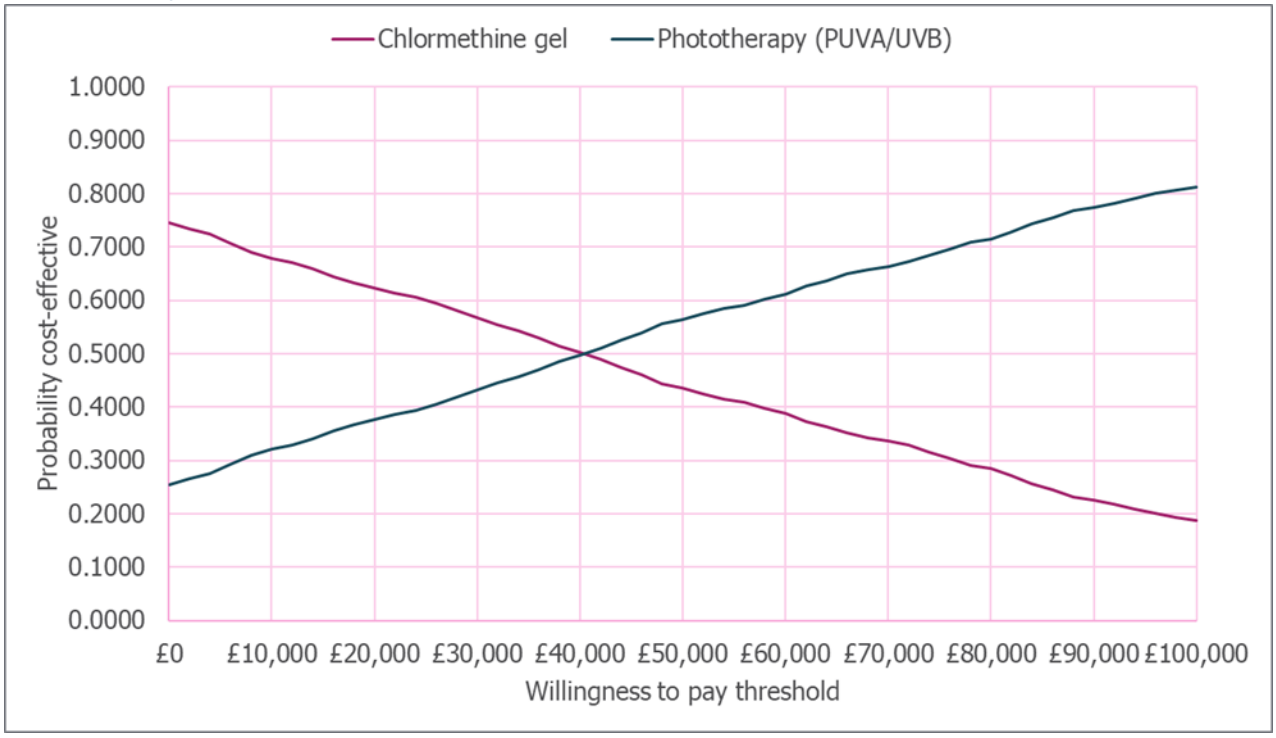
Figure 14: PSA scatterplot for chlormethine gel versus phototherapy (PUVA/UVB)



Abbreviations: PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; WTP: willingness-to-pay.

Cost-effectiveness acceptability curves for chlormethine gel versus phototherapy (PUVA/UVB) are presented in Figure 15.

Figure 15: Cost-effectiveness acceptability curve for chlormethine gel versus phototherapy (PUVA/UVB)



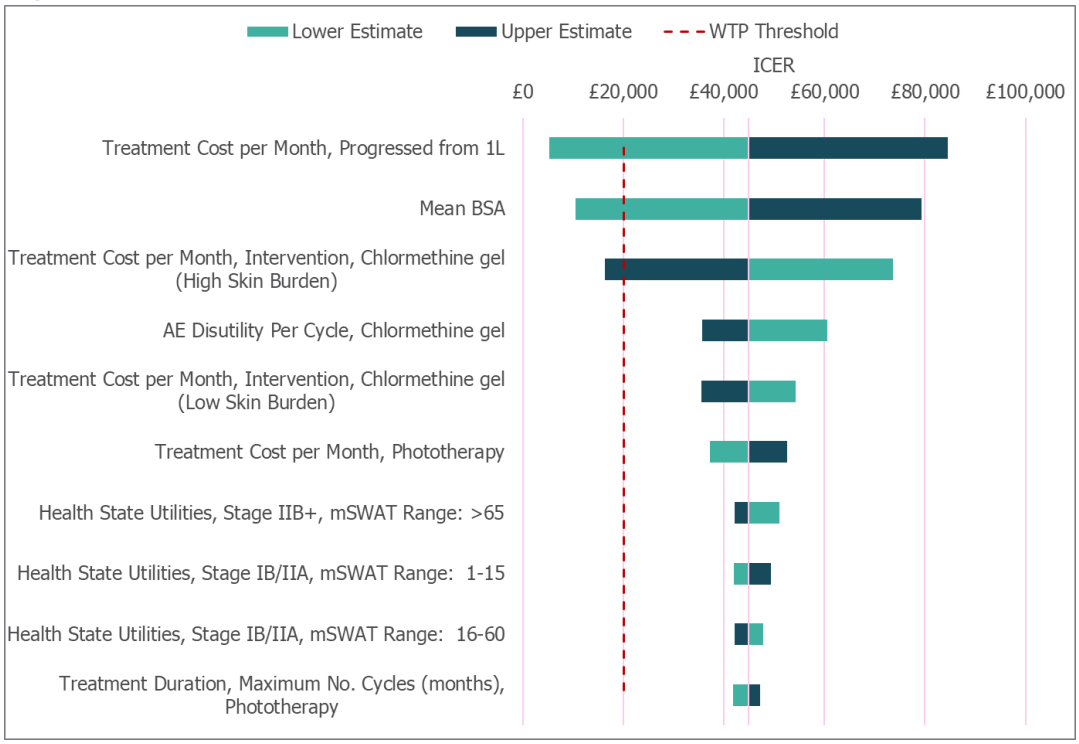
Abbreviations: PUVA: psoralen-ultraviolet A; UVB: ultraviolet B.

B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted by varying all parameters for which there were single input values in the model. Health state utility values within the model were varied using the standard deviation obtained directly from the vignettes which informed the mean values, with the upper and lower values of each adjacent utility value bound by one another in order to maintain appropriate ordering. In the absence of data on the variability around a particular value, all other model inputs were varied by ±20% in the DSA. Finally, transition probabilities were not included within the DSA given that they are dependent variables.

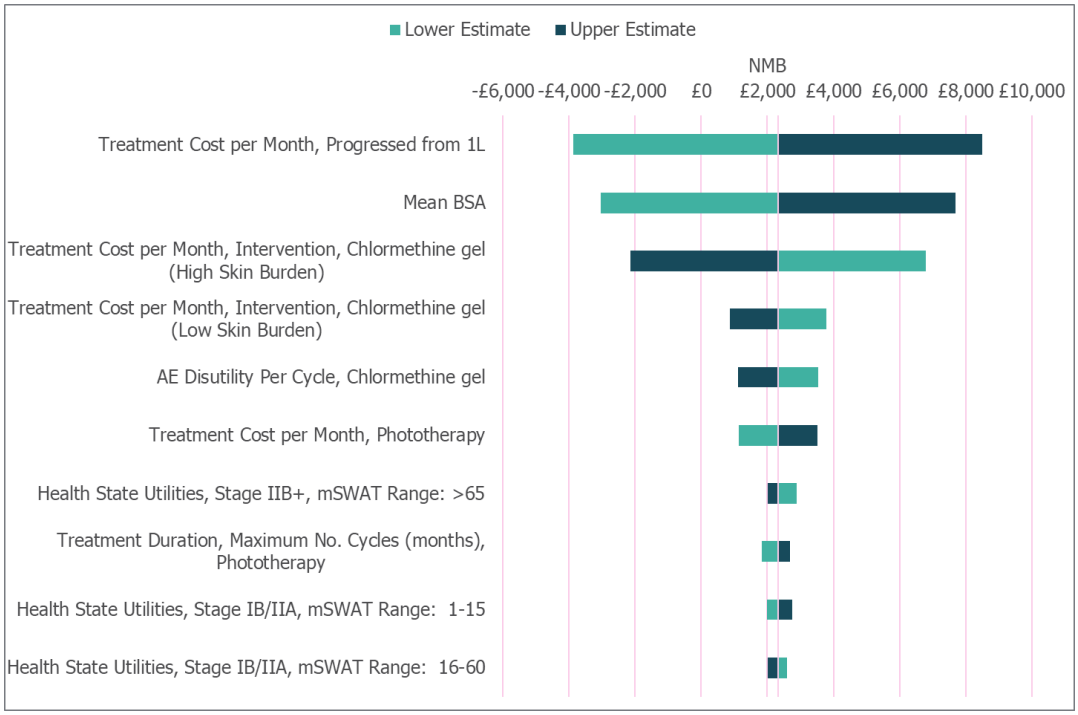
Tornado diagrams showing the top ten drivers of cost-effectiveness in the comparison of chlormethine gel versus phototherapy (PUVA/UVB) are presented in Figure 16 to Figure 19. The ICERs reported in Figure 16 are interpretable as the ICER for phototherapy versus chlormethine gel, given the south-west nature of the ICERs for chlormethine gel. Across these tornado plots, the most influential parameters were the treatment cost per month for Progressed from 1L, the mean BSA (m^2) and the treatment cost per month for chlormethine gel (High Skin Burden). Figure 16 shows that the finding that the ICER for phototherapy versus chlormethine gel is above £20,000 per QALY gained holds under most parameter variations in the DSA.

Figure 16: DSA – ICER tornado plot of the top ten most influential parameters



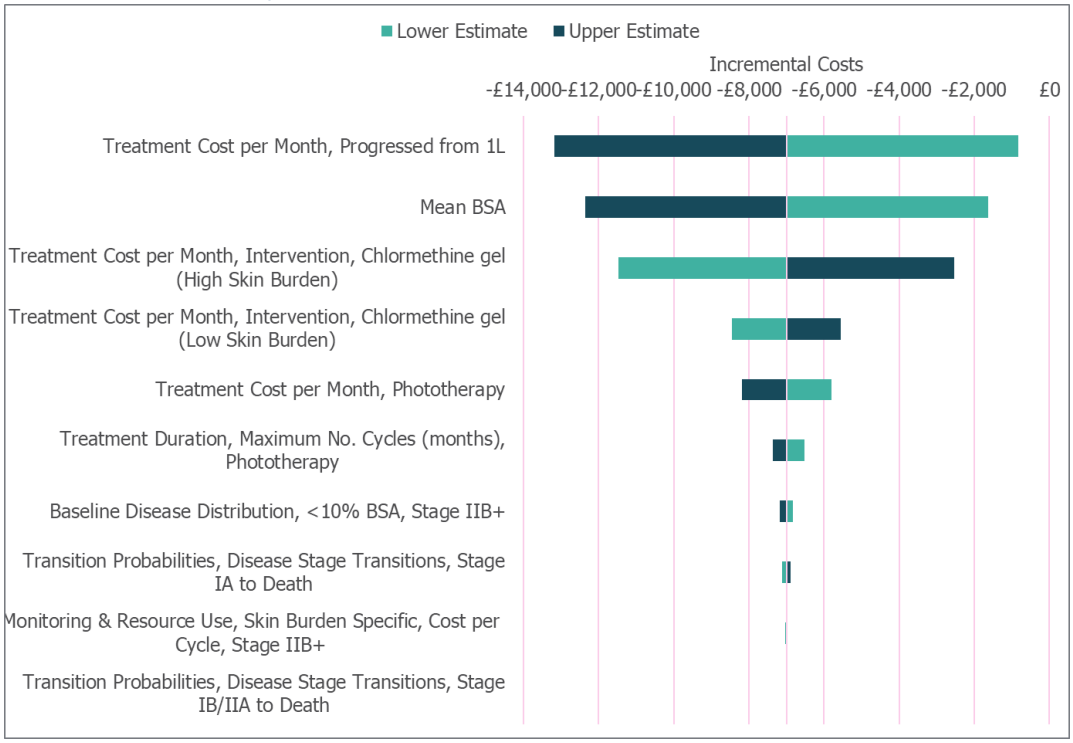
Abbreviations: 1L: first line; AE: adverse event; BSA: body surface area; DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; mSWAT: modified Severity Weighted Assessment Tool; PUVA: psoralen-ultraviolet A; UVB: ultraviolet B; WTP: willingness-to-pay.

Figure 17: DSA – NMB tornado plot of the top ten most influential parameters versus phototherapy (PUVA/UVB)



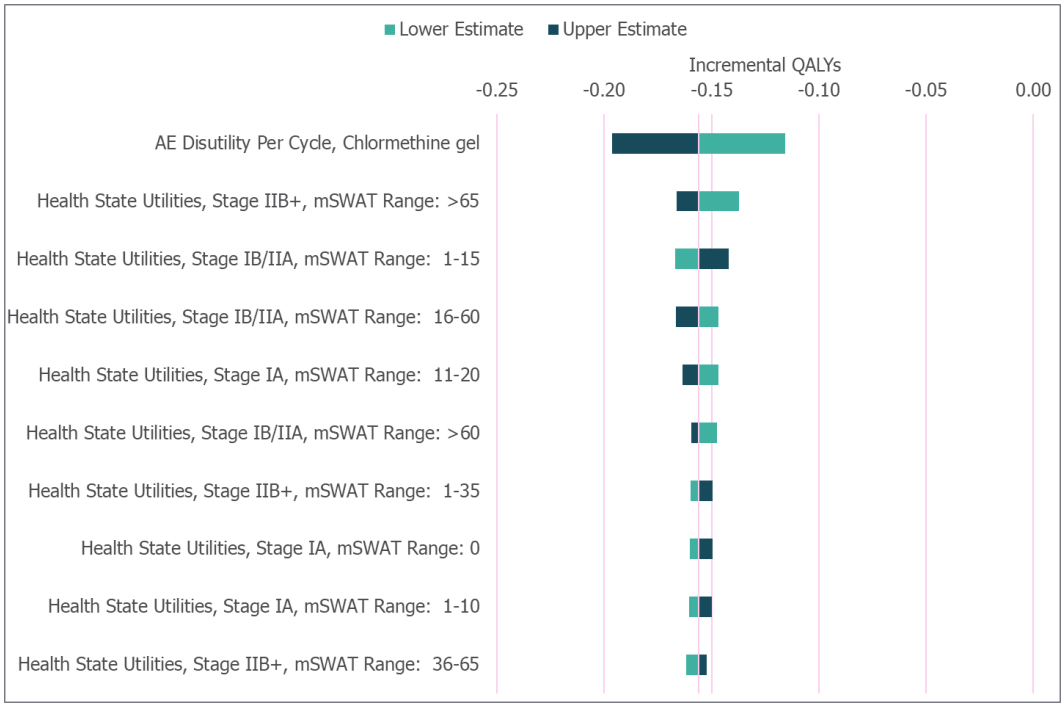
Abbreviations: 1L: first line; AE: adverse event; BSA: body surface area; DSA: deterministic sensitivity analysis; mSWAT: modified Severity Weighted Assessment Tool; NMB: net monetary benefit; PUVA: psoralen-ultraviolet A; UVB: ultraviolet B; WTP: willingness-to-pay.

Figure 18: DSA – incremental cost tornado plot of the top ten most influential parameters versus phototherapy (PUVA/UVB)



Abbreviations: 1L: first line; BSA: body surface area; DSA: deterministic sensitivity analysis; PUVA: psoralen-ultraviolet A; UVB: ultraviolet B.

Figure 19: DSA – incremental QALYs tornado plot of the top ten most influential parameters versus phototherapy (PUVA/UVB)



Abbreviations: AE: adverse event; DSA: deterministic sensitivity analysis; mSWAT: modified Severity Weighted Assessment Tool; PUVA: psoralen-ultraviolet A; QALY: quality-adjusted life year; UVB: ultraviolet B.

B.3.8.3 Scenario analysis

Various scenario analyses were conducted to explore the impact of assumptions and sources of parameter or structural uncertainty. The results of these scenarios are presented from Table 71 to Table 79 below. All ICERs presented in the below tables (with the exception of scenarios where the result is 'dominant' or 'dominated') represent south-west ICERs (i.e. chlormethine gel associated with fewer QALYs but lower costs than phototherapy), and should therefore be interpreted as the ICER for phototherapy versus chlormethine gel.

Scenario 1: Phototherapy efficacy

As discussed in Section B.3.3.2 above, it was not possible to perform a network meta-analysis or unanchored ITC in order to derive adjusted estimates of the relative effectiveness of phototherapy and chlormethine gel. A number of studies of phototherapy were identified as being more appropriate for naïve comparison to the results of Study 201 for chlormethine gel, though such naïve comparison remained subject to considerable limitations with regards to comparability of study populations and outcome measures, and study quality. Furthermore, estimates of the efficacy of phototherapy in terms of response rates were seen to vary quite considerably across the identified studies. Therefore, there remains considerable uncertainty regarding the estimates for response rates with phototherapy. Data from the PROCLIPI registry on response rates (definition of response not reported) support that the estimate of phototherapy effectiveness used in the base case analysis may represent an optimistic assessment of expected response rates in clinical practice. Thus, scenario analyses were conducted to explore the uncertainty surrounding the estimates for response rates with phototherapy, as presented in Table 71 below:

- Scenario 1: Weighted average of CR rates, excluding Oguz *et al.* (2003) and Anadolu *et al.* (2005), as these studies did not provide any information on the duration of phototherapy treatment over which responses were achieved (i.e. no time to response information)[89, 90]
- Scenario 2: CR and PR rates from NCT0168659, as this was the only study identified that used the same outcome measure for determination of response rates as Study 201 (mSWAT). This represents a more optimistic scenario with regards to phototherapy effectiveness, given the CR and PR rates observed in NCT0168659.
- Scenario 3: CR and PR rates from EORTC 21011, weighted to exclude non-assessable patients. This represents a more pessimistic scenario with regards to the estimated effectiveness of phototherapy (the CR rate observed in this study was markedly lower than for the other studies summarised in Table 26)

Table 71: Alternative phototherapy efficacy

Phototherapy efficacy scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Base case	Chlormethine gel	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,000	0.00	-0.16	£44,915
Scenario 1	Chlormethine gel	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,899	9.96	6.57	-£7,774	0.00	-0.15	£52,525
Scenario 2	Chlormethine gel	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,288	9.96	6.59	-£7,163	0.00	-0.18	£40,878
Scenario 3	Chlormethine gel	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£251,848	9.96	6.57	-£12,724	0.00	-0.15	£85,760

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

Time horizon

As discussed in B.3.2.2, a lifetime time horizon was considered an appropriate duration over which to fully capture the costs and benefits of chlormethine gel and thus was employed in the base case analysis. However, given the uncertainty associated with extrapolating the available data into the long term, it was considered informative to explore scenarios with shorter time horizons. Scenario analyses where the time horizon was varied are presented in Table 72 below.

Table 72: Time horizon scenarios

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)

Base case (lifetime)	Chlormethine gel	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,000	0.00	-0.16	£44,915
5 years	Chlormethine gel	£88,139	4.06	2.72	-	-	-	-
	Phototherapy (PUVA/UVB)	£93,263	4.06	2.87	-£5,124	0.00	-0.15	£33,735
10 years	Chlormethine gel	£149,292	6.56	4.37	-	-	-	-
	Phototherapy (PUVA/UVB)	£156,040	6.56	4.53	-£6,749	0.00	-0.15	£43,541

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

Chlormethine gel dose

The daily chlormethine gel dose in the base case economic analysis was calculated assuming that the dose would be proportional to the average baseline BSA % at each stage (IA [and those in Stage IIB–IV with Low Skin Burden]) and IB/IIA [and those in Stage IIB–IV with High Skin Burden]), given that chlormethine gel is a topical treatment, whilst preserving the median daily dose of 1.80 g received across all patients in Study 201 as stated in the SmPC (see Section B.3.2.3).[11] This lead to Low (Stage IA and those in Stage IIB–IV with Low Skin Burden) and High Skin Burden (Stage IB/IIA and those in Stage IIB–IV with High Skin Burden) daily doses of 0.99 g and 2.93 g, respectively.[11] However, a scenario was also conducted where the effect of setting the median daily chlormethine gel dose equal (at 1.80 g) for Low and High Skin Burden patients in the model was explored. The results of this analysis are presented in Table 73 below.

Table 73: Chlormethine gel dose scenario

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Base case (daily dose based on disease stage)	**Chlormethine gel**	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,000	0.00	-0.16	£44,915
	Chlormethine gel	£236,514	9.96	6.42	-	-	-	-

Equal daily dose between Low and High Skin Burden patients	**Phototherapy (PUVA/UVB)**	£246,125	9.96	6.57	-£9,611	0.00	-0.16	£61,664

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

Chlormethine gel dose frequency

The base case analysis assumes that chlormethine gel is administered daily, based on the SmPC.[11] However, real-world evidence from the French ATU Early Access Program suggests that in clinical practice, a lower dosing frequency may occur.[68] Therefore, a scenario analysis considering an average dosing frequency for chlormethine gel of 3.44 times per week (based on data from the French ATU Early Access Program) is reported in Table 74.

Table 74: Chlormethine gel dose frequency scenario

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Base case (daily dosing)	**Chlormethine gel**	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,000	0.00	-0.16	£44,915
Dosing frequency based on French ATU Early Access Program data	**Chlormethine gel**	£224,055	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£22,070	0.00	-0.16	£141,604

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

Chlormethine gel AEs

In the base case analysis, AEs at Grade 3 or greater that occurred in ≥5% of patients for chlormethine gel or the comparator (phototherapy) were included, as it was considered that these AEs would be the ones associated with a substantial cost and/or quality of life burden. However, safety data from the PROVe real-world evidence study suggest that there were [redacted] serious AEs that occurred in ≥5% patients receiving chlormethine gel (even

when given in combination with concomitant therapies), reflecting that perhaps in clinical practice (where concomitant administration of corticosteroids to manage adverse events would be permitted) adverse events with chlormethine gel may be lower than observed in Study 201 (where concomitant steroid use was not permitted). Therefore, a scenario analysis in which the chlormethine gel AE rates are set to 0% was conducted. The results of this analysis are presented in Table 75 below.

Table 75: Chlormethine gel AEs scenario

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Base case (AEs from Study 201)	Chlormethine gel	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,000	0.00	-0.16	£44,915
AEs from PROVe	Chlormethine gel	£239,119	9.96	6.62	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,006	0.00	0.05	Phototherapy is dominated

Abbreviations: AE: adverse event; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

Subsequent treatment costs

As described in Section B.3.2.2, the base case analysis assumed that patients who transitioned to Progressed from 1L remained in this health state until Death. The Progressed from 1L health state represented a simplification of skin symptom progression/improvement and subsequent treatments; patients were assumed to receive either bexarotene or pegylated IFN-α in a 50:50 split. However, in order to explore the extent to which the assumed subsequent treatment costs impact on cost-effectiveness results, a scenario where subsequent treatment costs for both chlormethine gel and phototherapy (PUVA/UVB) are set to £0 was conducted. The results of this analysis are presented in Table 76 below.

Table 76: Subsequent treatment cost scenario

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus

								baseline (£/QALY)
Base case	Chlormethine gel	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,000	0.00	-0.16	£44,915
Zero subsequent treatment cost	Chlormethine gel	£95,529	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£71,624	9.96	6.57	£23,905	0.00	-0.16	Phototherapy is dominant

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

Utility values

In the base case analysis, the responses from seven clinicians were used to inform the vignettes for the cost-effectiveness analysis. However, one clinician who responded to the questionnaire, was also involved in the design and validation of the vignettes. Therefore, a scenario was conducted in which the input from respondent A was excluded, in order to account for any potential bias that may have resulted from this participant both developing and responding to the study. The alternative mean values for the vignettes (with respondent A excluded) are presented in Table 77 below, with the results of this scenario analysis presented in Table 78 below.

Table 77: Alternative mean values from the vignette study (based on responses excluding respondent A)

Vignette	Base case mean values	Alternative mean values
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]

9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]

Table 78: Alternative utility values scenario

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Base case	**Chlormethine gel**	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,000	0.00	-0.16	£44,915
Alternative utility values	**Chlormethine gel**	£239,125	9.96	6.37	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.52	-£7,000	0.00	-0.15	£45,889

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

Source of chlormethine gel relapse post-CR transition probability

In the base case analysis, the transition probability from the No Skin Burden health state to the Progressed from 1L health state for both chlormethine gel and phototherapy (PUVA/UVB) was informed using data from Whittaker *et al.* (2012).[91] However, an assumption of equal duration of response between chlormethine gel and phototherapy may fail to reflect clinical experience that, as noted in the BAD guidelines, 'duration of response is often limited' with phototherapy.[3] Therefore, a scenario was conducted where this transition for chlormethine gel was informed by Kim *et al.* (2003) (combining the results for both aqueous and ointment formulations of chlormethine). [63] The results of this scenario analysis are presented in Table 79 below.

Table 79: Alternative chlormethine gel relapse post-CR transition probability scenario

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus

								baseline (£/QALY)
Base case	**Chlormethine gel**	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,000	0.00	-0.16	£44,915
Alternative source of chlormethine gel relapse post-CR TP	**Chlormethine gel**	£229,717	9.96	6.53	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£16,408	0.00	-0.04	£384,277

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; TP: transition probability; UVB: ultraviolet B.

B.3.8.4 Summary of sensitivity analyses results

The base case deterministic analysis finds chlormethine gel to be associated with fewer QALYs but cost savings compared to phototherapy, resulting in a south-west ICER. This ICER, interpretable as the ICER for phototherapy versus chlormethine gel, is above NICE's conventional range of cost-effectiveness of £20,000-£30,000 per QALY gained, indicating that chlormethine gel represents a cost-effective use of NHS resources. Results of the PSA, DSA and scenario analyses show this base case result to be robust to exploration of model parameter and structural uncertainty, and the adoption of alternative assumptions. Key drivers of cost-effectiveness results were identified as the cost of subsequent therapies received in the Progressed from 1L health state, mean BSA and treatment cost of chlormethine gel. All economic analyses remain subject to the inherent uncertainty in the relative effectiveness of chlormethine gel and phototherapy. However, chlormethine gel remained a cost-effective use of resource under scenarios exploring alternative assumptions (both more optimistic and more pessimistic) for phototherapy effectiveness.

B.3.9 *Subgroup analysis*

The population of interest in the base case analysis considers all stages of MF-CTCL and this aligns with the full licensed population for chlormethine gel in the UK and the expected use of chlormethine gel for the treatment of skin lesions as discussed in Section B.3.2.1. However, given that the patient population of Study 201 included only patients with early stage disease (Stage IA–IIA), a subgroup analysis for the early stage population specifically was conducted. For this scenario analysis, the baseline disease stage distribution and mSWAT scores were adjusted to reflect the inclusion of early stage patients only. All other parameters remained the same, as the source of efficacy data used in the base case was already reflective of early stage patients.

The base case deterministic results of this scenario analysis are presented in Table 80 below. PSA, DSA and scenario analyses when considering only the early stage population are provided in Appendix J.3. As for the full population base case results, chlormethine gel was found to be associated with fewer QALYs but lower costs than phototherapy. The ICER for chlormethine gel is therefore a south-west ICER, and hence the reported ICER should be interpreted as the ICER for phototherapy versus chlormethine gel.

Table 80: Subgroup analysis – early stage population

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Base case (all stages of MF-CTCL)	Chlormethine gel	£239,125	9.96	6.42	-	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,000	0.00	-0.16	£44,915

Early stage MF-CTCL (Stage IA-IIA)	Chlormethine gel	£239,938	11.28	7.49	-	-	-	-
	Phototherapy (PUVA/UVB)	£249,433	11.28	7.66	-£9,494	0.00	-0.17	£57,389

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

No relevant published studies were identified that considered the cost-effectiveness of chlormethine gel in this population. Therefore, cost-effectiveness results could not be compared with others in the literature. However, comprehensive clinician input was sought during the development of the cost-effectiveness analysis, to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice and reflected the treatment pathway. Additionally, where appropriate, assumptions concerning treatments have been validated against BAD Guidelines.[3]

As detailed throughout the submission, there was agreement from clinicians with the approaches and assumptions taken in the development of the cost-effectiveness analysis, and full details of the clinical validation are provided in the reference pack accompanying this submission.

Each component of the model was systematically reviewed for errors, inconsistencies and plausibility.

B.3.11 *Interpretation and conclusions of economic evidence*

A *de novo* economic analysis was conducted to evaluate the cost-effectiveness of chlormethine gel versus phototherapy for the topical treatment of MF-CTCL. The population of the economic analysis considered all adult patients with MF-CTCL regardless of disease stage, which is consistent with both the NICE final scope and licensed indication for chlormethine.[5, 11] Furthermore, the economic analysis was conducted from the perspective of the UK NHS and PSS, and can therefore be considered directly applicable to clinical practice in England. Resource use assumptions were based on the input of UK expert clinicians, experienced in the treatment of MF-CTCL and costs included were all derived from UK sources (e.g. NHS Reference Costs, the BNF or the eMIT) where possible.[112-114]

As acknowledged in Section B.1.3.2, phototherapy (PUVA/UVB), bexarotene and pegylated IFN-α may all be considered relevant comparators to chlormethine gel; however, a paucity of evidence for bexarotene and pegylated IFN-α precluded their inclusion in the cost-effectiveness analysis. In addition, the (naïve) comparison of chlormethine gel and phototherapy is associated with a high degree of uncertainty due to the reasons elaborated upon in Section B.2.9 and Appendix D. However, it is considered unlikely that the base case inputs represent an underestimate of phototherapy effectiveness.

A limitation of the cost-effectiveness analysis is that Study 201 did not include patients with advanced stage MF-CTCL, therefore, efficacy observed in early stage populations was assumed

to translate to advanced stage populations with the same skin burden. However, clinical expert opinion suggests that chlormethine gel would be used for the treatment of the skin symptoms of MF-CTCL irrespective of disease stage, and the licensed indication for chlormethine gel does not limit by stage. A subgroup analysis is presented for the early stage population only, in respect of the population of Study 201. The other notable limitation for the economic analysis is the lack of available published utility values for model health states, or quality of life data collected in Study 201. In light of this, utility values were derived using a vignettes study, meaning the utility values are associated with some uncertainty. However, utility values were not seen to be a key driver of cost-effectiveness results in DSA.

Extensive scenario analyses were also conducted and showed the model to be robust to the majority of assumptions employed in the base case analysis. Overall, the results suggest that chlormethine gel is a cost-effective treatment option versus phototherapy in the context of the decision problem. The probability of chlormethine gel being cost-effective is 62.40% at the £20,000 per QALY gained threshold.

As an innovative therapy with a convenient method of application, distinct mechanism of action, demonstrated efficacy and tolerability (with no evidence to suggest an increased risk of secondary malignancies) both in the clinical trial setting and in real-world clinical practice, chlormethine gel is a viable, flexible and cost-effective treatment option for the treatment of the skin symptoms of MF-CTCL.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Clarification questions

May 2020

File name	Version	Contains confidential information	Date
ID1589 ERG Clarification Questions Response_AIC_REDACTED_v2	2	Yes	13th May 2020

Notes for company

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Square brackets and [redacted] 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 [redacted] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Single technology appraisal

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Dear Yelan,

Thank you for the opportunity to respond to the clarification questions from the Evidence Review Group. We thank the team for their comments on the submission and hope that our responses to the individual questions in turn below provide clarity for our approach in the submission and the necessary additional information where this has been possible.

As requested, we have uploaded to NICE Docs two versions of this response letter: one with academic/commercial-in-confidence information clearly marked and one with this information removed. Accompanying these response letters is also a zipped folder data package, containing the references referred to within this response.

Please do not hesitate to get in touch should you have any questions regarding our response.

Kind regards,

Fabian Schmidt

Section A: Clarification on effectiveness data

Methodology of the relevant clinical effectiveness evidence

A1. PRIORITY. Please provide the Clinical Study Report for Study 201 as this is missing from the reference package we have received.

An updated reference pack with references renamed in accordance with their numbering in the Document B bibliography, and including the clinical study report (CSR) for Study 201, was uploaded to NICE Docs on the 4th February 2020.

A2. Document B, Section B.2.9 and Appendix D.7 of the company submission. The company refer to quality assessment of the RCTs and non-randomised studies presented in the clinical submission. Please clarify:

- **the methodological tool/checklist used for assessing the risk of bias (including the risk of bias of the phototherapy efficacy studies presented in Table 26, page 75 of the company submission);**
- **how many reviewers carried out the risk of bias assessment;**
- **whether the reviewers worked independently.**

The quality of RCTs (including EORTC 21011, El Mofty *et al.* [2012] and NCT01686594 from Table 26, page 75 of the Company Submission) was assessed using the criteria provided by the York Centre for Reviews and Dissemination,[1] and this was provided in Table 15, page 79 of the Company Evidence Submission appendices.[2-4]

The quality of the non-randomised studies presented in Table 26, page 75 of the Company Evidence Submission (Pavlotsky *et al.* [2006], Herrmann *et al.* [1995], Oguz *et al.* [2003], Anadolu *et al.* [2005]) have been assessed using the Downs and Black checklist,[5] and are presented in Table 1 below.[6-9]

All quality assessments were undertaken by one reviewer and evaluated by a second independent reviewer. Discrepancies between the reviewers were resolved through discussion or adjudicated by a third independent reviewer if necessary.

Table 1: Risk of bias assessment of non-RCTs (using the Downs and Black checklist)[5]

Domain	Pavlotsky *et al.* (2006)[6]	Herrmann *et al.* (1995)[7]	Oguz *et al.* (2003)[8]	Anadolu *et al.* (2005)[9]
1. Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes	Yes	Yes
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes	No – Outcomes are not clearly described prior to the Results section	Yes
3. Are the characteristics of the patients included in the study clearly described?	Yes – Baseline characteristics stratified by treatment group are presented	Yes – Baseline characteristics are presented	No – Few baseline characteristics are reported	Yes – Baseline characteristics are clearly presented for each disease stage
4. Are the interventions of interest clearly described? (if relevant)	Yes – The intervention is clearly described	Yes – The intervention is clearly described	Yes – The intervention is clearly described	Yes – The intervention is clearly described
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes – The variables suspected of influencing the response to treatment were examined by chi-square test and multivariate logistic regression analysis	N/A – Single-arm	N/A – Single-arm	No – Confounding could not be ascertained because confounders were not reported
6. Are the main findings of the study clearly described?	Yes – Study reports CR for each treatment group	Yes – Study reports survival and CR to PUVA therapy	Yes – Study reports response and course of disease	Yes – Study reports response rate for different treatments
7. Does the study provide estimates of the random variability in the data for the main outcomes?	N/A – Only non-continuous outcomes considered	No – Random variability estimates are not reported for survival	N/A – Only non-continuous outcomes considered	N/A – Only non-continuous outcomes considered
8. Have all important AEs that may be a consequence of the intervention been reported?	No – AEs are not reported	Yes – AEs are reported	No – AEs are not reported	No – AEs are not reported
9. Have the characteristics of patients lost to follow-up been described?	Unclear – No details provided	Unclear – No details provided	Unclear – No details provided	Unclear – No details provided

10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes – Actual p-values have been reported	Yes – Single-arm but actual p-values are provided for comparisons with other studies and between patients with different disease stages	Yes – Single-arm but actual p-values are provided for comparison between doses	Yes – Actual p-value reported for comparison between early- and late-stage disease
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unclear – Unable to determine if subjects were representative of the entire population	Unclear – Unable to determine if subjects were representative of the entire population	Unclear – Unable to determine if subjects were representative of the entire population	Unclear – Unable to determine if subjects were representative of the entire population
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unclear – Unable to determine if subjects were representative of the entire population	Unclear – Unable to determine if subjects were representative of the entire population	Unclear – Unable to determine if subjects were representative of the entire population	Unclear – Unable to determine if subjects were representative of the entire population
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes – Patients were treated within a dermatology department within a medical centre, which is likely to be representative of the treatment that the majority of patients receive	Unclear – It is unclear where patients were treated and whether treatment was representative of that received by the source population	Unclear – It is unclear where patients were treated and whether treatment was representative of that received by the source population	Yes – Patients were treated within a dermatology department within a university medical faculty, which is likely to be representative of the treatment that the majority of patients receive
14. Was an attempt made to blind study subjects to the intervention they have received?	Unclear – Blinding details were not reported	No – Subjects were not blinded to the intervention	No – Subjects were not blinded to the intervention	No – Subjects were not blinded to the intervention
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	Unclear – Blinding details were not reported	No – Those measuring the main outcomes were not blinded to the intervention	No – Those measuring the main outcomes were not blinded to the intervention	No – Those measuring the main outcomes were not blinded to the intervention
16. If any of the results of the study were based on “data dredging”, was this made clear?	Yes – No unplanned analyses were reported	Yes – No unplanned analyses were reported	No – Outcomes were not defined	Yes – No unplanned analyses were reported

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes – Because of the difference in treatment groups regarding the length of the follow-up, further Kaplan–Meier disease-free analysis was performed using log rank test	N/A – Study design not applicable	N/A – Study design not applicable	Unclear – No analyses were conducted to account for the different lengths of follow-up
18. Were the statistical tests used to assess the main outcomes appropriate?	N/A – No statistical tests were used to assess the main outcomes, only used to determine patient characteristic variability between treatment groups	Yes – A specific log rank test was used to compare disease stages	Unclear – Statistical tests used were not reported	Unclear – Statistical tests used were not reported
19. Was compliance with the intervention/s reliable?	Unclear – Compliance not reported	Unclear – Compliance not reported	Unclear – Compliance not reported	Unclear – Compliance not reported
20. Were the main outcome measures used accurate (valid and reliable)?	Yes – The outcome measures were clearly described	Yes – The outcome measures were clearly described	No – Measurement of CR was not clearly described	Yes – The outcome measures were clearly described
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Unclear – Source population unclear	N/A – Single arm	N/A – Single-arm	Unclear – Source population unclear
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?	Yes – Patients were treated between 1996 and 2002	N/A – Single-arm	N/A – Single-arm	Yes – Patients were recruited between March 1984 and June 2001
23. Were study subjects randomised to intervention groups?	No – Patients were not randomised	N/A – Single-arm	N/A – Single-arm	No – Patients were not randomised

24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A – Non-randomised	N/A – Non-randomised	N/A – Non-randomised	N/A – Non-randomised
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes – Confounding variables were measured and because of the difference in treatment groups regarding the length of the follow-up, further Kaplan–Meier disease-free analysis was performed using log rank test	N/A – Single-arm	N/A – Single-arm	No – The effect of confounders was not investigated
26. Were losses of patients to follow-up taken into account?	Unclear – 2% of patients dropped out and it is unclear whether this was accounted for	Unclear – Three patients dropped out and it is unclear whether this was accounted for	Unclear – No details provided	Yes – For patients who failed to return for follow-up after CR, the term “unknown remission duration” was used
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%?	Unclear – No details provided	Unclear – No details provided	Unclear – No details provided	Unclear – No details provided

Abbreviations: AE: adverse event; CR: complete response; N/A: not applicable; PUVA: psoralen-ultraviolet A.

A3. Document B, section B.2.4, Table 13, page 47 of the company submission. For Study 201, it was determined that chlormethine gel would be considered non-inferior to chlormethine ointment if the lower limit of the 95% CI around the ratio of response rate was >0.75. Please clarify the rationale for choosing this 'cut off' (>0.75).

As described in Document B of the Company Evidence Submission (Section B.2.4), the non-inferiority of chlormethine gel to chlormethine ointment was established if the lower bound of the 95% confidence interval (CI) around the ratio of the response rate (complete response [CR] + partial response [PR] for chlormethine gel/chlormethine ointment) was >0.75 i.e. demonstrating a retention effect of 75%. The lower bound of this CI was calculated based on the likelihood ratio-based methods of Miettinen and Nurminen (1985),[10] and if this value was greater than 0.75 then it was concluded that using the ratio of the proportions for chlormethine gel was no worse (i.e. non-inferior) to chlormethine ointment.

Unfortunately, the details regarding the methodology and justification for choosing the 0.75 threshold are not specified in the statistical analysis plan or study protocol available for Study 201; we have therefore been unable to confirm the rationale for a 0.75 threshold for this response.[11, 12] However, the Company note that chlormethine ointment is not used in UK clinical practice and is therefore not a relevant comparator to chlormethine gel. Thus, the comparison between chlormethine gel and chlormethine ointment in Study 201 is not directly relevant to the decision problem addressed within this submission or used to otherwise inform relative efficacy estimates for alternative comparators within the model.

Section B: Clarification on cost-effectiveness data

Comparators included in the economic model

B1. Document B, Section B.1.1 of the company submission. Table 1 suggests that bexarotene and pegylated-IFN-α would be considered in about 10% of patients, i.e. patients who would not be suitable for phototherapy. Please clarify why the comparator group consisting of a mixture of phototherapy (90%), bexarotene (5%) and pegylated-IFN-α (5%) was not considered for the economic model?

As discussed in Sections B.2.1 and B.2.9 of Document B, a clinical systematic literature review (SLR) and review of studies cited in the British Association of Dermatologists (BAD) guidelines was conducted with the aim of identifying relevant clinical evidence for the efficacy and safety of chlormethine gel and relevant comparators (phototherapy, bexarotene and pegylated-interferon-α [pegylated IFN-α]) for treatment of adult patients with MF-CTCL.[13]

For IFN and bexarotene only three RCTs and no RCTs, respectively, were identified by the clinical SLR;[14-16] and only three studies and one study, respectively, were cited in the BAD

guidelines.[17-20] No clinical trials were identified from either the SLR, or the review of the BAD guidelines, that directly compared chlormethine gel to either IFN or bexarotene. Furthermore, for the reasons outlined in Appendix D (Section D.5.1) of the Company Submission, none of these studies were considered to provide appropriate evidence for conducting an unanchored ITC, or for informing a naïve indirect comparison with Study 201. Therefore, there is a distinct lack of robust clinical studies investigating bexarotene and pegylated IFN-α in MF-CTCL patients to allow modelling of the clinical effectiveness of these therapies (relative to that of chlormethine gel, even as a naïve comparison) as part of a cost-effectiveness analysis. In light of the challenges with explicitly modelling effectiveness of these treatments, to include pegylated-IFN-α and bexarotene in the model as part of a comparator group with phototherapy would require including these comparators on the basis of cost alone (i.e. assuming implicitly that the effectiveness of these comparators is the same as that of phototherapy). Such an assumption of equivalent clinical effectiveness is not evidence-based, hence why this approach was not considered appropriate.

In addition, the Company is aware that an approach whereby multiple comparators are bundled and proportionally weighted according to their anticipated use in clinical practice has been criticised in previous NICE appraisals, as it may obscure the true cost-effectiveness of individual comparator treatments.[21-24]

For these reasons, combined with consideration that pegylated IFN-α and bexarotene represent the relevant comparators in a relative minority of patients (10%), the Company did not consider it appropriate to include these comparators in the cost-effectiveness analysis as stand-alone comparators or as part of a comparator group.

Nevertheless, in light of the ERG's question, the Company has conducted a scenario analysis where the costs of 5% of patients receiving each of bexarotene and pegylated IFN-α, respectively, are included in the economic analysis (alongside 90% patients receiving phototherapy). The results of this scenario analysis are presented in Table 2 below, indicating that this change from the base case assumptions has limited effect on the ICER. Please note that this scenario accounts for the costs of 5% patients receiving bexarotene and 5% receiving pegylated IFN-α; however, the efficacy modelled for this bundled comparator is assumed to be that of phototherapy, given the lack of robust data sources to inform the efficacy of bexarotene or pegylated IFN-α specifically, as explained above.

Table 2: Scenario – bundled comparator approach (costs only)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Base case	Chlormethine gel	£239,125	9.96	6.42	-	-	-	-
	Bundled comparator (phototherapy [PUVA/UVB], bexarotene and pegylated IFN-α)	£246,125	9.96	6.57	-£7,000	0.00	-0.16	£44,915
Scenario	Chlormethine gel	£239,125	9.96	6.42	-	-	-	-
	Bundled comparator (phototherapy [PUVA/UVB], bexarotene and pegylated IFN-α)	£245,746	9.96	6.57	-£6,621	0.00	-0.16	£42,485

Note that the base case presented in this table is aligned with the base case presented in the Company Submission, rather than the updated base case presented in the response to question B4. This is to demonstrate the effects of this scenario only, rather than confounding these results with additional changes to model inputs.
Abbreviations: ICER: incremental cost-effectiveness ratio; IFN-α: interferon alpha; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

Model structure and transition probabilities

B2. PRIORITY. Document B, section B.3.3.2, Tables 46 to 49 of the company submission. The transition probabilities to "progressed from 1L" are substantially higher from the "no skin burden" state (sourced from Whittaker, 2012) than from the "low skin burden" state (sourced from Study 201). The implication is that increasing complete response (CR) in the model leads to higher proportions of the cohort in the "progressed from 1L" state, incurring higher costs of subsequent treatments and lower utility. This leads to counter-intuitive results where a high partial response (PR) results in a slower progression to 2nd line treatment than a high CR. For example, the least favourable cost-effectiveness scenario for chlormethine gel would be to increase its CR to 100%. Please comment on the face validity of these results and consider using alternative data or assumptions to generate more plausible progression through the model health states.

As highlighted in the Company Evidence Submission (Section B.3.3.2), data to inform transitions to the Progressed from 1L health state are available from the initial Low/High Skin Burden health states (i.e. transition from Low/High Skin Burden to Progressed from 1L) and from No Skin Burden to Progressed from 1L (i.e. relapsing after achieving a CR). However, no data were available on relapse rates following a PR (i.e. transition from Reduced Skin Burden to Progressed from 1L) and therefore, assumptions were necessary.

Based on the definitions of CR and PR employed in Study 201 (and therefore the economic analysis), as well as input received from clinical expert opinion, the Company believes the transition probabilities employed are clinically plausible and have face validity. Specifically, the Company affirms that it is the intention to have the transition probability from the No Skin Burden health state to Progressed from 1L (representing relapse of skin lesions following a CR) as higher than that from the Reduced Skin Burden health state (representing relapse of skin lesions following a PR).

The reason for this is two-fold. Firstly, patients who achieve a CR (and hence transition to the No Skin Burden health state) discontinue treatment of skin-directed therapies. In contrast, patients who achieve a PR (and subsequently transition to the Reduced Skin Burden health state) continue to receive active treatment (the same as prior to achieving a PR). Therefore, it is reasonable to believe (and has been clinically validated) that patients achieving CR may be less likely to maintain a response (i.e. avoid skin progression) than patients in the Reduced Skin Burden health state who achieve only PR and continue to receive active treatment.[25, 26]

Secondly, relapse, as defined in clinical practice and hence the economic analysis, is the point at which a patient loses a response. For a patient in CR, any subsequent reappearance of skin lesions would result in the patient no longer having 100% remission of skin lesions (i.e. loss of response), and hence constitute a relapse that would require a patient to recommence treatment. In contrast, for patients who achieve PR (50-99% reduction in skin lesions), loss of response may

require a greater increase in skin lesions than for a loss of response from CR, and hence patients in PR will not be considered to lose their response as quickly. For example, a patient in PR may experience an increase in skin lesions but remain within a net 50–99% reduction (from baseline), and therefore not be considered to have relapsed. Therefore, it is reasonable to expect that patients who have achieved a CR (in the No Skin Burden health state) are more likely to lose this response than a patient with a PR (in the Reduced Skin Burden health state). This assumption was clinically validated, confirming that it was more reasonable to assume relapse rates for a PR patient to be equal to the probability of a patient without prior response having PD, than to assume PR relapse rates to be equal to a CR patient.

Furthermore, the Company would like to highlight that the aim of skin-directed treatment in clinical practice (as informed by expert opinion) is the management of symptoms, and not necessarily achieving CR, given the ability to achieve and maintain CR is very rare.[25] Achievement of CR is not necessarily related to how likely a patient is or is not to relapse in the future.

Adverse events

B3. PRIORITY. Document B, Section 3.3.4, page 125 of the company submission. Please provide a table with the frequency of adverse events from Study 201 (excluding NYU centre), categorised by grade of severity.

As described in Section B.2.4 of Document B of the Company Submission, the analysis of adverse events (AEs) in Study 201 was carried out using the safety set (N=255), which included all patients who received at least one application of either chlormethine gel (n=128) or chlormethine ointment (n=127). This represented the ITT including NYU population (n=260), minus five patients. AE data are not available for the intention-to-treat (ITT) excluding New York University (NYU) patient population, therefore, in response to this question, the number and percentage of AEs, graded by severity, are provided for the safety set in Table 3 and Table 4 for chlormethine gel and chlormethine ointment, respectively.

Table 3: AEs by severity in patients treated with chlormethine gel in Study 201 (safety set)

AE, n (%)	Severity[a]					
	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Moderately severe)	Grade 4 (Severe)	NR	Total
Any AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin irritation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis contact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Skin hyperpigmentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actinic keratosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blister	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin ulcer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Furuncle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Impetigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain of skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus generalised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Seborrhoeic keratosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin burning sensation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin papilloma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Application site irritation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blister infected	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis psoriasiform	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised erythema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hidradenitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkeratosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Intertrigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphomatoid papulosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onychomycosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash papular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash pruritic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Seborrhoeic dermatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tinea versicolour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria contact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngolaryngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pleuritic pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary fibrosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Rhinitis allergic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinus congestion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Folliculitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Herpes simplex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Staphylococcal infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta haemolytic streptococcal infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Escherichia infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia klebsiella	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Staphylococcal abscess	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tinea pedis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tooth abscess	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrooesophageal reflux disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal hernia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Haemorrhoids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ileus paralytic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inflammatory bowel disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Irritable bowel syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Xerosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Face oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hernia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperhidrosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rheumatoid arthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shoulder pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tenosynovitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac murmur	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymph node palpable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood pressure increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood urea increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Differential white blood cell count abnormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eosinophil count increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Global amnesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperaesthesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lethargy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Urinary incontinence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthropod bite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tooth fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rib fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rotator cuff syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunburn	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thermal burn	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign (including cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Benign neoplasm of thyroid gland	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nodule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Polyp colorectal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uterine polyp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aortic aneurysm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haematoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral vascular disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Otitis media	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Otitis media acute	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphadenopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myelodysplastic syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypercalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperparathyroidism primary	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye discharge	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid ptosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hypersensitivity	[redacted]					
Neoplasms malignant	[redacted]					
Basal cell carcinoma	[redacted]					
Squamous cell carcinoma	[redacted]					
Thyroid gland cancer	[redacted]					
Reproductive system and breast disorders	[redacted]					
Endometrial hypertrophy	[redacted]					
Menorrhagia	[redacted]					
Prostatitis	[redacted]					
Metabolism and nutrition disorders	[redacted]					
Decreased appetite	[redacted]					
Hyperkalaemia	[redacted]					
Cardiac disorders	[redacted]					
Atrial fibrillation	[redacted]					
Renal and urinary disorders	[redacted]					
Cystitis	[redacted]					
Surgical and medical procedures	[redacted]					
Parathyroidectomy	[redacted]					

[a] The maximum intensity ever recorded was used to categorise AEs.
Abbreviations: AE: adverse event; NR: not reported.
Source: Study 201 CSR Appendix (2011).[11]

Table 4: AEs by severity in patients treated with chlormethine ointment in Study 201 (safety set)

AE, n (%)	Severity[a]					
	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Moderately severe)	Grade 4 (Severe)	NR	Total
Any AE	[redacted]					
Skin and subcutaneous tissue disorders	[redacted]					

Pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis contact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin irritation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin hyperpigmentation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash papular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin burning sensation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actinic keratosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blepharitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intertrigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphomatoid papulosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neurodermatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash erythematous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash vesicular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin erosion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin ulcer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blister	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Body tinea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Campbell de Morgan spots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis atopic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyshidrosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ecchymosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkeratosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Impetigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Milia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nail dystrophy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onychomycosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pityriasis alba	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus generalised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Purpura	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin fissures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin papilloma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Skin warm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tinea infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wound	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngolaryngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lung disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Postnasal drip	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory tract congestion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis allergic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinus congestion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Folliculitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fungal infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Helicobacter infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Herpes simplex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Staphylococcal infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abscess	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corynebacterium infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enterococcal infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Escherichia infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gingival infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Groin abscess	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perineal abscess	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash pustular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subcutaneous abscess	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tinea pedis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tonsillitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tooth abscess	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wound infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Irritability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Night sweats	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pitting oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Swelling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flank pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shoulder pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint effusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint sprain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint swelling	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Limb discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carpal tunnel syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diplopia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sciatica	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacunar infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nerve compression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flatulence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hiatus hernia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stomach discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excoriation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthropod bite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle strain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Procedural pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunburn	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wound secretion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign (including cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fibrous histiocytoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Breast cyst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Breast mass	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mass	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Melanocytic naevus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mouth cyst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nodule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Polyp colorectal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Neoplasms malignant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Breast mass	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neuroendocrine carcinoma of the skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphadenopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Seasonal allergy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronary artery occlusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palpitations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatine increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood triglycerides increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Breath sounds abnormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac murmur	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate irregular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed mood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arteriosclerosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flushing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hot flush	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysuria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyuria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract obstruction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Breast microcalcification	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysmenorrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prostatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hearing impaired	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacrimation increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mycosis fungoides	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biliary colic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] The maximum intensity ever recorded was used to categorise AEs.
Abbreviations: AE: adverse event; NR: not reported.
Source: Study 201 CSR Appendix (2011).[11]

B4. Document B, section B.3.4.5, Page 131 of the company submission & tab: "Adverse events", Cells: I49:I50" of the submitted economic model. An initial inspection of the economic model suggests that an annual probability of experiencing adverse events may have been applied in each monthly cycle, suggesting a stable proportion of patients continue to experience adverse events for the full duration of time on treatment. The SmPC suggests that adverse events should be managed by discontinuation or temporary pausing of treatment and dose frequency modification. This would suggest that

adverse events may have a shorter acting impact on health state utility than assumed in the model.

- **Please confirm the intended approach to modelling adverse events.**
- **Please check the calculations in tab: "Adverse events", Cells: I49:I50" of the submitted economic model and provide a revised cost-effectiveness analysis if appropriate.**

The Company would like to acknowledge that AE probabilities were not adjusted correctly in the economic analysis, and this has now been corrected. The updated Company base case analysis assumes a constant monthly probability of experiencing each AE (for the intervention) in line with the cycle length of the economic model. Both the original and updated monthly probabilities are provided in Table 5.

Table 5: AE per cycle probabilities

AE	Original Model	Updated Model
Original model		
Dermatitis contact	[redacted]	[redacted]
Erythema	[redacted]	[redacted]
Skin irritation	[redacted]	[redacted]

Abbreviations: AE: adverse event.

Updated base case analyses utilising a monthly probability of experiencing of each annual event are provided in Table 6.

Table 6: Updated model base case

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Original model base case					
Chlormethine gel	£239,125	6.42	-		
Phototherapy (PUVA/UVB)	£246,125	6.57	-£7,000	-0.16	£44,915
Updated model base case					
Chlormethine gel	£239,120	6.60	-		
Phototherapy (PUVA/UVB)	£246,125	6.57	-£7,005	0.03	Phototherapy Dominated

B5. Document B, section B.3.5.2, Table 65 and 66, page 141 of the company submission. The ERG believes that the economic model may under-estimate the cost implications of treating grade 3 *(severe but not life threatening, hospitalisation required)* and grade 4 *(life threatening, urgent intervention required)* adverse events. Given these definitions, the ERG would expect secondary care resource use to be included in the calculation of adverse event

costs. Please justify your approach to costing adverse events or provide a revised set of cost-effectiveness analyses as appropriate.

Grade 3 and Grade 4 AEs with an incidence ≥5% were included in the economic analysis. Only three AEs met these criteria based on the chlormethine gel arm data from the safety set of Study 201 (skin irritation, erythema and dermatitis contact). As provided in response to clarification question B3, it is worth highlighting that [redacted], with the remainder being Grade 3. The Company base case economic analysis did not account for secondary care resource use costs in the calculation of AE treatment costs, as based on clinical expert opinion, the majority of occurrences (of this severity) would resolve without intervention, when treatment is paused.[27]

Specifically, it was confirmed by clinical expert opinion that these AEs would not require hospitalisation, and that patients experiencing them would pause/discontinue treatment, resulting in self-resolution.[27] This aligns with the protocol-defined guidelines for managing AEs, as found in the Study 201 CSR (Section 9.4.6): patients were recommended to reduce/suspend treatment for two and four weeks (for Grade 3 and Grade 4 respectively) until irritation improves to Grade 2 or lower, and patients may restart treatment.[28] Consistent with this, a number of patients in the trial experienced temporary dose reductions, temporary suspensions and permanent suspensions (data available on request), indicating that these protocol-defined approaches were adopted in practice in the trial. As such, it is not expected that patients would require hospitalisation, and therefore the inclusion of any additional secondary resource use cost would be unwarranted.

Based on clinical expert opinion, in some cases patients would be treated with corticosteroids to help manage AEs.[26] Corticosteroid use to manage AEs was included in the Company's economic analysis, as described in Section B.3.5.2 of the Company Evidence Submission. In absence of data to indicate the specific proportion of patients that would receive these (concomitant steroid use was not permitted in Study 201, and therefore data for this are not available from this study), corticosteroid acquisition costs were conservatively applied for all patients.

Lastly, it is worth noting that, as explained in the Company Evidence Submission (Section B.3.8.3), safety data from the PROVe real-world evidence study (where concomitant administration of corticosteroids to manage AEs occurred) suggest that there were [redacted] serious AEs that occurred in ≥5% patients receiving chlormethine gel (even when given in combination with concomitant therapies).[29] This reflects that in clinical practice (where concomitant administration of corticosteroids to manage AEs would be permitted) AEs with chlormethine gel may be expected to be lower than observed in Study 201 (where concomitant steroid use was not permitted).

Based on this, the Company consider it reasonable to not include any further costs for treating AEs, and hence no additional cost-effectiveness analyses have been provided in response to this question.

B6. Document B, section B.3.5.2, Adverse events of 2nd line therapies. The ERG notes that the proportion of the cohort that progress from 1L receive either bexarotene or pegylated IFN-α and incur the costs of those treatments.

However, any related adverse events of second line therapy have not been included. Please comment on the likely cost-effectiveness implications.

Owing to the lack of adequate data to inform AEs for these therapies, it was not deemed appropriate to include AEs for bexarotene and pegylated IFN-α in the economic model. Specifically, none of the studies of bexarotene and IFN identified by the clinical SLR and review of BAD guidelines reported in Appendix D of the Company Evidence Submission reported AEs by severity grade to allow identification of the most common Grade 3 or 4 AEs occurring with these therapies. Therefore, including AEs for these treatments would have required several assumptions, which would likely increase the uncertainty in the economic analysis.

As an alternative to published trial data, clinical expert opinion was sought to understand common (≥5%) Grade 3 and Grade 4 AEs for these treatments, and it was confirmed that these would be uncommon (at such severity) and patients would temporarily suspend/reduce treatment dosing, where AEs would self-resolve.[27] Patients would therefore likely not incur significant costs such as hospitalisation, or other secondary-care resource use. Therefore, inclusion of AEs for these second line therapies would be expected to have only a minimal impact on the cost-effectiveness results.

Furthermore, the decision not to include AE costs for second line therapy represents a conservative modelling approach in the base case, from the perspective of cost-effectiveness of chlormethine gel. Specifically, patients in the phototherapy (PUVA/UVB) comparator arm transition to second-line therapies more quickly than patients receiving chlormethine gel (given the maximum duration of 13 weeks for phototherapy). Therefore, increasing the total costs of second-line therapies (e.g. by including AE, and associated treatment costs), would be expected to disproportionately affect the comparator.

Costs of chlormethine gel

B7. Document B, Section 3.5.1 of the company submission. Please clarify how treatment discontinuation or temporary pausing of treatment and dose frequency modification due to adverse events have been accounted for in the economic model. Please clarify if the approach to modelling adverse events is in line with the EMA summary of product characteristics (Section 4.2).

The base case economic analysis assumes that the dosing and efficacy data included in the model account for any potential treatment discontinuation, temporary pausing of treatment and dose frequency modification due to AEs, as dosing and efficacy data are derived directly from Study 201, the protocol of which permitted treatment adjustments due to toxicity that are likely reflective of treatment adjustments discussed in the SmPC and that might occur in clinical practice.[12, 30] Therefore, it is deemed that no additional adjustments to efficacy or treatment discontinuation are required.

B8. Document B, Section 3.5.1 of the company submission. Please confirm that the median daily dose from Study 201 of 1.8g per person used in the economic model accounts for discontinuation, suspension and dose modifications.

The median daily dose used in the economic analysis (1.8 g) has been derived from Study 201 treatment data. Therefore, it is expected that this implicitly accounts for patient discontinuation, suspension and dose modifications. For transparency, unfortunately the details of the specific calculations conducted to arrive at the 1.8 g figure are not available to the Company in the timeframe of this response, and hence the Company cannot claim this with 100% certainty.

The Company believes it would be reasonable to assume the median daily dose from Study 201 accounts for treatment discontinuation, suspension and dose modifications, given treatment instructions to patients, as noted in the CSR and SmPC.[28, 30] Specifically, patients enrolled in Study 201 were instructed to apply treatment topically once daily, and frequency of application could be reduced for toxicity.[28] Clinical opinion also confirmed that dosing would be discontinued or reduced when patients experienced toxicities.[27] On this basis it was deemed reasonable to assume that these factors are accounted for in the analyses on treatment dosing data from the trial.

B9. <u>PRIORITY</u>. Document B, Section 3.5.1 of the company submission. Please provide further details regarding treatment dosing from Study 201 for chlormethine gel. Specifically, please provide:

- **Mean (SD) daily on treatment dose of chlormethine gel (including and excluding NYU centre)**
- **Mean (SD) intention to treat dose of chlormethine gel (including and excluding NYU centre).**

Please also provide an analysis reporting cost-effectiveness using mean rather than median dosage.

At the time of the Company Evidence Submission, no mean daily chlormethine gel dose consumption (including and excluding NYU centre) were available in data on file, and therefore, a median dosage (1.8 g), as reported in the Ledaga SmPC, was used.[30] In absence of alternative data, this was considered the most appropriate estimate of dosing for use within the Company base case economic analysis

In considering this question, a number of alternative approaches to attempt to reflect a mean daily dose of chlormethine gel for Low and High Skin Burden patients in the economic analysis have been considered. These are discussed in detail in turn below, with cost-effectiveness analyses provided in Table 8. All analyses were calculated following the update which was made to the AE probabilities, as detailed in response to clarification question B4, and so also incorporate the impact of that adjustment on results.

Mean Dose Scenario 1: A mean dose of 2.80 g was reported in the Valchlor (US brand name for chlormethine gel) Summary of Product Characteristics (SmPC).[31] The Company's understanding is that this dose is derived from Study 201; however, we have been unable to definitively confirm this within the timeframe of this response. For this scenario analysis, a mean daily dose for Low and High Skin Burden patients was calculated, based on the overall mean of 2.80g, the % BSA affected for Stage IA and Stage IB/IIA (from Study 201) and proportion of patients who are Stage IA and Stage IB/IIA (again, from Study 201). This is described in further detail in response to Question B10. This method preserved the mean dose of 2.8 g received across all patients in Study 201, but derived separate Low and High Skin Burden daily doses of [redacted] g and [redacted] g, respectively, for use in the model. Similar to the response to Question B8, details of the specific calculations conducted to arrive at the 2.8 g estimate reported in the Valchlor SmPC are unfortunately not available to the Company in the timeframe of this response. Therefore, it is not possible to within the timeframe of this response to confirm whether this value represents a mean daily on treatment dose or a mean intention to treat dose.

Mean Dose Scenario 2: An alternative scenario analysis was conducted, also using the mean dose reported from the Valchlor gel SmPC (2.80 g) but assuming this mean dose to be equal for the Low and High Skin Burden patients.[31] This aligns with the scenario that was presented in the original Company economic analysis, where the median dose (1.80 g) was assumed equal for Low and High Skin Burden patients.

Mean Dose Scenario 3: Finally, a scenario was conducted whereby a mean chlormethine gel dose was approximated from the median dose (1.80 g) as reported in Study 201, as discussed with the ERG on the NICE Clarification call (Tuesday 18th February). This was performed by assuming that the proportional difference between the mean and median BSA % affected for Stage IA (Low Skin Burden) and Stage IB/IIA (High Skin Burden) patients, as reported in the Study 201 CSR, was the same as the proportional difference between the mean and median daily dose for Low and High Skin Burden patients.[11] The implicit rationale for this assumption is that dose is directly related to BSA%. The mean, median and percentage differences for % BSA affected are presented in Table 7.

Table 7: Mean and median BSA percentages affected

Disease stage	Median BSA (%)	Mean BSA (%)	Proportional Difference (%)
Stage IA	[redacted]	[redacted]	[redacted]
Stage IB/IIA	[redacted]	[redacted]	[redacted]

Abbreviations: BSA: body surface area.

These percentage differences were then applied to the median dose calculated for Low and High Skin Burden patients as reported for the base case analysis in the Company Evidence Submission in order to derive the approximate mean dose for Low and High Skin Burden patients, respectively. This method resulted in approximated mean doses of 0.99 g and 3.59 g for Low and High Skin Burden patients, respectively. It should be noted that the Low Skin Burden dose was artificially increased to 0.99 g, based on clinical opinion which confirmed that for a Low Skin Burden patient, the estimated number of tubes per year should not fall below six tubes per year (and to align with the 2 month expiration of tubes; necessitating a minimum of six tubes per year).[26] This 'artificial increase' was also done for the calculated median dose for Low Skin Burden patients in the original Company Evidence Submission, for the same reason. The cost-effectiveness results of this scenario are also presented in Table 8.

In summary, the three scenarios presented in Table 8 are as follows:

1. Mean daily dose of Valchlor gel as reported in the SmPC,[31] and assuming that consumption between Low and High Skin Burden patients is in proportion to the relative baseline % BSA affected from Study 201
2. Equal mean daily chlormethine gel dose as per the Valchor SmPC (2.80 g), for Low and High Skin Burden patients[31]
3. Approximating a mean chlormethine gel dose from the median dose (1.80 g), based on the relationship between the mean and median average baseline % BSA, for Low and High Skin Burden patients

The above three scenario analyses were conducted based on the updated Company base case economic analysis provided in response to clarification question B4, in order to explore the impact of alternative chlormethine gel treatment doses on cost-effectiveness results. All scenarios have no impact on treatment QALYs, affecting only chlormethine gel costs. Caution should be taken when interpreting these results as ICERs, given the minor differences in treatment QALYs which mean that small changes in incremental costs between scenarios can translate to substantial changes in ICER values due to the nature of the ICER as a ratio statistic.

Table 8: Alternative dosing assumptions for updated model base case

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Updated model base case					
Chlormethine gel	£239,120	6.60	-		
Phototherapy (PUVA/UVB)	£246,125	6.57	-£7,005	0.03	Phototherapy dominated
Scenario 1					
Chlormethine gel	£256,836	6.60	-		
Phototherapy (PUVA/UVB)	£246,125	6.57	£10,711	0.03	£380,444
Scenario 2					
Chlormethine gel	£251,521	6.60	-		
Phototherapy (PUVA/UVB)	£246,125	6.57	£5,396	0.03	£191,650
Scenario 3					
Chlormethine gel	£244,161	6.60	-		
Phototherapy (PUVA/UVB)	£246,125	6.57	-£1,964	0.03	Phototherapy dominated

Abbreviations: ICER: incremental cost-effectiveness ratio; PUVA: psoralen-ultraviolet A; QALY: quality-adjusted life year; UVB: ultraviolet B.

B10. Document B, Section B.3.2.3; Page 115 of the company submission. The company submission states that *"The dose for patients in Stage IB/IIA and those in stage IIB-IV with high skin burden was then calculated such that the overall weighted average daily dose for all patients was equal to the median daily dose of 1.80g received in Study 201."*

The median daily dose of 1.80g obtained from Study 201 is based on patients with less severe disease overall (58.5%, 40% and 1.5% were in stage IA, IB and IIA, respectively) compared to the PROCLIPI registry used in the economic model ([redacted] in stages IA, IB/IIA and IIB-IV, respectively).

Therefore, the modelled cohort would likely require a greater amount of gel usage than observed in Study 201, due to the greater proportion of body surface area affected. Furthermore, the ERG considers the use of median, rather than mean dosage to be inappropriate for the calculation of expected costs.

Please comment on why a median daily dose of 1.8g is appropriate in this scenario. If appropriate, please provide an alternative scenario where the <u>mean</u> daily dosage and cost of chlormethine gel is increased to better reflect the level of skin burden, as per the PROCLIPI registry (and hence the modelled patient cohort).

As noted in the response to B8 and B9, the median daily dosage of chlormethine gel, as reported in the EMA regulatory submission, was used for the economic analysis, as at time of submission this was the only data available on file, and therefore, the best estimate of average treatment dose.[30] As described in B9, a mean daily dosage is reported in the US regulatory submission (2.8 g) which appears to be derived from Study 201 data.[31]

With regards to calculating an average (median or mean) dose for Low and High Skin Burden patients, the Company believes that the approach taken in the economic analysis is consistent with both the dose administered in Study 201, and the disease stage distribution in clinical practice (from PROCLIPI).[32] To clarify, in the Company Evidence Submission base case analysis the relevant dosing for Low and High Skin Burden patients was estimated as follows: the Study 201 patient proportions for Stage IA and Stage IB/IIA respectively were used to estimate the required Low and High Skin Burden dose to achieve a weighted average of 1.8 g in total – consistent with the dose administered in Study 201. In other words, taking 1.8 g as the starting point for the median dose used in Study 201, the Company back-calculated the corresponding median dose that would have been used for Stage IA and Stage IB/IIA patient groups. Then, in order to reflect that the distribution of Low and High Skin Burden in clinical practice may differ from that of Study 201, these two doses (0.99 g and 2.93 g respectively, as can be found on the 'Chlormethine Gel Consumption' tab of the economic model) were then applied separately in the model for Low and High Skin Burden patients with proportions of Low and High Skin Burden based on the PROCLIPI registry.[32]

An alternative scenario, where the mean dose (2.8 g) rather than the median dose (1.8 g) is used to calculate doses for Low and High Skin Burden ([redacted] g and [redacted] g respectively) is provided in

response to B9. With the exception of the use of mean rather than median, the same approach was applied for this scenario analysis.

Costs of 2nd line treatments in advanced stage disease

B11. Document B, section B.3.5.1, Page 134 of the company submission and trace tabs of economic model. The ERG notes that [redacted] are included as treatment options in the model for both advanced disease treatment and as 2nd line treatment for skin burden. Please comment on whether this represents a double counting of systemic treatment costs for patients with advanced disease who are progressed from L1. It suggests that these patients will receive two systemic therapies. The ERG's concern is that costs may be counted under both column 'CB' and 'DB' on the 'Trace' tabs of the economic model.

The Company agree that including [redacted] may be double counting the cost of systemic treatments for patients with advanced disease in the Progressed from 1L health state. However, it should be noted that in clinical practice, advanced disease stage patients might receive both treatments in combination, in which case, these costs would not be double counted.

Removing [redacted] from the advanced disease stage treatment basket has no impact on the ICER (only slightly affecting total costs), given that advanced disease stage costs and rates of progression to advanced stage disease are equal between treatment arms (Table 9).

Table 9: Results with the exclusion of [redacted] from the advanced disease stage treatment basket

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Original model base case					
Chlormethine gel	£239,125	6.42	-		
Phototherapy (PUVA/UVB)	£246,125	6.57	-£7,000	-0.16	£44,915
Scenario: exclusion of [redacted] from the advanced disease stage treatment basket					
Chlormethine gel	£233,894	6.42	-		
Phototherapy (PUVA/UVB)	£240,894	6.57	-£7,000	-0.16	£44,915

Abbreviations: ICER: incremental cost-effectiveness ratio; IFN-α: interferon alpha; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; UVB: ultraviolet B.

Section C: Textual clarification and additional points

C1. Document B, section B.3.3.2, Table 49 of the company submission. Transition probabilities in Table 49 ("progressed from 1L") do not match to what is reported in the economic model, (tab: "transition probabilities", cells: L84 and L86). Please clarify which transition probabilities are correct and provide a revised cost-effectiveness analysis, if necessary.

Thank you for highlighting this inconsistency. The transition probabilities reported in the economic model are correct. The corrected version of Table 49 from Section B.3.3.2 of Document B is presented below (Table 10).

Table 10: Transition probabilities for Stage IB/IIA patients receiving phototherapy in the cost-effectiveness model

Initial health state	End health state			
	High Skin Burden	No Skin Burden	Reduced Skin Burden	Progressed from 1L
High Skin Burden	0.559	0.356	0.075	0.010
No Skin Burden	-	0.873	-	0.127
Reduced Skin Burden	-	0.020	0.970	0.010

C2. Document B, Page 130 and table 56 of the company submission. The disutility of adverse events is reported in the company submission as "0.003". However, the disutility used in the economic model [Tab: "Adverse Events", Cells: "I41:I43"] is "0.03". Please confirm that the data used in the model are correct and that "0.003" is a typographical error in the company submission?

Thank you for highlighting this inconsistency. This is a typographical error; the correct disutility value is 0.03, as reported in the economic model.

C3. Please clarify where chlormethine gel should be positioned in relation to the use of steroids. Please provide further clarity on the role of chlormethine gel in the subgroup of patients who may be able to have their skin burden managed well with steroids. Should chlormethine gel be compared against steroids, or would it only ever be considered for those who would not be treated with topical steroids alone?

As described in the Company Evidence Submission (Section B.1.3.2), and supported by the Final Scope issued by NICE, topical (cortico)steroids are not considered to be a comparator to chlormethine gel.

Clinical expert feedback sought for the Company Evidence Submission suggested that almost all patients diagnosed with MF-CTCL, and hence considered for treatment with chlormethine gel, would have received topical (cortico)steroids for treatment of non-specific symptoms prior to diagnosis of MF-CTCL (due to delayed diagnosis of MF-CTCL in practice). Clinical expert feedback also highlighted that (cortico)steroids treat the skin inflammation associated with MF-CTCL, rather than being considered anti-MF-CTCL therapies specifically, as they do not have an impact on malignant T-cells (in contrast to chlormethine gel). As such, the use of (cortico)steroids in MF-CTCL patients is typically to manage skin toxicities such as dermatitis and pruritis and (cortico)steroids are therefore used as a concomitant therapy alongside existing treatments for MF-CTCL (and would be used concomitantly to chlormethine gel).[25, 26]

The Company understanding based on clinical expert feedback is therefore that there is not a subgroup of patients that are currently treated with (cortico)steroids alone that would have otherwise been treated with chlormethine gel should this have been an available treatment option. Patients diagnosed with MF-CTCL are expected to have either already received (cortico)steroids, as specified above, or otherwise not be suitable to receive (cortico)steroids (i.e. are contraindicated). (Cortico)steroids alone would not be considered for the management of skin symptoms upon a diagnosis of MF-CTCL, and use of (cortico)steroids is in the context of concomitant therapy. Use of (cortico)steroids would therefore not be expected to be displaced should chlormethine gel be introduced as a treatment option and (cortico)steroids therefore do not represent a comparator.[25, 26]

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma ID1589

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 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.

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 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):
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 matrix.]	**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.)	The population to treat would be all patients with CTCL with symptomatic or troublesome patch/plaque lesions of MF.
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?	There is a huge unmet need for patients with patch / plaque lesions of MF which cause pain, itch, functional disability and disfigurement. There are few treatment options and after failure of topical steroids patients have either to come to hospital for courses of light treatment (phototherapy) which are limited in number as they cause other skin cancers with more frequent use or radiotherapy with significant local and long term side effects. A topical preparation which is effective and safe is needed. Patients with CTCL have painful, itchy and often unsightly skin lesions and as a result suffer a reduced HRQoL [ref 1,2]. 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 3]. Those with earlier stages often exhaust the small repertoire of anti-CTCL treatments and have to be managed with supportive therapy alone. 1. 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 2. 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 3. Gilson D, Whittaker S, Child F, Scarisbrick J, Illidge T, Parry E, Rezvani K, Dearden C, Morris S. British Association of Dermatologists and UK Cutaneous Lymphoma Group Guidelines for the Management of Primary Cutaneous Lymphomas. *Br J Dermatol.* 2019 Mar;180(3):496-526
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?	
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?	Yes, add pruritus score, the assessment should be of clinical benefit this may include various clinical responses from stable disease 0-50% improvement plus better HRQL, to partial responses >50% or occasional CR 100% better
• 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(s) since the publication of NICE technology appraisal guidance [TA577]?	The best comparators would be phototherapy, bexarotene of sc interferon alpha – but all have a completely different side effect profile and application / dosing/ monitoring
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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Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma ID1589

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.

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- 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	Recordati Rare Diseases - £3000 (sponsorship of education and training events) Helsinn Healthcare SA - NA

months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
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	People with mycosis fungoides (MF) 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.

experience when caring for someone with the condition?	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 MF 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. MF 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 MF. They are often the main source of emotional and psychological support for a loved one with MF. They 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?	Existing topical treatments and phototherapy for MF can improve symptoms but they are not effective in all patients and symptoms tend to recur. Often patients have only a short period before they need 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 phototherapy or existing topical treatments may need systemic treatments, including chemotherapy or radiotherapy. Patients with advanced MF 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, including some forms of phototherapy, 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 a convenient topical therapy that improves symptoms and could have the potential to delay the need for more onerous treatments.
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 chlormethine, either as a gel or in ointment or lotion formulations. However, patients reported that existing treatments did not keep symptoms under control for long and they needed repeated courses of phototherapy, radiotherapy and topical treatments. A convenient treatment that improves symptoms with few side effects would be welcomed. Chlormethine gel is applied once a day by the patient themselves (or their carer). This offers a big advantage over therapies that have to be administered in an outpatient setting or at specialist treatment centres. It is more convenient than previous formulations of chlormethine (either a lotion that had to be made up every day by the patient at home, or an ointment only prepared by specialist pharmacy departments).

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. However, other formulations of chlormethine are already well established in the management of MF and are generally well tolerated.
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:

- Mycosis fungoides has a significant negative impact on the quality of life of patients and their carers.
- Current treatments for mycosis fungoides often improve symptoms for only a short period of time. Many patients require repeated courses of phototherapy, radiotherapy or existing topical treatments even for early stage disease.
- Current treatments can involve travelling considerable distances for repeated appointments at specialist treatment centres, which is time-consuming, expensive and can require significant amounts of time off work for patients and carers.
- There is a clear unmet need for a convenient topical therapy that improves symptoms and could have the potential to delay the need for more onerous treatments.
- Chlormethine is well established in the management of mycosis fungoides. The new gel formulation has significant advantages over previous formulations in terms of easier preparation and storage and simpler administration.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Sean Whittaker**
2. Name of organisation	**Guys and St Thomas NHS Foundation Trust and Kings College London**

3. Job title or position	**Consultant Dermatologist and Professor of Cutaneous Oncology**
4. Are you (please tick all that apply):	☐ 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)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X** 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

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.)	Various treatments are available dependent on stage of disease specifically skin directed treatment (SDT) options for early stage IA-IB and systemic options for late stages (IIB-IV). The primary aim of treatment is to reduce the extent of skin involvement in early stages of disease and improve symptoms. In a minority of patients SDT can induce a prolonged remission but cures are rare. Approximately 25% of patients with early stage disease at diagnosis progress and die of their disease. Whilst SDT may reduce this progression risk, there is a lack of a good evidence base to support this aim. For early stage patients refractory to SDT and late stage patients, there are several systemic biologic and chemotherapeutic options but once again durable remissions are rare. The only exception is the use of reduced intensity allogeneic stem cell transplantation for a highly selected and small group of patients with advanced disease.
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 have published clinical trial endpoints for CTCL (Olsen et al JCO 2011 29; 2598-607) defining partial and complete response (ORR) criteria in terms of skin assessment based on mSWAT analysis (as well as global response criteria based on combined skin, node and blood responses for those patients with advanced disease). Whilst ORR is key, durability of response or time to next treatment (TTNT) are also important for early stage disease whereas survival (OS and PFS) are key for late stage patients. In addition patients with CTCL suffer from significant disease related morbidity and symptom control notably itch and skin pain as well as secondary infection risk are important secondary endpoints captured by various QoL metrics.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes undoubtedly there is an unmet need for CTCL. The lack of durable complete remissions in early stage disease is a significant issue and the limited impact on survival for late stage disease means that patients continuously cycle through different treatment regimes often with only palliative intent. The only exception is use of stem cell allogeneic transplantation but this is only feasible for a small proportion of patients with late stage disease due to co-morbidities, lack of matched donor, a failure to obtain at least a good partial response and age.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	UK cutaneous lymphoma group (UKCLG) guidelines published 2019 (Gilson et al Br J Dermatol 2019; 180) and referenced in the UK haematology guidelines. This is consistent with published US National Comprehensive Cancer Network (www.nccn.org) and European guidelines (EORTC: Trautinger et al Eur J Cancer 2017 77; 57-74 and ESMO: Willemze et al Ann Oncol 2018 29 30-40)
• 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.)	Yes please see NICE improving outcomes guidance for skin tumours including melanoma (www.nice.org.uk/guidance/csg8) which provides the model of care for CTCL in the UK with a recommendation for supra-network MDTs and access to specialised treatments such as TSEB and ECP as well as trial access through this supra-network model. Please note that CTCL pathways of care are not directly covered by the NICE improving outcomes guidance for haematologic malignancies.
• What impact would the technology have on the current pathway of care?	The technology would be part of the skin directed treatment option for early stage disease. Specifically the technology would provide an effective topical therapy which currently is not available as potent topical steroids have limited benefit for CTCL. The technology would educe our reliance on the use of localised radiotherapy for selected skin lesions and phototherapy.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes there would be no change to current NHS care as the technology would be a topical component of skin directed treatment. Indeed the technology was used for CTCL until 9/11 when mechlorethamine, in view of its chemical relationship to mustard gas, was classed as a “biologic weapon” by the US Govt and MERCK discontinued its manufacture.

• How does healthcare resource use differ between the technology and current care?	Currently both radiotherapy (localised and whole skin – TSEB) and phototherapy (both PUVA and UVB – TLO1) are used as alternatives to the technology and so there will be some reduced use of both if the technology becomes available.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics with some supervision of treatment in secondary sector as recommended by specialist clinical services
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Minimal – mainly patient education for appropriate topical use.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes both radiotherapy and phototherapy have potential adverse effects which would be mitigated by the use of the techonology
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the	Possibly as topical treatment of localised early stage skin disease is likely to be easier for CTCL patients

technology to increase health-related quality of life more than current care?	than use of alternatives such as prolonged or repeated courses of radiotherapy and phototherapy
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More appropriate for early stage patients with limited skin disease with patches/thin plaques (stage IA/IB) Less effective for patients with severe skin disease such as tumours (stage IIB) or erythroderma (stage III)
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 example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Little impact compared to current options although the technology will require less frequent OP visits. Accurate monitoring of topical drug use might be a sensible option to assess efficacy and compliance and reduce risks of repeated prescriptions over prolonged periods. There might be a benefit in restricting duration and frequency of use to manage resource impact.

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?	As mentioned above, it might be sensible to limit the duration of topical use to assess efficacy based on published data.
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 as there will be no impact on survival and benefits of the technology will be restricted to skin disease and symptom control.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	The technology is a unique topical approach to managing CTCL patients which has been unavailable since 9/11, contributing to an increased use of alternatives such as radiotherapy and phototherapy both of which have significant resource implications and require prolonged courses of treatment and attendance at hospital often 2-3 times weekly for 3-4 months for phototherapy.

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?	It is more re-emergence of a treatment option that became unavailable following 9/11
• Does the use of the technology address any particular unmet need of the patient population?	Yes it addresses the lack of an effective topical therapy for early stage disease as most other topical therapies have only been reported in small cohort studies without inclusion of appropriate endpoints or have shown no significant benefits in comparative studies.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Only significant adverse effect is the risk of an irritant or allergic contact dermatitis which can limit duration of treatment and efficacy. This can be mitigated by use of topical steroids to reduce the associated inflammatory response (de Quatrebarbes J et al Arch Dermatol 2005 141; 1117-20)
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK	Yes as inferiority comparison was to a compounded version of mechlorethamine (Chlormethine) which was the product in use prior to 9//1.

clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	ORR and symptom control
• 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 but have come to light subsequently?	None
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Recent data (Jones et al in press) has shown that UV is a major contributor to the mutational burden in CTCL. Whilst this is likely to be primarily relevant for disease initiation, this might discourage use of phototherapy for early stage CTCL patients and encourage use of systemic biologic agents such as Bexarotene and alpha Interferon for limited skin disease with associated toxicity and significant resource

	implications. The technology would provide an alternative to systemic treatment for such patients.
21. How do data on real-world experience compare with the trial data?	ORR reported in the trial for both the compounded product and the technology are similar to real world experience pre 9/11
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None apparent in the NHS
22b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Effective topical treatment option for early stage CTCL
- Well tolerated with manageable side effects
- Will reduce reliance on complex treatments such as radiotherapy and phototherapy with associated adverse effects
- Will reduce resource implications for more complex treatment options above requiring frequent and often prolonged hospital visits
- Will potentially limit introduction of systemic treatment options such as Bexarotene and alpha Interferon

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

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About you	
1. Your name	**Julia Scarisbrick**
2. Name of organisation	**Br Association Dermatology**

3. Job title or position	**Consultant Dermatologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** 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):
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 Yes I wrote it just to add in this COVID pandemic the availability of a home treatment for our patients would be a massive advantage for safety of our vulnerable patients

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.)	The treatment improves symptoms, stops progression and improves quality of life
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.)	50% improvement seen in at least 60%
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Huge unmet need , no comparator, at present patients have to come into hospital for phototherapy which is inconvenient , time consuming and risky during COVID pandemic
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	phototherapy
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	**Yes our BR J Dermatology guidelines include topical nitrogen mustard which is the same as chlormethine gel** Gilson D, Whittaker S, Child F, **Scarisbrick J**, Illidge T, Parry E, Rezvani K, Dearden C, Morris S. British Association of Dermatologists and UK Cutaneous Lymphoma Group Guidelines for the Management of Primary Cutaneous Lymphomas. *Br J Dermatol.* 2019 Mar;180(3):496-526. *IF=4.28*
• 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.)	No guidelines above may be followed
• What impact would the technology have on the current pathway of care?	Massive benefit to patients Ease of application, efficacy, new option

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	n/a
• How does healthcare resource use differ between the technology and current care?	n/a
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics only
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	none
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, this will be a massive benefit to the armoury against CTCL where currently there is no active chemotherapy creams/gels available

• Do you expect the technology to increase length of life more than current care?	No known
• Do you expect the technology to increase health-related quality of life more than current care?	Yes , it will vastly improve symptom burden , functionality and emotional well being
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	MF is rare disease all patients with early stage lesions should be considered
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	Easier , it's a topical application applied by patient No monitoring needed

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?	Specialists will assess patients and provide repeat prescriptions according to response as they would with any anti CTCL therapy
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 – see earlier

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 – see responses
• Is the technology a 'step-change' in the management of the condition?	Yes , new topical chemotherapy agent no comparator
• Does the use of the technology address any particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Few adverse effects most common is skin drug rash that resolves on reduced application / topical steroids and very rarely allergic contact reaction

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 mSWAT response and skindex HRQOL
• 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?	no

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?	Very well this treatment has been FDA approved 2017
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
22b. Consider whether these issues are different from issues with current care and why.	n/a
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Novel topical chemotherapy for early MF lesions
- No comparators
- Patients have poor quality of life and live with symptoms of pain, itching and disfiguring lesions
-
-

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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. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
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

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

No competing interests to disclose.

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Clare Robertson and Mari Imamura summarised and critiqued the company's definition of the decision problem and the clinical effectiveness evidence reported within the company submission. Dolapo Ayansina critiqued the statistical methods and analyses presented in the company submission and checked all the numerical results related to the review of the clinical effectiveness evidence. Dwayne Boyers and Elisabet Jacobsen critiqued the cost-effectiveness evidence submitted by the company, checked their economic model, and conducted further sensitivity analyses. Paul Manson critiqued the methods used for identifying relevant studies and checked the search strategies presented in the company submission. Gavin Preston provided clinical advice during the appraisal. Miriam Brazzelli acted as lead for the clinical effectiveness side of the appraisal. Dwayne Boyers acted as lead for the cost-effectiveness side of the appraisal. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

AE	Adverse event
BAD	British Association of Dermatologists
BSA	Body surface area
CAILS	Composite Assessment of Index Lesion Severity
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CR	Complete response
CTCL	Cutaneous T-cell lymphoma
DSA	Deterministic sensitivity analyses
ECP	Extracorporeal photopheresis
EE	Efficacy evaluable
ERG	Evidence review group
HRG	Healthcare Resource Group
HRQOL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
MF-CTCL	Mycosis fungoides-type cutaneous T-cell lymphoma
mSWAT	Modified Severity Weighted Assessment Tool
NYU	New York university (study centre)
OS	Overall survival
PD	Progressed disease
PFS	Progression free survival
PR	Partial response
PUVA	psoralen-ultraviolet A
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QoL	Quality of Life
SAE	Serious adverse event
SD	Stable disease
SDT	Skin directed therapy

TNMB	Tumour, Nodes, Metastasis, Blood
TP	Transition Probability
TSEB	Total skin electron beam
TTO	Time trade off
UVB	Ultraviolet B.

1 EXECUTIVE SUMMARY

1.1 Critique of the decision problem in the company's submission

The company (Recordati Rare Diseases/Helsinn Healthcare SA) provided clinical and cost-effectiveness evidence for chlormethine gel (Ledaga®) for treating mycosis fungoides-type cutaneous T-cell lymphoma. As highlighted in Chapter 2 of this report, the decision problem addressed by the company is aligned with the final scope issued by NICE, with a few minor differences in the choice of comparators. These differences are outlined in Table 1 below.

Table 1 Differences between the company's decision problem and the final scope issued by NICE

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	Company's rationale if different from the final NICE scope	ERG comments
Comparator(s)	Skin directed therapies such as photo therapy (PUVA, UVB) and total skin electron beam therapy. In patients for whom the above skin directed therapies are contraindicated: • Established clinical management without chlormethine gel (including systemic therapies such as interferons and retinoids)	Phototherapy (PUVA, UVB) In patients for whom the above skin directed therapies are unsuitable: • Bexarotene • Pegylated IFN-α	TSEB is not considered a comparator to chlormethine gel. Firstly, whilst both treatments are used to target the skin symptoms of MF-CTCL, these therapies may be used to treat patients with notably different degrees of skin involvement in MF-CTCL. Chlormethine gel is anticipated to be used on specific thin patches and plaques, whilst TSEB, as a treatment for the whole body, would more likely be considered for patients with very widespread plaques covering most of the body. Clinical expert opinion supports this, and although it was acknowledged that there may be minor overlap in the patient populations treated with chlormethine gel and TSEB, the introduction of chlormethine gel is not anticipated to displace the majority of TSEB use. Secondly, the use of TSEB is very limited in UK clinical practice, supported by	The ERG agrees with the company that TSEB, localised radiotherapy, cortico(steroids) and ECP are not valid comparators for chlormethine gel. In the case of TSEB, this is primarily because availability in the UK is very limited. The ERG agrees with the company that phototherapy, is a suitable comparator for chlormethine gel. The ERG clinical expert agrees that the number of patients requiring systemic therapy, as IFN or bexarotene alone, as a first line treatment would be around 10% of the patient population who are eligible for chlormethine gel, and that bexarotene and IFN-α are suitable comparators. The ERG clinical expert also agrees that IFN-α will soon be replaced by the pegylated form in UK clinical practice.

			data from the PROCLIPI registry; therefore, it is not considered standard of care. Wording regarding contraindication to phototherapy in the NICE final scope has been updated to 'unsuitable' in the submission decision problem. This is because there are reasons beyond contraindication as to why patients may not receive phototherapy; these include prior receipt of phototherapy (as there is a maximum number of cycles that patients can receive), restricted access geographically, and low levels of lesional coverage for which the risk benefit ratio for phototherapy precludes its use. Although we consider a broader definition of "unsuitable" to be more appropriate to the clinical setting than "contraindicated", it should be noted that the proportion of patients who would not be considered suitable for phototherapy and who would receive bexarotene or pegylated IFN-α remains low (approximately 10% of the eligible patient population for chlormethine	

			gel addressed in the submission, based on clinical expert feedback). Finally, it should be noted that the decision problem addressed specifies pegylated IFN-α specifically; based on feedback from a UK clinical expert, IFN-α will soon no longer be available in UK clinical practice and the pegylated form will be used in its place.	

1.2 Summary of the key issues in the clinical effectiveness evidence

Overall, the ERG considers the methods used by the company to conduct their systematic review of clinical effectiveness evidence to be satisfactory and in line with current methodological standards. The key clinical effectiveness evidence presented by the company consists of one Phase II trial, Study 201, which compared chlormethine gel (n=130) with chlormethine ointment (n=130).[1] As Study 201 enrolled patients with early-stage MF-CTCL (stage IA-IIA), the study population is narrower than that specified in the NICE final scope and by the marketing authorisation for chlormethine gel; in particular, Study 201 does not provide evidence for the efficacy and safety of chlormethine gel for patients with advanced stage (stage IIB, III and IV). The ERG also notes that the comparator in Study 201, chlormethine ointment, is no longer in use in UK clinical practice. Additional effectiveness data are provided from two real-world data sources: the French ATU (Temporary Use Authorisation) study and the PROVe study.[2, 3] Evidence for the safety profile of chlormethine gel is provided from Study 202, the Phase II, multicenter, open-label extension of Study 201.[4] Additional adverse event data are presented from the French ATU and PROVe studies and from MIDAS, an ongoing split-face, open-label, non-randomised study.[2, 3, 5]

Results of Study 201 indicate that chlormethine gel is non-inferior to chlormethine ointment for the primary endpoint, which was defined as a ≥50% improvement (complete or partial response) in the validated CAILS score from baseline.[1] The ratio of these response rates, stratified by MF-CTCL Stage IA versus IB/IIA, was 1.226 (95% CI: 0.974–1.552, [redacted]). Estimated time to achieve a 50% CAILS response rate was significantly shorter in the gel treatment arm compared with the ointment arm (26 weeks [95% CI 20.71, 35.14] versus 42 weeks [95% CI 29.14, 53.00], $p<0.012$). Non-inferiority was also demonstrated for several other secondary clinical endpoints. Sensitivity analyses excluding the NYU population (as there was a protocol violation at the NYU study centre) showed results akin to those of the full ITT population. The safety profile of chlormethine gel is in keeping with the known toxicity profile. The ERG agrees that no new safety issues were identified.

Nine RCTs of comparators were identified by the company but no connected network could be formed. The company identified seven phototherapy studies (3 RCTs and 4 non-RCTs) to inform a naïve unadjusted comparison with chlormethine gel. The average response rate across these studies was 94% for phototherapy (CR rate of 73% and PR rate of 21%). The ERG has limited confidence in the results of the naïve comparison as they were not adjusted for any difference in study characteristics and agree with the company that they should be taken as highly uncertain. It is also worth noting that the company did not conduct a separate search for non-RCTs for comparator treatments and, therefore, it is unclear whether all relevant evidence on phototherapy has been identified and taken into consideration. An additional search conducted by the ERG has identified a number of potentially eligible phototherapy studies missed by the company but due to time constraints a full-text assessment of these studies was not feasible.

1.3 Summary of the key issues in the cost-effectiveness evidence

The company's base case ICER (original submission) was £44,915 based on modelled cost savings and QALY losses. However, the ERG identified an error in the company's economic model that over-estimated the rate of adverse events, impacting particularly on incremental QALYs. The company corrected this error in response to clarification queries. The company's preferred base case assumptions generate cost savings (£7,005) and QALY gains (+0.03), with chlormethine gel dominating the phototherapy comparator.

The ERG considers the following to represent key issues of uncertainty for decision making:

- The true incremental clinical effectiveness of chlormethine gel vs. phototherapy is unknown. There is substantial heterogeneity across phototherapy studies, using the company's and the ERGs preferred data sources, particularly in terms of the definition of complete / partial response, the comparability of that definition to Study 201, and the approach used to calculate time to progression of skin burden following a CR or PR. In the absence of data to formulate an indirect treatment comparison, a naïve comparison is required, but this introduces substantial uncertainty for decision making.

- The treatment acquisition costs for chlormethine gel are based on the proportion BSA affected, by MF-CTCL stage, from Study 201. However, it is unclear how representative the %BSA within each MF-CTCL stage from Study 201 is to that seen in UK clinical practice, especially for Stage IIB+ disease as these patients were not included in Study 201. The ERG note that small changes to the % BSA affected have a substantial impact on incremental costs and hence the ICER. A judgement is required as to whether the proportion BSA affected in in each stage in Study 201 is generalisable to the UK clinical setting in which chlormethine gel may be used.
- The company use the median daily dosage of chlormethine gel (1.8g) from Study 201 to calculate treatment acquisition costs. However, the ERG prefers the use of mean daily dosage (2.8g) and considers the mean to be more appropriate than the median for costing purposes.
- Substantial uncertainty exists with regard to the proportion of the cohort in each modelled arm that transition into the 'progressed from 1L' health state (i.e. require second line therapy for progression of skin symptoms) and the time to progression following an initial response to first line treatments. Furthermore, the distribution of post-progression therapy, the duration of its usage, it's potential to deliver a favourable response and the associated impact on costs and QALY add additional uncertainty to the base case ICER. The greater the proportion of the cohort that enter this model health state, the higher the overall costs and lower the overall QALYs for any given treatment arm. The ERG considers the progression into this state in the phototherapy arm of the model to be over-estimated and consider alternative sources of data as plausible scenario analyses.
- The appropriateness of using N=7 clinician proxy responses to the EQ-5D to assign health status to vignettes based on mSWAT score in each CTCL disease stage to inform utilities in each of the modelled health states. The ERG accepts the lack of data, but would have considered patient completed responses to the vignettes to be preferable. The ERG also notes substantial differences in the elicited utility scores across states with differential skin burden, despite concerns that the EQ_5D may not be sufficiently sensitive to capture changes in skin burden.

1.4 Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred base case ICER incorporates the cumulative impact of the following assumptions:

1. The ERG prefers treatment acquisition costs for chlormethine gel calculated using the mean daily dosage (2.8g) from Study 201 as opposed to the median (1.8g). The ERG's approach leads to a substantial increase in incremental costs for chlormethine gel.
2. The ERG prefers the use of 2017/18 NHS reference costs to inform the treatment administration costs (HRG code: JC47Z, consultant led outpatient attendance) for phototherapy, as opposed to the company's approach which used 2006/7 reference costs, as reported in Fonia et al. inflated to 2017/18 values[7]. The ERG's preferred approach reduces phototherapy administration costs from £3,458.52 per month to £1,093.28 per month and thus leads to a substantial increase in the ICER for chlormethine gel.
3. The ERG prefers the use of data from Agar et al. as opposed to Wernham et al. to determine the progression between CTCL stages in the model.[23, 61] Agar et al. is a substantially larger cohort and estimate a slower rate of underlying disease progression compared to Wernham et al. The impact of the ERG's preferred assumption is an increase in overall survival (as mortality is dependent on stage), and an improvement in the cost-effectiveness of chlormethine gel.
4. Based on clinical expert opinion, the ERG prefers an assumption that Stage IA mortality is equal to that of the general population. The impact of this assumption is a further improvement in the cost-effectiveness of chlormethine gel.
5. The ERG prefers phototherapy effectiveness (i.e. CR and PR) obtained from the review by Phan et al. (N=7 studies) because it is possible to derive response data by phototherapy type (PUVA / UVB).[9] The company's preferred approach took a weighted average across seven different studies identified as being potentially comparable to Study 201, obtained from the BAD guidelines[19].
6. The ERG also prefers the use of Phan et al. to inform the time to progression following a CR and PR, applied separately to PUVA / UVB, by MF-CTCL stage. By contrast, the company's approach uses data from Whittaker et al., a

small study of PUVA vs. PUVA + bexarotene restricted to Stage IB/IIA MF-CTCL to inform progression following a CR / PR that is based on a different set of studies. The use of Phan et al. ensures a consistent data source for all phototherapy transition probabilities in the model.

7. The ERG prefers the use of Kim et al. considered as a scenario analysis in the CS, as the source of progression following a CR for chlormethine gel, as opposed to the company's preferred assumption that progression following CR is independent of treatment.[3] The ERG's preferred source improves the cost-effectiveness of chlormethine gel relative to the company's preferred base case assumptions. The net impact of the ERG's preferred phototherapy and chlormethine transition probabilities is a reduction in the cost savings associated with chlormethine gel and negative rather than positive incremental QALYs compared to the company's preferred base case analysis where phototherapy was dominated.
8. The ERG prefers the inclusion of an outpatient consultation with a dermatologist for the management of all grade 3 and 4 adverse events included in the model compared to the company's preferred assumption that only corticosteroid treatment is required.
9. The ERG prefers the removal of ECP and methotrexate from the advanced treatment bundle while the cohort is receiving phototherapy, based on clinical expert opinion that these treatments cannot be provided together.
10. The ERG prefers the use of the data from Dalal et al. as an approximation of the proportion of the cohort in the progressed skin burden state that might obtain a CR, and the duration of that response following treatment with bexarotene or IFN-a - as opposed to the company's assumption that 100% of patients with progressed skin burden remain on costly treatment and incur QALY losses for their remaining life years.[67]

The ICER under the set of model assumptions preferred by the ERG is £1.83m per QALY gained (see Table 2). The corresponding probabilistic ICER is £2.61m, and the probability that chlormethine gel and phototherapy are the most cost-effective strategy at a WTP threshold of £30,000 per QALY gained is 11.1% and 86.6% respectively. Despite the magnitude of the ICER under the ERG's base case assumptions, it is important to acknowledge that the ICER is based on small differences in QALYs, and

is highly sensitive to different plausible assumptions about key model parameters. Ultimately, it is the ERG's view is that it that determining a robust and accurate base case ICER in light of the data limitations is problematic.

Table 2 ICER resulting from ERG's preferred assumptions

	Total costs	**Total QALYs**	**Δ costs**	**Δ QALYs**	**ICER £/QALY**
Chlormethine gel	£248,355	9.0429	-		
Phototherapy	£231,983	9.0339	£16,372	0.0089	£1,830,197

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has explored the impact of several different scenario analyses applied to both the company's (see Table 28) and the ERG's set of preferred assumptions (see Table 30). A summary of the results of scenario analyses applied to the ERG preferred set of base case assumptions is provided in Table 3. Full details and justification of each scenario analysis undertaken can be found in Table 27 of this report.

The ERGs base case ICER is most sensitive to changes in treatment acquisition costs and assumptions about post progression treatments that might be used in clinical practice. It should be noted that plausible changes in these parameters have a substantial impact on the ICER. The ERG cautions that there remains substantial uncertainty regarding the most plausible base case ICER.

Table 3 Exploratory analyses undertaken by ERG

Scenario	ERG base-case	Δ Cost	Δ QALY	ICER £/QALY
ERG base case		+£16,372	+0.0089	£1,830,197
Treatment acquisition cost scenarios (Chlormethine gel)				
50% reduction in mean BSA affected.	Mean BSA for low and high skin burden from Study 201.	-£5,995	+0.0089	Phototherapy dominated
50% increase in mean BSA affected.		+£44,093	+0.0089	£4,929,092
Phototherapy treatment distribution scenarios				
All phototherapy delivered as PUVA	PUVA = [redacted]% and UVB = [redacted]%	+£30,707	-0.1550	Phototherapy dominant
All phototherapy delivered as UVB		+£11,306	+0.0695	£162,723
Treatment effectiveness / skin burden transition scenarios				
CR and PR for phototherapy from Phan et al. pooled across CTCL stage	CR and PR for phototherapy from Phan et al. applied by CTCL stage	+£16,196	+0.0086	£1,875,923
Time to progression post CR and PR (for phototherapy) pooled across PUVA/UVB (Phan et al.[9])	Time to progression post CR and PR (for phototherapy) applied separately to PUVA and UVB (Phan et al.[9])	+£24,507	-0.0896	Phototherapy dominant
Subsequent treatment scenarios				
Remove costs of 2nd line treatment for PR in phototherapy arm	Include costs of 2nd line treatment for PR in phototherapy arm	+£20,205	+0.0089	£2,258,701
2nd line treatment: 100% bexarotene	2nd line treatment: 50% bexarotene, 50% IFN-a	-£8,766	+0.0099	Phototherapy dominated
2nd line treatment: 100% IFN-a		+£41,313	+0.0080	£5,184,531
Methodological uncertainty scenarios				
Discount rate = 0%	Discount rate = 3.5%	+£14,608	+0.0368	£396,505
Discount rate = 6%		+£17,194	-0.0060	Phototherapy dominant

Scenario	**ERG base-case**	**Δ Cost**	**Δ QALY**	**ICER £/QALY**
Subgroup analyses				
Model population = Stage IA / IIA MF-CTCL	Model population = all stages of MF-CTCL	+£11,988	+0.0295	£406,773
Model population = Stage IIB+ MF-CTCL		+£33,690	-0.0709	Phototherapy dominant

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

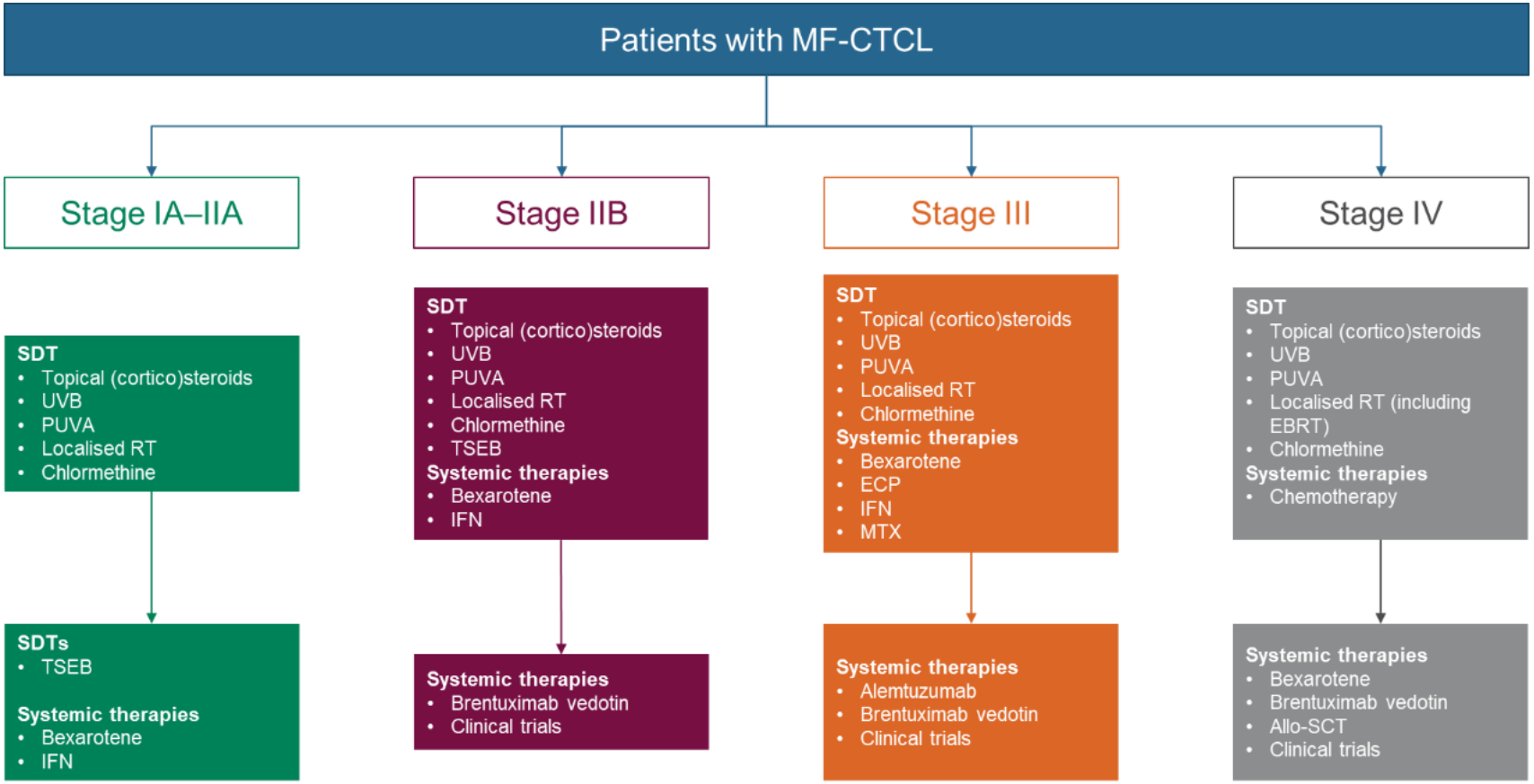
The relevant health condition for this submission is mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL). The company's description of MF-CTCL in terms of prevalence, symptoms and complications appears generally accurate and in keeping with the decision problem. The relevant intervention for this submission is chlormethine gel (Ledaga®).

2.2 Background

Cutaneous T-cell lymphoma (CTCL) is a rare type of non-Hodgkin lymphoma. MF-CTCL is a subtype of CTCL and is characterised by visible oval patches and plaques (raised areas) on the skin, which can be painful and itchy and may progress into tumours over time. The skin symptoms of MF-CTCL are associated with substantial patient burden and can cause physical discomfort, sleep disruption, embarrassment, social withdrawal and absenteeism.[12-17] MF-CTCL patients are also more likely to experience depression and anxiety than the general population and patients with particularly visible lesions may experience substantial impact on their normal daily activities and social interactions. MF-CTCL is also associated with extensive healthcare resource use as patients may require regular hospital visits to receive treatment and disease monitoring.[12] MF -CTCL can be mistaken for other skin conditions like eczema or psoriasis, which can lead to a substantial delay in diagnosis. MF-CTCL is incurable and, in the early stages, has a low mortality rate.

MF-CTCL is usually diagnosed in older, adult patients, although it can affect people of all ages. The peak age of incidence is 50-74 years of age. A total of 920 cases of MF-CTCL were reported in England between 2009 and 2013. The company state that this corresponds to an estimated 182 new diagnoses of MF-CTCL in England each year. MF-CTCL diagnosis is 1.5 times more common in males than females. Prevalence is estimated to be 3515 patients in England and 4077 patients for the UK, but data are limited.[18]

Grading and staging of the disease are based on the TNMB (Tumour, Nodes, Metastasis, Blood) classification system from the British Association of Dermatologists (BAD) guidelines.[19-21] The disease is classified into stages IA to IVB according to the number and type of skin lesions, lymph node involvement, metastasis or visceral organ and peripheral blood involvement. Stages IA, to IIA are classed as early stage disease and stages IIB to IVB are classed as advanced disease.[20, 22] The company provides details of each of the disease stages in Table 4, Document B, of the CS. Patients with early stage disease can have a very good prognosis with 5-year progression free survival (PFS) rates ranging from 75% to 95% and overall survival (OS) ranging from 78% to 97%.[19, 23] Advanced disease stages are associated with worsening prognosis. OS at 5 and 10 years has been reported as 69% and 51% for stage IIB disease. Prognosis for stage IV is extremely poor, with a 5-year survival rate of 24%.[24] The aim of treatment at all stages is to reduce the visibility and body surface area (BSA) coverage of lesions to reduce physical symptoms as well as reducing the social and psychological burden associated with lesions that are visible. A partial response (PR) to treatment is usually a more realistic expectation of treatment than a complete response (CR). Treatment may also be given with the aim of delaying or preventing progression of the underlying disease in advanced stage patients, although patients are not expected to achieve cancer remission. The company presents a summary of the treatment options for MF-CTCL in Figure 2, Document B, of the CS and this is reproduced by the ERG as Figure 1 in this report. The ERG clinical expert agrees that this accurately reflects current UK practice.



Abbreviations: allo-SCT: allogeneic stem cell transplantation; EBRT: external beam radiotherapy; ECP: extracorporeal photopheresis; IFN: interferon; MTX: methotrexate; PUVA: psoralen-ultraviolet A; RT: radiotherapy; SDT: skin-directed therapy; TSEB: total skin electron beam therapy; UVB: ultraviolet B.
Source: Adapted from Gilson et al. (2019)[19]

Figure 1 A summary of the treatment options for MF-CTCL (both SDTs and systemic therapies) in UK clinical practice [reproduced from Figure 2, Document B of the CS]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 4. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 4. The ERG agrees that there are no foreseen equality issues related to chlormethine gel.

Table 4 Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Company's rationale if different from the final NICE scope	ERG comments
Population	Adults with mycosis fungoides-type cutaneous T-cell lymphoma	Adults with mycosis fungoides-type cutaneous T-cell lymphoma	N/A – in line with the final NICE scope	The clinical evidence submitted by the company matches the patient population described in the NICE final scope and is comparable with the characteristics of the patient population eligible for this treatment in clinical practice.
Intervention	Chlormethine gel	Chlormethine gel	N/A – in line with the final NICE scope	The intervention described in the company's submission matches the NICE final scope. At the time of this appraisal, there are no relevant NICE guidelines for the management of MF-CTCL, although published guidance for CD30-positive CTCL is available in TA577. There are additionally various clinical guidelines available.[25] The ERG clinical expert agrees with the company that, of these, the UK-specific BAD guidelines are most commonly used to inform clinical practice in the UK.[12, 19] The company presents the BAD treatment recommendations in Figure 2, Document B of the CS. The company state that they expect chlormethine gel would be used as a first line therapy across all disease

				stages for the treatment of skin symptoms associated with MF-CTCL, except for patients with erythroderma, as these patients may not be able to tolerate a topical therapy due to skin inflammation, and in patients where over 80% of BSA is affected, due to toxicity associated with systemic absorption. The company state that chlormethine gel would be used as monotherapy in early stages of the disease and in combination with systemic therapies for more advanced disease stages. The Committee for Orphan Medicines designated chlormethine gel as an orphan medicinal product on 22nd May 2012.[26] The Committee for Medicinal Products for Human Use recommended granting marketing authorisation for chlormethine gel for the treatment of MF-CTCL on 15th December 2016[26] and the European Commission granted marketing authorisation on 3rd March 2017.[27]
Comparator(s)	Skin directed therapies such as photo therapy (PUVA, UVB) and total skin electron beam therapy.	Phototherapy (PUVA, UVB)	TSEB is not considered a comparator to chlormethine gel. Firstly, whilst both treatments are used to target the skin symptoms of MF-CTCL, these therapies may be used to treat patients	The ERG agrees with the company that TSEB, localised radiotherapy, cortico(steroids) and ECP are not valid comparators for chlormethine gel. In the case of TSEB, this is primarily because

	In patients for whom the above skin directed therapies are contraindicated: • Established clinical management without chlormethine gel (including systemic therapies such as interferons and retinoids)	In patients for whom the above skin directed therapies are unsuitable: • Bexarotene • Pegylated IFN-α	with notably different degrees of skin involvement in MF-CTCL. Chlormethine gel is anticipated to be used on specific thin patches and plaques, whilst TSEB, as a treatment for the whole body, would more likely be considered for patients with very widespread plaques covering most of the body. Clinical expert opinion supports this, and although it was acknowledged that there may be minor overlap in the patient populations treated with chlormethine gel and TSEB, the introduction of chlormethine gel is not anticipated to displace the majority of TSEB use.[28] Secondly, the use of TSEB is very limited in UK clinical practice, supported by data from the PROCLIPI registry; therefore, it is not considered standard of care. Wording regarding contraindication to phototherapy in the NICE final scope has been updated to 'unsuitable' in the submission decision problem. This is because there are reasons beyond contraindication as to why patients may not receive phototherapy; these include prior receipt of phototherapy (as there is a maximum number of cycles that patients can receive),	availability in the UK is very limited The ERG agrees with the company that phototherapy, is a suitable comparator for chlormethine gel. The ERG clinical expert agrees that the number of patients requiring systemic therapy, as IFN or bexarotene alone, as a first line treatment would be around 10% of the patient population who are eligible for chlormethine gel, and that bexarotene and IFN-α are suitable comparators. treatment would be around 10% of the eligible population. The ERG clinical expert also agrees that IFN-α will soon be replaced by the pegylated form in UK clinical practice.

			restricted access geographically, and low levels of lesional coverage for which the risk benefit ratio for phototherapy precludes its use.[12, 19] Although we consider a broader definition of "unsuitable" to be more appropriate to the clinical setting than "contraindicated", it should be noted that the proportion of patients who would not be considered suitable for phototherapy and who would receive bexarotene or pegylated IFN-α remains low (approximately 10% of the eligible patient population for chlormethine gel addressed in the submission, based on clinical expert feedback).[28] Finally, it should be noted that the decision problem addressed specifies pegylated IFN-α specifically; based on feedback from a UK clinical expert, IFN-α will soon no longer be available in UK clinical practice and the pegylated form will be used in its place.[12, 28]	
Outcomes	• Skin symptoms (for example erythema, scaling and pruritus) • Response rates • Duration of response	• Skin symptoms (via CAILS) • Response rates • Duration of response	N/A – in line with the final NICE scope	The outcomes described in the company's submission matches the NICE final scope. The company state that skin symptoms were measured via the Composite Assessment of Index Lesion Severity (CAILS). The ERG

	• Adverse effects of treatment • Health-related quality of life • Mortality	• Adverse effects of treatment • Health-related quality of life • Mortality		notes that skin symptoms in the CS are reported only in terms of symptom reduction rather than measures of actual skin symptoms, including the location of symptoms. While CAILS is a validated tool and the ERG clinical expert believes it would accurately correspond with skin symptoms, the impact of skin symptoms on HRQOL is uncertain as visible skin lesions, for example in areas such as the face, potentially have greater impact on HRQOL than lesions that are less visible.
Subgroups	None specified	• A cost-effectiveness analysis in the subgroup of patients with early stage MF-CTCL (Stage IA-IIA) only is performed, as this reflects the population of Study 201	N/A	

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS provides full details of the searches used to identify the studies included in the systematic review of clinical effectiveness evidence. An appropriate range of databases was searched, as well as ClinicalTrials.gov and applicable conference proceedings for the previous three years. The search strategies are documented in full in Appendix D of the CS. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible.

It is of note that the systematic literature review (SLR) research question, as formulated in Appendix D, is limited to RCTs of any comparator treatment for the treatment of cutaneous T-cell lymphoma (CTCL) and non-RCTs of chlormethine for the treatment of CTCL. The search for the SLR of clinical evidence did not include non-RCTs for comparator treatments and the company did not conduct a separate search for non-randomised evidence of clinical comparators due to time constraints. Additionally, searches for identifying relevant systematic reviews are limited to the Cochrane Database of Systematic Reviews (Issue 7 of 12, July 2019) and the DARE database, which was last updated in 2015. These restrictions may limit the evidence available for the clinical effectiveness review.

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The ERG appraisal of the company's systematic review methods is summarised in Table 5 below.

Table 5 ERG appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Possibly	A search for non-RCTs was conducted to identified studies assessing chlormethine for the treatment of CTCL but a separate search for non-RCTs for comparator treatments was not performed (see section B.2.9, Document B and Appendix D of the CS). It is unclear to the ERG whether all relevant phototherapy non-RCTs were identified.
Were appropriate bibliographic databases/sources searched?	Yes	
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	
Was study selection conducted by two or more reviewers independently?	Yes	See Appendix D.4 of the CS.
Was data extraction conducted by two or more reviewers independently?	Possibly	In Appendix D.4 of the CS, it is stated that data were extracted by a single reviewer and were verified by a second reviewer.

Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	See Appendix D.4 of the CS.
Was risk of bias assessment conducted by two or more reviewers independently?	Possibly	In Appendix D.4 of the CS, it is stated that the quality of eligible RCTs was assessed by a single reviewer and verified by a second reviewer.
Was identified evidence synthesised using appropriate methods?	Not applicable	As the SLR identified only one RCT, meta-analysis was not conducted.

Overall, The ERG considers the methods used by the company to conduct the systematic review of clinical effectiveness evidence to be acceptable according to current methodological standards.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria; results are presented in Table 6.

Table 6 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included study

The evidence for the clinical efficacy and safety of chlormethine gel for adults with mycosis fugoides-type cutaneous T-cell lymphoma (MF-CTCL) consists of one Phase II non-inferiority trial, Study 201, conducted in the USA and supported in part by Ceptaris Therapeutics.[1] An overview of the study is presented in Table 8, Section B.2.2 of the CS. Study methods are summarised in Section B.2.3 and the participant flow of the study is presented in Figure 4, Section B.2.4.1 of the CS.

Study 201 is a multicentre, randomised, observer-blind, active comparator Phase II clinical study comparing chlormethine gel (0.02%) with chlormethine ointment (0.02%). The study population comprises a total of 260 participants with Stage IA, IB or IIA MF-CTCL, previously treated with at least one SDT (skin directed therapy) for MF-CTCL (approximately 40% of these patients had received prior phototherapy). Patients were randomised in a 1:1 ratio to receive either chlormethine gel (n = 130) or chlormethine ointment (n = 130). Although the study was conducted in the USA, the ERG's clinical expert is of the opinion that the study participants are similar to those with early-stage MF-CTCL who would be seen in clinical practice in the UK. In study 201, other therapies to treat MF-CTCL were prohibited, while topical steroids were permitted only on non-MF-CTCL lesions. Participants remained on study treatment for up to 12 months. Patients were then followed off-study for an additional 12 months to assess for secondary non-melanoma skin cancers associated with topical use of chlormethine.

Concurrently with the 12-month follow-up period of Study 201, participants who completed 12 months of treatment with either chlormethine gel or ointment but did not achieve a complete response (CR) could enrol in Study 202, an open-label 7-month study investigating an unlicensed dose of 0.04% chlormethine gel.[4] In the CS, given the higher-than-licensed dose of chlormethine gel used, Study 202 provides only supportive safety data, rather than safety and efficacy data.

The company performed a risk of bias assessment of Study 201 using the University of York Centre for Reviews and Dissemination guidance (Table 14, Appendix B.2.5 of the CS).[29] The ERG does not agree with the company judgement that the methods of randomisation and allocation concealment were appropriate and considers them to be at unclear risk of bias. This is on the basis that the method used for generating random number sequence was not reported; and the method used to conceal the allocation sequence was not described in sufficient details (i.e. the envelopes used to conceal random treatment allocation were described as numbered but it was unclear whether these envelopes were also sealed and opaque; an example of the envelopes was mentioned as Appendix 16.1.7 to the Study 201 CSR but the relevant Appendix was not supplied to the ERG). In view of the fact that the drug formulations (chlormethine ointment and chlormethine gel) were different in their appearance (as stated in the study 201 CSR, page 26[1]), the ERG has some doubts about the blinding of the care providers and patients. On the other hand, the ERG agrees that outcome assessors for tumour response and toxicity were blinded to treatment allocation. The ERG considers that the assessment on other criteria performed by the company to be adequate.

Study 201 was well balanced for baseline characteristics including demographics, disease characteristics and prior therapies (Table 11, Section B.2.3.3 of the CS). At baseline, 54.2% of the participants had stage IA disease (58.5% and 50.0% for chlormethine gel and ointment, respectively) and 44.2% had stage IB disease (40.0% and 48.5% for chlormethine gel and ointment, respectively), while two participants (1.5%) within each of the two treatment groups had stage IIA disease. There was a protocol violation in one of the study centres (New York University or NYU) where patients were incorrectly randomised with stage IA patients assigned to the chlormetine gel group ([redacted]) and stage IB/IIA patients to the chlormethine ointment group ([redacted]). Effectiveness data were therefore analysed in the intention-to-treat (ITT) population including (full population) and excluding NYU within the CS.

As Study 201 enrolled patients with early-stage MF-CTCL (stage IA-IIA), the study population is narrower than that specified in the NICE final scope and by the marketing authorisation for chlormethine gel. In particular, Study 201 does not

provide evidence for the efficacy and safety of chlormethine gel for patients with advanced stage (stage IIB, III and IV). To complement data from Study 201, the company provided additional efficacy and safety data from three observational studies.

Additional effectiveness data were presented in the CS from the following studies:

- French Temporary Use Authorisation (ATU) study[2,30]
- PROVe study[3,31]

Additional adverse event data were presented in the CS from the following studies:

- MIDAS study[5,32]
- French ATU study[2]
- PROVe study[3]

It is not stated in the CS how these observational studies were identified. The publications are from conferences that took place after the date of the company's literature search (17th July 2019), therefore, they were not discoverable by the company's search, nor were the associated conferences included in the company's grey literature search.

Characteristics of these additional observational studies, as well as of Study 201 and Study 202, are summarised in Table 7 below. The ERG notes that these observational studies were identified outside the systematic review of clinical effectiveness evidence. The interventions and populations from these observational studies are not directly comparable to those reported in Study 201, and there was heterogeneity with regard to study characteristics across studies. To the ERG, it is unclear how participants were selected from a wider patient population for these studies, how representative the included participants are, and whether the findings are applicable to the general patient population with MF-CTCL. The CS does not provide information on the risk of bias assessment of these observational studies.

Table 7 Characteristics of Study 201, Study 202 and relevant observational studies that provide additional data on the effectiveness and safety of chlormethine gel

Characteristics	Study name						
	Study 201[1]			Study 202[4]	ATU study[2]	PROVe study[3]	MIDAS study[5]
Country	USA			USA	France	USA	USA
Study design	RCT			Open-label follow-up trial of Study 201	Single-arm study	Ongoing, prospective, open-label single-arm study	Ongoing split-face, open-label, non-randomised study
Treatment	Chlormethine 0.02% gel; Concomitant treatments prohibited; Topical steroids were permitted only on non-MF-CTCL lesions			Chlormethine 0.04% gel	Chlormethine 0.02% gel; Concomitant treatments permitted.	Chlormethine 0.02% gel; Concomitant treatments permitted.	Two therapies administered concurrently to the same individual but on different lesions: • chlormethine gel (0.02%), or • chlormethine gel (0.02%) and triamcinolone ointment (0.1%)
Treatment duration	Median (range) [redacted] weeks and [redacted] weeks for chlormethine gel and ointment groups respectively (based on safety set)			Median [redacted] weeks	Median [redacted] months	Not reported	Not reported
Number of participants	Including NYU		Excluding NYU	[redacted] (FAS); Stage IA-IIA disease	[redacted]	[redacted]	[redacted] Stage IA-IB disease
	Chlormethine gel (n=130)	Chlormethine ointment (n=130)	Chlormethine gel (n=[redacted])	Chlormethine ointment (n=[redacted])			

MF-CTCL stage (n, %)									
IA	76 (58.5)	65 (50.0)	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	[redacted]	Not reported
IB	52 (40.0)	63 (48.5)	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	[redacted]	Not reported
IIA	2 (1.5)	2 (1.5)	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	[redacted]	-
IIB	-	-	-	-	-	[redacted]	[redacted]	[redacted]	-
III-IV*	-	-	-	-	-	[redacted]	[redacted]	[redacted]	-
Other/ Missing/ unknown	-	-	-	-	-	[redacted]	[redacted]	[redacted]	-
Data within the CS	Effectiveness and adverse events				Supportive safety data only	Effectiveness and adverse events		Effectiveness and adverse events; QoL	Adverse events
Source	Tables 11, 27				Table 34	Tables 19, 20		Table 22	B.2.2; B.2.10.3

* includes Sézary Syndrome

Abbreviations: ATU: temporary use authorisation; CS: company submission; FAS: full analysis set; MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; NYU: New York University (study centre); SD: standard deviation; QoL: quality of life; RCT: randomised controlled trial

3.2.2 Primary and secondary efficacy endpoints

The following outcomes were assessed in Study 201: CAILS response rate, mSWAT response rate, time to confirmed CAILS response, time to progression on CAILS score and extent of cutaneous disease. The company provides a summary of the definitions for each outcome in Table 9, Document B, of the CS, which is reproduced as Table 8 below. Study 201 did not collect quality of life outcomes.

Table 8 Outcome definitions in Study 201 [reproduced from Table 9, Document B of the CS]

Outcome	Definition
CAILS or mSWAT response categories	
Confirmed response	Any response which had a duration of ≥28 days
CR	No evidence of disease; 100% improvement from baseline score (score of 0), confirmed at the next visit ≥28 days later
PR	Partial but incomplete clearance of disease (evidence of disease remains); ≥50% improvement from baseline score, confirmed at the next visit ≥28 days later
SD	Disease has not changed from baseline score; <50% improvement or <25% increase from baseline
PD	Disease has worsened since baseline; ≥25% increase from baseline score
(CAILS/mSWAT) response rate	Proportion of patients with ≥50% improvement (CR+PR) from the baseline score, confirmed at the next visit ≥28 days later
Other CAILS/mSWAT endpoints	
Duration of confirmed CAILS response	Time from the first appearance of confirmed response (CR or PR) to the first assessment where the response was no longer apparent (i.e. when SD or PD was subsequently documented)
Time to progression based on CAILS score	Time from baseline to progressive disease (≥25% increase from baseline CAILS score)
Time to confirmed CAILS response	Time from baseline to the first confirmed CAILS response (CR or PR)
Extent of cutaneous disease	Change from baseline in the total percentage of the BSA component of the mSWAT score calculation

Abbreviations: CAILS: Composite Assessment of Index Lesion Severity; CR: complete response; mSWAT: modified Severity Weighted Assessment Tool; PD: progressive disease; PR: partial response; SD: stable disease
Source: Study 201 CSR (2011);[1] Lessin et al. (2013)[33]

Primary endpoints: Response rates

The primary efficacy endpoint in Study 201 was a ≥50% improvement (CR or PR) in CAILS score from baseline. The CAILS score is calculated by adding a severity score for the following skin symptoms: erythema and scaling (both scored on a severity scale of 0-8), and plaque elevation (scored on severity scale of 0–3) and surface area (scored on a severity scale of 0-9). In Study 201, physicians chose up to five representative index lesions for each patient at baseline and these were assessed throughout the study. Patients with no baseline or post-baseline CAILS assessment were classed as 'unevaluable'.[1] The company provides a summary of the CAILS responses for both the ITT populations including and excluding the NYU population in Table 15, Document B, of the CS. In the ITT including NYU population, the confirmed response rate (CR+PR) was higher for chlormethine gel than for chlormethine ointment, although this was not statistically significant (p=[redacted], stratified by MF-CTCL Stage [IA versus IB/IIA]). In the full ITT population, the CAILS response rates for chlormethine gel was 58.5% and that for chlormethine ointment 47.7%, with a response ratio of 1.226 (95% CI: 0.974–1.552). Similarly, in the in the ITT population excluding NYU the CAILS response rates for chlormethine gel was [redacted] and that for chlormethine ointment [redacted], with a response ratio of [redacted] (95% CI: [redacted]). The company state that these data confirmed that the chlormethine gel formulation was non-inferior to the compounded ointment formulation - as the lower limit of the 95% CI was ≥0.75. The company also provide data for CAILS response by stage IA (gel n=76, ointment n=65) and stages IB/IIA (gel n=54, ointment n=65). These data are summarised in Table 16, Document B of the CS and, as for previous results, indicate that the gel formulation is non-inferior to the ointment formulation.

A further post-hoc analysis to evaluate the efficacy of chlormethine gel using a by-time approach was conducted to identify any trends in treatment response via CAILS and mSWAT. Only patients who had data available at each assessment timepoint were included in the analysis. Patients who withdrew due to lack of efficacy or progressive disease were counted as non-responders. Clinically relevant response rates (CAILS: 8.5% [n=118]; mSWAT 5.9% [n=119]) occurred from month 1. Peak response rates for CAILS was 78.9% (visit 8; n=90) and the peak mSWAT response rate was 60.7% (final visit; n=90). The company state that these results demonstrate that response

rates increased over time in Study 201, and that maximum response to the gel treatment typically occurs in the 8–10-month timeframe.

Secondary endpoints

In section B.2.6 Document B of the CS the company present also the secondary endpoints of Study 201: Modified Severity Weighted Assessment Tool (mSWAT) response rate, time to confirmed CAILS response, duration of confirmed CAILS response, time to progression based on CAILS score, and extent of cutaneous disease. Definitions of these endpoints are presented in Table 8 above.

The mSWAT response rate (CR+PR) was measured at each study visit for up to 12 months of treatment. The mSWAT score is obtained by classifying each lesion on a patient into one of three categories: patch, plaque and tumour. The BSA covered by that lesion is then multiplied by 1, 2 or 4 for a patch, plaque or tumour, respectively, to weight the score based on lesion severity.[1, 19] The company present the mSWAT response rates of Study 201 in Table 17, Document B, of the CS.

For time to CAILS response patients who had no baseline CAILS assessment were excluded from the analysis ([redacted] patient in the chlormethine gel arm and [redacted] patients in the chlormethine ointment arm). Patients with a baseline CAILS assessment but no post-baseline assessment were censored at time 0 ([redacted] patients in the chlormethine gel arm and [redacted] patient in the chlormethine ointment arm). The company presents the Kaplan-Meier data for both ITT populations in section B.2.6.3 and Figures 5 and 6, Document B, of the CS.

Duration of confirmed CAILS response was defined in the Study 201 as the time from the first appearance of confirmed response (CR or PR) to the first assessment where stable disease (SD), defined as disease is unchanged from baseline; <50% improvement or <25% increase in CAILS score from baseline, or progressive disease was documented (see Table 8). Patients were not withdrawn if the response was lost and response could be re-attained with continued treatment.[1] Duration of CAILS response was analysed in patients who achieved a response. Seventy-six chlormethine gel patients and 62 chlormethine ointment patients for the ITT including NYU population were analysed. Of these patients, 65/76 (85.6%) gel patients and 51/62

(82.2%) ointment patients maintained their response to the end of the trial at 12 months. Kaplan-Meier data for the duration of confirmed CAILS response are presented in section B.2.6.4 and Figures 7 and 8, Document B, of the CS.[1]

With regard to time to progression, patients who had no baseline and no post-baseline CAILS assessments were excluded from the analysis. In Study 201, among the ITT population (including NYU population) 15 patients treated with gel (11.5%) and ten treated with ointment (7.7%) had progressive disease at some point during the course of the study.[33] The company state that most of these patients remained on treatment. Kaplan-Meier data for time to progression based on CAILS score are presented in section B.2.6.5 and Figures 9 and 10, Document B, of the CS.

In Study 201, the overall extent of cutaneous disease was measured by the total percentage of the body surface area (BSA) component of the mSWAT score. To assess non-inferiority, response was defined as ≥50% improvement from baseline in percentage BSA that was confirmed at the next visit ≥28 days later. The percentage BSA response rates for both ITT populations including and excluding the NYU population are presented in Table 18, Document B, of the CS.

A summary of the main results for the full ITT population including NYU related to the secondary endpoints are shown in Table 9 below. Based on the Kaplan-Meier analysis, a 50% CAILS response rate would occur 16 weeks sooner in patients treated with chlormethine gel than those treated with chlormethine ointment ($p<0.012$). The remaining secondary endpoints were not statistically different between the two treatment arms. The reported sensitivity analyses excluding the NYU population show results broadly consistent with those of the full ITT population.

Table 9 Secondary endpoints in Study 201 (ITT population including NYU)

Outcome	**Chlormethine gel (n=130)**	**Chlormethine ointment (n=130)**	
Estimated time to a 50% CAILS response rate	n=130 26 weeks (95% CI 20.71, 35.14)	n=130 42 weeks (95% CI 29.14, 53.00)	p<0.012
mSWAT response rate CR +PR, n (%)	n=130 61 (46.9%)	n=130 60 (46.2%)	response rate ratio 1.017 (95% CI: 0.783–1.321) p=[redacted], X^2=[redacted]
Duration of CAILS response (% maintained response) Week 24 Week 40	n=76 [redacted] [redacted]	n=62 [redacted] [redacted]	p=[redacted] unadjusted log-rank p=[redacted] stratified log-rank
Time to progression based on CAILS score (% who do not have ≥25% increase from Baseline CAILS score) Week 24 Week 52	n=130 [redacted]	n=130 [redacted]	p=[redacted]
Extent of cutaneous disease (n, % with ≥50% improvement from baseline in percentage BSA) Responders Non-responders	n=130 [redacted] [redacted]	n=130 [redacted] [redacted]	Response rate ratio [redacted] (95% CI: [redacted]), p<[redacted]

Abbreviations: CAILS, Composite Assessment of Index Lesion Severity; mSWAT, Modified Severity Weighted Assessment Tool; CR, complete response; PR, partial response; BSA, body surface area.

Although Study 201 was designed to test non-inferiority of chlormethine gel versus chlormethine ointment, a post-hoc analysis, using the data cut-off date of 1st June 2011, was conducted to test superiority of the gel versus ointment for the CAILS response rate. Data for the post-hoc analyses are presented in section B.2.6.7. The company state that, because the lower bound of the 95% CI around the ratio of response rates exceed the non-inferiority threshold of ≥0.75 in the ITT population and was above 1 in the efficacy evaluable population at 1.301 (95% CI: 1.065–1.609), this post-hoc approach demonstrates that the [redacted].

Efficacy data from the French ATU report and the PROVe study

In addition to Study 201, the company presents efficacy data from two evidence sources for chmormethine gel: the French Temporary Use Authorisation (Autorisations Temporaires d'Utilisation [ATU]) data and the PROVe study. The results of these studies are summarised by the company in section B.2.6.8 of the CS.

Efficacy data were available for [redacted] patients who returned at least one follow-up form in the French ATU study. Of these [redacted] achieved an overall response (OR) that was defined as PR, "nearly CR" or CR following treatment with chlormethine gel, and [redacted] were classed as achieving a 'favourable' response, defined as OR or SD. The company states that the majority ([redacted], [redacted]) of these patients were Stage IA/IB, and that [redacted] patients with advanced disease experienced a favourable response of OR or SD (<50% reduction from baseline score).[2] The ERG notes that the results for patients with advanced disease are based on a small number of data (only [redacted]). The company also notes that the measures used to evaluate response rate are unknown as clinicians were not required to report this information in the ATU study. The ERG is, therefore, uncertain on whether participants were assessed using the same response measures and the extent to which these are comparable to the CAILS and mSWAT measures used in Study 201. As the company acknowledges, the data set is also limited due to missing follow-up data. Data for response rates in the ATU study are provided by the company in Table 21, Document B, of the CS.

The company presents preliminary response data from the PROVe trial, as of September 2019, in the CS. A response was defined as a ≥50% reduction in pre-enrolment baseline BSA percentage coverage of lesions.[3] With regard to Stage IA and IB patients, [redacted] responded to gel treatment at 12 months. The peak response rate of [redacted] was achieved at 18 months. In the whole (Stage IA–IV) evaluable patient population the response rate was [redacted] ([redacted]) at 12 months.[3, 31] While these data are supportive of the Study 201 efficacy results for chlormethine gel, the ERG notes the small numbers of participants with advanced stage disease in the PROVe trial.

A summary of the numbers of patients experiencing a response in Study 201, the French ATU study and PROVe trial are presented in Table 10.

Table 10 Summary response data for Study 201, French ATU study and PROVe study

Response n (%)	Study 201				ATU[1, 2]	PROVe [3]
	CAILS response [1]		mSWAT response [1]			
	ITT including NYU		ITT including NYU			
	Chlormethine gel (n=130)	Chlormethine ointment (n=130)	Chlormethine gel (n=130)	Chlormethine ointment (n=130)	Chlormethine gel [redacted]	Chlormethine gel [redacted]
OR	76 (58.5)	62 (47.7)	61 (46.9)	60 (46.2)	[redacted]	[redacted]
CR	18 (13.8)	15 (11.5)	[redacted]	[redacted]	[redacted]	-
"nearly CR"	-	-	-	-	[redacted]	-
PR	58 (44.6)	47 (36.2)	[redacted]	[redacted]	[redacted]	-
Non-response	54 (41.5)	68 (52.3)	[redacted]	[redacted]	-	-
SD	42 (32.3)	61 (46.9)	[redacted]	[redacted]	[redacted]	-
PD	5 (3.8)	3 (2.3)	[redacted]	[redacted]	[redacted]	-
Unevaluable	7 (5.4)	4 (3.1)	[redacted]	[redacted]	-	-
No baseline mSWAT assessment	-	-	[redacted]	[redacted]	-	-
No post-baseline mSWAT assessment	-	-	[redacted]	[redacted]	-	-
Unspecified	-	-	-	-	[redacted]	-

Abbreviations: ATU: temporary use authorisation, CAILS: Composite Assessment of Index Lesion Severity; CR: complete response; ITT: intention-to-treat; NYU: New York University; OR: overall response, PD: progressive disease; PR: partial response,

a Includes patients with no Baseline CAILS assessment or no post-Baseline CAILS assessment. For the ITT including NYU population for the primary endpoint, five patients never received study drug and six patients were withdrawn without any post-Baseline assessment (one for non-compliance and five due to treatment-limiting toxicity).
1 Source: Lessin et al. (2013);[33] Study 201 CSR (2011). Concomitant cortico(steroid) treatment not allowed during study[1]
2 Source French ATU Report (2019). Concomitant cortico(steroid) treatment allowed[30]
3 Source: Kim et al. Oral Presentation (2019). Concomitant cortico(steroid) treatment allowed[31]

3.2.3 Health-related quality of life (HRQOL) measures

HRQOL data were not collected in Study 201. The company describe their systematic review to identify relevant HRQOL studies and the *de novo* utility (vignette) study in Appendix H of the CS. A critique of the review and vignette study will be presented in chapter 4.

3.2.4 Adverse effects of treatment

The Study 201 safety set comprised all patients who received at least one topical application of chlormethine (128 gel patients and 127 ointment patients). The median duration of exposure was [redacted] weeks in the gel and [redacted] weeks in the ointment arms, respectively The methods for assessing and reporting adverse effects (AEs) in Study 201 are reported by the company in section B.2.10.1. The ERG considers these methods appropriate.

The criteria for reducing the frequency, temporarily suspending dosing or discontinuing study medication in Study 201, and data for the numbers of patients experiencing these events are presented in Tables 28 and 29, Document B, of the CS. Significantly more patients treated with chlormethine gel experienced at least one reduction in frequency of dosing or had their study medication temporarily suspended at least once during the trial than patients treated with chlormethine ointment ([redacted] versus [redacted] p=[redacted] and [redacted] versus [redacted] p=[redacted], respectively).[1] The numbers of patients who discontinued treatment due to a drug-related AE associated with toxicity were similar between the two treatment arms (20.3% in the gel arm and 17.3% in the ointment arm, p=0.631).[33]

61.7% of the patients treated with chlormethine gel and 50.4% of patients treated with chlormethine ointment experienced at least one AE that was considered to be possibly, probably, or definitely related to a study drug.[33] The most commonly reported AEs were skin and subcutaneous disorders, ([redacted] of gel patients and [redacted] of ointment patients), and were mainly due to skin irritation, which was experienced by more patients who received the gel formulation than those who received the ointment formulation (25.0% versus 14.2% p=0.040).[33] Similar numbers of patients experienced a serious adverse event (SAE) in both treatment arms ([redacted] versus [redacted] p=[redacted]). None of the SAEs were considered drug-related. More gel patients

experienced a grade 3 or grade 4 AE than ointment patients ([redacted] versus [redacted] and [redacted] versus [redacted] respectively). The company present summary data for AEs in Study 201 in Tables 30 to 33, Document B, of the CS. It is the ERG clinical expert's opinion that the type and frequency of AEs reported in Study 201 are representative of UK clinical practice.

Patients were monitored for the development of secondary non-melanoma skin cancers for 24 months (12 months during the trial and for an additional 12-month follow-up period).[33] During this time, three patients treated with chlormethine gel and eight treated with chlormethine ointment were diagnosed with 20 non-melanoma skin cancers. The non-melanoma skin cancers included nine squamous cell carcinomas (SCCs) of the skin, ten basal cell carcinomas (BCCs) and one Merkel cell carcinoma. The company state that, for all these cases, the skin cancer cannot be attributed to topical chlormethine treatment as 14/20 cases occurred in untreated areas of the skin, on sun exposed areas, and in patients with a prior history of skin cancers or who had received prior skin-directed therapy for MF-CTCL, including phototherapy, which is known to increase the risk of skin cancer. The ERG agrees with the company that these data do not support an obvious association between the development of secondary non-melanoma skin cancer and topical chlormethine treatment, although the ERG believes these data are inconclusive.

Supportive safety data from [redacted] patients enrolled in Study 202 are presented in section B.2.10.2 of the CS. Study 202 enrolled both gel and ointment patients from Study 201 who had not achieved a CR from either treatment. Patients in Study 202 received chlormethine gel only and at an unlicensed (higher) dose than in Study 201. The month 12 assessment for Study 201 served as the baseline assessment for the Study 202 extension. Study 202 patients were then assessed at months 2, 4, 6 and 7 during the 7-month study period.[4] Patients were treated with chlormethine gel for a median duration of [redacted]. The most frequently reported AEs were skin and subcutaneous disorders, reported by [redacted]) patients, which were mainly classed as Grade 1 ([redacted] patients) or Grade 2 ([redacted] patients) in severity.[4] Grade 3 skin AEs occurred in [redacted] patients, and only [redacted] patient reported a Grade 4 skin AE. The most frequently reported AEs were skin irritation in [redacted] patients, erythema in [redacted] patients, and pruritus in

[redacted] patients. [redacted] patients experienced a SAE, although the company state that none of these were considered to be drug related. [redacted] non-melanoma skin cancer was reported 80 days after completing treatment with chlormethine gel (0.04%), although this was also considered to be unrelated to gel treatment.

The company present summary data for any AEs, and skin and subcutaneous tissue disorders experienced by >5% of patients for study 201 and Study 202 in Table 37, document B, of the CS.

The company present AE data for the ongoing MIDAS trial in section B.2.10.3. MIDAS (NCT03380026) is an investigator-initiated, split-face, open-label, non-randomised study designed to investigate the incidence and severity of common adverse reactions to topical chlormethine gel (0.02%) treatment, with an emphasis on contact dermatitis. Patients in the MIDAS trial were all treated concurrently with two different therapies but on different lesions: either chlormethine gel once nightly, or gel once nightly plus triamcinolone (steroid) ointment (0.1%) once daily, for four months.[5] Of the [redacted] patients who were enrolled as of September 2019, [redacted] patients experienced allergic contact dermatitis and [redacted] experienced irritant contact dermatitis.[5] [redacted] of these patients also had reactions to various other allergens. [redacted] patients were unable to continue with chlormethine gel treatment.[5]

The company also presents AE data for the French ATU and PROVe studies. In the ATU study, [redacted]) patients reported experiencing [redacted] adverse events:[redacted] treatment-related AEs and [redacted] AEs not linked to chlormethine gel treatment. [redacted] cases of cutaneous AEs were reported, including [redacted] serious cases.[30] AEs which were reported in >5% of the population were contact dermatitis ([redacted]), skin irritation ([redacted]) and erythema ([redacted]).[2] The company note that patients could receive concomitant medications in the ATU study that were not allowed in Study 201.

In the PROVe study, [redacted]/298 patients experienced an AE. All AEs which affected ≥3% patients were skin related AEs, the most common of whic was dermatitis

([redacted]), followed by pruritis ([redacted]) and skin irritation ([redacted]). Data for all AEs and AEs occurring in ≥3% patients in the PROVe study are presented in Table 39, Document B, of the CS.[31]

The company note the lower incidence of skin-related AEs in the ATU and PROVe studies compared with Study 201.

With regard to mortality, [redacted] death was recorded among patients treated with chlormethine gel (due to widely disseminated metastatic colorectal cancer and considered unrelated to the study drug), and [redacted] among those treated with chlormethine ointment in Study 201.[1] No deaths were reported in Study 202 during the study duration or within 30 days of stopping the chlormethine gel (0.04%) treatment.[34] [redacted] treatment-related deaths were reported in the French ATU study.[30]

A summary of the AE data reported in the CS is presented in Table 11.

3.2.5 Subgroup analyses

Subgroup analyses of the CAILS response rates in Study 201 were conducted for sex (Male, Female), race (Caucasian, African American, Other), age (<18, 18–64, 65–74, ≥75) and the stratification variable, MF-CTCL stage (Stage IA, Stage IB/IIA) for both ITT populations (including and excluding the NYU population). Results were consistent among subgroups and both strata were consistent for non-inferiority of chlormethine gel versus chlormethine ointment. Results for the subgroup analyses are presented in Tables 24 and 25, Document B, of the CS. The company acknowledge also that a subgroup analysis for the CAILS or mSWAT scores based on whether patients had received previous phototherapy or not was not feasible due to data constraints.

3.2.6 Meta-analyses

As only Study 201 was identified by the company as relevant to address the decision problem of this appraisal, no meta-analyses were performed.

Table 11 Summary of adverse events (AEs) reported in Study 201, Study 202, MIDAS study, French ATU study and PROVe study

Adverse event n (%)	**Study 201[1]**		**Study 202[2]**	**MIDAS[3]**	**ATU[5]**	**PROVe[6]**
	Chlormethine gel 0.02% (n=128)	Chlormethine ointment 0.02% (n=127)	Chlormethine gel 0.04% ([redacted])	Chlormethine gel 0.02% ([redacted])	Chlormethine gel 0.02% ([redacted])	Chlormethine gel 0.02% ([redacted])
Any AE	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	-	-	-
Skin irritation	32 (25.0)	18 (14.2)	[redacted]	-	[redacted]	[redacted]
Pruritis	25 (19.5)	20 (15.7)	[redacted]	-		[redacted]
Erythema	22 (17.2)	18 (14.2)	[redacted]	-	[redacted]	[redacted]
Dermatitis contact	19 (14.8)	19 (15.0)		[redacted][4]	[redacted]	[redacted]
Skin hyperpigmentation	7 (5.5)	9 (7.1)	-	-	-	-
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	-	-	-	-
Upper respiratory tract infection	11 (8.6)	10 (7.9)	-	-	-	-
Infections and infestations	[redacted]	[redacted]	-	-	-	-
Folliculitis	7 (5.5)	5 (3.9)	-	-	-	-
Rash	-	-	-	-	-	[redacted]
Skin burning sensation	-	-	-	-	-	[redacted]
Drug-related AEs	79 (61.7)	64 (50.4)	-	-	-	-
SAE not drug-related	[redacted]	[redacted]	[redacted]	-	-	-
Grade 3 (moderate severe) drug-related skin and subcutaneous AEs	[redacted]	[redacted]	[redacted]	-	-	-
Grade 4 (severe) drug-related skin and subcutaneous AEs	[redacted]	[redacted]	[redacted]	-	-	-
Discontinuation due to AEs	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Discontinuation due to drug-related AEs	[redacted]	[redacted]	-	-	-	-
Deaths	[redacted]	[redacted]	[redacted]	-	[redacted][8]	

1. AEs occurring in ≥5% patients in the Study 201 safety set.[1]
2. AEs occurring in ≥5% patients in the Study 202 full analysis set.[4]
3. Trial is ongoing at time of CS. Data as of September 2019.[5]
4. [redacted] allergic contact dermatitis and [redacted] irritant contact dermatitis
5. AEs occurring in >5% patients in the French ATU study.[30]
6. AEs occurring in ≥3% patients in the PROVe trial.[31]
7. No drug-related
8. Treatment-related

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

3.3.1 Indirect treatment comparison (ITC)

In the absence of direct clinical evidence, the company considered the feasibility of conducting an indirect treatment comparison (ITC) on the basis of ten RCTs (Study 201 and nine comparator RCTs) identified by the SLR to assess the relative effectiveness of chlormethine gel versus other treatments for MF-CTCL.

The company present the results of the risk of bias assessment for Study 201 and the nine comparator RCTs in Table 15 of Appendix D.7 of the CS. The ERG considers the company's methods for risk of bias assessment to be acceptable.

No connected network could be formed between Study 201 and any of the nine identified comparator RCTs as there was not a common comparator. In addition to the lack of connectivity the company identified heterogeneity across included studies in terms of treatment regimens, patient populations, study design, outcomes definitions and quality of reporting. Details of the differences between studies and their potential limitations are discussed in Appendix D.5.1 of the CS. The company considered also whether these studies could be used to inform a formal unanchored ITC with Study 201 or a naïve unadjusted comparison with Study 201. The characteristics of the nine comparator RCTs including the company's judgement about the appropriateness of the studies for informing a formal unanchored ITC or a naïve comparison are summarised in Table 12 below.

3.3.2 Naïve indirect comparison

The company subsequently provide efficacy estimates for phototherapy as a naïve comparison to chlormethine gel. The naïve unadjusted indirect comparison involved seven phototherapy studies - including three of the nine comparator RCTs identified for the ITC and four additional non-randomised studies identified from the BAD (British Association of Dermatologists) guidelines. The company acknowledge in the CS that they did not conduct a separate SLR for non-RCTs of clinical comparators due to time constraints and, therefore, their SLR did not include non-RCTs for comparator treatments in the eligibility criteria. While the ERG considers that the selection of the seven studies of phototherapy based on the BAD guidelines is

presented in a transparent way, argues that in the absence of a comprehensive search for non-randomised evidence it is not possible to exclude with certainty that some relevant studies have not been missed.

Characteristics of the seven studies of phototherapy included in the naïve indirect comparison is summarised in Table 13 below. The methodological quality of the three RCTs (EORTC 21011, El Mofty et al. 2012 and NCT01686594)[36-38] was conducted in accordance with the criteria provided by the University of York Centre for Reviews and Dissemination guidance.[29] The assessment of the four non-randomised studies (Pavlotsky et al. 2006, Herrmann et al. 1995, Oguz et al. 2003, Anadolu et al. 2005)[39-42] was conducted in accordance with the Downs and Black checklist.[43] At clarification, the company clarified that two reviewers were involved in the risk of bias assessment of the studies included in the naïve indirect comparison but the methods were not described in sufficient details to establish whether the two reviewers worked truly independently. The company provide information on the methods used for the risk of bias assessment of the included phototherapy studies in the CS (Table 15, Appendix D.7 for the 3 RCT) and in their clarification response (for the 4 non-RCTs). The ERG considers the company's methods for risk of bias assessment to be acceptable and agrees that the majority of the included studies of phototherapy were of poor quality.

Table 12 Summary of the characteristics of the 9 comparator RCTs considered for the indirect treatment comparison (ITC) (adapted from Table 26, Section B.2.9, and Tables 12 and 13, Appendix D.5.1, of the CS)

Study	Identified in SLR or BAD guidelines	Intervention	Sample size and study design	Population	Definition of response	Judgement about appropriateness
Kaye (1989)[44]	SLR	TSEB + chemotherapy vs. Aqueous chlormethine	Sample size not reported in the CS RCT	Not reported in the CS	CR = the absence of all evidence of clinical disease, confirmed in every case by negative results of a skin biopsy and biopsies of any other previously involved nodal or visceral site.	TSEB + chemotherapy does not represent a relevant comparator for the decision problem; the pooling of the gel and aqueous chlormethine formulations is considered inappropriate; only 30% of patients with stage IA, IB or IIA disease.
Child *et al.* (2004)[45]	SLR; not cited in BAD guidelines	PUVA vs ECP (PUVA arm represents relevant comparator)	N = 16 (10 PUVA; 6 ECP) Crossover RCT	• Stage IB/T2 • Slightly higher proportion male than Study 201 (75% versus 59%)	CR = clinical remission; however, the precise measurement and definition of this was not reported. Specific skin scoring system used with outcomes summarised as quantitative skin scores (thresholds for degrees of response not defined).	Small sample size, confounding due to crossover design and differences in definition of response.
Aydogan *et al.* (2014)[46]	SLR; not cited in BAD guidelines	Low dose UVA	N = 19 RCT	• Early stage MF (Stage IA, IB or IIA) • Longer median duration of disease than Study 201	CR = >95% clearance of lesions. PR = 50-95% clearance of lesions.	Small sample size and differences in definition of response.

Study	Identified in SLR or BAD guidelines	Intervention	Sample size and study design	Population	Definition of response	Judgement about appropriateness
Aviles *et al.* (2015)[47]	SLR; not cited in BAD guidelines	IFN 5 MU subcutaneously, three times a week plus retinoids vs. IFN 5 MU subcutaneously, three times a week plus methotrexate Interferon not used as monotherapy	N = 377 (201 IFN/methotrexate vs 176 IFN/retinoids) RCT	Advanced stage patients only (Stage IIB to Stage IVB)	Unclear from text.	Only advanced stage patients; does not reflect use of interferon as monotherapy.
Vonderheid (1987)[48]	SLR; not cited in BAD guidelines	Recombinant IFN-α 2b	N = 6 RCT	Early stage (Stage IA, IB and IIA *et al.*)	Outcomes not response-based: outcomes reported in terms of degree of erythema and induration (graded as absent/mild/moderate/marked); global response (a composite assessment defined in terms of percentage reduction in lesion induration, erythema and scaling.	Small sample size, differences in definition of response and historical nature of study.
Wolff *et al.* (1985)[49]	SLR; not cited in BAD guidelines	Recombinant IFN-α 2 x 10^6 units, intralesionally, three times weekly vs. Control	N = 12 RCT Historical study (1985)	Early stage patients (Stage IA or IB)	Outcomes not response-based: outcomes reported in terms of change in size of lesions, change in clinical lesional score and overall disease status.	Small sample size, differences in definition of response and historical nature of study.

Study	Identified in SLR or BAD guidelines	Intervention	Sample size and study design	Population	Definition of response	Judgement about appropriateness
EORTC 21011 (Whittaker *et al.* 2012)[36]	SLR; also cited in BAD guidelines	PUVA alone vs PUVA plus bexarotene (PUVA alone arm represents relevant comparator)	N = 45 (receiving PUVA alone) RCT	Early stage MF-CTCL (all patients stage IB or IIA)	CR = complete resolution of all clinically apparent cutaneous disease for at least 4 weeks. PR = >50% reduction of cutaneous disease burden based on tumour burden index score compared with baseline score and sustained for at least 4 weeks (not based on CAILS or mSWAT).	Relatively small sample size and differences in definition of response.
El Mofty *et al.* (2012)[37]	SLR; not cited in BAD guidelines	PUVA vs broad band UVA	N = 30 (15 PUVA; 15 broad band UVA) RCT	Early stage MF (Stage IA, IB); Notably lower mean age of patients than Study 201	CR = complete clinical and histopathological clearance. PR = not measured.	Small sample size and differences in definition of response.
NCT01686594[38]	SLR; not cited in BAD guidelines	PUVA vs observation (PUVA arm represents relevant comparator)	N = 27 RCT	Early stage MF (Stage IA–IIA)	CR = mSWAT score reduced to zero. PR = mSWAT score reduction of more than 50%.	Small sample size.

Note 1: Studies described as historical studies if published >20 years ago (i.e. before the year 2000)

Abbreviations: BAD: British Association of Dermatologists; BB-UVB: broadband ultraviolet B; CAILS: Composite Assessment of Index Lesion Severity; CR: complete response; ECP: extracorporeal photopheresis; EORTC: European Organisation for Research and Treatment of Cancer; IFN(-α): interferon (alpha); ITC: indirect treatment comparison; MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; mSWAT: modified Severity Weighted Assessment Tool; MU: million unit; N/A: not applicable; NB-UVB: narrowband ultraviolet B; PR: partial response; PUVA: psoralen-ultraviolet A; RCT: randomised controlled trial; SLR: systematic literature review; TSEB: total skin electron beam; UVA: ultraviolet A; UVB: ultraviolet B.

Table 13 Summary of the 7 phototherapy efficacy studies (3 RCTs and 4 non-RCTs) considered for the naïve unadjusted indirect comparison (adapted from Table 26, Section B.2.9, and Tables 12 and 13, Appendix D.5.1, of the CS)

Study ID and design	Identified in SLR or BAD guidelines	Intervention	Sample size	Population	Definition of response	CR rate	PR rate
EORTC 21011 (Whittaker *et al.* 2012)[36] RCT	Identified by SLR and cited in BAD guidelines	PUVA alone vs PUVA plus bexarotene (PUVA alone arm represents relevant comparator)	N = 45 (receiving PUVA alone)	Early stage MF-CTCL (all patients stage IB or IIA)	CR = complete resolution of all clinically apparent cutaneous disease for at least 4 weeks PR = >50% reduction of cutaneous disease burden based on tumour burden index score compared with baseline score and sustained for at least 4 weeks (not based on CAILS or mSWAT)	22%	49%
El Mofty *et al.* (2012)[37] RCT	Identified by SLR but not cited in BAD guidelines	PUVA vs broad band UVA	N = 30 (15 PUVA; 15 broad band UVA)	Early stage MF (Stage IA, IB); Notably lower mean age of patients than Study 201	CR = complete clinical and histopathological clearance PR = not measured	77% (weighted average across PUVA and BB-UVA)	Not reported
NCT01686594[38] RCT	Identified by SLR but not cited in BAD guidelines	PUVA vs observation (PUVA arm represents relevant comparator)	N = 27	Early stage MF (Stage IA–IIA)	CR = mSWAT score reduced to zero PR = mSWAT score reduction of more than 50%	70% (over initial 12-24 week period)	30% (over initial 12-24 week period)
Pavlotsky *et al.* (2006)[39] Retrospective non-randomised study	BAD guidelines	NB or BB-UVB	N=111	Patient population generally aligned to Study 201 in terms of disease stage and disease duration	CR = complete clinical clearance PR = >50% clearance (not CAILS or mSWAT)	79% (weighted average across Stage IA and IB)	7%

Study ID and design	Identified in SLR or BAD guidelines	Intervention	Sample size	Population	Definition of response	CR rate	PR rate
Herrmann *et al.* (1995)[40] Non-randomised study	BAD guidelines	PUVA	N = 74	Study included early stage patients (83% of study population); No information on disease duration	CR = total clinical and histologic clearing for a minimum of 4 weeks PR = Minimum of 50% reduction in the size of measurable lesions, or clinical clearance but continuation of atypical cells on histologic examination or more than 5% Sézary cells in peripheral blood	66%	Not comparable to Study 201 due to additional criteria around atypical cells.
Oguz *et al.* (2003)[41] Non-randomised study (case series)	BAD guidelines	PUVA	N = 58 (early stage patients)	Study included early stage patients (89% of study population); Limited information on other patient characteristics	CR = unclear, but likely complete clearance PR = definition not provided	98%	Not comparable to Study 201, as definition of PR not provide.
Anadolu *et al.* (2005)[42] Retrospective non-randomised study	BAD guidelines	PUVA (and various other treatments)	N = 92 (early stage treated with PUVA)	Study included early stage patients (96% of study population treated with PUVA alone); Slightly higher proportion of female patients than Study 201	CR = no clinical or dermopathologic evidence of disease PR = >50% decrease in skin involvement with no new lesions or an improvement resulting in a lower stage	80%	Not comparable to Study 201 due to additional criteria around improvement resulting in a lower stage.
Overall range						**22–98%**	**7–49%**
Weighted average						**73%**	**21%**

Note 1: Studies described as historical studies if published >20 years ago (i.e. before the year 2000)

Abbreviations: BAD: British Association of Dermatologists; BB-UVB: broadband ultraviolet B; CAILS: Composite Assessment of Index Lesion Severity; CR: complete response; ECP: extracorporeal photopheresis; EORTC: European Organisation for Research and Treatment of Cancer; IFN(-α): interferon (alpha); ITC: indirect treatment comparison; MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; mSWAT: modified Severity Weighted Assessment Tool; MU: million unit; N/A: not applicable; NB-UVB: narrowband ultraviolet B; PR: partial response; PUVA: psoralen-ultraviolet A; RCT: randomised controlled trial; SLR: systematic literature review; TSEB: total skin electron beam; UVA: ultraviolet A; UVB: ultraviolet B.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Indirect Treatment Comparison (ITC)

The company did not conduct an ITC because no connected network for chlormethine gel and other formulations and relevant comparators could be formed. Moreover, considerable heterogeneity across studies was observed in terms of patient population, treatment regimens, study design and outcomes assessed. In the absence of a connected network, the company gave consideration to alternative population-adjusted ITC methods such as the matching-adjusted indirect comparison (MAIC). However, they considered the MAIC not appropriate as it was not possible to meet the assumption that there were no unmeasured confounders in any matching procedure and because it was not possible to adjust for inconsistencies in terms of outcome definitions and treatment regimens. The ERG agrees that an ITC (anchored or unanchored) was not feasible given the paucity and heterogeneity of available evidence.

3.4.2 Naïve indirect comparison

The naïve comparison of efficacy estimates from Study 201 and the seven phototherapy studies identified by the company is fraught with uncertainties, as it does not adjust for any differences in study characteristics.

Table 13 above summarises the results of the naive indirect comparison based on 7 studies of phototherapy: 3 RCTs and 4 non-RCTs. The company selected the 4 non-RCTs from the BAD guideline but did not conduct a separate search for non-randomised evidence. The company states in the CS that the observed weighted average estimates for phototherapy (CR rate of 73%, PR rate of 21% and overall response rate of 94%) may represent an optimistic assessment of its efficacy and should be taken as highly uncertain. The ERG considers the company's interpretation of the naïve comparison results to be fair.

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG carried out a scoping search to get an indication of non-RCT evidence on interventions for mycosis fungoides-type CTCL, which was not specifically included in the company's search. In line with the CS, the search covered MEDLINE (Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions; 1946 to March 10, 2020) and Embase (1974-2020 Week 10); the other databases included in the company's search (CDSR, CENTRAL, and DARE) were not relevant for non-RCTs. The

ERG's search strategy used index and text terms for mycosis fungoides-type CTCL, non-randomised study design, and phototherapy as an indicative intervention. The search identified 418 citations. The ERG removed duplicates and studies already identified by the company or those included in the BAD guideline and screened 398 citations. Using the eligibility criteria for study selection outlined in Appendix D.4 of the CS the ERG identified 140/398 citations as potentially relevant to the decision problem of this appraisal. Due to time constraints the ERG was not in the position to assess the full text copies of the identified potentially relevant articles and confirm their eligibility.

The ERG also identified a recent systematic review and meta-analysis conducted by Phan et comparing narrowband UV-B (NBUVB) with psolaren-UV-A (PUVA) phototherapy for patients with early-stage MF-CTCL.[9] This systematic review published in JAMA Dermatology in 2019 includes seven studies with a total of 778 patients (527 treated with PUVA and 251 with NBUVB). These studies were missed from the company submission. The ERG assessed this systematic review and meta-analysis using the AMSTAR-2 criteria[50] (see Appendix 1) and concluded that it was conducted according to acceptable methodological standards even though the authors did not use satisfactory techniques for assessing the risk of bias of included studies. A summary of the characteristics of the studies included in the Phan et al.'s systematic review is presented in Table 14 below. Definitions of CR and PR do not always match those of Study 201. Information reported in Table 14 are taken from the primary studies included in the Phan et al.'s systematic review, with the exception of Unal et al. 2015, a paper published in Turkish with an accompanied English abstract.[51] The numbers of patients receiving and responding to treatments in the Unal et al. 2015 study have been derived from the Phan et al.'s systematic review. It is worth noting that all the studies included in the Phan et al.'s systematic review with the exception of the Unal et al.'s paper published in Turkish were identified by the additional search conducted by the ERG. The Phan et al.'s systematic review is further discussed in the cost-effectiveness section of this report.

Table 14 Summary of the studies comparing psoralen–UV-A phototherapy (PUVA) with narrowband UV-B (NBUBV) included in the Phan et al. (2019) systematic review

Study ID and design	Total sample size	Number of patients who received PUVA	Number of patients who received NBUVB	Population	Definition of response	CR rate	PR rate
Ahmad 2007[52] Retrospective cohort	40	28	12	The majority of the patients (79%) had stage IA and IB disease PUVA: IA (n=7), IB (n=14), IIA (n=3), IIB (n=2), III (n=1) and IVA (n=1) NBUVB: IA (n=6), IB (n=4), IIA (n=1) and IIB (n=1)	CR = disappearance of all skin lesions, PR = ≥50% improvement	64% PUVA 50% NBUVB	21% PUVA 33% NBUVB
Almohideb 2017[53] Retrospective cohort	267	158	109	Early stage IA-IB	CR = as defined by the International Society for Cutaneous Lymphomas PR = >50% lesion improvement	77% PUVA 58% NBUVB	11% PUVA 30% NBUVB
Diederen 2003[54] Retrospective cohort	56	35	21	Early stage IA-IB	CR = no disease activity present PR = decrease of disease activity > 50%	71% PUVA 81% NBUVB	29% PUVA 19% NBUVB
El-Mofty 2005[55] Prospective cohort	20	10	10	Early stage IA, IB and IIA	CR = ≥80% improvement of the lesions. PR = 80-60% improvement of the lesions Assessed by physicians	70% PUVA 70% NBUVB	10% PUVA 20% NBUVB
Nikolaou 2018[56] Retrospective cohort	227	175	52	Early stage IA-IB	CR = complete clearance of all skin lesions, PR = >50% remission of skin lesions	77% PUVA 54% NBUVB	17% PUVA 33% NBUVB

Study ID and design	Total sample size	Number of patients who received PUVA	Number of patients who received NBUVB	Population	Definition of response	CR rate	PR rate
Ponte 2010[57] Retrospective cohort	114	95	19	Early stage IA, IB and IIA	CR = more than 95% clearing of skin lesions. PR = 50% clearing of lesions was achieved, despite continuing treatment	62% PUVA 68% NBUVB	25% PUVA 26% NBUVB
Unal 2015[51] Retrospective cohort	54	26	28	Early stage IA, IB and IIA	CR = more than 95% clearance of skin lesion PR = more than 50% clearance of skin lesion	85% PUVA 71% NBUVB	Unclear

Abbreviations: CR, complete response; NBUVB, narrowband ultraviolet B; PR, partial response; PUVA, psoralen plus ultraviolet A
a The total sample size is reported in Unal 2015 as 61 patients. Data for the numbers of patients receiving PUVA and NBUVB are taken from the Phan review.

3.6 Conclusions of the clinical effectiveness section

For the assessment of the clinical effectiveness of chlormethine gel for treating MF-CTCL, the company focuses on Study 201, a single non-inferiority trial that compares two formulations of chlormethine (gel and ointment). The ERG agrees that no other RCTs of chlormethine gel meeting the decision problem specified in the NICE final scope have been missed.

The ERG considers that the data from Study 201 were reported and analysed in a transparent way and agree with the company's approach for the analysis of the primary and secondary endpoints.

However, the ERG notes that Study 201 only recruited patients with early disease (Stage IA-IIA) and therefore there is no evidence from the trial on the use of chlormethine gel in people with more advanced disease; although the company suggest that in advanced disease chlormethine gel can be used as an adjunct to treat the patches and plaques of MF-CTCL alongside systemic therapies to treat the underlying cancer. The trial also did not collect data on quality of life outcomes and the company submission relies on a vignette study for its quality of life outcomes.

The ERG also notes that even though non-inferiority was demonstrated in Study 201, chlormethine ointment is no longer in use in UK clinical practice and is not one of the comparators specified in the decision problem. Considering that there is no other available comparative evidence (direct or indirect) of the efficacy of chlormethine gel against any of the comparators relevant to the decision problem, the ERG is of the opinion that the evidence base for assessing the clinical effectiveness of chlormethine gel is currently very limited.

The company conducted a naïve unadjusted comparison using seven phototherapy studies (3 RCTs and 4 non-RCTs). The non-RCTs were selected from the BAD guidelines as the company did not conduct a search to identify non-randomised evidence for comparator treatments. The ERG agrees that given the paucity of available evidence, a naïve comparison was the only viable option. However, as naïve comparisons are prone to bias and unadjusted comparisons represent only a very limited level of evidence, the ERG has limited confidence in the reliability of the naïve comparison estimates and agree with the company that they should be taken as highly uncertain.

4 COST-EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

Details of the company's review of cost-effectiveness evidence are provided in Section 3.1 of the CS and results of included studies summarised in Table 40 of the CS. The company have conducted a broad search of economic evaluations, utility studies and resource studies in CTLC. Four economic evaluations were identified and included in the review but none of these assessed the cost-effectiveness of chlormethine gel in adult patients with MF-CTCL. The ERG has replicated the company's search strategy and are satisfied that the searches have been conducted appropriately (see Chapter 3, Section 3.1). The ERG is satisfied that all relevant studies have been included in the cost-effectiveness review, and the interpretation of the evidence presented in those studies is accurate. Table 15 describes the ERG's interpretation of the relevance of the identified studies to both the current decision problem and as a source of information / data to populate the company's *de novo* economic model.

Table 15 Relevance of studies identified in the company's literature review

Study, year	Perspective	Population	ERG: Relevance to decision problem?	ERG: Relevance to population of economic model?
Geskin et al[58]	US payer	Advanced CTCL	No	Yes, assessment of cost-effectiveness of 8 different treatments (Methotrexate, IFN-α, ECP, Denileukin diftitox, Vorinostat, Pralatrexate, Romidepsin, Bexarotene) for advanced stage CTCL may be appropriate to inform the selection (and distribution) of cost-effective treatments for advanced stage treatments in the *de novo* economic model. However, the ERG accepts that the distribution of advanced stage treatments is not an important driver of cost-effectiveness in the *de novo* model.
NICE TA577[25]	UK NHS and PSS	Advanced CTCL (Stage IIB and above)	No	Partially, whilst the evaluation provides information regarding cost-effectiveness of brentuximab vedotin as treatment for advanced stage disease, brentuximab vedotin is only recommended by NICE for stage IIB patients who have had at least 1 systemic therapy. Given that the company's *de novo* model does not model progression to 2nd line systemic therapy for advanced stage disease, the relevance of this assessment is limited.

Study, year	Perspective	Population	ERG: Relevance to decision problem?	ERG: Relevance to population of economic model?
Semenov et al[59]	US Societal	CTCL patients	No	No, not an assessment of long-term cost-effectiveness.
Xia et al[60]	US Societal	Stage IA MF-CTCL	Partially – includes an assessment of the cost-effectiveness of Nitrogen Mustard. Chlormethine gel is a form of nitrogen mustard but may have different formulation and therefore different stability which could impact on adverse events. However, the study may be relevant in validating any potential for differential impact between phototherapy and nitrogen mustard on underlying disease. The ERG notes that the modelled response rates, and time to relapse in Xia et al. both favour phototherapy, especially PUVA, over topical nitrogen mustard. Topical nitrogen mustard was associated with a low probability of cost-effectiveness	Partly, model structure is relevant, but in a different setting (US rather than UK). For example, relative response rates and time to progression post a response may be informative for the *de novo* economic model, but costs are not.

The ERG notes that one of the included studies (Xia et al.) reports[60] the cost-effectiveness from a US societal perspective of alternative treatments in a state transition model (topical nitrogen mustard, local radiation, NB-UVB, PUVA, topical corticosteroids and topical bexarotene) for MF-CTCL. The ERG's considers that a comparison of treatment effectiveness parameters for topical nitrogen mustard versus phototherapy treatments (PUVA and NB-UVB) may be relevant given the similarity of the modelled population (early stage MF-CTCL) to the NICE decision problem and the study 201 population. The ERG's clinical expert confirms that chlormethine gel is a type of nitrogen mustard. Chlormethine gel may have a different formulation and stability to other studies included in a broader definition of nitrogen mustard which improves the adverse event profile, but it is likely to have a similar impact on progression of underlying disease.

Xia et al. reported life year gains for phototherapy (total modelled life years were 15.17 and 15.07 for NBUVB and PUVA respectively) compared to nitrogen mustard (total modelled life years: 14.29).[60] In contrast, the company's *de novo* economic model structure assumes an equal risk of disease progression for chlormethine gel and phototherapy, and hence equal life year gains regardless of CR or PR rate. The modelled life year gains in Xia et al. were likely driven by a superior complete remission probability for PUVA (65% at 7.2 months) and UVB (78% at 12.3 months) compared to topical nitrogen mustard (36% at 9 months). It appears as if Xia et al. have assumed that patients who achieve a complete remission from Stage IA disease achieve a lower overall mortality risk. However, the ERG's clinical expert considers this assumption to be questionable, given that there is no clear clinical reason why mortality should be higher for Stage IA patients than general population.

The ERG appreciates that the Xia et al. model is not directly relevant to the NICE reference case. For example, it applies a societal rather than healthcare and PSS perspective, measures outcomes in terms of life years gained rather than QALYs and uses US based rather than UK costing. However, it is an important study to contextualise the treatment effectiveness outputs of the company's *de novo* model.

The ERG agrees with the company's assessment that the results of Geskin et al. are not appropriate for decision making in the context of this assessment. Whilst the cost-effectiveness assessment of alternative treatments (e.g. i.e. Methotrexate, IFN-α, ECP) is relevant for the selection of subsequent (downstream) therapies for advanced disease (Stage

IIB+) in the *de novo* model, the decision is unlikely to impact on the ICER, given the company's assumption that disease progression is independent of the decision to treat with phototherapy or chlormethine gel.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 16 reports the ERGs assessment of the company submission (CS) against the NICE reference case.

Table 16 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes, the economic model includes health effects for patients. Carer outcomes have not been considered but this would not be appropriate, particularly for the population with early stage disease.
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, a lifetime horizon has been used.
Synthesis of evidence on health effects	Based on systematic review	Yes, the company conducted a systematic review of clinical effectiveness, and did not identify sufficient data to develop an indirect treatment comparison between chlormethine gel and phototherapy. However, the ERG are concerned that the clinical effectiveness review may have been incomplete and may have missed some important studies, especially for the phototherapy comparator (see Section 3.5) A systematic review of utilities was also conducted and no studies were identified that matched the NICE

		reference case. The ERG consider this latter conclusion to be reasonable.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes, QALYs were based on EQ-5D-5L responses to 12 vignettes with different mSWAT score and underlying MF-CTCL disease stage.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No, EQ-5D-5L responses to the 12 vignettes were provided by N=7 clinicians (dermatologists and oncologists), including 1 clinician who helped design the vignettes. One patient validated the vignette descriptors but did not provide EQ-5D-5L responses directly. EQ-5D-5L responses were therefore not based on the responses of a representative patient sample with MF-CTCL disease. Their appropriateness for use in the economic model is questionable.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, EQ-5D-5L responses were cross walked to 3L and valued using UK general population TTO tariffs.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes, NHS sources were used where possible. Most costs were valued using national average unit cost sources for 2018. However, phototherapy treatment cost and end-of-life care costs have been inflated from a 2010 and 2015 study, respectively. The approach to calculate the phototherapy treatment cost was by indirectly, through Fonia et al.[7] applying a unit cost from 2006/07 NHS reference costs (inflated) instead of using the most recent NHS reference costs directly. The approach to end of life care costing was consistent with the approach in NICE TA577.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes, but the ERG notes that the discount rate was not varied in sensitivity analysis.
EQ-5D, standardised instrument for use as a measure of health outcome.; PSS, personal social services; QALYs, quality-adjusted life years; TTO, time trade off		

4.2.2 Model structure

The company submitted a Markov cohort state transition model developed in Microsoft Excel to determine the cost-effectiveness of chlormethine gel compared to phototherapy for adults with MF-CTCL. The model included 3 health states to capture disease progression of MF-CTCL: "Stage IA", "Stage IB/IIA" and "Stage IIB+" and five health states within each disease stage to capture the effect of changes in skin burden: "Low skin burden", "High skin burden", "Reduced skin burden", "No skin burden" and "Progressed from 1L". The cohort could enter the "Death" state from any state in the model, based on median survival time reported in Agar et al. or general population mortality, whichever is higher. [23] Figure 12, Company submission, Document B, page 110 describes the state transition model.

MF-CTCL disease

The economic model assumes that MF-CTCL disease is progressive and the cohort cannot revert from more to less severe states or be cured. The ERG agrees that this is an appropriate assumption. The ERG notes that the company's model assumes that progression of underlying disease (and hence mortality risk) is independent of treatment on chlormethine gel or phototherapy. This assumption is in contrast to the assumptions applied in Xia et al. where life year gains were predicted for phototherapy relative to topical nitrogen mustard, driven by assumed differences in complete remission. This information suggests that phototherapy could prevent or slow underlying disease progression in Stage IA patients compared to chlormethine gel. If this is the case, and if the modelled life year gains from Xia et al. are plausible, it is likely that the company's restriction of the model structure to assume progression independent of treatment generates a substantial bias in favour of chlormethine gel. Further details of the relevance of Xia et al. to this assessment are provided in Section 4.1 above.

Skin burden

The definition of each skin burden health state is provided in Table 17.

Table 17 Definitions of skin burden health states

Health state	Definition / criteria for transition to health state
Low skin burden	<10% BSA affected
High skin burden	10-80% BSA affected
Reduced skin burden	PR
No skin burden	CR
Progressed from 1L	Multiple definitions (routes to transition into state): ➔ Progression following CR (from 'no skin burden state) ➔ Progression following PR (from 'reduced skin burden state) ➔ Progression from 'initial skin burden' state, low or high (the proportion of the cohort failing to achieve CR or PR)

Abbreviations: BSA: Body Surface Area

The company economic model used % body surface area (BSA) affected to determine the two categories of skin burden: high and low. Patients enter the model in the high and low skin burden health states, which were determined by the TNMB classification system which classified those with stage IA to have <10% BSA affected (i.e. low skin burden) and those with stage IB and most of those with stage IIA to have at least 10% BSA affected (all assumed to have high skin burden in the company's economic model). Those with stage IIB+ were assumed to have low ([redacted]) and high ([redacted]) skin burden respectively, with the distribution of skin burden derived from the PROCLIPI registry. The ERG considers the company's approach to categorising the skin burden levels in the economic model to be reasonable. The proportion of the cohort that have a relapse in skin burden symptoms are all assumed to progress onto second line skin therapy, and thus enter the 'progressed from 1L' state, where they remain on second line treatment (either bexarotene or IFN-α) for their remaining life years.

This simplifying modelling assumption is associated with several limitations.

The assumption that all patients who have a relapse of their skin burden progress to 2nd line therapy has questionable face validity. The ERG's clinical expert's opinion is

that some patients who achieve a complete and sufficiently long response to initial treatment may revert to their initial successful treatment should their skin burden relapse. A second round of phototherapy may be suggested if phototherapy provided the patient with at least 5 years of remission. The ERG also notes that the BAD guidelines suggest that patients having more than 200 (PUVA) or 500 (UVB) sessions in a lifetime would require annual checks for skin cancer.[19] However, for patients initially treated with chlormethine gel, the required duration of response before re-instating treatment would be shorter, likely around 2 years. The implication is that the current model structure may over-estimate the proportion of the cohort who ultimately progress to 2nd line treatment as well under-estimating the average time to progression.

The current model structure prevents the cohort from transiting out of the 'progressed from 1L' health state. This means that the costs of 2nd line therapies and the quality of life decrements associated with progressive skin burden are incurred for the remainder of the patient's life years in the 'progressed from 1L' state, regardless of whether they have achieved a response to second line skin treatments or not. The ERG queries the validity of this assumption for two reasons. First, the ERG's clinical expert opinion is that there is value in providing patients with a second line treatment, many patients receive an adequate response to treatment and some achieve a complete response. Secondly, there is some evidence from a recently conducted systematic review by Dalal et al. 2020 to suggest that a complete response is feasible for patients with relapsed disease. The review reported an average complete response of 21% (6 studies) and 64% (4 studies) for bexarotene and IFN-α respectively[67]. The average duration of response was approximately 9 months (data reported for bexarotene only). Those that have a CR, mostly those with Stage IA disease would then subsequently have their 2nd line skin treatment discontinued and have an improvement in QoL. The implication of this assumption is that the current model structure over-estimates the costs and QALY losses associated with entering the 'progressed from 1L' state, thereby generating a bias in favour of chlormethine gel due to the greater proportion of the cohort who enter this state in the phototherapy arm of the model under the company's base case assumptions. The ERG accepts that the review conducted by Dalal et al. 2020 may not have been available to the company at the time of submission[67]. However, the ERG consider the review to be a relevant source of data

and conduct an analysis using the available data to approximate the proportion of the cohort in the 'progressed from 1L' state that may have a response, and thus no longer incur treatment costs or QoL decrements.

4.2.3 Population

The population for the company's economic model was adults with mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL). The population is in line with the NICE scope and the marketing authorisation for chlormethine gel. The modelled cohort were age [redacted] and [redacted] were female, based on Study 201 data. The distribution of MF-CTCL disease severity was obtained from the PROCLIPI registry where [redacted] have stage IA, IB-IIA and IIB+ disease respectively. By comparison, Study 201 excluded patients with Stage IIB+ disease and the distribution of disease severity, pooled across both arms of the study, was [redacted] with stage IA, IB/IIA and IIB+, respectively. The mean %BSA obtained from Study 201, where low and high skin burden patients had a mean %BSA of [redacted] and [redacted] BSA affected, respectively was used to inform the base case model characteristics. Comparable BSA data from the PROCLIPI registry were not reported in the CS. The ERG accepts that such data may not have been available to the company. However, if %BSA data were available by MF-CTCL stage from the registry, they would have been a preferable and more UK relevant source to define the model cohort and inform treatment acquisition costs for chlormethine gel.

The ERG accept that the distribution of disease severity from the PROCLIPI registry is appropriate for use in the economic model as it reflects the UK population with MF-CTCL and is in line with the marketing authorisation for chlormethine gel which does not preclude use of chlormethine gel for Stage IIB+ disease. However, the ERG raises two concerns regarding the use of Study 201 data to populate model parameters for a more severe disease cohort. First, it is unclear whether effectiveness parameters for chlormethine gel (i.e. CR, PR etc.) are transferable to patients with more severe disease. ERG clinical expert opinion was that patients with more advanced disease may be expected to remain on treatment for longer and response rates may feasibly be lower. If this is the case, then it is feasible to assume that any bias, of uncertain magnitude, would be in favour of chlormethine gel. The ERG accepts that the company have noted this limitation in their submission and conducted a scenario analysis to explore the impact of restricting the population to Stage IA/IIA (early stage) or to IIB+ (later stage) disease only. The ERG notes that chlormethine gel is more likely to be a

cost-effective use of resources when the model cohort is restricted to those with early stage MF-CTCL disease.

4.2.4 Interventions and comparators

Intervention: topical chlormethine gel (0.02%)

The modelled intervention was topical chlormethine gel (0.02%), Ledaga ® applied once daily in line with its marketing authorisation for the "topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients". This includes all stages of MF-CTCL, regardless of skin burden. However, the ERG's clinical expert opinion is that in real-world clinical practice, use of chlormethine gel would be unlikely in patients with very high skin burden, for example those with >50% BSA covered in patches and plaques, because of the practical difficulties of covering a large proportion of the body with gel. In such cases, a systemic treatment would be preferred.

Chlormethine gel is available in 60g tubes and the daily dose of gel required is proportional to the %BSA affected. It should be noted that the shelf-life for chlormethine gel once opened is 2 months meaning a minimum of 6 tubes are required in any one year. Daily dosage calculations and the associated impact on treatment acquisition costs are discussed in Section 4.2.8.

Comparator: phototherapy

The comparator arm in the economic model is phototherapy, specifically PUVA and UVB. The base case model used data from the PROCLIPI registry to assume [redacted] of phototherapy was PUVA and [redacted] was UVB. The ERG accepts that the PROCLIPI registry is likely an accurate reflection of average phototherapy usage in the UK. However, both the ERG's clinical expert and the BAD guideline documents suggest that the use of PUVA is more common in current clinical practice than UVB for the treatment of MF. The ERG queries whether the PROCLIPI registry reflects historical usage of phototherapy and note that perhaps clinical practice has changed in recent years. The ERG has conducted scenario analyses varying the proportion of phototherapy delivered as PUVA and UVB respectively.

The ERG also notes that there are several inconsistencies between the NICE final scope and CS; however the company have provided justifications for each of these inconsistencies in their CS and in response to clarification queries. Specifically:

- The company excluded TSEB as a comparator because of its limited use in UK practice. ERG's clinical expert agrees that TSEB is rarely used in the UK due to only very few hospitals providing the treatment in the UK.

- The company excluded topical steroids from their comparator based on clinical expert opinion that: 1) most patients diagnosed with MF-CTCL would already have received topical steroids, 2) there is no impact on the malignant T-cells (unlike chlormethine gel) and 3) clinicians would typically retain topical steroids for the management of adverse skin reactions following chlormethine gel (e.g. dermatitis). In response to clarification queries (clarification question C3, pages 39-40), the company clarified that patients eligible for chlormethine gel could not have their symptoms adequately managed using topical steroids alone and therefore chlormethine gel and topical steroids should not be considered direct comparators in the modelled population. The ERG's clinical expert agrees with the company's reasoning for positioning the gel alongside rather than replacing topical steroids.

- Table 1 of the CS notes that the comparator is phototherapy (PUVA / UVB) plus the use of bexarotene or pegylated IFN-α in patients for whom skin directed therapies are unsuitable. The company consider the proportion of the population unsuitable would be approximately 10%. However, the ERG note that the economic model excludes bexarotene and pegylated IFN-α as direct comparators and that these treatments were only included as second line skin therapies or within the advanced disease stage bundle. The ERG queried (clarification question B1) why the comparator group was not 90% phototherapy, 5% bexarotene and 5% pegylated IFN-α. The company responded (Clarification response document, page 9-11) that this was due to a lack of evidence on the use of bexarotene and pegylated IFN-α for MF-CTCL patients. The company also pointed out that previous NICE appraisals have criticised the use of bundled comparators as it is unclear which treatments are delivering the modelled benefit. However, the company provided a scenario analysis where the comparator costs consisted of (phototherapy (90%), bexarotene (5%) and IFN-α (5%)) assuming clinical effectiveness remained unchanged. The ERG notes that the impact on the

ICER is small and favours the cost-effectiveness of chlormethine gel under the company's base case assumptions.

4.2.5 Perspective, time horizon and discounting

An NHS perspective was adopted for the costs, in line with NICE's reference case. The model was run for a cohort with average [redacted] for a time horizon of [redacted]. The model therefore ran to [redacted] which was assumed to be a lifetime horizon. The ERG note that 99% of the cohort have died within the [redacted] and are satisfied that the company's time horizon is appropriate. Costs and QALYs were discounted by 3.5% per annum, according to the NICE reference case. However, the company have not provided any sensitivity analysis around this source of methodological uncertainty. The ERG therefore vary the annual discount rate between 0% and 6% for costs and QALYs in scenario analyses.

4.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness and hence QALY gains are driven by the potential for treatment to impact on skin burden. It is assumed that the progression of underlying disease severity is independent of treatment, hence incremental life years gained in the model are always 0.

Overall survival, by stage

In the economic model, mortality is based on the median survival time reported in Agar et al. by disease stage, or general population mortality, whichever is higher. The ERG agrees that Agar et al. are an appropriate source to populate disease stage specific overall survival. Whilst the longer-term extrapolation function of OS is uncertain, the ERG accepts that an exponential survival function (i.e. continuous with respect to time) is a reasonably plausible assumption given the available data.

Progression of underlying disease

Whilst progression is assumed to be treatment independent, assumptions about disease progression may still impact on incremental treatment acquisition costs (1st and 2nd line) and QALYs due to differential mortality rates across stages. For example, any modelled differences in treatment acquisition costs are magnified the longer patients remain in early stage disease, with lower mortality risk.

The ERG considers that the rate of progression between the underlying disease stages may have been over-estimated. Transition between different MF-CTCL stages (IA, IB/IIA, IIB+) was based on a research letter (Wernham et al.) that reported results from a single database study identified by a clinical expert.[61] The database included N=86 patients with early stage disease, with a median follow up of 60 months (range 5–423). It was assumed that the rate of transition was continuous over time beyond the median of 60 months for the duration of the modelled time horizon. The advantage of the study is that it allows calculation of transitions between all modelled health states, including directly from stage IA to IIB+. The ERG is concerned that there was no assessment of the validity or generalisability of this source against the rates of progression observed in UK clinical practice. Furthermore, the source was not identified based on literature review and relevant alternative studies may have been missed. Indeed, the ERG have identified an alternative study (Agar et al. summarised in Wilcox et al.)[23, 62] that is based on a larger sample (1502 patients, 1061 of whom had Stage IA, IB or IIA at baseline) of UK patients with MF-CTCL that provides data on risk of disease progression. The ERG considers this to be a more robust source to populate disease progression in the economic model. The ERG also note that this source is advantageous as it is the same source used by the company to populate overall survival by disease stage, thereby maintaining consistency of source. It is unclear why the company did not consider this a relevant source of disease progression data. The only disadvantage of Agar et al. is that data to populate the direct transition between stages IA and IIB+ are not available. However, in a monthly cycle, such a direct transition is possible, but unlikely. The ERG's approach is thus a more conservative estimate of underlying disease progression. The ERG also notes that using Agar et al. as the source to populate both disease progression and overall survival by MF-CTCL stage increases the modelled life-years gained by 1.95 years overall compared to the company's preferred data source (see Section 5.1).

The ERG considers the larger Agar et al. study with longer follow up to offer a more robust estimate of transition probabilities for use in the model. Table 18 compares the company preferred transition probabilities (black font) using Wernham et al. and the ERG preferred transition probabilities (red font) using Agar et al.[23, 61] The ERG's preferred source suggests slower progression overall. The magnitude of the impact on the ICER depends on the range of other assumptions applied in the model (see Chapter 6), but the ERG notes that applying slower disease progression to the company's preferred base case improves the cost-effectiveness of chlormethine gel.

Table 18 Alternative sources of transition probabilities for underlying disease progression [A]

Stage from:	Stage to:		
	IA	IB/IIA	IIB+
IA	CS: 0.9952 ERG: 0.9990	CS: 0.0032 ERG: 0.0010	CS: 0.0017 ERG: 0.0000[B]
IB/IIA		CS: 0.9943 ERG: 0.9984	CS: 0.0057 ERG: 0.0016
IIB+			CS: 1.0000 ERG: 1.0000

Abbreviations: CS: Company submission; ERG: Evidence review group

[A] Note that the numbers reported in the CS, Table 45 do not match those used in the economic model. Numbers reported here are as per the economic model, which the ERG assumes reflects the company's intended source. The ERG was however unable to replicate the numbers reported in the table. [B] The ERG's preferred source requires the assumption that direct monthly transition from Stage IA to Stage IIB+ is 0.

Progression of skin burden

The incremental impact of chlormethine gel vs. phototherapy on skin burden, specifically treatment effectiveness in terms of partial (PR) or complete response (CR) and durability of response (i.e. time to progression onto costly 2nd line skin burden treatments) are all important drivers of cost-effectiveness. There is no available evidence that directly compares the effectiveness of chlormethine gel and phototherapy, and there is insufficient evidence to inform an indirect comparison, for example a matched adjusted indirect comparison. The ERG appreciates the lack of evidence and accepts that the only reasonable option open to the company was to conduct a naïve indirect comparison to populate the economic model. This is consistent with the modelling approach taken by Xia et al. However, the ERG caution that such a naïve indirect comparison, based on heterogeneous phototherapy studies (in terms of study population, disease stage, and definition of response) introduces substantial uncertainty in the economic model, under both the company's and ERGs preferred set of assumptions. It is difficult therefore to select a definitive set of parameters to inform a robust estimate of a base case ICER as all sources of data and all potential assumptions are open to methodological criticism. Exploring a range of different plausible assumptions and scenarios regarding response rates and time to progression onto 2nd line treatment can lead to substantial differences in the ICER and it is important to demonstrate the impact of this uncertainty on the ICER through extensive scenario analyses.

Chlormethine gel

CR and PR data for Chlormethine gel are based on the mSWAT response rates from Study 201.[1] Response rates from Study 201 (Stages IA and IB/IIA) were assumed to be transferable to the proportion of the modelled cohort (sourced from the PROCLIPI registry) with Stage IIB+ disease. Whilst noting that the response may differ by disease stage, it is unclear to the ERG how this parameter could be reasonably modified given the current available data. It is also unclear in what direction any biases may affect the ICER. Overall, the ERG accept that Study 201 provides the best available evidence to populate the treatment effectiveness (i.e. response rates) of chlormethine gel.

Phototherapy

The company selected a total of 7 studies (Table 26, page 75, Document B of the CS) from the sub-set of studies included in the BAD guidelines (see Appendix D.5.1 of the CS) that reported CR and PR data that were deemed potentially relevant for comparison to Study 201. However, the ERG notes that only 1 of the identified studies used a directly comparable definition based on mSWAT (NCT01686594).[38] The overall response from that study was 100%, but its appropriateness for use in the economic model is questionable based on the small sample size (N=27), hence it was only considered as a scenario analysis in the CS. The company base case response rates for phototherapy are calculated as a weighted average of the CR and PR from the 7 identified studies (see section 3.3, table 13 for further details of these studies). It is assumed that response to phototherapy is not disease stage dependent and that response rates from PUVA and UVB are equal.

The ERG is concerned that the approach taken by the company to identify phototherapy studies is not systematic and may have missed relevant studies. For example, the ERG identified Phan et al. 2019, a recent published systematic review and meta-analysis that provides data on CR, PR, and time to relapse following a response for PUVA and UVB separately, and by MF-CTCL disease stage.[9] Only one of the studies identified by Phan et al. was included in the BAD guidelines, thereby raising questions about the completeness of the evidence review conducted to populate phototherapy effectiveness in the economic model. Further details of the studies included in Phan et al. are summarised in Section 3.5, table 14 of the ERG report.

The different response rates and associated monthly transition probabilities considered for use in the economic model by both the company and the ERG are summarised in Table 19. Response rates for PUVA and UVB obtained from Phan et al. were applied by MF-CTCL disease stage to the proportion of phototherapy delivered as PUVA / UVB based on the PROCLIPI registry in the ERG's preferred base case analysis.

Table 19 Sources of alternative CR and PR considered for use in the economic model

Scenario	Description		Parameter	CR	PR
Company base case	Weighted average of available CR and PR rates across 7 identified studies		Response rate	0.732	0.208
			Monthly TP	**0.356**	**0.075**
Company scenario 2	Weighted average of CR rates, excluding Oguz 2003 and Anadolu 2005. Weighted average of PR across all 7 studies.		Response rate	0.659	0.208
			Monthly TP	**0.302**	**0.075**
Company scenario 3	CR and PR rates from NCT0168659 (most comparable definition to Study 201)		Response rate	0.704	0.296
			Monthly TP	**0.335**	**0.111**
Company scenario 4	CR and PR rates from EORTC 21011, weighted to exclude non-assessable patients		Response rate	0.263	0.579
			Monthly TP	**0.097**	**0.251**
ERG analyses	CR and PR sourced from Phan et al. 2019,[9] applied to each stage (ERG preferred base case assumption)	Stage IA	PUVA %	0.821	0.129
			UVB %	0.621	0.292
			Weighted %	0.702	0.226
			Monthly TP	**0.333**	**0.082**
		Stage IB	PUVA	0.676	0.276
			UVB	0.578	0.145
			Weighted	0.618	0.198
			Monthly TP	**0.275**	**0.071**
	CR and PR sourced from Phan et al.[9] 2019, weighted for PUVA / UVB & pooled across stages		PUVA	0.738	0.180
			UVB	0.622	0.275
			Weighted	0.669	0.236
			Monthly TP	**0.309**	**0.086**

Abbreviations: CR: Complete response; ERG: Evidence Review Group; PR: Partial response; TP: Transition probability

Time to achieve a response was calculated as 13.8 weeks from the included studies that reported the relevant data. Based on the assumption that phototherapy is delivered over 13 weeks and a response would be most likely whilst on treatment, the ERG considers it appropriate that the company have assumed a time to response of 13 weeks in their model.

Progression to 2nd line skin therapy following CR and PR

Time to relapse following a response is an important driver of cost-effectiveness. The shorter the durability of response on treatment, the faster the cohort progresses to expensive 2nd line therapies (bexarotene and IFN-α) and quality of life decrements incurred in the semi-absorbing 'progressed from 1L state'. At the clarification stage, the ERG queried the face validity of the transition probabilities to the 'progressed from 1L' state, whereby increasing CR for a treatment increased total costs and reduced total QALYs. This was driven by assumptions in the company's base case analysis whereby the transition probability from "no skin burden" (i.e. those having a CR) state to "progressed from 1L" is substantially greater than the transition from "initial skin burden" or "reduced skin burden" (i.e. PR) to "progressed". For example, the company model predicts that for those in stage IA, at 12 months, ~4% in the gel arm and ~22% in the phototherapy arm have progressed to 2nd line treatment, despite phototherapy having better response rates. In response to clarification (question B2, pages 12-13), the company argued that the assumption was valid and in line with their clinical expert opinion that patients who have a CR discontinue treatment and are therefore more likely to suffer a subsequent relapse or progression to 2nd line treatment than those with a PR or no response that remain on treatment. The ERG's expert opinion was this may be plausible, but there is no evidence to support the assumption.

<u>Chlormethine gel</u>

It was not possible to inform time to progression to 2nd line therapy following a complete or partial response based on the data available from Study 201. The company have therefore assumed that time to progression post a CR is equal for chlormethine gel and phototherapy. However, the ERG prefers the company's scenario analysis using data from Kim et al. which reports time to progression following a CR for an alternative nitrogen mustard treatment to inform the transition probability from 'no skin burden' to 'progressed from 1L'.[3] The opinion of the ERG's clinical expert is that treatment from Kim et al. is more likely to reflect time to progression following CR on chlormethine gel than assuming this is equal to phototherapy. The ERG notes that the company have assumed that progression to 2nd line therapy following

a PR on chlormethine gel is equal to progression following no response based on expert opinion. The ERG accepts this may be the only reasonable assumption in the absence of data and accepts that a corresponding assumption was applied to the phototherapy arm of the model. However, the assumption is not evidence based and introduces further uncertainty regarding the trajectory of changes in skin burden over time.

Phototherapy

The ERG disagrees with the company's sources and assumptions to estimate time to progression following CR / PR in the phototherapy arm of the model. The company used data from Whittaker et al. to inform the transition between "no skin burden" (i.e. CR) and "progressed from 1L".[36] The population in Whittaker et al. 2012 (stage IB-IIA MF-CTCL only) have more advanced disease compared to the PROCLIPI registry or Study 201 and may therefore over-estimate the risk of progression onto 2nd line treatments. Furthermore, the sample with a CR for whom time to progression could be calculated was only N=25, pooled across two arms of a trial comparing PUVA vs. PUVA + bexarotene. The median time to relapse was: PUVA: N=10; 10.68 months, PUVA + bexarotene: N=15; 3.81 months and pooled: N=25; 6.48 months. The ERG notes the substantial differences across arms of the study with respect to median time to relapse, driven by the small sample available to inform the calculation and the lack of potential to account for any confounding factors.

For the remaining phototherapy transitions to 'progressed from 1L', the company base case assumed an equal split of progressive and stable disease based on the EORTC study, with time to progression assumed equal to the maximum treatment duration (i.e. time to initial response). The ERG is unclear as to the justification for assuming time to progression is equal to maximum treatment duration. The ERG note that data on time to relapse is available for PUVA and UVB by MF-CTCL disease stage from Phan et al and that it is possible to calculate differential time to progression following CR and PR from the reported data that is in line with the company's argument that time to progression following CR is shorter than following PR.[9] Phan et al. meta-analyse data from seven different phototherapy studies and the data are consistent with those used to populate the ERG's preferred source of CR and PR rates. The disadvantage of Phan et al. is that data are reported for a relapse following an overall response, rather than separately following a CR and PR. To get around this, the ERG have calculated the ratio of median time to OR: median time to CR and median time to PR from Whittaker et al., and applied these ratios to the median response reported from Phan et

al.[9, 36] thereby allowing estimation of monthly transition probabilities based on median time to progression following a CR and median time to progression following a PR obtained from Phan et al. The additional advantage of Phan et al. as a data source is that the time to progression data are available by type of phototherapy (PUVA / UVB) and by stage of MF-CTCL disease. The impact of the company's base case assumptions and the ERG's alternative assumptions on transition probabilities into the 'progressed from 1L' state are detailed in Table 20 below.

Table 20 Transition to 2nd line treatment following a CR and PR on phototherapy, comparing company and ERG alternative assumptions.

	Relapse post CR			Relapse post PR		
	Company preferred approach (Whittaker et al.)[36]	ERG preferred approach [B] (Phan et al.)[9]		Company preferred approach (Assumption)	ERG preferred approach [B] (Phan et al.) [9]	
		PUVA	UVB		PUVA	UVB
Number of patients with response	25			N/A		
Observed number of events	18			N/A		
Median (months)	6.48	28.86[A]	12.87[A]	N/A	35.98[A]	16.05 [A]
Rate	0.107	0.0240	0.0538	N/A	0.0193	0.0432
Estimated mean (months)	9.351	N/A		N/A	N/A	
Monthly TP	0.127	0.0237	0.0524	0.01	0.0191	0.0423

[A] Time to relapse from Phan et al. are reported for OR only. To obtain time to progression following PR and following CR, it was assumed that the ratio of median time to OR: time to CR and time to PR from Whittaker et al. could be applied to the median time to OR reported in Phan et al. From Whittaker et al., we know that 69/69, 25/69 and 44/69 had an OR, CR and PR, respectively. Using data from Figure 3 and Figure 4 in Whittaker et al. the median time to relapse (in months) from Whitaker et al. was calculated as 7.5 and 6.48 months for OR and CR, respectively. Using this information, the median time (months) to relapse post PR is calculated as: $PR_{time\ to\ relapse}$ = (7.5 - (6.48*(25/69)))/(1-(25/69)) = 8.08 months. Since we know that $CR_{time\ to\ relapse}$ = 6.48 the ratio for CR:OR =6.48/7.5=0.864 and for PR:OR = 8.08/7.5=1.077. These ratios are applied to the median time to relapse for the overall responders obtained from Phan et al.; [B] The ERG considered a further scenario analysis that applies a weighted average time to progression for phototherapy based on the proportion of patients receiving PUVA (527/778) and UVB (251/778) respectively, as opposed to the ERG's preferred approach of applying transition probabilities separately for PUVA and UVB.

4.2.7 Health related quality of life

Health state utility values used in the economic model

The company conducted a literature review and identified 11 publications reporting from 4 different studies that were deemed potentially relevant to populate the model (see Appendix H, Table 32 of the CS). However, on further reflection, none were deemed appropriate for population of the economic model as they either did not match the NICE reference case (e.g. HUI) or were not relevant to the decision problem (e.g. more advanced disease). The company have therefore undertaken a *de novo* vignette study with 12 vignettes developed in conjunction with a clinical expert and validated by a patient representative to obtain utility values congruent with the model health states. The 12 vignettes were based on 4 categories of mSWAT score to reflect skin burden that varied by 3 underlying MF disease stages (Stage: IA, IB/IIA and IIB-IVB). Seven clinicians provided proxy EQ-5D-5L responses (including one who helped develop the vignettes) based on their anticipation of how a patient might value each vignette. Responses were then cross-walked to the EQ-5D-3L and valued using UK general population time-trade off tariffs.

The utility values applied to each health state in the model were independent of treatment (chlormethine gel or phototherapy) and are summarised in Table 21 where:

1. Initial skin burden utility for each MF stage was calculated as a weighted average of the proportion of patients with each mSWAT category from the PROCLIPI registry multiplied by the corresponding utility value from the vignette study.
2. Complete response was assigned a utility equal to mSWAT score of 0 (by MF stage).
3. Partial response and progressive disease incurred a utility by MF stage that was based on the percentage change in mSWAT score observed from Study 201 for PR and PD respectively.

Table 21 Health state utility values applied in the economic model

Disease Stage	Initial Skin Burden (SD)	Reduced Skin Burden (PR)	No Skin Burden (CR)	Progressed from 1L (PD)
Stage IA	[redacted]	[redacted]	[redacted]	[redacted]
Stage IB/IIA	[redacted]	[redacted]	[redacted]	[redacted]
Stage IIB+ (Low)	[redacted]	[redacted]	[redacted]	[redacted]
Stage IIB+ (High)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CR: Complete response; PD: Progressive disease; PR: Partial response; SD: Stable Disease

The ERG is satisfied that the company's review has not missed any important and relevant utility studies and accepts that there are no available utility data that perfectly match both the NICE reference case and the definition of the modelled health states.

The ERG accepts that vignettes are sometimes required to elicit utility data in the absence of published sources. However, the health states associated with those vignettes should be elicited from a patient sample rather than clinician proxies. It is unclear whether the proxy completion accurately reflects the EQ-5D health state that patients would assign to these vignettes. Furthermore, as the vignettes have been described in a manner that is inconsistent with the domains of the EQ-5D, it may have been particularly difficult for respondents to assign an EQ-5D response. This may have led to over or under estimation of the impact of the vignettes on quality of life. Therefore, the direction and magnitude of any bias that this creates is unclear.

The ERG notes that the only feasible study from the company's literature review that could have been used to reasonably inform the model was the HUI study conducted by Semenov 2019.[59] However, Semenov could not elicit the impact a direct utility impact of response to skin treatment or progression in skin burden. As an assessment of the face validity of the vignette utilities assigned to underlying MF disease stage, the ERG notes that the HUI data from Semerov et al. are reasonably comparable with those obtained from the company's elicitation exercise. The average utility associated with early (IA to IIA) and later (IIB to IVB) stage disease was mean (SE): 0.72 (0.04) and 0.56(0.07) respectively. The utilities are similar to those used in the CS for initial skin burden (average IA and IB/IIA: [redacted] and average IIB+: [redacted], using unrounded data from the company model), respectively. Therefore, despite the methodological limitations of the company approach the ERG is satisfied that the initial skin burden utilities applied in each MF-disease stage appear to have acceptable face validity.

In relation to the face validity of the health state utilities and the magnitude of difference across low and high skin burdens, he ERG notes that previous NICE technology appraisals have acknowledged the limited sensitivity of EQ-5D to assess the impact of skin burden (TA577) on QoL. However, the data provided in the CS suggests substantial differences in utility across different skin burden states. This may be driven by the company's use of the 5L version of the EQ-5D, but may also represent the uncertainty of the company's utility

estimation approach and it is unclear how reliable the magnitude of utility difference across skin burden states is for decision making.

A further concern, driven by the model structure, is that the proportion of the cohort entering the progressed skin burden state all incur the same utility value, that is lower than the initial skin burden state, regardless of whether they had previously obtained a satisfactory response or not. Consider a patient who has a CR and subsequently relapses. It may be more appropriate to assume such a patient would incur a utility equal to their initial skin burden. Furthermore, the company's approach implicitly assumes that no patients entering the progressed state will observe an improvement in their symptoms, despite the model assumption that they receive life-long treatment with either bexarotene or IFN-α for their skin burden. It may be reasonable to assume that at least a proportion of patients treated receiving systemic therapy for skin lesions will observe a response and improvement in their QoL. Therefore, the ERG's clinical expert opinion was that the utilities assigned to progressed disease in the model may have under-estimated the true utility of that state by failing to account for potential improvements from successful second line therapies. The ERG considers a scenario analysis where a proportion of the cohort in the 'progressed from 1L' state are assigned the full treatment cost and QoL decrement, based on response data from the review by Dalal et al. 2020[67].

Adverse event dis-utilities

Utility decrements associated with grade 3 or 4 contact dermatitis, erythema and skin irritation adverse events that occurred in 5% or more of the Study 201 population were included in the economic model. The disutility (-0.03: note this was incorrectly reported in the CS as -0.003) associated with these adverse events was based on the disutility for a rash reported by Nafees et al. and was consistent with the utility decrement applied in TA577.[25, 63] The ERG identified an error in the application of adverse event disutility in the economic model where the annual probability of adverse events was applied in each month without adjustment, thereby substantially over-estimating the QALY losses associated with adverse events for chlormethine gel. The company corrected this error in response to clarification queries and the impact on the ICER is illustrated in Section 5.1. The ERG is satisfied that adverse event utility decrements for chlormethine gel have been correctly applied in the company's revised economic model. The ERG further notes the company assumption that there were no adverse events associated with phototherapy treatment. The ERG accepts that

Grade 3 and Grade 4 adverse events following phototherapy may be rare in appropriately managed patients. Nonetheless, this assumption likely generates a bias against chlormethine gel in terms of the ICER.

Age adjustment of utilities

The ERG notes that the company have age adjusted all utilities in the economic model to account for reducing utility as the general population age. The ERG considers the approach taken to be appropriate.

4.2.8 Resources and costs

Treatment acquisition costs:

The list price for chlormethine gel is £1000.00 per 60g tube. The treatment acquisition costs for chlormethine gel are incurred for the proportion of the cohort with low, high or reduced skin burden. The proportion of the cohort with a CR were assumed to discontinue treatment. The daily dosage of chlormethine gel is directly proportional to the proportion of BSA covered in patches and plaque. The company's preferred base case analysis calculates treatment acquisition costs based on the median daily dosage observed in Study 201 (1.8g per day).[1] Based on data from Study 201, those with low and high skin burden are assumed to have a mean of [redacted]% and [redacted]% BSA affected respectively. In the base case analysis, the company calculated that the median daily usage of gel would equate to less than the minimum 6 tubes per year required by the 2-month shelf life. Therefore, to account for wastage, the gel usage was set to the minimum annual requirement, equating to 0.99g per day. The daily requirement of gel for a patient with high skin burden was back calculated as 2.93g per day to ensure that the overall weighted median daily dosage of 1.8g from Study 201 was maintained. This calculation approach is inappropriate and under-estimates the true median gel dosage required in a real-world setting for patients with high skin burden. After appropriately increasing the low skin burden dosage to account for gel shelf life and associated wastage, the company's calculation approach required the artificial reduction of the dosage required for high skin burden patients to retain the overall median from Study 201. The assumed low and high doses were then applied to the appropriate disease stage and skin burden category based on distribution of disease stage obtained from the PROCLIPI registry. The calculated monthly cost for a patient with low (<10% BSA covered) and high (10-80% BSA covered) was £500.00 and £1486.91 respectively.

Furthermore, basing the calculation of treatment acquisition cost on median, rather than mean daily gel dosage, is inappropriate. Given that costs are proportional to %BSA affected, and the distribution of %BSA is likely to be right skewed, it is reasonable to infer that the mean daily dosage is substantially higher than the median. In response to a clarification question asking for re-calculation of costs based on the mean daily dosage, the company provided three alternative methods for calculating daily gel usage, and hence the costs for use in the economic model (see clarification questions response document, B9 for further details), though retained the median daily dosage of 1.8g as their preferred base case. The ERG's preferred approach to costing (company scenario 1) applies a mean daily mean dose (2.8g) obtained from the summary of product characteristics of Valchlor®, chlormethine gel's US brand name, which the company assume has been sourced from Study 201, but could not be confirmed with certainty. The associated mean daily dose calculated for low and high skin burden was [redacted] and [redacted] respectively. Therefore, the ERG preferred monthly costs of chlormethine gel acquisition costs are [redacted] and [redacted] for low and high skin burden respectively. The resultant impact on the ICER is substantial.

It is unclear whether the mean %BSA within each disease Stage from study 201 is a fair reflection of the mean BSA within each stage for patients in the PROCLIPI registry. The ERG notes that the % BSA affected has a substantial impact on the costs of chlormethine gel treatment, and thus a substantial impact on the most appropriate ICER. As it is unclear whether the %BSA of the Study 201 population (by disease stage) is an accurate representation of the % BSA that would be observed in clinical practice, the ERG consider scenario analyses where the %BSA is increased and decreased. The ICER is highly sensitive to changes in this parameter.

The company have costed phototherapy administration using an inflated price from Fonia et al.[7] On further investigation of this source, the ERG note that the cost is based on an outpatient consultation for providing phototherapy and photo chemotherapy treatment from 2006/07 reported in Fonia et al. and inflated to 2017/18 values for use in the model (inflated costs = £294.20)[7]. However, the most recent available NHS reference cost data from 2017/18 show that the current consultant led outpatient clinic cost for phototherapy and photo chemotherapy (HRG code: JC47Z) is £93. The ERG's clinical expert confirms that phototherapy is delivered in the outpatient setting. The ERG therefore prefer the use of the most recent NHS reference costs for phototherapy to inform the model. The impact is that

the company's base case model has over-estimated the treatment acquisition costs of phototherapy.

Furthermore, the cost of the comparator, phototherapy, consisted of a weighted average cost of PUVA ([redacted]%) and UVB ([redacted]%) based on the PROCLIPI registry data, resulting in a monthly treatment cost of £3,459 given for a maximum of 13 weeks. The company assumed that PUVA would be administered 3 times per week and UVB 2-3 times per week, according to BAD guidelines. The company therefore assumed UVB would be delivered on average 2.5 times per week. As the cost of administration is the same for PUVA and UVB, the total costs associated with PUVA are higher than UVB in the company's base case model. The ERG's clinical expert noted that the number of doses per week for phototherapy treatment is a reasonable reflection of UK practice. However, the ERG's clinical expert felt that PUVA would be more likely to be used as the phototherapy treatment of choice and this appears to be consistent with the BAD guidance. The ERG therefore considers exploratory scenario analyses that vary the proportion of phototherapy treatments delivered as PUVA and UVB.

Second line treatment for skin symptoms:

The economic model assumes that 50% of patients requiring second line systemic treatment for skin burden receive bexarotene (monthly cost: £2,184) and 50% receive pegylated IFN-α (monthly cost: £333), with the distribution of treatment based on expert opinion. The ERG's clinical expert agrees that this is a reasonable assumption. However, the ERG notes that increasing the proportion of patients assumed to receive bexarotene would increase the total cost of progressive disease substantially and improve the cost-effectiveness case for chlormethine gel in the model.

The cost of 2nd line skin treatment is applied in the model to:

A) the full proportion of the modelled cohort that progress from first line treatment for the remainder of their lives. As noted in Section 4.2.2, the ERG considers this an important limitation of the model structure as it is unreasonable to assume that all patients would be treated with bexarotene or IFN-α for the rest of their lives as some patients would achieve a complete response and thus no longer require treatment. Similarly, ineffective treatments would not be continued indefinitely. The ERG has therefore conducted scenario analyses that assume only a proportion of those in the

'progressed from 1L' state receive the costs of 2nd line skin therapy indefinitely. The ERG conducted an additional analysis using data from Dalal et al. to approximate the proportion of the cohort in the 'progressed from 1L' state that would be removed from bexarotene or IFN-α treatment based on having a CR, and the duration of treatment withdrawal based on reported response duration[67].

B) the full proportion of the phototherapy cohort who achieve no response or PR. The ERG's clinical expert noted that when partial response is achieved on phototherapy, a systemic treatment would often, but not always be considered as an additional treatment. Some patients who have a PR on phototherapy would be satisfied with that progress and would not immediately progress onto further treatment once their course of phototherapy finished. Additionally, it is feasible that some patients achieving only a PR on chlormethine gel would change treatment and consider moving to systemic treatments, rather than remaining on chlormethine gel indefinitely. The net impact of these uncertainties on incremental costs is unclear. The ERG considers the impact of an exploratory scenario analysis that assumes no further treatment following PR on phototherapy until progression of skin burden.

Advanced disease treatments:

The cost of advance disease treatments consists of a bundle of five common treatments for advanced stage MF according to the PROCLIPI registry. The treatments are: pegylated IFN-a [redacted], ECP [redacted], methotrexate [redacted], bexarotene [redacted] and gemcitabine [redacted] The registry included [redacted]. The ERGs clinical expert considers the treatment distribution for advanced disease to be reasonable. Given that progression into advanced disease is independent of treatment with chlormethine gel or phototherapy, the impact of these cost parameters on the ICER is minimal. However, the ERG notes that the BAD guidelines recommend that patients receiving phototherapy should not receive methotrexate (or any other treatment that limits the immune system, such as ECP) at the same time, or for 2 weeks after treatment ends. The ERG has therefore updated the bundle of advanced treatments in the phototherapy arm to apply this restriction. The impact on the ICER is minimal.

Adverse event costs

The company incorporated grade 3 and 4 adverse events of chlormethine gel that occurred in 5% or more of the Study 201 sample. The company assumed that all adverse events would be treated with [redacted] hydrocortisone cream for 2-3 weeks, priced at £0.81 for [redacted] (sourced from eMIT 2019).[64] However, the ERG believes that the cost to the NHS of treating the adverse events have been underestimated. In response to a clarification query, the company noted that skin related adverse events would be managed by discontinuation of chlormethine gel and use of corticosteroids and would not require hospital admission. However, ERG's clinical expert noted that if patients experience grade 3 or 4 adverse events, their treatment would be reviewed prior to recommending discontinuation, and this would require an additional outpatient appointment with a dermatologist. The ERG therefore included an additional cost of £115 for a consultant led appointment to manage each adverse event. This was applied in the ERG's preferred base case analysis.

A summary of the adverse events included in the model as well as company and ERG preferred costing assumptions are provided in Table 22 below.

Table 22 Summary of modelled adverse events and costs

	Annual probability		Company preferred cost of treatment	ERG preferred cost of treatment
Adverse Event	**Chlormethine gel**	**Phototherapy (PUVA/UVB)**		
Dermatitis contact	[redacted]	0.00%	£0.81	£115.81
Erythema	[redacted]	0.00%	£0.81	£115.81
Skin irritation	[redacted]	0.00%	£0.81	£115.81

Other costs

Other disease related treatment costs included in the model were administration costs (associated with having phototherapy, ECP and Gemcitabine), consultations, appointments and different tests common for patients with MF-CTCL. A de novo survey was sent to seven clinicians based in the UK (the same clinicians as in the de novo vignette study). This survey was used to inform the outpatient/inpatient appointments, home visits, radiotherapy treatment, wound dressings required and tests such as complete blood count, liver function test or CT scan (see Tables 60 and 61 Document B of the CS). Resource use was costed using

NHS reference costs (2017/18).[65] The ERG considers the costing of these items to be appropriate.

5 COST-EFFECTIVENESS RESULTS

5.1 Company's cost-effectiveness results

Markov model traces, disaggregated costs (by disease stage: drug acquisition, adverse events, advanced disease treatment, monitoring and end of life care) and disaggregated QALYs (by disease stage: skin burden state QALYs and AE QALYs) calculated from the economic model are all reported in Appendix J of the CS. The initial company submission included an error in the economic model that over-estimated the QALY losses associated with adverse events in the chlormethine gel arm of the model. The error was corrected in response to clarification queries. The company's preferred base case ICER (with and without the error corrected) is provided in Table 23 below for information. All further analyses in this section are implemented using the company's updated model base case.

Table 23 Company preferred deterministic base-case results

Intervention	Total costs (discounted)	Total LYGs	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Original company base case						
Chlormethine gel	£239,125	9.96	6.42	-		
Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,000	-0.16	£44,915
Updated company base case						
Chlormethine gel	£239,120	9.96	6.60	-		
Phototherapy (PUVA/UVB)	£246,125	9.96	6.57	-£7,005	0.03	Phototherapy Dominated

Abbreviations: ERG: Evidence review group; ICER: incremental cost-effectiveness ratio; PSA: Probabilistic sensitivity analysis; QALY: Quality adjusted life year
(Source: Company response to clarification, Table 6, page 31)

Under the company's preferred set of assumptions, the base case ICER indicates that Chlormethine gel is less costly and generates higher QALYs than the phototherapy comparator.

The main drivers of cost-effectiveness are:

A) the treatment acquisition costs for chlormethine gel, including assumptions about the %BSA for an average patient and the associated required daily dosage of chlormethine gel

B) assumptions surrounding time to progression of skin burden, particularly the assumption that progression to 2nd line skin therapy is faster post a CR compared to no response or PR. In the company's base case model, the phototherapy cohort progress to costly 2nd line skin treatment and incur utility decrements of progressive skin burden much faster than the chlormethine gel arm, due to the higher phototherapy CR rate. The impact is that the phototherapy arm accumulates greater costs and quality of life decrements compared to chlormethine gel over a lifetime horizon. The model predicts that patients spend most of their life years in the 'Progressed from 1L' state: 8.91 (i.e. 89% of the time) and 7.23 (i.e. 73% of the time) life years for patients on phototherapy and chlormethine gel, respectively. This is despite, the phototherapy cohort having 0.28 more life years with no skin burden and 0.17 less life years with high skin burden compared to chlormethine gel due to the base case assumption that phototherapy response rates are superior to chlormethine gel.

C) the treatment acquisition costs (bexarotene and IFN-α) for the proportion of the cohort in the 'progressed from 1L' health state, that accounted for 73% of the cost difference (Results Overview tab in the economic model).

The model assumes that mortality risk is only dependant on the MF-CTCL stage, i.e. independent of the level of skin burden or initial treatment. The proportion in each disease stage at any given time is equal between the modelled cohorts, therefore, the life expectancy is the same (9.96 life years discounted).

5.2 Company's sensitivity analyses

Probabilistic sensitivity analysis

As described in Section 5.1, the company revised their preferred set of base case model assumptions in response to a clarification query from the ERG to correct an error in the modelling of adverse event disutility. However, the company have not provided a revised

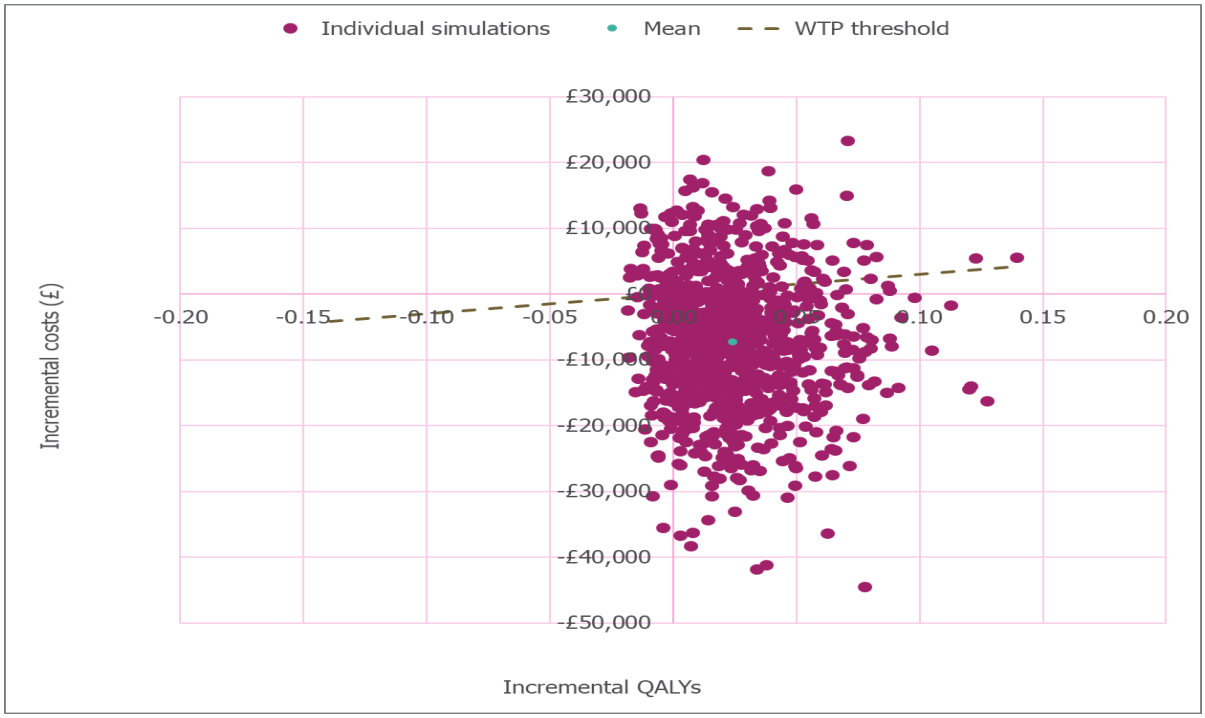
PSA to accompany the new preferred set of model assumptions. The ERG therefore re-ran the PSA. The results are reported in Table 24, using 1000 monte-carlo simulations, applied to the company's preferred base case model assumptions.

Table 24 Probabilistic sensitivity analysis results (company's preferred base case analysis)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Chlormethine gel	£242,028	6.76	-	-	-
Phototherapy (PUVA/UVB)	£249,274	6.73	-£7,246	0.02	Phototherapy dominated

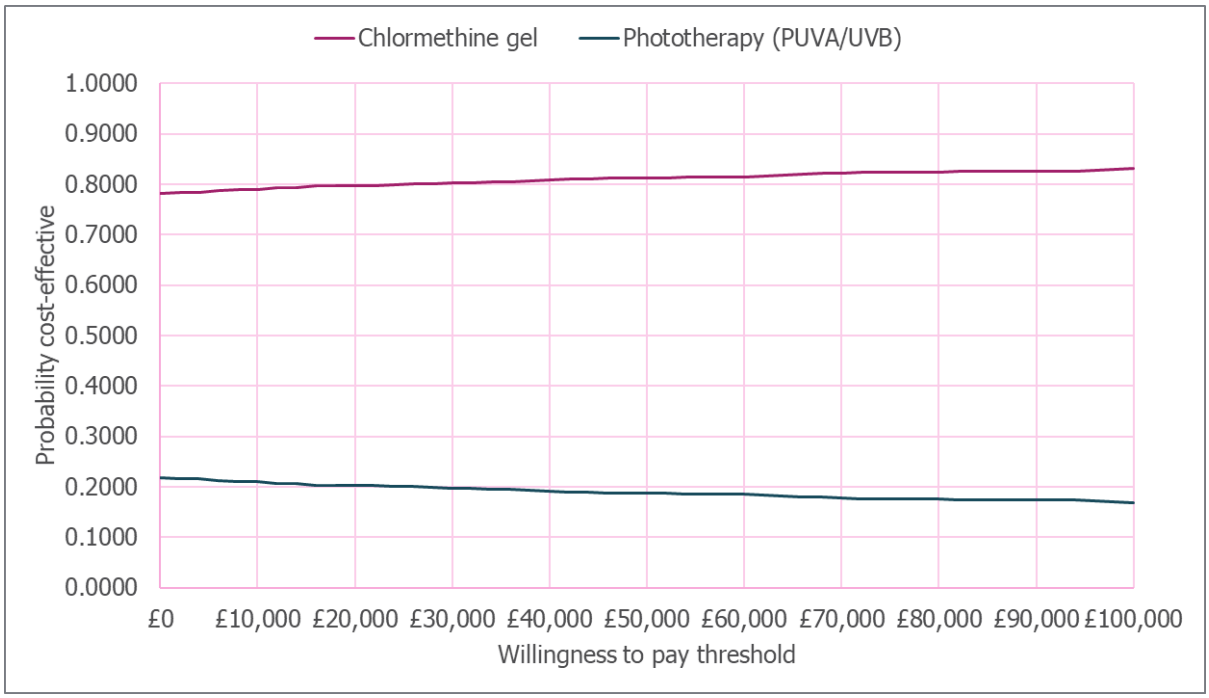
Abbreviations: ERG: Evidence review group; ICER: incremental cost-effectiveness ratio; PSA: Probabilistic sensitivity analysis; QALY: Quality adjusted life year
(Source: the ERG re-ran the PSA on the company's updated base-case)

The probability of chlormethine gel being cost-effective at a threshold willingness to pay of £30,000 per QALY was 80.20%. Figures 2 and 3 illustrate the parameter uncertainty surrounding the company's preferred base case analysis using scatterplots of the PSA simulations on the cost-effectiveness plane cost-effectiveness acceptability curves (CEACs) respectively.



Abbreviation: PSA: Probabilistic sensitivity analysis
(Source: Re-produced by the ERG from the company's revised, preferred base case model)

Figure 2 Scatter plot of PSA results on the cost-effectiveness plane (company's preferred base case analysis)



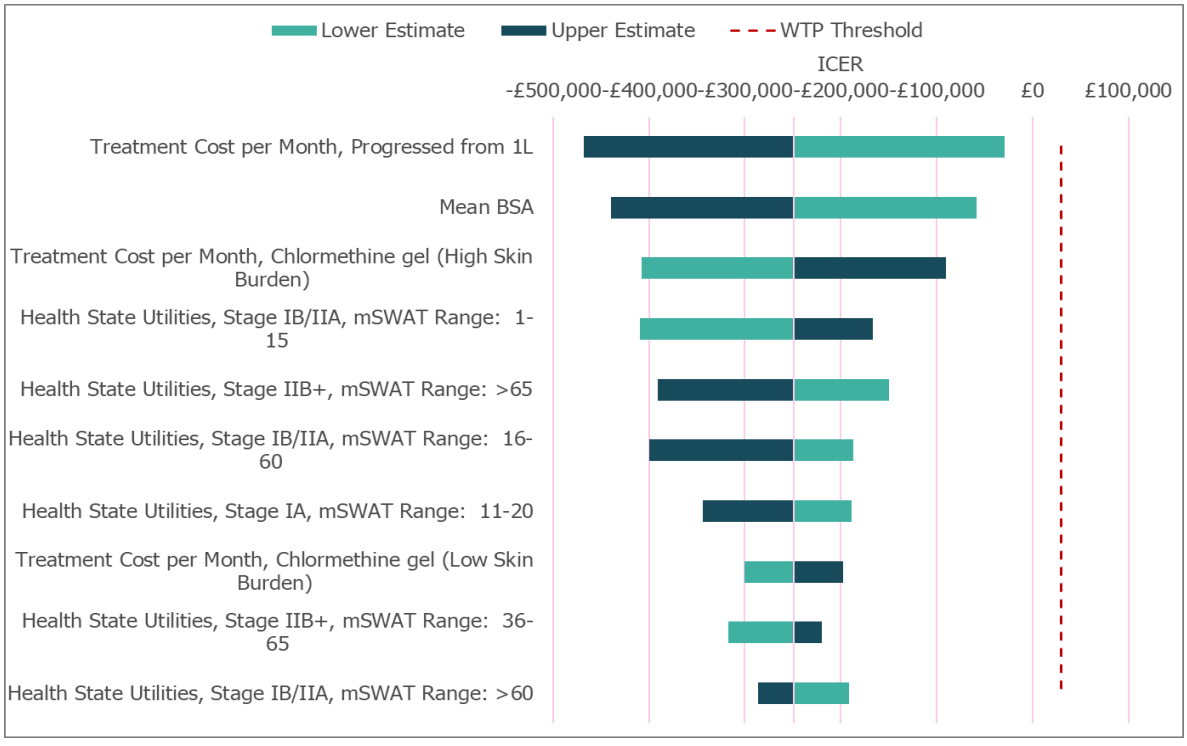
Abbreviations: CEAC: Cost-effectiveness acceptability curve; ERG: Evidence Review Group
(Source: Re-produced by the ERG from the company's revised, preferred base case model)

Figure 3 CEAC (company's preferred base case analysis)

The simulations indicate that under the company's preferred set of assumptions, the probability of cost-effectiveness of chlormethine gel is greater than 80% at threshold values of WTP for a QALY gained up to £100,000. The scatterplot shows that incremental costs are more uncertain than incremental QALYs. However, it should be noted that these results illustrate parameter uncertainty only, and do not account for feasible alternative scenario analyses which could have a substantial impact on cost-effectiveness. A range of scenario analyses are reported in Table 25 (company scenario analyses) and Table 28 (ERG scenario analyses).

Deterministic sensitivity analysis

The ERG also re-ran deterministic sensitivity analyses to illustrate the impact of uncertainty in the most influential model parameters on the company's revised preferred set of model assumptions. The results are reported in the tornado diagram, Figure 4, which illustrates the impact of ±20% variability in the important model parameters, in terms of the impact on the ICER.



Abbreviations: 1L: first line; AE: adverse event; BSA: body surface area; DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; mSWAT: modified Severity Weighted Assessment Tool; PUVA: psoralen-ultraviolet A; UVB: ultraviolet B; WTP: willingness-to-pay.
(Source: the ERG re-ran the DSA and tornado plot using the company's updated base-case model)

Figure 4 ICER tornado diagram (company's preferred base case analysis)

The most influential parameters on the company's preferred base case analysis are the treatment costs of 2nd line treatment, the mean BSA (m^2), the cost of treating high skin burden with chlormethine gel and the health state utilities applied in the model. However, under the company's preferred base case assumptions, the ICER remains below the WTP threshold of £20,000-£30,000 per QALY gained across the range of variation in the parameter inputs.

Company conducted scenario analyses

Section 3.8.3 of the CS (pg. 154 to 163) describes several scenario analyses conducted by the company in their original submission. However, the ERG notes that these scenario analyses were not replicated on the company's updated preferred base case analysis following response to clarification queries. The company conducted several further scenario analyses in response to clarification queries, and these were applied to the company's updated preferred base case. The ERG has re-produced a full set of company conducted scenario analyses (from the original submission and in response to clarification queries) and applied these to the company's updated base case analysis in Table 25.

Table 25 Scenario analysis results – applied to company's revised preferred base case analysis

	Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
Company updated base case analysis						
	Chlormethine gel	£239,120	6.60	-	-	-
	Phototherapy (PUVA/UVB)	£246,125	6.57	-£7,005	+0.03	Phototherapy dominated
Phototherapy efficacy scenarios						
Scenario 1 (weighted average CR rates but exclude Oguz et al. (2003)[41] and Anadolu et al. (2005)[42])						
	Chlormethine gel	£239,120	6.60	-	-	-
	Phototherapy (PUVA/UVB)	£246,899	6.57	-£7,779	+0.04	Phototherapy dominated
Scenario 2 (response rates obtained from NCT01686594[38] study)						
	Chlormethine gel	£239,120	6.60			
	Phototherapy (PUVA/UVB)	£246,288	6.59	-£7,168	+0.01	Phototherapy dominated

	Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
Scenario 3 (response rates obtained from EORTC 21011 study[36])						
	Chlormethine gel	£239,120	6.60			
	Phototherapy (PUVA/UVB)	£251,848	6.57	-£12,729	+0.04	Phototherapy dominated
Time horizon						
5 years						
	Chlormethine gel	£88,135	2.88			
	Phototherapy (PUVA/UVB)	£93,263	2.87	-£5,128	+0.01	Phototherapy dominated
10 years						
	Chlormethine gel	£149,287	4.56			
	Phototherapy (PUVA/UVB)	£156,040	4.53	-£6,754	+0.03	Phototherapy dominated
Gel dose/frequency						
Equal daily median dose between Low and High Skin Burden patients						
	Chlormethine gel	£236,509	6.60			
	Phototherapy (PUVA/UVB)	£246,125	6.57	-£9,616	+0.03	Phototherapy dominated
Dosing frequency based on French ATU Early Access Program data[30]						
	Chlormethine gel	£224,050	6.60			
	Phototherapy (PUVA/UVB)	£246,125	6.57	-£22,075	+0.03	Phototherapy dominated
AE source						
AEs from PROVe[3]						
	Chlormethine gel	£239,119	6.62			
	Phototherapy (PUVA/UVB)	£246,125	6.57	-£7,006	+0.05	Phototherapy dominated
2nd line treatment cost						
Zero subsequent treatment cost						
	Chlormethine gel	£95,524	6.60			

	Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
	Phototherapy (PUVA/UVB)	£71,624	6.57	+£23,900	+0.03	£848,895
Alternative utility values (see Table 77 in the CS, page 159-60)						
	Chlormethine gel	£239,120	6.55			
	Phototherapy (PUVA/UVB)	£246,125	6.52	-£7,0054	+0.03	Phototherapy dominated
Alternative source of chlormethine gel relapse post-CR TP , derived from Kim *et al.* (2003) [10]						
	Chlormethine gel	£229,712	6.72			
	Phototherapy (PUVA/UVB)	£246,125	6.57	-£16,413	+0.14	Phototherapy dominated
Subgroup analysis						
Model population: early Stage (IA/IIA only) MF-CTCL						
	Chlormethine gel	£239,933	7.68			
	Phototherapy (PUVA/UVB)	£249,433	7.66	-£9,499	+0.03	Phototherapy dominated
Model population: late Stage (IIB+) MF-CTCL only						
	Chlormethine gel	£235,938	2.38			
	Phototherapy (PUVA/UVB)	£233,189	2.35	+£2,749	+0.03	£79,461
Additional scenarios provided by the company at the clarification letter stage						
Comparator arm: phototherapy [PUVA/UVB] (90%), bexarotene (5%) and pegylated IFN-α (5%). Only the proportional costs are applied, effectiveness assumed to be equal to phototherapy						
	Chlormethine gel	£239,120	6.60			
	Bundled comparator	£245,746	6.57	-£6,626	+0.03	Bundled comparator dominated
Apply mean dose (2.8g)						
	Chlormethine gel	£256,836	6.60			
	Phototherapy (PUVA/UVB)	£246,125	6.57	+£10,711	+0.03	£380,444
Equal daily mean dose between Low and High Skin Burden patients						

	Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
	Chlormethine gel	£251,521	6.60			
	Phototherapy (PUVA/UVB)	£246,125	6.57	+£5,396	+0.03	£191,650
Apply approximated mean dose from the median dose (1.8g)						
	Chlormethine gel	£244,161	6.60			
	Phototherapy (PUVA/UVB)	£246,125	6.57	-£1,964	+0.03	Phototherapy dominated
Exclusion of bexarotene and pegylated IFN-α from the advanced disease stage treatment basket						
	Chlormethine gel	£233,889	6.60			
	Phototherapy (PUVA/UVB)	£240,894	6.57	-£7,005	+0.03	Phototherapy dominated

Abbreviations: CR: complete response; ICER: incremental cost-effectiveness ratio; IFN-α: interferon alpha; LYG: life years gained; PUVA: psoralen-ultraviolet A; QALYs: quality-adjusted life years; TP: Transition probability UVB: ultraviolet B.

Source: ERG reproduced table in the CS (pages 154-161) on the company's updated base case. ERG also reproduced some additional scenarios provided by the company in the clarification letter response to ensure all scenarios are conducted on the company's updated base case.

The following points summarise the main findings of the company's scenario analyses:

- There is substantial heterogeneity in the definition of response rates across seven phototherapy studies identified by the company for use in the model[36-42]. Furthermore, the definition of response is often inconsistent with the definition of response for chlormethine gel, obtained from Study 201[1]. The company therefore conducted several scenario analyses using alternative sources for response rates of phototherapy. Study NCT0168659 was the only study using the same outcome measure for determining response rates (mSWAT) as in Study 201[1]. However, the sample size was small. The impact of using this source (Scenario 2) increased the total QALYs for phototherapy but did not change the cost-effectiveness conclusions. In all phototherapy efficacy scenarios, phototherapy remained dominated.
- Chlormethine gel remained cost-saving and more effective at 5- and 10-year time horizons.
- Equalising the dose between patients with high and low skin burden reduced the total treatment cost of the chlormethine gel and phototherapy remained dominated.

- Reducing the dosing frequency in accordance with the French ATU study reduced the treatment acquisition cost of chlormethine gel and hence increased the cost savings further.
- If chlormethine gel adverse events can be managed with concomitant therapies, i.e. setting the adverse event rates to 0% increases the QALY gain for chlormethine gel.
- Assuming no subsequent treatment costs had a substantial impact on the ICER and resulted in chlormethine gel not being cost-effective with an ICER of £848,895.

The key findings of the additional scenario analyses provided in response to clarification queries are as follows:

- Including the costs of bexarotene and IFN-α in a comparator bundle (90% phototherapy, 5% interferon-alpha and 5% bexarotene) to account for the 10% of patients for whom phototherapy may be unsuitable reduced the comparator cost slightly, reducing the cost savings, but chlormethine gel remained the dominant strategy.
- Three scenario analyses conducted in response to clarification question B9, using alternative dosing assumptions to calculate the treatment acquisition cost of chlormethine gel had a substantial impact on cost-effectiveness. For example, applying the mean (2.8g) as opposed to the company's preferred base case scenario applying the median (1.8g) daily dosage substantially increased the costs of chlormethine gel and led to an ICER of £380,444 per QALY gained.

5.3 Model validation and face validity check

The ERG has undertaken a range of verification tests, based on an adaption of those proposed by Tappenden et al.[66] The results of these verification checks are provided in Table 26 below, applied to the company's revised base case analysis following clarification queries. The ERG has not identified any further errors in the company's submitted model functionality or formulae.

Table 26 Black box' verification checks conducted on the company submitted model

Model component	Model test	Unequivocal criterion for verification	Issues identified
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	None
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	None
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	None
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	None
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	None
Cost estimation	Set intervention costs to 0	ICER is reduced*	None
	Increase intervention cost	ICER is increased*	None
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter (e.g., samples from beta distribution lie in range 0\x \1, samples from lognormal distribution lie in range x[0, etc.)	None
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	None
	Amend value of each individual model parameter*	ICER is changed	None
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	None
ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year * Note this assumes that the parameter is part of the total cost function and/or total QALY function			

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 27 provides details of the additional work conducted by the ERG in relation to cost-effectiveness. The ERG have conducted several scenario analyses to explore the impact of uncertainty in the base case ICER, based on issues raised throughout Chapter 4. Where possible, the ERG have implemented all additional scenarios using switches in the company's revised economic model to enable easy reproduction of the results.

Table 27 ERG justification for additional exploratory and sensitivity analyses

Scenario No.	Parameter/Analysis	Company base case assumptions	Scenario explored	Justification for ERG's assumption
1	Company preferred base case assumptions			
Mortality and disease progression scenarios				
2*	Disease progression (between MF-CTCL disease stages)	Wernham et al. [61]	Apply alternative source Agar et al. for disease progression.[23]	Agar et al. is a larger UK study that provides a source for both overall survival by disease stage and risk of disease progression by disease stage in a single source.[23]
3*	Stage IA mortality source	Stage IA mortality calculated from 5-year overall survival reported by MF-CTCL disease stage in Agar et al.[23]	Stage IA mortality assumed to equal that of the UK general population.	The ERG's clinical expert opinion is that there is no clear clinical reason why overall survival should be different between patients with Stage IA disease and the corresponding age and sex specific general population survival.
Treatment effectiveness / skin burden transitions scenarios				
4	CR and PR rates for phototherapy	Weighted average of N=7 phototherapy studies identified in the CS, based on selection	Use meta-analysed response data from N=7 studies included in the systematic review conducted by Phan et al., with response rate data pooled across	The ERG has identified a systematic literature review conducted by Phan et al. that reports CR and PR data by type of phototherapy, using meta-analysis methods. [48] The ERG prefers the use of Phan because

Scenario No.	Parameter/Analysis	Company base case assumptions	Scenario explored	Justification for ERG's assumption
		of studies reported in BAD guidance that were deemed potentially comparable to Study 201.	PUVA and UVB and across MF-CTCL disease stages [48]	it allows assignment of different CR and PR rates to PUVA and UVB in the model (see Section 3.5 for further details on Phan et al.)
5*			As per 4 above, but with data from Phan et al. applied separately to PUVA and UVB	
6	Time to progression post CR and PR for phototherapy:	Data obtained from Whitaker et al. [36] and time to progression post PR assumed equal to maximum treatment duration	Apply weighted average time to progression from PUVA/UVB by MF-CTCL stage (Phan et al.)[48]	The ERG prefer the use of Phan et al. because: - The data source is consistent with the ERG's preferred CR and PR rate source - Whittaker et al. is a single small study that excludes stage IA disease. [36] - The data allow the potential for applying time to progression by type of phototherapy (PUVA / UVB) and by MF-CTCL disease stage.
7*			Apply time to progression separately for PUVA/UVB and by MF-CTCL stage (Phan et al.)[48]	
8*	Time to progression post CR for chlormethine gel	Assumed equal to phototherapy, based on Whitaker et al. [36]	Use data from Kim et al.[10]	The ERG believes that the true time to progression following a CR on chlormethine gel is more likely to be reflected by Kim et al., a study of an alternative nitrogen mustard compound than it is by Whitaker et

Scenario No.	Parameter/Analysis	Company base case assumptions	Scenario explored	Justification for ERG's assumption
				al. Also, Kim et al includes a larger sample and may be more robust. [10]
9	Transition probabilities (ERG's preferred combination)	5+7+8 above	5+7+8 above	The ERG considers it more appropriate to use single sources of evidence across multiple parameters where possible to do so, to ensure the face validity of model transition probabilities for phototherapy (i.e. Phan et al.). The ERG also considers it more appropriate to assume that progression following a CR on chlormethine gel based on a study of nitrogen mustard than on a study of phototherapy.
Treatment acquisition costs – chlormethine gel				
10	%BSA affected	Mean BSA calculated as [redacted]% and [redacted]% BSA affected for low and high skin burden, respectively	Assume a lower %BSA affected in the low and high skin burden group (50% lower) [A]	It is unclear how representative the %BSA affected within each MF-CTCL stage in Study 201 is to patients with a similar disease stage in UK clinical practice. These scenarios illustrate the magnitude of the impact of uncertainty in %BSA on treatment acquisition costs and the ICER.
11			Assume a higher %BSA affected in the low and high skin burden group (50% higher) respectively [B]	

Scenario No.	Parameter/Analysis	Company base case assumptions	Scenario explored	Justification for ERG's assumption
12*	Chlormethine gel daily dose	Treatment costs calculated using **median** daily gel usage (1.8g)	Treatment costs calculated using **mean** daily gel usage (2.8g)	The ERG considers a mean daily gel dosage more appropriate for calculation of the chlormethine gel treatment acquisition costs.
Treatment administration costs – phototherapy				
13*	Treatment administration costs for phototherapy	Based on 2006/07 NHS reference costs (outpatient appointment) as reported in Fonia et al., inflated to 2017/18 values.[7]	Apply the cost of a consultant led outpatient clinic for phototherapy / photo chemotherapy (HRG code: JC47Z) obtained directly from NHS reference costs 2017/18[6]	The ERG prefers using the most up to date NHS reference cost data.
14	Proportion of phototherapy delivered as PUVA / UVB	PUVA = [redacted]% and UVB = [redacted]%	Assume all phototherapy delivered as PUVA	The ERG's clinical expert opinion was that the use of PUVA in clinical practice may be greater than that included in the model. Also phan et al. suggest differential effectiveness by type of phototherapy. The ERG considered it appropriate to explore the impact of this on cost-effectiveness.
15		PUVA = [redacted]% and UVB = [redacted]%	Assume all phototherapy delivered as UVB	

Scenario No.	Parameter/Analysis	Company base case assumptions	Scenario explored	Justification for ERG's assumption
Cost and resource use scenarios				
16*	Advanced treatment stage costs	Costs of ECP and Methotrexate included in the advanced treatment bundle while patients are also receiving phototherapy.	Remove costs of ECP and Methotrexate as advanced treatment, while on phototherapy and for 2 weeks after stopping treatment	Based on clinical expert opinion that these treatments cannot be provided together with phototherapy.
17*	Adverse event costs	Assume that grade 3 or 4 skin related adverse events can be managed with corticosteroids only and an additional consultation with a dermatologist is not required.	Include outpatient visit with a dermatologist for treating grade 3 and 4 skin related adverse events	According to ERG's clinical expert opinion, patients experiencing a grade 3 or 4 skin related adverse event are referred to a dermatologist outpatient appointment to review treatment.
18	2nd line treatment costs for phototherapy patients who achieve a PR.	Costs of 2nd line treatment (50% bexarotene and 50%	Remove 2nd line treatment (bexarotene and IFN-α) therapy from PR in phototherapy arm	To explore the sensitivity of the ICER to this assumption and to reflect the ERG's clinical expert's opinion that not all patients having a PR on phototherapy will always go on to 2nd line treatment.

Scenario No.	Parameter/Analysis	Company base case assumptions	Scenario explored	Justification for ERG's assumption
		IFN-α) included for PR in phototherapy arm.		
19	Treatment costs in the 'progressed from 1L' state	Assumes 50% bexarotene, 50% IFN-α	Assume all 2nd line skin therapy delivered as bexarotene	Company assumption based on clinical expert opinion and validated as reasonable by ERG's clinical expert. However, the true breakdown of treatments remains unknown. This exploratory analysis investigates the impact of varying the distribution of 2nd line treatments between bexarotene and IFN-α on the ICER.
20			Assume all 2nd line skin therapy delivered as IFN-α	
Scenario analyses surrounding costs and QoL in progressed skin burden state				
21*	Proportion of cohort in 'progressed from 1L' health state that incur the treatment costs of bexarotene and IFN-α and the QALY losses of progressed disease	Assumes 100% incur additional costs and QALY losses for all remaining life years	Only a proportion (chlormethine gel: 97.8%; phototherapy:98.1%) incur costs and QoL decrements of progressed disease (approximated from CR and duration of response reported by Dalal et al. 2020)[67]	The ERG's clinical expert opinion, supported by studies included in the Dalal et al suggests that some patients will receive a CR on 2nd line treatments for progressed skin burden and would come off treatment.[67] The ERG considers it reasonable to assume that such patients would not remain on treatment and would not incur the QoL decrements associated with the progressed health state for the duration of their CR.

Scenario No.	Parameter/Analysis	Company base case assumptions	Scenario explored	Justification for ERG's assumption
Methodological scenario analyses				
22	Discount rate for costs and QALYs	3.5% per annum	0% per annum	Standard scenario analysis to explore the impact of discounting on the ICER.
23			6% per annum	
Subgroup analyses				
24	Model population	Model run for all MF-CTCL stages, based on stage distribution from the PROCLIPI registry	Early stage MF-CTCL only (Stage IA-IIA)	Company conducted subgroup analysis replicated by the ERG on our preferred base case to illustrate the impact of restricting the economic model to the population defined as part of Study 201 (Stage IA-IIA) only, and contrasting results against the model run only for a cohort with Stage IIB+ disease.
25			Late stage MF-CTCL only (Stage IIB+)	

Abbreviations: BAD: British Association of Dermatologists; BSA: Body surface area; CR: Complete response; ERG: Evidence Review Group; HRG: Healthcare Resource Group; ICER: Incremental cost-effectiveness ratio; IFN-α: interferon alpha MF-CTCL: Mycosis fungoides-type cutaneous T-cell lymphoma; PR: Partial response; QALY: Quality adjusted life year; QoL: Quality of Life.

*Identifies analyses / scenarios that contribute to the ERG's preferred base case ICER.

[A] Grams per 1%BSA=[redacted]%/100=0.23. %BSA = [redacted]% (Low skin burden) and =[redacted]% (High skin burden).

[B] Grams per 1%BSA=[redacted]%/100=0.23. %BSA = [redacted]% (Low skin burden) and =[redacted]% (High skin burden).

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG has undertaken several further scenario analyses, in addition to those undertaken by the company (see Table 25 above) to explore the impact on the ICER of plausible alternative assumptions about key model parameters. Table 28 describes the impact of the additional scenario analyses undertaken by the ERG on the company's base case ICER. The ERG's preferred scenarios are provided in bold. The cumulative impact of the ERG's preferred assumptions is then provided in Section 6.3 (Table 29).

Table 28 ERG's scenario analyses surrounding company's base case (ERG's preferred assumptions in bold)

Scenario No.	Scenario description	Company base case	Incremental cost	Incremental QALY	ICER (£/QALY)	ERG report Section:
1	Company preferred base case		-£7,005	0.0282	Phototherapy Dominated	5.1
Mortality and disease progression scenarios						
2*	Apply alternative source Agar et al. for disease progression[23]	Wernham et al.[61]	-£8,415	0.0385	Phototherapy dominated	4.2.6
3*	Apply general population mortality to those with stage IA	Stage IA mortality sourced from Agar et al. [23]	-£7,449	0.0289	Phototherapy dominated	4.2.6
Treatment effectiveness / skin burden transitions scenarios						
4	CR and PR rate for phototherapy: Use data from Phan et al. for PUVA and UVB separately, pooled across CTCL disease stages[48]	Weighted average of N=7 studies identified in the CS	-£7,710	0.0309	Phototherapy dominated	4.2.6
5*	CR and PR rate for phototherapy: Use data from Phan et al. applied separately to PUVA and UVB and by CTCL disease stages[48]	Weighted average of N=7 studies identified in the CS	-£7,611	0.0285	Phototherapy dominated	4.2.6

Scenario No.	Scenario description	Company base case	Incremental cost	Incremental QALY	ICER (£/QALY)	ERG report Section:
6	Time to progression post CR and PR for phototherapy: Apply weighted average of PUVA/UVB (Phan et al.)[48]	Time to progression post CR obtained from Whitaker et al. [36] and time to progression post PR assumed equal to maximum treatment duration	£2,871	-0.0982	Phototherapy dominant	4.2.6
7*	Time to progression post CR and PR for phototherapy: Apply separate time to progression for PUVA and UVB (Phan et al.) for those on phototherapy [48]	Time to progression post CR obtained from Whitaker et al. [36] and time to progression post PR assumed equal to maximum treatment duration	-£657	-0.0497	£13,217[A]	4.2.6
8*	Time to progression post CR for chlormethine gel: Use data from Kim et al.[10]	Assumed equal to phototherapy, based on Whitaker et al. [36]	-£16,413	0.1413	Phototherapy dominated	4.2.6
9*	ERGs preferred treatment effectiveness scenarios (5+7+8)	--	-£4,268	-0.0119	£358,285[A]	4.2.6
Treatment acquisition cost scenarios – Chlormethine gel						
10	Assume a lower %BSA affected in the low and high skin burden group (50% lower) i.e. daily dose of [redacted] and [redacted]	Mean BSA calculated as [redacted] and [redacted] BSA affected for low and high skin burden respectively,	-£9,867	0.0282	Phototherapy dominated	4.2.3 & 4.2.8

Scenario No.	Scenario description	Company base case	Incremental cost	Incremental QALY	ICER (£/QALY)	ERG report Section:
	grams for low and high skin burden groups, respectively [A]	based on mean daily dosage of 2.8g as per Study 201 (i.e. [redacted]g and [redacted]g for low and high skin burden respectively)				
11	Assume a higher %BSA affected in the low and high skin burden group (50% higher) i.e. [redacted] and [redacted] grams for low and high skin burden groups, respectively [B]		£34,385	0.0282	£1,221,294	4.2.3 & 4.2.8
12*	Chlormethine gel treatment acquisition costs based on mean daily gel usage	Chlormethine gel treatment acquisition costs based on median daily gel usage	£10,711	0.0282	£380,444	4.2.8
Treatment administration – Phototherapy						
13*	Treatment administration costs for phototherapy obtained from NHS reference costs 2017/18[6] (HRG code: JC47Z)	Treatment administration costs obtained from Fonia et al[7], based on 2006/07 NHS reference costs inflated to 2017/18 values.	-£2,934	0.0282	Phototherapy dominated	4.2.8
14	Assume all phototherapy delivered as PUVA	PUVA = [redacted]% and UVB = [redacted]%	-£7,658	0.0282	Phototherapy dominated	4.2.8
15	Assume all phototherapy delivered as UVB	PUVA = [redacted]% and UVB = [redacted]%	-£6,557	0.0282	Phototherapy dominated	4.2.8

Scenario No.	Scenario description	Company base case	Incremental cost	Incremental QALY	ICER (£/QALY)	ERG report Section:
Cost and Resource use scenarios						
16*	Remove costs of ECP and Methotrexate as advanced treatment, while on phototherapy and for 2 weeks after stopping treatment	Costs of ECP and Methotrexate included as advanced treatment, while on phototherapy	-£7,135	0.0282	Phototherapy dominated	4.2.8
17*	Include outpatient visit with a dermatologist for treating grade 3 / 4 skin related adverse events	Outpatient consultation not included for treatment of adverse events	-£6,938	0.0282	Phototherapy dominated	4.2.8
18	Remove 2nd line treatment (bexarotene and IFN-a) therapy from PR in phototherapy arm	Costs of 2nd line treatment included for PR in phototherapy arm	-£1,869	0.0282	Phototherapy dominated	4.2.2 & 4.2.8
19	Assume all 2nd line skin therapy delivered as bexarotene	Assumes 50% bexarotene, 50% IFN-a	-£29,741	0.0282	Phototherapy dominated	4.2.8
20	Assume all 2nd line skin therapy delivered as IFN-a	Assumes 50% bexarotene, 50% IFN-a	£15,731	0.0282	£558,743	4.2.8
Scenario analyses surrounding costs and QoL in progressed skin burden state						
21*	Proportion of cohort in 'progressed from 1L' health state that incur costs of bexarotene and IFN-a and QoL	Assumes 100% incur cost and get reduced QoL for all remaining life years	-£6,679	0.0273	Phototherapy dominated	4.2.2, 4.2.7 & 4.2.8

Scenario No.	Scenario description	Company base case	Incremental cost	Incremental QALY	ICER (£/QALY)	ERG report Section:
	decrements of progressed disease (approximated from CR and duration of response reported in Dalal et al. 2020[67])					
Methodological scenario analyses						
22	Set the discount rate to 0% for both costs and QALYs	3.5%	-£7,955	0.0376	Phototherapy dominated	4.2.5
23	Set the discount rate to 6% for both costs and QALYs	3.5%	-£6,445	0.0225	Phototherapy dominated	4.2.5
Subgroup analyses						
24	Model population = early stage MF-CTCL (Stage IA / IIA) only	Model population = all stages of MF-CTCL	-£9,499	0.0265	Phototherapy dominated	4.2.3
25	Model population = later stage MF-CTCL (Stage IIB+ only)	Model population = all stages of MF-CTCL	£2,749	0.0346	£79,461	4.2.3

*Identifies analyses / scenarios that contribute to the ERG's preferred base case ICER.

[A] Note that analyses where incremental costs and incremental QALYs are both negative, lie in the south-west quadrant of the cost-effectiveness plane, therefore higher ICERs are preferable in terms of cost-effectiveness.

Abbreviations: BSA: Body surface area; CR: Complete response; ERG: Evidence Review Group; HRG: Healthcare Resource Group; ICER: Incremental cost-effectiveness ratio; IFN-α: interferon alpha; MF-CTCL: Mycosis fungoides-type cutaneous T-cell lymphoma; PR: Partial response; QALY: Quality adjusted life year; QoL: Quality of Life.

6.3 ERG's preferred assumptions

The ERG's preferred base case ICER reflects the following assumptions and amendments to the company's economic model:

1. The ERG prefers treatment acquisition costs for chlormethine gel calculated using the mean daily dosage (2.8g) from Study 201 as opposed to the median (1.8g). The impact of the ERG's preferred approach is a substantial increase in the ICER.
2. The ERG prefers the use of the most up to date NHS reference costs to inform the treatment administration costs associated with phototherapy, as opposed to the company's approach which used reference costs from 2006/7 as reported in Fonia et al. inflated to 2017/18 values. The ERG's preferred approach reduces phototherapy administration costs from £3,458.52 per month to £1,093.28 per month and thus leads to a substantial increase in the ICER for chlormethine gel.
3. The ERG prefers the use of data from Agar et al. as opposed to Wernham et al. to determine the progression between CTCL stages in the model. Agar et al. is a substantially larger cohort and estimate a slower rate of underlying disease progression than Wernham et al. The impact of the ERG's preferred assumption is an increase in overall survival (as mortality is dependent on stage), and an improvement in the cost-effectiveness of chlormethine gel.
4. Based on clinical expert opinion, the ERG prefers an assumption that Stage IA mortality is equal to that of the general population. The impact of this assumption is a further improvement in the cost-effectiveness of chlormethine gel.
5. The ERG prefers phototherapy effectiveness (i.e. CR and PR) obtained from the review by Phan et al. because it is possible to derive response data by phototherapy type (PUVA / UVB) and also by MF-CTCL disease stage. The ERG also prefers time to progression following a CR and PR calculated from Phan et al. applied separately to PUVA / UVB, with the assumption that the ratio of time to progression following OR:CR is the same as the company's preferred source (Whittaker et al). The use of Phan et al. ensures a consistent data source for the phototherapy transition probabilities. The net impact of the ERG's preferred phototherapy transition probabilities is a substantial reduction in the cost-savings associated with chlormethine gel and negative as opposed

to positive incremental QALYs, due primarily to the substantially slower rate of progression into the progressed skin burden state following a complete response and the assumed higher CR rate for phototherapy compared to chlormethine gel.

6. The ERG prefers the use of Kim et al. considered as a scenario analysis in the CS, as the source of progression following a CR for chlormethine gel, as opposed to the company's preferred assumption of equality with phototherapy. The ERG's preferred source improves the cost-effectiveness of chlormethine gel relative to the company's preferred base case assumptions.
7. The ERG prefers the inclusion of an outpatient consultation with a dermatologist for the management of all grade 3 and 4 adverse events included in the model. This slightly reduces the cost savings for chlormethine gel compared to the company's preferred base case assumption that only the treatment cost of corticosteroids should be included for the management of grade 3 and 4 adverse events.
8. The ERG prefers the removal of ECP and methotrexate from the advanced treatment bundle while the cohort is receiving phototherapy, based on clinical expert opinion that these treatments cannot be provided together. The impact on the ICER is minimal.
9. The ERG prefers the use of data from Dalal et al. as an approximation of the proportion of those in the progressed skin burden state that might obtain a CR, and the duration of that response following treatment with bexarotene or IFN-a. Such patients may be discontinued from treatment and achieve an improvement in QoL. The ERG prefers this approach to the company's assumption that the full proportion of the cohort in the progressed skin burden state will incur additional treatment costs and QALY losses for the remainder of their life years in that state. The impact is a reduction in the cost savings and QALY gains for chlormethine gel because the company's base case assumptions assume that the chlormethine gel cohort enter the progressed state earlier, and thus spend a greater number of life years in that state compared to the phototherapy cohort.

The cumulative impact of all the ERG's preferred assumptions on the ICER is provided in Table 29.

Table 29 Cumulative impact of ERG preferred assumptions on the ICER

Scenario:	Incremental costs	Incremental QALYs	Chlormethine gel ICER (£/QALY)	Reference to section in ERG report
Company updated base case	-£7,005	+0.0282	Phototherapy dominated	5.1
+ Apply alternative source Agar et al. for disease progression[23]	-£8,415	+0.0385	Phototherapy dominated	4.2.6
+ Apply general population mortality to those with stage IA	-£8,986	+0.0395	Phototherapy dominated	
+ CR and PR rate for phototherapy: Use data from Phan et al. applied separately to PUVA and UVB and by CTCL disease stages[48]	-£9,591	+0.0396	Phototherapy dominated	4.2.6
+ Time to progression post CR and PR for phototherapy: Apply separate time to progression for PUVA and UVB (Phan et al.) for those on phototherapy [48]	-£4,115	-0.0267	£154,249[A]	4.2.6
+ Time to progression post CR for chlormethine gel: Use data from Kim et al.[10]	-£7,572	+0.0109	Phototherapy dominated	4.2.6
+ Chlormethine gel treatment acquisition costs based on mean daily gel usage	+£11,700	+0.0109	£1,075,201	4.2.8
+ Treatment administration costs for phototherapy obtained from NHS reference costs (HRG code: JC47Z), 2017/18[6]	+£16,158	+0.0109	£1,484,862	4.2.8

Scenario:	Incremental costs	Incremental QALYs	Chlormethine gel ICER (£/QALY)	Reference to section in ERG report
+ Remove costs of ECP and Methotrexate as advanced treatment, while on phototherapy and for 2 weeks after stopping treatment	+£16,031	+0.0109	£1,473,167	4.2.8
+ Include outpatient visit with a dermatologist for treating grade 3 / 4 skin related adverse events	+£16,107	+0.0109	£1,480,109	4.2.8
+ Proportion of cohort in 'progressed from 1L' health state that incur costs of bexarotene and IFN-a and QoL decrements of progressed disease (approximated from CR and duration of response reported in Dalal et al. 2020[67])	+£16,372	+0.0089	£1,830,197	4.2.2 & 4.2.7 & 4.2.8
ERG preferred base case analysis (deterministic)	**+£16,372**	**+0.0089**	**£1,830,197**	
ERG preferred base case analysis (probabilistic)	**+£16,160**	**+0.0062**	**£2,613,493**	

Abbreviations: BSA: Body surface area; CR: Complete response; ERG: Evidence Review Group; HRG: Healthcare Resource Group; ICER: Incremental cost-effectiveness ratio; IFN-α: interferon alpha; MF-CTCL: Mycosis fungoides-type cutaneous T-cell lymphoma; PR: Partial response; QALY: Quality adjusted life year; QoL: Quality of Life.

Table 30 Scenario analyses surrounding ERG preferred base-case

Scenario	ERG base-case	Incremental cost	Incremental QALY	ICER (£/QALY)
ERG base case		+£16,372	+0.0089	£1,830,197
Treatment acquisition cost scenarios (Chlormethine gel)				
Assume a lower %BSA affected in the low and high skin burden group ([redacted] lower) i.e. daily dose of [redacted] and [redacted] grams for low and high skin burden groups, respectively [A]	Mean BSA calculated as [redacted] and [redacted] BSA affected for low and high skin burden respectively, based on mean daily dosage of 2.8g as per Study 201 (i.e. [redacted] and [redacted] for low and high skin burden respectively)	-£5,995	+0.0089	Phototherapy dominated
Assume a higher %BSA affected in the low and high skin burden group ([redacted] higher) i.e. [redacted] and [redacted] grams for low and high skin burden groups, respectively [B]		+£42,362	+0.0089	£4,735,641
Phototherapy treatment distribution scenarios				
Assume all phototherapy delivered as PUVA	PUVA = [redacted]% and UVB = [redacted]% based on PROCLIPI registry data	+£30,707	-0.1550	Phototherapy dominant
Assume all phototherapy delivered as UVB	PUVA = [redacted]% and UVB = [redacted]% based on PROCLIPI registry data	+£11,306	+0.0695	£162,723
Treatment effectiveness / skin burden transition scenarios				
Use pooled data from Phan et al. across CTCL disease stages for CR and PR (for phototherapy)[9]	CR and PR applied by CTCL stage	+£16,196	+0.0086	£1,875,923

Scenario	ERG base-case	Incremental cost	Incremental QALY	ICER (£/QALY)
Apply weighted average of PUVA/UVB (Phan et al.[9]) to progression post CR and post PR (for those on phototherapy)	PUVA/UVB CR and PR applied separately	+£24,507	-0.0896	Phototherapy dominant
Subsequent treatment scenarios				
Remove 2nd line treatment (bexarotene and IFN-α) therapy from PR in phototherapy arm	Costs of 2nd line treatment included for PR in phototherapy arm	+£20,205	+0.0089	£2,258,701
Assume all 2nd line skin therapy delivered as bexarotene	Assumes 50% bexarotene, 50% IFN-a	-£8,766	+0.0099	Phototherapy dominated
Assume all 2nd line skin therapy delivered as IFN-a	Assumes 50% bexarotene, 50% IFN-a	+£41,313	+0.0080	£5,184,531
Methodological uncertainty scenarios				
Discount costs and QALYs by 0% per annum, in line with NICE methods guide[68]	3.5% as per NICE reference case[68]	+£14,608	+0.0368	£396,505
Discount costs and QALYs by 6% per annum, in line with NICE methods guide[68]	3.5% as per NICE reference case[68]	+£17,194	-0.0060	Phototherapy dominant
Subgroup analyses				
Model population = early stage MF-CTCL (Stage IA / IIA) only	Model population = all stages of MF-CTCL	+£11,988	+0.0295	£406,773
Model population = later stage MF-CTCL (Stage IIB+ only)		+£33,690	-0.0709	Phototherapy dominant

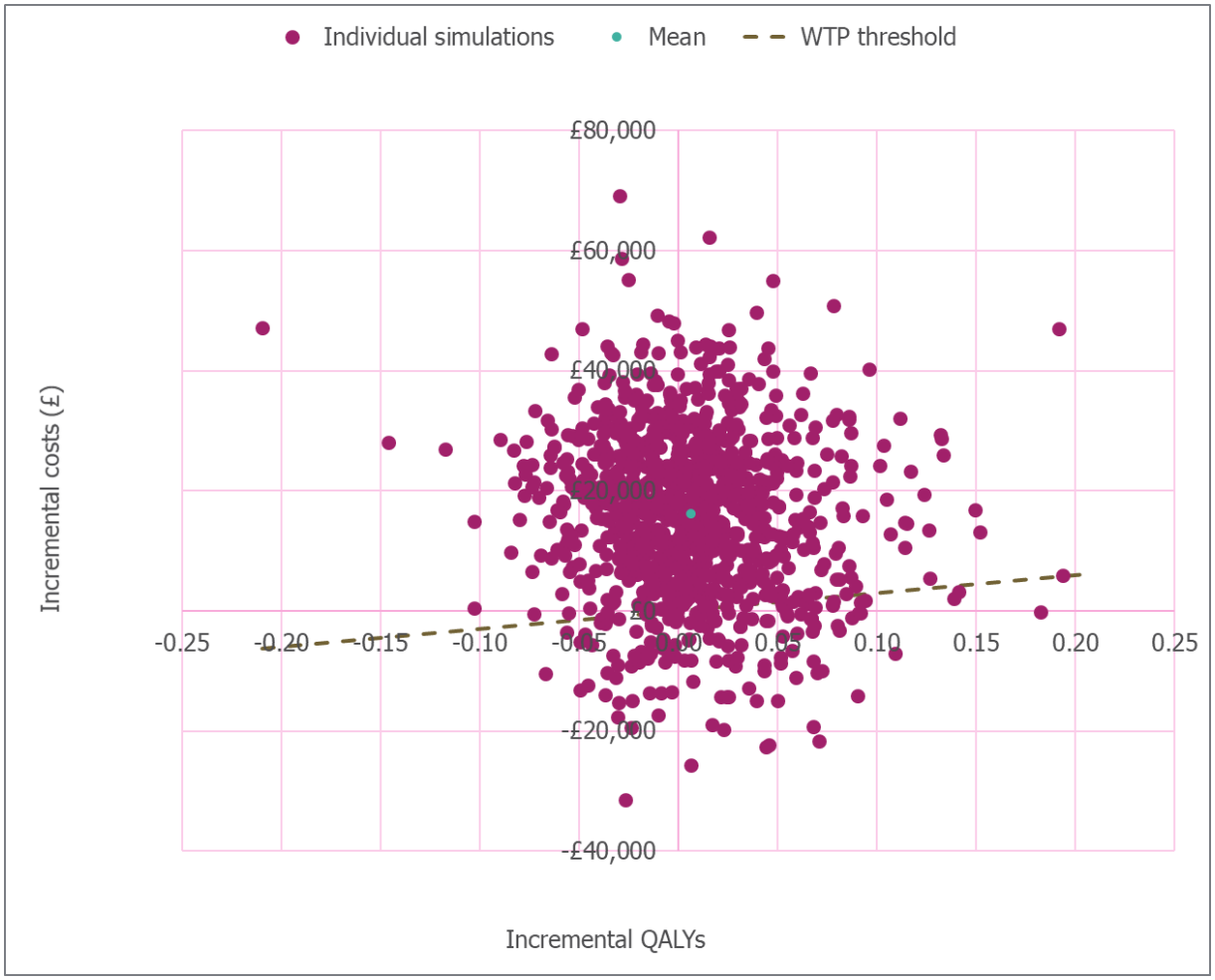
[A] Grams per 1%BSA=[redacted]%/100=0.23. %BSA = [redacted]% (Low skin burden) and =[redacted]% (High skin burden).
[B] Grams per 1%BSA=[redacted]%/100=0.23. %BSA = [redacted]% (Low skin burden) and =[redacted]% (High skin burden).
Abbreviations: BSA: Body surface area; CR: Complete response; ICER: Incremental cost-effectiveness ratio; IFN-α: interferon alpha; MF-CTCL: Mycosis fungoides-type cutaneous T-cell lymphoma; PR: Partial response; QALY: Quality adjusted life year.

The ERG's preferred set of base case assumptions suggests leads to an ICER of £1.83m per QALY gained. However, the ERG acknowledges the company's explanation in response to clarification queries that differences in the ICER are magnified due to the small magnitude of QALY differences. The ERG has undertaken a range of plausible scenario analyses surrounding its base case assumptions to explore the potential impact on the ICER of plausible variation in key important model parameters. The ERG's preferred base case ICER is also subject to substantial uncertainty. The most important parameters are the proportion of BSA affected and the distribution of second line treatment between bexarotene and IFN-α.

Proportion BSA affected is the key driver of the treatment acquisition costs for chlormethine gel. It is also a highly uncertain parameter and it is unknown how transferable the % BSA observed in Study 201, used for treatment acquisition costing, would be to the distribution of BSA observed in the UK general population. The ERG is unclear whether %BSA data were available to the company by CTCL stage from the PROCLIPI registry. If they were, these data may have been more appropriate for calculating the treatment acquisition costs for chlormethine gel. The true treatment acquisition costs associated with chlormethine gel are therefore difficult to ascertain with accuracy. For example, decreasing and increasing the %BSA by ±50% leads to incremental costs for chlormethine gel vs. phototherapy of -£5,995 and +£44,093 and ICERs for chlormethine gel ranging dominance to £4.93m per QALY gained respectively.

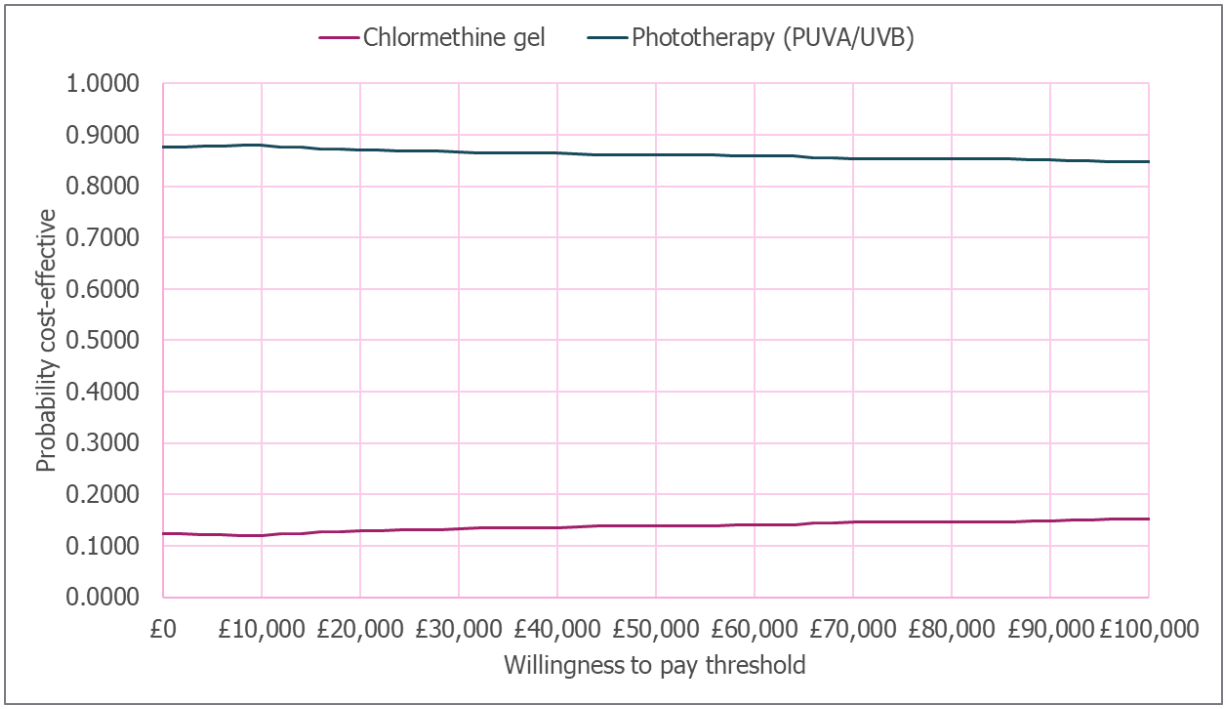
The distribution of downstream treatments for progressed skin burden has a substantial impact on the ICER. The company have assumed that an equal proportion of patients with progressed skin disease will be on bexarotene and IFN-a. Whilst the ERG's clinical expert considers this to be a reasonable assumption, it is noteworthy that the distribution is not based on any data. It is unclear to the ERG whether such data could have been obtained from the PROCLIPI registry. If this was possible, it would have been a preferred source of data. Assuming all patients in the 'progressed from 1L' state receive bexarotene results in an ICER where chlormethine gel dominates. However, assuming all receive the less costly IFN-a, increases the ICER to approximately £5.18m per QALY gained. Plausible variations in this important model parameter have a potentially very large impact on the ICER.

The results of the PSA using the ERG's preferred base case assumptions are illustrated using a scatter plot of the cost-effectiveness plane and CEACs in Figures 5 and 6 respectively.



WTP threshold = £30,000 per QALY
Abbreviations: ERG: Evidence Review Group; QALY: Quality adjusted life year; WTP: Willingness to pay
(Source: Produced by the ERG from the company's revised, preferred base case model)

Figure 5 Scatter plot of the cost-effectiveness plane for ERG's preferred base case analysis



Abbreviations: CEAC = Cost-effectiveness acceptability curve; ERG: Evidence review group
(Source: Produced by the ERG from the company's revised, preferred base case model)

Figure 6 CEAC for ERG's preferred base case analysis

Under the ERG's set of preferred assumptions there is a high chance that phototherapy is less costly than chlormethine gel overall. The greatest uncertainty now lies in whether chlormethine gel offers positive or negative incremental QALYs, as illustrated in the approximately equal number of Monte Carlo simulations on either side of the x-axis in Figure 5. This contradicts the PSA surrounding the company's preferred ICER where much of the uncertainty lay in incremental costs. Under the ERG's preferred analysis there is an 86.6% probability that phototherapy is the most cost-effective use of resources at a willingness to pay of £30,000 per QALY gained. The CEAC in Figure 6 confirms that this probability remains stable over increasing threshold values of WTP for a QALY gained up to £100,000.

6.4 Conclusions of the cost-effectiveness section

The company's base case ICER (original submission) was £44,915 per QALY gained based on modelled cost savings and QALY losses. However, the ERG identified an error in the company's economic model that over-estimated the rate of adverse events in the model, impacting particularly on incremental QALYs. The company corrected this error in response to clarification queries. The company's preferred base case assumptions generate cost

savings (-£7,005) and QALY gains (+0.03), with chlormethine gel dominating the phototherapy comparator.

The ERG's preferred analysis:

- Uses the mean (as opposed to median) daily dose of chlormethine gel to calculate treatment acquisition costs,
- Uses NHS reference costs for 2017/18 (as opposed to costs inflated from Fonia et al. based on NHS reference costs 2006/07) to determine phototherapy administration costs,
- Includes the cost of an outpatient consultation with a dermatologist to manage grade 3 and 4 skin related adverse events,
- Uses data from the systematic review by Phan et al.[9] to inform response rates and time to progression following a response on phototherapy,
- Uses data from Kim et al. to inform progression following a CR on chlormethine gel,[10]
- Uses data from a review by Dalal et al[67] to approximate the proportion of the cohort with progression of skin burden who will have a response to downstream bexarotene / IFN-a treatment.

The resultant deterministic ICER (~£1.83m per QALY gained) is considered to offer a plausible alternative to the company's base case analysis. The probabilistic analysis shows that under the ERG's suggested base case, there is an 86.6% probability that phototherapy is the most cost-effective use of resources at a willingness to pay of £30,000 per QALY gained. The probability of cost-effectiveness remains similar for alternative reasonable threshold values of WTP for a QALY gain. Despite the magnitude of the ICER under the ERG's base case assumptions, it is important to acknowledge that the ICER is based on small differences in QALYs, and is highly sensitive to different plausible assumptions. Ultimately, it is the ERG's view that determining an accurate base case ICER in light of the data limitations is problematic.

The ERG considers the following to represent key issues of uncertainty for decision making:

- The true incremental clinical effectiveness of chlormethine gel versus phototherapy is unknown. There is substantial heterogeneity across phototherapy studies, using the company's and the ERGs data sources, particularly in terms of the definition of

complete / partial response, the comparability of that definition to Study 201, and the approach used to calculate time to progression of skin burden following a CR or PR. In the absence of data from the company's literature review to formulate an indirect treatment comparison, a naïve comparison was undertaken. However, this introduces substantial uncertainty for decision making.

- The treatment acquisition costs for chlormethine gel are based on the proportion BSA affected, by CTCL stage, from Study 201. However, it is unclear how representative the %BSA within each CTCL stage from Study 201 is to the UK population, especially for Stage IIB+ disease where no data were available from Study 201. The ERG note that small changes to the % BSA affected have a substantial impact on the ICER. A judgement is required as to whether the proportion BSA affected in Study 201 is generalizable to the UK clinical setting in which chlormethine gel may be used, or whether it is possible for the company to source these data from the PROCLIPI registry, if available.
- The use of mean vs. median daily gel dosage to calculate the treatment acquisition costs of chlormethine gel. The company prefer the use of the median, but the ERG considers it inappropriate to use the median, and prefers the use of the mean for costing purposes.
- The proportion of the modelled cohort that ultimately progress onto 2nd line skin treatments (bexarotene and IFN-a), the distribution of post-progression therapy, the duration of its usage, it's potential to deliver a favourable response and the associated impact on costs and QALY. The greater the proportion of the cohort that enter this model health state, the higher the overall costs and lower the overall QALYs.
- The appropriateness of using N=7 clinician proxy responses to the EQ-5D to assign health status to vignettes based on mSWAT score in each CTCL disease stage to inform utilities in each of the modelled health states. The ERG accepts that there is a lack of utility data for MF-CTCL, but would have considered a survey where patients, as opposed to clinicians, completed responses to the vignettes to be preferable. The ERG also notes substantial differences in the elicited utility scores across states with differential skin burden, despite published literature indicating that EQ-5D is not sufficiently sensitive to capture changes in skin burden.

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8 APPENDICES

Appendix 1 ERG's assessment of the Phan et al 2019 systematic review using the AMSTAR-2 checklist

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- [X] Population
- [X] Intervention
- [X] Comparator group
- [X] Outcome

Optional (recommended)
- [ ] Timeframe for follow-up

- [X] Yes
- [ ] No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- [ ] review question(s)
- [ ] a search strategy
- [ ] inclusion/exclusion criteria
- [ ] a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- [ ] a meta-analysis/synthesis plan, if appropriate, *and*
- [ ] a plan for investigating causes of heterogeneity
- [ ] justification for any deviations from the protocol

- [ ] Yes
- [ ] Partial Yes
- [X] No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- [ ] *Explanation for* including only RCTs
- [ ] OR *Explanation for* including only NRSI
- [ ] OR *Explanation for* including both RCTs and NRSI

- [ ] Yes
- [X] No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- [X] searched at least 2 databases (relevant to research question)
- [X] provided key word and/or search strategy
- [X] justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- [X] searched the reference lists / bibliographies of included studies
- [ ] searched trial/study registries
- [ ] included/consulted content experts in the field
- [ ] where relevant, searched for grey literature
- [X] conducted search within 24 months of completion of the review

- [ ] Yes
- [X] Partial Yes
- [ ] No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- [X] at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- [ ] OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- [X] Yes
- [ ] No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- ☒ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☒ Yes
☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- ☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☐ Partial Yes
☒ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- ☒ described populations
- ☒ described interventions
- ☒ described comparators
- ☒ described outcomes
- ☒ described research designs

For Yes, should also have ALL the following:

- ☐ described population in detail
- ☐ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

☐ Yes
☒ Partial Yes
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:

- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☒ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

- ☐ from confounding, *and*
- ☐ from selection bias

For Yes, must also have assessed RoB:

- ☐ methods used to ascertain exposures and outcomes, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☒ No
☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☐ Yes
☒ No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☒ No meta-analysis conducted

For NRSI

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☒ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☒ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☐ Yes
☒ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ☐ included only low risk of bias RCTs
- ☒ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☒ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ☐ There was no significant heterogeneity in the results
- ☒ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☒ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ☒ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☒ Yes
☐ No
☐ No meta-analysis conducted

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

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 Friday 3 April 2020** 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.

Sections 1–3: Executive Summary, Introduction and Background and Clinical Effectiveness

Issue 1 Confidentiality highlighting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 5: 'The ratio of these response rates, stratified by MF-CTCL Stage IA versus IB/IIA, was 1.226 ([redacted], [redacted]).'	Please amend confidentiality highlighting as follows: 'The ratio of these response rates, stratified by MF-CTCL Stage IA versus IB/IIA, was 1.226 (95% CI: 0.974–1.552, [redacted]).'	Confidential data were incorrectly marked and should be updated.	The proposed revision is accepted. The ERG report has been amended.

Issue 2 Placeholder cross reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16: 'A summary of the company's decision problem in relation to the NICE final scope is presented in Table x.'	Please amend as follows: 'A summary of the company's decision problem in relation to the NICE final scope is presented in Table ~~x~~ 4.'	Updating this minor typographical error makes navigating the document easier.	The proposed revision is accepted. The ERG report has been amended.

Issue 3 Summary of the decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 (Table 4): 'At the time of this appraisal, there are limited NICE guidelines for the management of MF-CTCL, although various clinical guidelines are available. The ERG clinical expert agrees with the company that, of these, the	Please amend as follows: 'At the time of this appraisal, there are ~~limited~~ **no relevant NICE guidelines** for the management of MF-CTCL, although **published guidance for CD30-positive CTCL is available in TA577**. There are additionally various clinical guidelines ~~are~~ available; the	The statement is misleading regarding the level of guidance available from NICE for MF-CTCL. The Company believes that the lack of NICE guidance for the treatment of MF-CTCL is indicative of the unmet need in this rare disease, and the lack of robust clinical evidence	The proposed revision is accepted. The ERG report has been amended.

UK-specific BAD guidelines are most commonly used to inform clinical practice in the UK.'	ERG clinical expert agrees with the company that, of these, the UK-specific BAD guidelines are most commonly used to inform clinical practice in the UK.'	for comparator treatments for MF-CTCL.	
Page 18 (Table 4): 'The company state that chlormethine gel would be used as monotherapy in early stages of the disease and in combination with systemic therapies for more advanced disease stages.'	Please amend as follows: 'The company state that chlormethine gel would be used as monotherapy in early stages of the disease and in combination with systemic therapies for more advanced disease stages. **The company also note that topical (cortico)steroids may be used in combination with chlormethine gel (across disease stages) for the management of skin related adverse events and for symptomatic treatment of non-MF-CTCL skin symptoms, in UK clinical practice.**'	To ensure full clarity for the reader, the additional text clarifies the position of Recordati Rare Diseases/Helsinn Healthcare SA that although chlormethine gel will be used as a monotherapy in terms of MF-CTCL specific treatments at early stages of disease, patients may additionally be treated with (cortico)steroids to manage adverse events and MF-CTCL-related symptoms such as dermatitis and pruritis, in UK clinical practice.	Not a factual inaccuracy.

Issue 4 Critique of the methods of review(s)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22: 'Additionally, searches for identifying relevant systematic reviews are limited to the Cochrane Database of Systematic Reviews and the DARE database, which was last updated in 2015. These restrictions may limit the evidence available for the clinical effectiveness review.'	Please amend as follows: 'Additionally, searches for identifying relevant systematic reviews are limited to the Cochrane Database of Systematic Reviews (**Issue 7 of 12, July 2019**), and the DARE database, which was last updated in 2015. These restrictions may limit the evidence available for the clinical effectiveness review.'	The updated text improves clarity as to the fact that although the DARE database was last updated in 2015, the Cochrane Database of Systematic Reviews does contain more recent data, up to July 2019.	The proposed revision is accepted. The ERG report has been amended.

Issue 5 Characteristics of studies that provide data on the effectiveness and safety of chlormethine gel

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28 (Table 7): 'Study design of French ATU is reported as: "single-arm study"'.	Please amend as follows: '~~single-arm study~~ **early access programme**"	By referring the French ATU programme as a single-arm study, it could be misinterpreted as an experimental study; the Company therefore suggests the French ATU would be better described as an "early access programme"	Not a factual inaccuracy
Page 28 (Table 7): PROVe is described as an 'Ongoing, prospective, open-label single-arm study'.	Please amend as follows: "Ongoing, prospective, ~~open-label single-arm~~ **multicentre, observational study**"	The updated text improves clarity as to the fact that the PROVe study is an observational study of the use of chlormethine gel in the real-world in patients in the USA.	Not a factual inaccuracy. The ERG believes the text is clear.
Page 28 (Table 7): Treatment duration of the PROVe study is reported as: 'Mean [redacted]years'	Please amend as follows: '~~Mean [redacted]years~~ **Not reported**".	The figure reported by the ERG is the duration of MF-CTCL in years, not the duration of treatment with chlormethine gel. The duration of treatment in the PROVe study was not reported in the company submission (CS).	The proposed revision is accepted. The ERG report has been amended.
Page 29 (Table 7): Patients with Stage III–IV MF-CTCL, French ATU nominative cohort is reported as '[redacted]'.	Please amend as follows: '[redacted]'	Incorrectly reported data.	This is not a factual inaccuracy. However, the ERG accepts the proposed amendment for consistency in the rounding of numbers.
Page 29 (Table 7): Patients with Stage III–IV MF-CTCL, French ATU cohort is reported as	Please amend as follows: '[redacted]'	Incorrectly reported data.	This is not a factual inaccuracy. However, the ERG accepts the proposed amendment for

‘[redacted]’.			consistency in the rounding of numbers.

Issue 6 Description of the primary endpoint

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 31: ‘The CAILS score is calculated by adding a severity score for the following skin symptoms: erythema and scaling (both scored on a severity scale of 0-8), and plaque elevation and surface area (both scored on a severity scale of 0-9).’	Please amend as follows: ‘The CAILS score is calculated by adding a severity score for the following skin symptoms: erythema and scaling (both scored on a severity scale of 0-8), ~~and~~ plaque elevation (**scored on severity scale of 0–3)** and surface area (~~both~~ scored on a severity scale of 0–9).’	The scoring system used for CAILS, the primary endpoint in the trial, is incorrectly reported and so should be updated.	The proposed revision is accepted. The ERG report has been amended.

Issue 7 Reporting of secondary endpoints

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 (Table 9): ‘Time to progression based on CAILS score (% with ≥25% increase from Baseline CAILS score)’	Please amend as follows: ‘Time to progression based on CAILS score (% ~~with~~ **who do not have** ≥25% increase from Baseline CAILS score)’	The ERG has reported that the majority of patients at Week 24 and Week 52 have progressive disease (defined by ≥25% increase from Baseline CAILS score) where this should in fact be reporting the number of patients who did not have progressive disease.	The proposed revision is accepted. The ERG report has been amended.
Page 34 (Table 9): Patient numbers reported for estimated time to a 50% CAILS response rate are Chlormethine gel: n=129;	Please amend as follows: Patient numbers reported for estimated time to a 50% CAILS response rate: Chlormethine gel: n=~~129~~ 130; Chlormethine ointment: n=~~127~~ 130	The percentage responses reported are calculated from the whole population of n=130 (as per the CS and the CSR for Study 201).	The proposed revision is accepted. The ERG report has been amended.

Chlormethine ointment: n=127.			
Page 34 (Table 9): Patient numbers reported for time to progression based on CAILS score: Chlormethine gel: n=123; Chlormethine ointment: n=126.	Please amend as follows: Patient numbers reported for time to progression based on CAILS score: Chlormethine gel: n=~~123~~ 130; Chlormethine ointment: n=~~126~~ 130	The percentage responses reported are calculated from the whole population of n=130 (as per the CS and the CSR for Study 201).	The proposed revision is accepted. The ERG report has been amended.

Issue 8 Typo altering meaning of text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25: 'Although the study was conducted in the USA, the ERG's clinical expert is of the opinion that the study participants are similar to those with early-stage MR-CTCL who would be seen in clinical practice in the UK'	Please amend as follows: 'Although the study was conducted in the USA, the ERG's clinical expert is of the opinion that the study participants are similar to those with early-stage M**F**-CTCL who would be seen in clinical practice in the UK'	Updating this small inaccuracy allows this sentence to be interpreted more easily.	The proposed revision is accepted. The ERG report has been amended.

Issue 9 Confidentiality highlighting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35: 'The company states that the majority ([redacted], [redacted]) of these patients were Stage IA/IB, and that [redacted] patients with advanced disease experienced a favourable response of OR or SD (<50% reduction from baseline score).'	Please amend confidentiality highlighting as follows: 'The company states that the majority ([redacted], [redacted]) of these patients were Stage IA/IB, and that [redacted] patients with advanced disease experienced a favourable response of OR or SD (<50% reduction from baseline score).'	Confidential data were incorrectly marked and should be updated.	The proposed revision is accepted. The ERG report has been amended.

Issue 10 Summary of clinical efficacy data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 37 (Table 10): 'Unevaluable[a] [a] Patients with at least one follow-up form'	Please amend as follows: 'Unevaluable[ab] ~~a Patients with at least one follow-up form~~ b Includes patients with no Baseline CAILS assessment or no post-Baseline CAILS assessment. For the ITT including NYU population for the primary endpoint, five patients never received study drug and six patients were withdrawn without any post-Baseline assessment (one for non-compliance and five due to treatment-limiting toxicity).'	The incorrect footnote is indicated for the definition of unevaluable patients which makes the data unclear.	The proposed revision is accepted. The ERG report has been amended.

Issue 11 Adverse events reporting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 38: 'The most commonly reported AEs were skin and subcutaneous disorders, ([redacted] of gel patients and [redacted] of ointment patients), and were mainly due to skin irritation, which was experienced by more patients who received the gel formulation than those who received the ointment formulation (25.0% versus 14.2% p=0.040).'	Please amend as follows: 'The most commonly reported AEs were skin and subcutaneous disorders, ([redacted] of gel patients and [redacted] of ointment patients), and in the chlormethine gel arm, ~~were mainly due to~~ the most commonly reported skin disorder was skin irritation, which was experienced by more patients who received the gel formulation than those who received the ointment formulation (25.0% versus 14.2% p=0.040). In the chlormethine ointment arm the most commonly	It may be misleading to say that skin AEs were mainly due to skin irritation as the proportions of other skin AEs including contact dermatitis, erythema and pruritus also ranged from 14.8%–19.5% patients treated with chlormethine gel. Additionally, pruritis was the most commonly reported skin AE in chlormethine ointment treated patients.	Not a factual inaccuracy.

	reported skin AE was pruritis (15.7% of patients).'		
Page 39: 'The company state that, for all these cases, the skin cancer cannot be attributed to topical chlormethine treatment as 14/20 cases occurred in untreated areas of the skin, on sun exposed areas, and in patients with a prior history of skin cancers or who had received prior skin-directed therapy for MF-CTCL, which is known to increase the risk of skin cancer.'	Please amend as follows: 'The company state that, for all these cases, the skin cancer cannot be attributed to topical chlormethine treatment as 14/20 cases occurred in untreated areas of the skin, on sun exposed areas, and in patients with a prior history of skin cancers or who had received prior skin-directed therapy for MF-CTCL **including phototherapy**, which is known to increase the risk of skin cancer.'	The updated wording allows improved clarity as to the fact that it is phototherapy specifically not all prior skin-directed therapies that are known to increase the risk of skin cancers.	The proposed revision is accepted. The ERG report has been amended.
Page 40: 'The company present summary data for any AEs, and skin and subcutaneous tissue disorders experienced by >5% of patients for study 201 and Study 202 in Table 37, document B, of the CS.'	Please amend as follows: 'The company present summary data for any AEs, and skin and subcutaneous tissue disorders experienced by >5% of patients ~~for study 201 and~~ in Study 202, **including separate analysis by treatment group in Study 201 (i.e. chlormethine gel versus chlormethine ointment), and the full analysis set (FAS),** in Table 37, document B, of the CS.'	The updated wording allows improved clarity as to the fact that the data reported in Table 37 are for all patients in Study 202 stratified by both their original treatment arm in Study 201, and the FAS of Study 202.	Not a factual inaccuracy. The ERG believes this information is clear.
Page 40: 'Patients in the MIDAS trial were all treated concurrently with two different therapies but on different lesions: either chlormethine gel once nightly, or gel once nightly plus triamcinolone (steroid) ointment (0.1%) once daily, for four months.'	Please amend as follows: 'Patients in the MIDAS trial were all treated concurrently with two different therapies but on different lesions: either chlormethine gel once nightly, or **chlormethine** gel once nightly plus triamcinolone (steroid) ointment (0.1%) once daily, for four months.'	Updating this small inaccuracy allows this sentence to be interpreted more easily.	Not a factual inaccuracy. The ERG believes this statement is clear.

Page 41: '[redacted] treatment-related deaths were reported in the French ATU study.'	'[redacted] treatment-related deaths were reported in the French ATU study.~~35~~**30**'	The statement is incorrectly referenced; it should cite reference number 30.	The proposed revision is accepted. The ERG report has been amended.

Issue 12 Subgroup reporting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 41: 'Subgroup analyses of the CAILS response rates in Study 201 were conducted for sex (Male, Female), race (Caucasian, African American, Other), age (<18, 18–64, 65–74, ≥65) and the stratification variable, MF-CTCL stage (Stage IA, Stage IB/IIA) for both ITT populations (including and excluding the NYU population).'	Please amend as follows: 'Subgroup analyses of the CAILS response rates in Study 201 were conducted for sex (Male, Female), race (Caucasian, African American, Other), age (<18, 18–64, 65–74, ≥**75**) and the stratification variable, MF-CTCL stage (Stage IA, Stage IB/IIA) for both ITT populations (including and excluding the NYU population).'	The age range used for subgroup analysis was misreported and should be corrected to align with that utilised in Study 201.	The proposed revision is accepted. The ERG report has been amended.

Issue 13 Data reporting from the Phan et al. (2019) systematic review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 52 (Table 14): CR rates for El-Mofty 2005[55] are reported as: '70% PUVA' and '70% NBUVB'	Please amend as follows: ' ~~7~~80% PUVA' and '~~7~~90% NBUVB'	These results are incorrectly reported and should therefore be updated.	As documented in the ERG report, the ERG extracted data from the El-Mofty 2005 paper. El-Mofty 2005 reports Very good response (>=80%) (complete response); Good response (80–60%) (partial response); Fair response (60–40%) (minor response). The

			ERG extracted 'very good response' as CR and 'good response' as PR (as defined in the 6th column of Table 14 in the final report), whereas Phan et al. and the factual error document used 'Very good response' and 'Good response' as CR. Not a factual inaccuracy
Page 52 (Table 14): PR rates for El-Mofty 2005[55] are reported as: '10% PUVA' and '20% NBUVB'	Please amend as follows: '~~1~~20% PUVA' and '~~2~~10% NBUVB'	These results are incorrectly reported and should therefore be updated.	Please see above response.

Issue 14 The role of chlormethine gel in the treatment of late-stage patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54: 'However, the ERG notes that Study 201 only recruited patients with early disease (Stage IA-IIA) and therefore there is no evidence from the trial on the use of chlormethine gel in people with more advanced disease; although the company suggest that in advanced disease chlormethine gel can be used as an adjunct. The trail also did not collect data on quality of life outcomes and the company submission relies on a vignette study for its quality of life outcomes'	Please amend as follows: 'However, the ERG notes that Study 201 only recruited patients with early disease (Stage IA-IIA) and therefore there is no evidence from the trial on the use of chlormethine gel in people with more advanced disease; although the company suggest that in advanced disease chlormethine gel can be used ~~as an adjunct~~ **to treat the patches and plaques of MF-CTCL alongside systemic therapies to treat the underlying cancer.** The tri**a**l also did not collect data on quality of life outcomes and the company submission relies on a vignette study for its quality of life outcomes.'	Recordati Rare Diseases/Helsinn Healthcare SA wish to highlight that chlormethine gel will be a component of a combination therapy approach and will specifically be used for the treatment of the patches and plaques in advanced stage patients, alongside systemic therapies, rather than as an adjunct to therapy. There is also a minor typo in the second sentence that should be updated.	The proposed revision is accepted. The ERG report has been amended.

Sections 4–6: Cost-Effectiveness, Cost-Effectiveness Results and Evidence Review Group's Additional Analyses

Issue 15 Scenario analysis results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54 (Table 25): Results of scenario analysis comparing bundled comparator to chlormethine gel are reported as 'ICER: Phototherapy dominated'	'ICER: ~~Phototherapy dominated~~ Bundled comparator dominated'	These results are incorrectly reported and should therefore be updated.	This typographical error has been corrected.

Issue 16 Perspective on outcomes in the reference case checklist

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59 (Table 16): 'Yes, the economic model includes health effects for patients. Carer outcomes have not been considered but this would not be appropriate for this population with early stage disease.'	Please amend as follows: 'Yes, the economic model includes health effects for patients. Carer outcomes have not been considered **due to limited available evidence**, but inclusion of carer outcomes would not be appropriate, **particularly** for **the** population with early stage disease.'	Recordati Rare Diseases/Helsinn Healthcare SA wish to highlight that the CS considers patients with MF-CTCL at both early stage and advanced stage, whereas the previous statement implied that only early stage patients were included.	This is not a factual inaccuracy. However, the ERG have adapted the text to improve clarity.

Issue 17 Source of data for measurement of health-related quality of life in the reference case checklist

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59 (Table 16): 'No, EQ-5D-5L responses to the 12 vignettes were provided by N=7 clinicians (dermatologists and oncologists),	Please amend as follows: 'No, EQ-5D-5L responses to the 12 vignettes were provided by N=7 clinicians (dermatologists and oncologists), including 1	Without providing additional context the sample size of clinicians (N=7) may appear limited. However, these expert clinicians are responsible for	This is not a factual inaccuracy. No amendment required.

including 1 clinician who helped design the vignettes. One patient validated the vignette descriptors but did not provide EQ-5D-5L responses directly. EQ-5D-5L responses were therefore not based on the responses of a representative patient sample with MF-CTCL disease. Their appropriateness for use in the economic model is questionable.'	clinician who helped design the vignettes. One patient validated the vignette descriptors but did not provide EQ-5D-5L responses directly. **These dermatologists and oncologists are experts responsible for treating the majority of patients with MF-CTCL in the UK (as MF-CTCL is a rare disease treated in few centres).** EQ-5D-5L responses were therefore not based on the responses of a representative patient sample with MF-CTCL disease. Their appropriateness for use in the economic model is questionable.'	the management and treatment of almost all MF-CTCL patients in the UK, which is important context for understanding the robustness of the approach taken in terms of the representativeness of the clinicians engaged with.	

Issue 18 Transition to the "Death" health state in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61: 'The cohort could enter the "Death" state from any state in the model, based on median survival time reported in Agar *et al.*'	Please amend as follows: 'The cohort could enter the "Death" state from any state in the model, based on median survival time reported in Agar *et al.* **and also general population mortality.**'	In addition to transition probabilities to the "Death" health state to account for disease-specific mortality (i.e. those from Agar *et al.*), baseline general population mortality from the Office of National Statistics for England and Wales for 2016–2018 (by single year of age and by gender) was applied. A built-in constraint was applied to ensure that the modelled (i.e. disease-specific) mortality did not drop below that of the general population mortality at any time point.	The ERG accepts the company's explanation and indeed the ERG report (page 67) explicitly states that *"In the economic model, mortality is based on the median survival time reported in Agar et al. by disease stage, or general population mortality, whichever is higher"* For completeness, this has also been clarified on page 61.

Issue 19 Description of skin burden health states in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 62 (Table 17): 'Progression following no response (from 'initial skin burden' state, low or high)'	Please amend as follows: 'Progression following **PD** (from 'initial skin burden' state, low or high)'	Patients transitioning to 'Progressed from 1L' from the initial skin burden health states (low or high) are those who have experience a 'PD' response (from Study 201), defined as patients with a ≥25% increase from Baseline score. This is not the same as saying 'no response', as previously stated in the ERG report.	This is not a factual inaccuracy. The ERG use the term 'no response' to refer to the proportion of the cohort who do not achieve a PR or CR. However, the ERG has provided further clarity in Table 17 to remove any ambiguity.

Issue 20 Incorrect proportions of patients across disease stages from Study 201

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 64: 'By comparison, Study 201 excluded patients with Stage IIB+ disease and the distribution of disease severity was [redacted] with stage IA, IB/IIA and IIB+, respectively.'	Please amend as follows: 'By comparison, Study 201 excluded patients with Stage IIB+ disease and the distribution of disease severity was [redacted] with **S**tage IA, IB/IIA and IIB+, respectively.'	This is aligned with the proportions from Study 201 used within the Company's cost-effectiveness model.	The ERG accept the proposed change. Additional clarity regarding the source of data has been added. The changes do not affect any ICERs in the ERG report.

Issue 21 Typo altering meaning of text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 64: 'However, it %BSA data were available by MF-CTCL stage from the registry, they would have been a preferable and more UK relevant source to define the	Please amend as follows: 'However, **if** %BSA data were available by MF-CTCL stage from the registry, they would have been a preferable and more UK relevant source	Updating this small inaccuracy allows this sentence to be interpreted more easily.	This typographical error has been corrected.

model cohort and inform treatment acquisition costs for chlormethine gel.'	to define the model cohort and inform treatment acquisition costs for chlormethine gel.'		

Issue 22 Clarification on recency of PROCLIPI registry data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65: 'The ERG queries whether the PROCLIPI registry reflects historical usage of phototherapy and note that perhaps clinical practice has changed in recent years.'	The Company propose that the ERG remove this statement from the ERG report.	The PROCLIPI registry, used to inform the proportion of patients receiving PUVA versus UVB in the company submission, consists of data from 2015 until October 2019. Therefore, the Company does not believe it reasonable to question whether the PROCLIPI data reflects current clinical practice, given the recency of the data from this registry.	This is not a factual inaccuracy, as the dates were not provided in the company submission. However, the ERG thank the company for the clarity provided here. No amendment required.

Issue 23 Incorrect page number referencing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 70: 'The company selected a total of 7 studies (Table 26, page 75, Document B of the CS) from the sub-set of studies included in the BAD guidelines (see Appendix D.5.1 of the CS) that reported CR and PR data that were deemed potentially relevant for comparison to Study 201.'	Please amend as follows: 'The company selected a total of 7 studies (Table 26, page **76**, Document B of the CS) from the sub-set of studies included in the BAD guidelines **and/or captured by the clinical SLR** (see Appendix D.5.1 of the CS) that reported CR and PR data that were deemed potentially relevant for comparison to Study 201.'	Firstly, the seven phototherapy studies presented in Table 26 were not exclusively from the BAD guidelines; the El Mofty *et al.* (2012) and NCT01686594 studies were not cited in the BAD guidelines but were identified via the clinical SLR. Secondly, phototherapy studies from the BAD guidelines are	These are not factual inaccuracies • Page 75 is correct, as per the latest version of the CS. • Appendix D.5.1 (Table 13: "Summary of clinical comparator studies cited in BAD guidelines", pages 58 to 73) of the company's

		summarised in Table 26 of the CS, which is presented on Page 76, rather than Page 75. Correcting this small inaccuracy will allow this cross reference to accurately represent the location of key information within the CS.	submission includes both the El Mofty *et al.* (2012) and NCT01686594 studies noted here by the company. The ERG's text is an accurate reflection of the information provided in the company submission. No amendments required.

Issue 24 Formulae for calculating median time to relapse post-PR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 74 (Row 1 in Table 20 labelled "Number of patients with response"): ERG preferred approach for PUVA and UVB are reported as '527' and '251' for both Relapse post CR and Relapse post PR	Please amend as follows: Relapse post CR: PUVA '389' and UVB '156' Relapse post PR: PUVA '90' and UVB '64'	The numbers utilised by the ERG for their calculations and reported in Row 1 of Table 20 appear to be the total number of patients reported in Phan et al. rather than the number of patients that experience each response (CR or PR). It is not clear to the Company why the ERG has taken this approach; based on our understanding, the calculation should use the number of patients experiencing a response and these values should therefore be reported in Row 1 of Table 20.'	This is not a factual inaccuracy, but may be misleading. The ERG can clarify that: 1) The ERG's preferred base case analysis applies transition probabilities separately for PUVA and UVB, based on the data from Phan. However, the count data for PUVA and UVB are not used to calculate the transition probabilities 2) These counts are only used to inform the ERG's scenario analysis that used a pooled median time to progression for phototherapy, using N=527 and N=251 to apply the relative weightings PUVA and UVB respectively. An additional footnote has been added to Table 20 to provide further clarity.
Page 74 (footnote of Table 20): 'Using this information, the median	Please amend as follows:	The formulae to calculate the ratios for CR:OR and PR:OR were	These typos have been corrected in the ERG report.

time (months) to relapse post PR is calculated as: $PR_{time\ to\ relapse}$ = 7.5 / ((25/69)*6.48) + ((44/69) = 8.08 months. Since we know that $CR_{time\ to\ relapse}$ = 6.48 the ratio for CR:OR =8.08/7.5=1.077 and for PR:OR = 6.48/7.5=0.864.'	'Using this information, the median time (months) to relapse post PR is calculated as: $PR_{time\ to\ relapse}$ = (**7.5 – (25/69*6.48))*69/44** = 8.08 months. Since we know that $CR_{time\ to\ relapse}$ = 6.48 the ratio for **CR:OR = 6.48/7.5 = 0.864** and for **PR:OR = 8.08/7.5 = 1.077**.'	reported the wrong way around, meaning that these calculations were not aligned with the ERG preferred base case analysis.	We can confirm that these ratios were applied correctly in the economic model, and the text now aligns with the model calculations.

Issue 25 Incorrect table heading

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 (Table 21): 'Initial Skin Burden (SD)'	Please amend as follows: 'Initial Skin Burden ~~(SD)~~'	It is inaccurate to state that the Initial Skin Burden is represented by 'SD'.	This is not a factual inaccuracy, and is consistent with the description provided on page 108 of the company submission. No amendment required

Issue 26 Misreporting of information from the CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76: 'The utilities are similar to those used in the CS for initial skin burden (average IA and IB/IIA: [redacted] and average IIB+:[redacted]), respectively.'	Please amend as follows: 'The utilities are similar to those used in the CS for initial skin burden (average IA and IB/IIA: [redacted] and average IIB+:[redacted]), respectively.'	Misreporting of data from the CS should be corrected.	This is not a factual inaccuracy. The ERG report calculation is based on utilities rounded to 2 decimal places. The ERG accepts that using the unrounded utilities from the model generates an average as described by the company. For clarity, the ERG have updated the numbers to match

			the exact model calculation

Issue 27 Inconsistency in decimal places

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 78: 'The calculated monthly cost for a patient with low (<10% BSA covered) and high (10-80% BSA covered) was £500 and £1487 respectively.'	Please amend as follows: 'The calculated monthly cost for a patient with low (<10% BSA covered) and high (10-80% BSA covered) was £500**.00** and £148**6.91** respectively.'	Elsewhere in the ERG report, two decimal places are used; therefore, these values should be updated to align with this approach.	This is not a factual inaccuracy However, the ERG have made the requested change for consistency.

Issue 28 Appropriateness of the Company's cost for phototherapy in the cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 79: 'The ERG therefore prefer the use of the most recent NHS reference costs for phototherapy to inform the model. The impact is that the company's base case model has over-estimated the treatment acquisition costs of phototherapy.'	Please amend as follows: 'The ERG therefore prefer the use of the most recent NHS reference costs for phototherapy to inform the model. The impact is that the company's base case model ~~has~~ **may have** over-estimated the treatment acquisition costs of phototherapy.'	The Company wish to acknowledge that the approach for costing phototherapy that we have used aligns directly with the approach for costing phototherapy employed by other technology appraisals (e.g. TA596, TA575 and TA574; all published in 2019 and electing to inflate Fonia *et al.* rather than using latest reference costs), for which the respective ERGs agreed this was an appropriate approach. Therefore, the Company consider that based on this precedent it is not clear that direct use of most recent NHS reference costs is most appropriate and hence the	This is not a factual inaccuracy. Up to date NHS reference costs are clearly the most appropriate source of data to populate the economic model. No amendment required.

		statement that the Company model overestimates phototherapy acquisition costs should be phrased as subjective rather than objective accordingly.	

Issue 29 Further treatment beyond phototherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 81: 'The ERG's clinical expert noted that when partial response is achieved on phototherapy, a systemic treatment would often, but not always be considered as an additional treatment. Some patients who have a PR on phototherapy would be satisfied with that progress and would not immediately progress onto further treatment once their course of phototherapy finished. Additionally, it is feasible that some patients achieving only a PR on chlormethine gel would change treatment and consider moving to systemic treatments, rather than remaining on chlormethine gel indefinitely. The net impact of these uncertainties on incremental costs is unclear. The ERG considers the impact of an exploratory scenario analysis that assumes no further treatment	Please amend as follows: 'The ERG's clinical expert noted that when partial response is achieved on phototherapy, a systemic treatment would often, but not always be considered as an additional treatment. Some patients who have a PR on phototherapy would be satisfied with that progress and would not immediately progress onto further treatment once their course of phototherapy finished**, although this contrasts with the CS, where clinical expert opinion suggests that all patients who receive treatment with phototherapy would receive a subsequent treatment, with the exception of those who achieve a CR**. Additionally, it is feasible that some patients achieving only a PR on chlormethine gel **would be satisfied with that progress and would not immediately progress onto further treatment** ~~would change treatment and consider moving to systemic treatments, rather than remaining on chlormethine gel indefinitely~~. The net impact of these uncertainties on incremental costs is unclear. The ERG considers the impact of an	The Company clinical expert opinion sought for the CS was quite clear that all patients who receive treatment with phototherapy would receive a subsequent treatment, with the exception of those who achieve a CR. The Company feels that omitting this context of the potentially contrasting expert opinions has the potential to be misleading. In addition, should an alternative scenario be explored for phototherapy where patients discontinue treatment following a PR, then this scenario should also be explored for chlormethine gel for consistency, unless the ERG report provides a rationale for taking a differing approach for the two therapies in their scenario analysis. Otherwise the wording implied by the ERG suggests that patients may be satisfied with a PR when	This is not a factual inaccuracy. The ERG have clearly outlined the uncertainties surrounding any changes to treatment following a partial response on both phototherapy and chlormethine gel. The scenario analysis provided illustrates the potential impact of one such uncertainty on the ICER and does not form a part of the ERG's preferred base case assumptions. No amendment required.

following PR on phototherapy until progression of skin burden.'	exploratory scenario analysis that assumes no further treatment following PR on phototherapy until progression of skin burden.' **[Additional statement to clarify whether the scenario analysis also adopted this approach for chlormethine gel, or otherwise to justify why the ERG considered it appropriate to apply this assumption to phototherapy only in their scenario analysis]**	receiving phototherapy but would not be satisfied (and may switch to receive systemic treatment) if a PR is achieved on chlormethine gel. Notably, clinical expert opinion informing the CS indicated that patients would always continue treatment until CR (and therefore that PR is not considered 'satisfactory').	

Issue 30 Typo altering meaning of text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 82: 'However, ERG's clinical expert noted that if patients experience grade 3 or 4 adverse events, their treatment would be reviewed prior to recommending discontinuation, and this would require an additional outpatient appoint with a dermatologist.'	Please amend as follows: 'However, ERG's clinical expert noted that if patients experience grade 3 or 4 adverse events, their treatment would be reviewed prior to recommending discontinuation, and this would require an additional outpatient appoint**ment** with a dermatologist.'	Updating this small inaccuracy allows this sentence to be interpreted more easily.	This typographical error has been corrected.

Issue 31 Incorrect page number referencing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 91 (Table 25): 'Alternative utility values (see Table 77 in the CS, page 159-60)'	Please amend as follows: 'Alternative utility values (see Table 7**8** in the CS, page **160-61**)'	This scenario is presented on pages 160–61 in the CS (with the results presented in Table 78). Correcting this small inaccuracy will allow this cross reference to accurately represent the location of	This is not a factual inaccuracy. The cross-reference relates to the source of alternative utility data, which is correct. No amendment required.

		key information within the CS.	

Issue 32 Inconsistency in decimal places

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 91 (Alternative utility values scenario of Table 25): '-£7,005.14'	Please amend as follows: '-£7,005'	Decimal places for costs are not used elsewhere in this table. Therefore, the Company suggest that the approach be aligned to reflect this.	This is not a factual inaccuracy. However, the ERG has amended the text as requested to improve the consistency of the report.

Issue 33 Additional detail required for source of scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 91 (Alternative source of chlormethine gel relapse post-CR TP scenario of Table 25): 'Alternative source of chlormethine gel relapse post-CR TP'	Please amend as follows: 'Alternative source of chlormethine gel relapse post-CR TP **(derived from Kim *et al.* [2003])**'	This additional text provides the reference for the alternative source of the chlormethine gel relapse post-CR TP as specified in the CS (page 161).	This is not a factual inaccuracy. However, the ERG has made the proposed amendment to improve clarity.

Issue 34 Inconsistency in use of '+' signs to indicate positive incremental QALYs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 91 (Model population: early Stage (IA/IIA only) MF-CTCL subgroup analysis in Table 25): '+0.03'	Please amend as follows: '0.03'	'+' signs are not used elsewhere in this table. Therefore, the Company suggest that the approach be aligned to reflect this.	This is not a factual inaccuracy. However, the ERG has added directional signs to incremental costs and QALYs throughout the table to improve clarity

Issue 35 Incorrect calculation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 102 (footnote of Table 27) **AND** page 114 (footnote of Table 30): '[B] Grams per 1%BSA= [redacted]%/100=0.23. %BSA = [redacted]% (Low skin burden) and = [redacted]% (High skin burden).'	Please amend as follows: '[B] Grams per 1%BSA = [redacted]%/100 = 0.23. %BSA = [redacted]% (Low skin burden) and = [redacted]% (High skin burden).'	The calculation for High skin burden is incorrect as reported in the ERG report, as [redacted]% rather than [redacted]%.	The ERG has updated this typo in the report. The ERG has also updated the corresponding scenario analysis results in Tables 28 (scenario 11) and the corresponding scenario applied to the ERG's preferred base case in Table 30. The impact on the ICER in both cases is minimal.

Issue 36 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 106 (Treatment acquisition cost scenarios – Chlormethine gel in Table 27): 'Mean BSA calculated as [redacted] and [redacted] BSA affected for low and high skin burden respectively, based on mean daily dosage of 2.8g as per Study 201 (i.e. [redacted]g and [redacted]g for low and high skin burden respectively)'	Please amend as follows: 'Mean BSA calculated as [redacted] and [redacted] BSA affected for low and high skin burden respectively, based on mean daily dosage of [redacted]g as per Study 201 (i.e. [redacted]g and [redacted]g for low and high skin burden respectively)'	Dosing information from Study 201 is not publicly available and so should be marked as academic in confidence.	This is not a factual inaccuracy. The mean dosage is publicly available from the FDA website. However, the ERG accepts that the calculated dosage for low and high burden might be considered AIC and have marked up accordingly.

Issue 37 Misreporting of information from scenarios based on the ERG's preferred base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 106 (Treatment effectiveness / skin burden transition scenarios of Table 30): '+£25,507'	Please amend as follows: '+£2**4**,507'	Misreporting of data based on scenarios conducted from the ERG's preferred base case should be corrected.	The ERG has corrected this typo in the report. Table 3 in the Executive Summary has also been amended accordingly.

Issue 38 Misreporting of data sources

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 115: 'The ERG is unclear whether %BSA data were available to the company by CTCL stage from the PROCLIPI registry'	Please amend as follows: '%BSA data were not available to the company by CTCL stage from the PROCLIPI registry, at time of CS.'	While the Company recognises it would preferable to derive the %BSA affected by disease stage from PROCLIPI rather than Study 201, these data were not available at the time of CS.	This is not a factual inaccuracy, as the clarity regarding the availability of these data was not provided in the CS. However, the ERG accepts the company's clarification. No amendment required.
Page 115: 'Whilst the ERG's clinical expert considers this to be a reasonable assumption, it is noteworthy that the distribution is not based on any data. It is unclear to the ERG whether such data could have been obtained from the PROCLIPI registry. If this was possible, it would have been a preferred source of data.'	Please amend as follows: '**This assumption in the CS was based on clinical expert opinion and** ~~Whilst~~ the ERG's clinical expert **also** considers this to be a reasonable assumption~~, it is noteworthy that the distribution is not based on any data~~. **Such data were not available to the Company in sufficient granularity from PROCLIPI.** ~~If this was possible, it would have been a preferred source of data~~.'	While data from PROCLIPI provide an indication of the line of treatment for which each therapy is used, data are not granular enough to reliably inform the distribution of treatments patients receive following phototherapy. Therefore, the proportion of patients receiving bexarotene and IFN-α at second line was based on clinical expert opinion.	This is not a factual inaccuracy. However, the ERG accepts the company's clarification in this document. No amendment required.

Issue 39 Misreporting of information from the ERG's preferred base case model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 116 (Figure 5): 'WTP threshold = £20,000 per QALY'	Please amend as follows: 'WTP threshold = £**3**0,000 per QALY'	The Company believes that this figure uses a WTP threshold of £30,000 based on assessing where the dotted line crosses the -0.20 figure on the x-axis.	This typographical error has been corrected.

Issue 40 Typo altering meaning of text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 117: 'Under the ERG's set of preferred assumptions there is a high change that phototherapy is less costly than chlormethine gel overall.'	Please amend as follows: 'Under the ERG's set of preferred assumptions there is a high chan**c**e that phototherapy is less costly than chlormethine gel overall.'	Updating this small inaccuracy allows this sentence to be interpreted more easily.	This typographical error has been corrected.

Issue 41 Misreporting of information from the ERG's preferred base case model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 117 and page 118: 'Under the ERG's preferred analysis there is an 86.6% probability that phototherapy is the most cost-effective use of resources at a willingness to pay of £20,000 per QALY gained.'	Please amend as follows: 'Under the ERG's preferred analysis there is an **87.1**% probability that phototherapy is the most cost-effective use of resources at a willingness to pay of £20,000 per QALY gained.'	The correct probability that phototherapy is the most cost-effective use of resources at a willingness to pay of £20,000 is 87.1% rather than 86.6%. Therefore, this should be corrected in the ERG report.	The ERG have corrected the typo in the report, reporting the probability of cost-effectiveness at £30,000 per QALY.

Issue 42 Inconsistency of reporting in deterministic ICER for the ERG's suggested base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 118: 'The resultant deterministic ICER (~£1.83m per QALY gained) is considered to offer a plausible alternative to the company's base case analysis.'	Please amend as follows: 'The resultant deterministic ICER (£1.83m per QALY gained) is considered to offer a plausible alternative to the company's base case analysis.'	'~' is not used when reporting these deterministic results elsewhere in the ERG report. Therefore, the Company suggest that the approach be aligned to reflect this.	This is not a factual inaccuracy No amendment required.

Issue 43 Typo altering meaning of text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 119: 'The ERG also notes substantial differences in the elicited utility scores across states with differential skin burden, despite published literature indicating that EQ_5D is not sufficiently sensitive to capture changes in skin burden.'	Please amend as follows: 'The ERG also notes substantial differences in the elicited utility scores across states with differential skin burden, despite published literature indicating that EQ-5D is not sufficiently sensitive to capture changes in skin burden.'	Updating this small inaccuracy allows this sentence to be interpreted more easily.	This typographical error has been corrected.

Questions from TR for clinical experts

ID1589: Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL)

*The clinical need for chlormethine gel in consideration of the current treatment available for MF-CTCL, i.e., phototherapy (PUVA/UVB)

- Which patients would be offered chlormethine gel in practice; and why for them chlormethine gel might be offered as opposed to the current treatment available (PUVA/UVB);
- The population of patients would be early stage patients, normally treated with SDT option.
- 3 modalities of SDT for this group of patients
    - Topical
    - Photo
    - Radiotherapy
- None are curative. Very rarely do not see recurrence. Vast majority relapse or achieve PR.
- Used chlormethine/nitrogen mustard until September 11 – in house compounded products – disappeared from market as classed as biologic weapon. A lot of experience historical experience using it, know the value.
- Photo is a standard of care for early stage patients BUT drawbacks:
    - cumulative UV dose determines whether it is appropriate for intermittent long term use, likely they need repeated courses of photo, increase non-melanoma and melanoma skin cancer risk
    - expensive (2x weekly for 12-14 wks) – much longer courses than those treated with psoriasis
    - PUVA more effective than UVB – impact on duration of benefit BUT more carcinogenic (non melanoma skin cancer risks are greater with PUVA)
    - PUVA becoming less available as narrow band UVB as effective for inflammatory skin disorders therefore many skin centres just supplying UVB
    - Access to PUVA has decreased steadily over last 10 years
    - Research on mutational spectrum of MF-CTCL: UV is critical mutagen causing initiation of CTCL, research paper based on 400 cases (submitted under review currently). Anticipate that use of photo (PUVA especially) going to become more problematic for early stage disease for these reasons.

- Company's pivotal trail study 201 only included people with early-stage MF-CTCL, would chlormethine gel be a suitable adjunctive treatment option for advanced stage MF-CTCL and whether response to chlormethine gel is influenced by stage of disease.
- Advanced stage: exhausted multiple lines of treatment, looking for good PR or CR, for some patients looking at transplant options if fit enough

- Patients tend to be elderly with co-morbidities
- Advanced patients can relapse with limited mild skin disease (gradually may deteriorate), some relapse with more advanced disease and systemic involvement.
    - Sometimes CG could be used for limited mild disease – symptomatic treatment, in advanced stage patients

The clinical effectiveness of chlormethine gel in comparison with phototherapy (PUVA and UVB)

- No direct comparative data was available for the clinical effectiveness of chlormethine gel vs. phototherapy (PUVA and UVB), what is the experts' view of the relative effectiveness of chlormethine gel, and the uncertainties associated with the unadjusted comparison undertaken by the company?
- No comparative randomised data to establish CG v photo
- Don't know which one more effective – may not see difference – best guess would be similar patterns of efficacy
- PUVA/UVB may be given to advanced disease stage patients but may have exhausted the lifetime risk
- PUVA response rates ~70% (CR ~ 20-25%)
- Differences in selection will make comparison difficult
- Need to look at quality of photo studies. Until there is an RCT for chlormethine, most data is retrospective and very weak.

- *Are there differences between PUVA and UVB in terms of treatment effect? Is it appropriate to bundle them together to assess phototherapy's relative clinical effectiveness in comparison with chlormethine gel?
- PUVA more powerful form of phototherapy – UVA penetrates more deeply, using psoralens (DNA damaging agent) – quite different from UVB, therefore use PUVA for bulkier (thick plaques) early stage disease in skin
- Comparison to topical agent to UVB would be a better trial, would use for less bulky, early stage disease because PUVA more powerful, greater adverse events, cumulative dose more restricted, deeper penetration deeper response
- No good comparative data between the 2 (based on clinical experience)
- If there is a comparator to the gel, it would be narrow band UVB – 2 groups of patients would be similar (PUVA is for thick, bulky skin disease)
- Plaques are prognostically important on long term survival (T1a v T1b and T2a v T2b)

*The amount of chlormethine gel use and costing of it

Chlormethine gel is supplied in 60g tube, the company calculated the treatment acquisition costs based on median dosage (1.8g per day) and % BSA obtained from study 201 in the model. The ERG preferred mean daily dose (2.8g per day).

For the calculation of cost, clinical advice on the following will be appreciated:

- How long a tube would be expected to last in consideration of its shelf life (2 month), and as such whether there are prescribing limits (and whether such restrictions would mean less gel is applied, and so reducing its effectiveness)?
- How much wastage of a tube of chlormethine gel there would be?
- Are there any other external factors that would affect the amount of chlormethine gel used in practice?
- Thickened skin lesions (plaques) – less response than thinner patches
- Do not apply more to plaques on prescription (patients may apply more) – it is related to %BSA
- How best the cost of chlormethine gel should be calculated considering it is supplied in a 60g tube?
- Is the %BSA for low and high skin burdens from study 201 ([redacted] and [redacted] BSA affected for low and high skin burden, respectively) representative of what's seen in practice and appropriating for costing in the model?
- 10% BSA is the cut-off for low (T1a) and high skin (T2a) burdens, what reported in study 201 were mean values very similar to seen in clinical practice
- Which daily dosage of chlormethine gel, the median daily dosage of 1.8g from Study 201, or the mean daily dosage of 2.8g calculated by the ERG, is likely to be seen in clinical practice?
- Study 201: extremely rigorous to guide patients on amount they applied, patients had to return tubes back to pharmacy to measure amount of product used, measure amount of product used in trial very accurately. If they are providing median dose from study 201 that data should have a lot of support in background (trial accumulated a lot of data on that), whether they correlate that to %BSA per patient, must be based on data from the trial
- No guidance from company but there are techniques to monitor the duration and amount of use in practice
- Expensive product – clinician would have very careful instruction for patients on use (duration and frequency of use), e.g. how they guide steroid use (FTU, 1 index finger would represent X amount of skin), could manage that e.g. do not prescribe tube until old tube brought back (could insist patients do that), could manage in real life
- French study compared to steroids suggested you could apply once a week. There may be patients who get a good response, may get some symptoms but only need to use once a week. Being aware of cost. Could you have a duration of treatment: is it producing meaningful response? N – change treatment. Y – yes but still some symptoms, could reduce to once a week or once a month (maintaining suppression of disease in some parts of skin). Data suggests once daily for 12 months – proportion of patients would stop because of response or due to AEs.
- CG Gel gives good spread – can give small amount and spread well
- Time to response: about 6-8 weeks (2 months) according to the French study– check study 201 time to response

*Costing and distribution of PUVA and UVB phototherapy in practice

The company estimates the monthly administration costs to be **£3,458.52**, as reported in Fonia et al. 2010 and inflated to 2017/18 values. The ERG prefers the use of the most recent NHS reference costs 2017/18 for phototherapy to inform the model. The ERG's preferred approach reduces the phototherapy administration cost from £3,458.52 per month to **£1,093.28** per month.

- What the monthly cost of phototherapy would be, whether the 2017/18 NHS reference costs is an accurate estimate of the cost of phototherapy?
- 8 (PUVA) -12 (TLO1) visits per month for 3-4 months in CTCL
- Reimbursement cost (tariff), staff resource cost (supervision, switching machines on), PUVA (drug cost, not UVB)
- Tariff varies across country – some are reimbursed by day case tariff some are per outpatient tariff
- Tariffs changing as NHS switches to block contracts
- PUVA – patient takes pills 2 hours before (psoralen tablets) UVA – cost has gone up to ??£1000 for 3-4 months' treatment – need to check this, very expensive PUVA
- Based on PUVA – company's may be closer, ERG figure – based on outpatient tariff (may have excluded staff resource and drug cost)

- What proportion of patients with MF-CTCL would receive PUVA vs. UVB phototherapy in practice?
- Depends on local availability – if PUVA not available will be all UVB
- All early stage pts will have photo, many will have repeated courses over a decade
- Photo given 3-4x over decade with meaningful clinical responses
- 2-3x/wk for 12-14 wks for photo – should not base on short duration of treatment (do not use inflammatory regimen – 6-8wks)
- UVB 3x/wk for 12-14wks
- PUVA 2x/wk for 12-14wks
- If <10% skin burden --> UVB
- If >10% skin burden or thickened plaques --> PUVA
- Over a decade, patients will cycle between the 2 (after 250 sessions of PUVA should not give any more due to melanoma/non melanoma skin cancer risks), need to be more careful with PUVA than UVB (patients may go back to UVB as compromise)

- Is it correct that PUVA is used more in practice now than UVB?
- PUVA prescribed to those who have never had it and relapsing frequently
- Hope duration of response better
- Cycle through SDTs over long period – inevitable they will all get photo. Early stage will have UVB and PUVA due to accessibility of both services

- Shift to less PUVA

Progression of underlying disease

- Is it likely that the underlying disease progression of MF-CTCL (including mortality risk) is the same for chlormethine and phototherapy, i.e., independent of treatment?

- Symptomatic control of disease – not a cure. Exceptions are rare. Same comment for photo and gel.
- Will not change course of disease
- Lack of data on whether improvement of skin symptoms correlates to stage of disease
- Those have a good CR/PR tend to have a durable response. For those whose condition is refractory to treatment – the management of the condition is more challenging. – ultimately comes down to biology
- Sometimes use a watch and wait approach eg T1a if patients can accept
- *Would the treatment for topical skin symptoms affect the underlying disease progression? Or the cause of the disease?

- No robust data on this. Both chlormethine gel and phototherapy are not curative. Disease is likely to be biologically pre-set. Patients who present with early stage disease fall into 2 or 3 groups
    - Biologically set – mutations and biology limited/low grade, do not progress (majority)
    - Progress and die of disease (25-28%) – include biology that makes them refractory to SDT (relapse and get PRs), cycle through different therapeutic options
    - Progress – disease becomes very extensive in skin, produce tumours or erythrodema, nodal progression – sometimes present with early stage, others already have late stage disease by the time they present

Progression of skin burdens/progression to 2nd line skin therapy following complete response (CR), partial response (PR), and no response

- Is the progression to 2nd line skin therapy faster post a CR compared to no response or PR? And is this true for both chlormethine gel and phototherapy?

- No studies have used these endpoints
- Do not know if patients who have CR are less likely to progress to 2nd line therapy than if you have a PR.
- No difference between CRs in gel v photo in clinical practice – cannot be confident on this.

- Would the progression following a CR be the same for chlormethine gel and phototherapy?

- Don't know
- Do not have evidence

- Is the progression to 2nd line therapy following a PR on chlormethine gel equal to progression following no response? And is this the same for phototherapy?

- Do not escalate in most early stage patients
- Most early stage relapse with early stage disease – keep going back to topical / photo / radio (ie SDT options)
- Patients with refractory disease – will escalate to bexarotene or peg IFNa or TSEB if very extensive – more concerned here that biology suggests increase risk and go to 2nd line treatment options
- Patients with relapse – retry the initial treatments, as long as getting good meaningful responses
- Relapse: some are early relapse (24 months) some later
- Data: 6% CR for CG (much lower than photo)
- Longer duration of CR for phototherapy – 50% relapsing within 2 years, 50% beyond 2 years. 20% get a CR to photo. No data for CG on CR duration rates.

The proportion of patients that would stay in progressed skin burden state/"progressed from 1st line"

- What proportion of patients who have a relapse in skin symptoms would progress to 2nd line therapy? Do all patients who have a relapse progress to 2nd line therapy?
- For patients whose condition progressed into 2nd line therapy, would some of them obtain a CR by receiving treatments available at this stage (i.e., bexarotene or IFN-a)?
- How long on average do patients remain on second line therapy?
- Most patients refractory to SDTs are those who have progressed – 25-30%, they go on to 2nd line treatment
- Relapse so common in this disease, will respond again to same treatments; relapse is not refractory
- Only refractory get 2nd line
- Not true that relapses will then go to 2nd line
- Need to define refractory vs. relapse

- Limitations to this: irritant dermatitis secondary to gel, cumulative UV dose
- Progressive disease is implying refractory and these patients do progress to 2nd line
- Progressed skin burden on SDT implies refractory
- Will remain on 2nd line therapy for the rest of their life (very rarely may respond and have limited skin disease and can go back to SDTs – but small numbers)
- May still be stage IB and refractory – at higher risk of systemic progression – biological difference drives systemic progression. This is the group of early stage patients who die from their disease. Some may progress slowly over 5 - 10 years.

Distribution of post progression treatments in clinical practice

- For patients whose condition progressed and advanced treatment needed, what proportion of them would be receiving bexarotene or IFN-a, respectively, in the UK clinical practice?

- 25-30% of early stage patients are refractory and progress to 2nd line
- 70-75% cycle between SDTs and responsive to SDT
- Maintenance treatments – prescribed continuously (2nd line with the exception of TSEB which has a 2-5 week course)
- Only those who are refractory would receive this
- 60:40 bex/IFNa or 2:1 – bexarotene is better tolerated (IFN – 1/3 find it difficult to tolerate, problems with accessibility recently)
- Response rates similar
- Then disease becomes more resistant would give TSEB – much more for refractory early stage than standard SDTs
- Half a dozen centres across UK (limited) and very expensive – full dose 5 weeks

If patients have limited skin disease (Low %BSA) and want treatment

- Do use photo, alternatively could use radiotherapy (localised, superficial)
- 2-3 fractions of low dose skin superficial radiotherapy
- Not as dangerous as PUVA – very low energy, very well-tolerated, counselled on secondary malignancies, main issues are for those who have whole skin radiotherapy ie TSEB
- Have multiple course of photo and then whole skin radiotherapy – can develop skin cancers

- Radio only used for isolated areas, not curative
- Extensive therapy – TSEB, arduous, 45 minutes for each of 8 sessions (4 sessions/wk for two weeks – low dose regime or for 5 weeks – full dose), lots of potential complications, very expensive

Questions from TR for clinical experts

ID1589: Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL)

*The clinical need for chlormethine gel in consideration of the current treatment available for MF-CTCL, i.e., phototherapy (PUVA/UVB)

- Which patients would be offered chlormethine gel in practice; and why for them chlormethine gel might be offered as opposed to the current treatment available (PUVA/UVB);
- Phototherapy – time consuming, several times a week for 3-4 months. 1500 treatments over life time. Patients with fair skin in particular have increased risk of other skin malignancies. Responses are typically short lived (months) relapse is frequent
- Topical steroids may be used early in skin disease and have limited efficacy. Literature shows they have an anti inflammatory effect no proven anti CTCL effect. Now looking for creams/gels to allow normal home life without it being interrupted
- Years ago had topical nitrogen mustard solution equivalent to CG but solution – problems with chemotherapy spillage, safety risk in dispensing
- Advantages of CG is that there is no blood monitoring and can be used at home.

- Company's pivotal trail study 201 only included people with early-stage MF-CTCL, would chlormethine gel be a suitable adjunctive treatment option for advanced stage MF-CTCL and whether response to chlormethine gel is influenced by stage of disease.

- Use for early stage lesions – could have localised radiotherapy, but may have e.g. 30 areas, where CG would be more appropriate
- Patients cannot downgrade stage of MF-CTCL. May use CG in advanced disease but in early stage lesions. Use of CG is based on current status of patient rather than overall stage.
- Use systemic treatments for high grade lesions – low grade lesions benefit most from chlormethine gel.

The clinical effectiveness of chlormethine gel in comparison with phototherapy (PUVA and UVB)

- No direct comparative data was available for the clinical effectiveness of chlormethine gel vs. phototherapy (PUVA and UVB), what is the experts' view of the relative effectiveness of chlormethine gel, and the uncertainties associated with the unadjusted comparison undertaken by the company?

- Similar efficacy. CG may get longer clearance as can use it for longer (photo have to stop due to carcinogenic risks)
- Patients relapse quickly after photo as have to come off treatment, could stay on CG for longer, CG has excellent side effect profile main ae is skin drug reaction
- Average treatment length of CG reasonable – shortest 2 months (vary between 2 months or 3 years), an average of 6months would be reasonable for costing

- *Are there differences between PUVA and UVB in terms of treatment effect? Is it appropriate to bundle them together to assess phototherapy's relative clinical effectiveness in comparison with chlormethine gel?

- Psoralens likey to be withdrawn – PUVA more effective for plaques than NB-UVB
- Currently using both so reasonable to combine the two
- Not just cost of treatment, patients have to take time off work etc with phototherapy, travel costs
- Favour PUVA for patients with thicker plaques but not big enough difference in treatment effect to separate out PUVA/UVB

*The amount of chlormethine gel use and costing of it

Chlormethine gel is supplied in 60g tube, the company calculated the treatment acquisition costs based on median dosage (1.8g per day) and % BSA obtained from study 201 in the model. The ERG preferred mean daily dose (2.8g per day).

For the calculation of cost, clinical advice on the following will be appreciated:

- How long a tube would be expected to last in consideration of its shelf life (2 month), and as such whether there are prescribing limits (and whether such restrictions would mean less gel is applied, and so reducing its effectiveness)? 1 tube per month would be reasonable average
- How much wastage of a tube of chlormethine gel there would be? Mostly would expect a tube to be used in 2 months
- Are there any other external factors that would affect the amount of chlormethine gel used in practice? Correlate with body surface area treated
- How best the cost of chlormethine gel should be calculated considering it is supplied in a 60g tube? 1 tube a month
- Is the %BSA for low and high skin burdens from study 201 ([redacted] and [redacted] BSA affected for low and high skin burden, respectively) representative of what's seen in practice and appropriating for costing in the model? IA would be 1 tube every 2 months (BSA<10%) and IB would vary 1-4 tubes month, average for all =~1 month
- That is reasonable, could be a little bit higher (20-40% in the high skin burden) but overall not unreasonable estimates

- Conservative estimates
- Which daily dosage of chlormethine gel, the median daily dosage of 1.8g from Study 201, or the mean daily dosage of 2.8g calculated by the ERG, is likely to be seen in clinical practice?
- Average 60g every 2 months from Lessin trial
- Very few patients would need tube per week
- Reasonable to say maximum of 1 tube/week
- Would be monitoring patients who you would be giving tube to frequently
- With Covid: having a drug that does not need monitoring and could use in own home could be very helpful

*Costing and distribution of PUVA and UVB phototherapy in practice

The company estimates the monthly administration costs to be **£3,458.52**, as reported in Fonia et al. 2010 and inflated to 2017/18 values. The ERG prefers the use of the most recent NHS reference costs 2017/18 for phototherapy to inform the model. The ERG's preferred approach reduces the phototherapy administration cost from £3,458.52 per month to **£1,093.28** per month.

- What the monthly cost of phototherapy would be, whether the 2017/18 NHS reference costs is an accurate estimate of the cost of phototherapy? and
- What proportion of patients with MF-CTCL would receive PUVA vs. UVB phototherapy in practice?
- Is it correct that PUVA is used more in practice now than UVB?

- Would not know about how much it costs – lots of factors that are included in this calculation

Progression of underlying disease

- Is it likely that the underlying disease progression of MF-CTCL (including mortality risk) is the same for chlormethine and phototherapy, i.e., independent of treatment?

- Just treats the topical symptoms would not change the disease stage
- Phototherapy may have an effect on disease stage? No a stage is never down graded and the disease has no cure

- *Would the treatment for topical skin symptoms affect the underlying disease progression? Or the cause of the disease?

Progression of skin burdens/progression to 2nd line skin therapy following complete response (CR), partial response (PR), and no response

- Is the progression to 2nd line skin therapy faster post a CR compared to no response or PR? And is this true for both chlormethine gel and phototherapy?

- Not **more** likely – **as** likely

- Would the progression following a CR be the same for chlormethine gel and phototherapy?

- Could be the same, could have a better response if have a CR
- A CR does not mean the disease is cured, disease waxes and wanes
- CR is < 20% for both treatments, if you have a CR the likelihood of lasting 6-9 months is very low, most relapse within the year

- Is the progression to 2nd line therapy following a PR on chlormethine gel equal to progression following no response? And is this the same for phototherapy?

- The same – relapse from PR same as from CR
- Would stop photo if you have a PR
- Photo cannot be given longer than 12 weeks
- Patients usually treated with multiple consecutive treatments
- Could give CG for 1 year – could come back on treatment in few years time if symptoms comes back

The proportion of patients that would stay in progressed skin burden state/"progressed from 1st line"

- What proportion of patients who have a relapse in skin symptoms would progress to 2nd line therapy? Do all patients who have a relapse progress to 2nd line therapy?
- SDTs can be given at any point throughout duration and stages – not just early stage. It can be adjuvant in later stage.
- For patients whose condition progressed into 2nd line therapy, would some of them obtain a CR by receiving treatments available at this stage (i.e., bexarotene or IFN-a)?

- Could obtain a CR on advanced treatment and revert back to earlier treatments

- How long on average do patients remain on second line therapy?
- Chemo – give 4-6 cycles
- Photophoresis – could give until loss of response
- Time on subsequent systemic treatment could vary according to patient – will not stay on this for life

Distribution of post progression treatments in clinical practice

- For patients whose condition progressed and advanced treatment needed, what proportion of them would be receiving bexarotene or IFN-a, respectively, in the UK clinical practice?

- 50/50 about right

- Stage IA – would not go on to advanced treatment from phototherapy

- Stage IB – once you have had photo, no where else to go, would go to bexaroten as no other treatment options (25% progress to advanced stage, 25% stay in 1b)

Additional Information

- Photo very different treatment modality
- Not an ideal comparison with CG
- Lifeline for patients – a gel could help their symptoms
- At time of covid, could be very helpful
- Benefit is that patient does not need to go to hospital

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

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. Topic background

1.1 Disease background

Non-Hodgkin lymphomas (NHLs) are cancers that develop within the network of vessels in which lymph circulates throughout the body (the lymphatic system) and the glands through which it is filtered (lymph nodes). In NHL, lymphocytes (B- and T-cells) that circulate within the lymphatic system multiply abnormally and then group together in particular locations in the body, for example in the lymph nodes themselves, or outside of these nodes ('extra-nodally').

Primary cutaneous lymphomas are extra-nodal NHLs that only affect the lymphatic cells in the skin, with no extracutaneous disease at the time of diagnosis. Cutaneous lymphomas can affect either the T-cells (cutaneous T-cell lymphoma [CTCL]) or B-cells (cutaneous B-cell lymphoma [CBCL]). CTCLs are the larger group of primary cutaneous lymphomas, accounting for approximately 75–80% of all cases, and represent the second-most common type of extra-nodal NHL. There are a number of sub-types of CTCL, of which mycosis fungoides-type CTCL (MF-CTCL) and Sézary Syndrome (SS; a leukaemic disorder related to MF-CTCL), are the most common.

1.2 Incidence

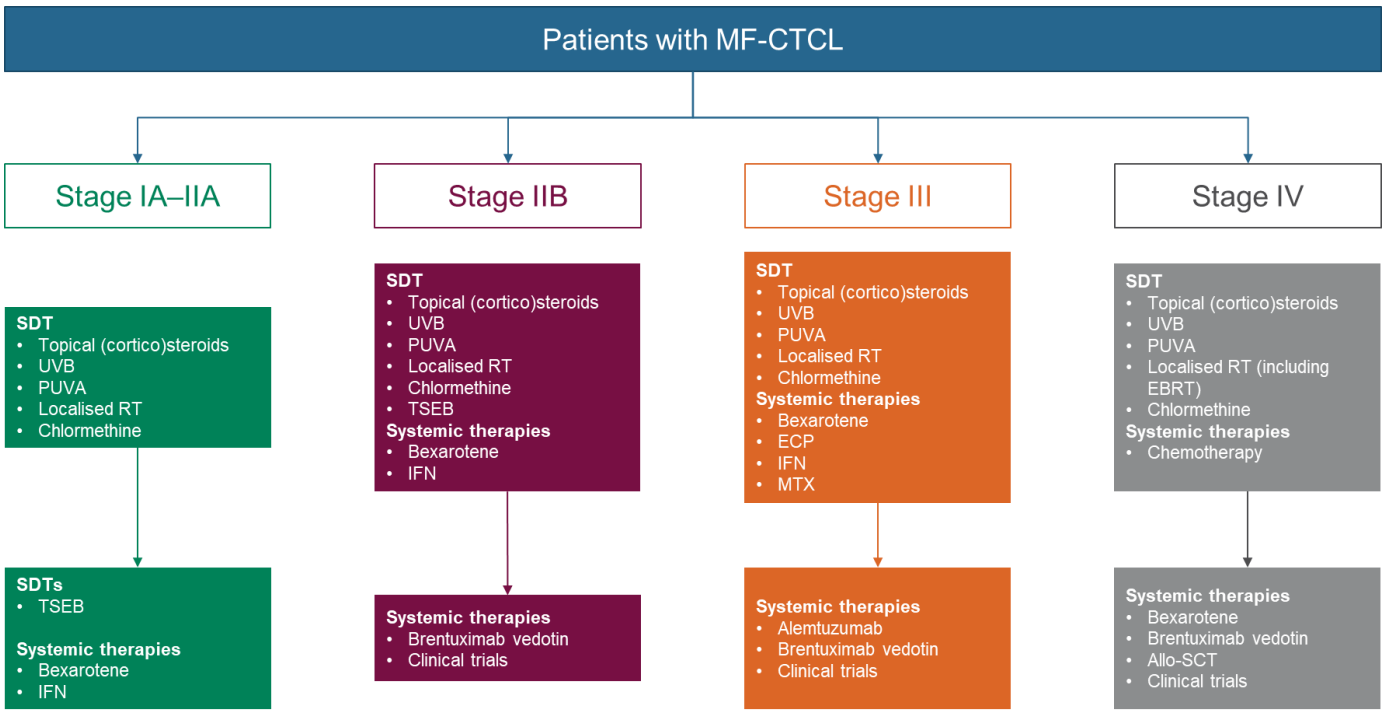
Epidemiological data on CTCL (and MF-CTCL) for England specifically is available from a Public Health England National Cancer Registration and Analysis Services Short Report on registration of CTCL in England between 2009 and 2013. This indicates that there are 182 new diagnoses of MF-CTCL on average in England each year. The age-standardised incidence rate of MF-CTCL was reported as 0.42 and 0.29 per 100,000 for males and females, respectively, meaning that MF-CTCL diagnosis was found to be 1.5 times more common in males than females. MF-CTCL is usually diagnosed in older, adult patients but can affect individuals of all ages; the peak age of incidence of CTCL is 50–74 years of age.

1.3 Chlormethine gel (Ledaga, Recordati Rare Diseases/Helsinn Healthcare SA)

Mechanism	Chlormethine is a cytotoxic, bifunctional DNA alkylating agent which inhibits rapidly proliferating (i.e. malignant cancer) cells by disrupting DNA replication through various mechanisms, such as DNA cross-linking, abnormal base pairing, or nucleic acid depurination. When absorbed into the affected areas of the skin, chlormethine could have a cytotoxic (fatal) effect on the malignant T-cells underlying patches and plaques, thus reducing the appearance of the skin lesions Chlormethine gel was developed to address skin symptoms (patches and plaques) rather than the underlying causes of MF-CTCL.
Marketing authorisation	Chlormethine gel has a marketing authorisation in the UK for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma in adult patients.
Administration and dose	• Topical therapy • Chlormethine gel contains chlormethine hydrochloride at a concentration of 0.016% (w/w) (160 micrograms/gram), equivalent to 0.02% (w/w) chlormethine. • A thin film of chlormethine gel should be applied to affected areas of skin once daily
Indicative list price	£1,000 per 60g tube (excluding VAT; BNF online accessed 13 May 2020)
Other indications	N/A

1.4 Treatment pathway

The aim of treatment for MF-CTCL for all stages is to reduce the visibility and body surface area (BSA) coverage of lesions. Overall, there are two main types of therapy for MF-CTCL: skin directed therapies (SDTs) and systemic therapies. SDTs are used for local treatment of the disease (skin lesions) and are the first choice of treatment in early stage disease, whilst also often being used in combination with systemic therapies in later stage disease. Chlormethine gel would be expected to be used as an option at first line in the treatment of the skin symptoms of MF-CTCL. Referring to the treatment pathway from the British Association of Dermatologists guidelines, chlormethine gel would therefore be expected to be added as an additional SDT option in the first row of treatment options, across all disease stages.



BAD guidelines for the treatment of MF-CTCL. Source: company submission

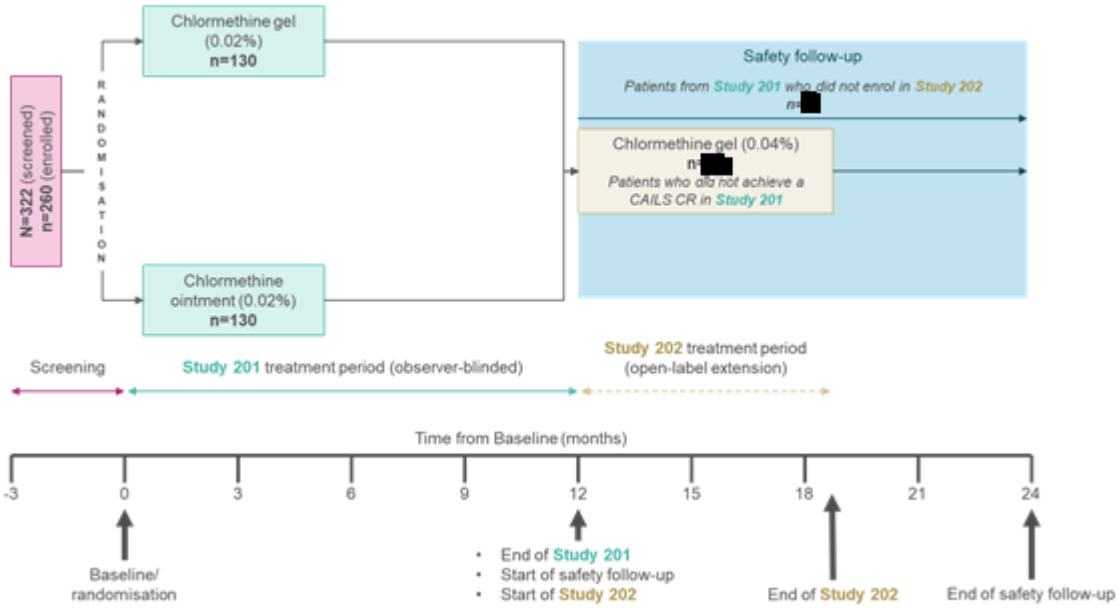
1.5 Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission
Population	Adults with mycosis fungoides-type cutaneous T-cell lymphoma	Adults with mycosis fungoides-type cutaneous T-cell lymphoma
Intervention	Chlormethine gel	Chlormethine gel
Comparator	Skin directed therapies such as photo therapy (PUVA, UVB) and total skin electron beam therapy. In patients for whom the above skin directed therapies are contraindicated: • Established clinical management without chlormethine gel (including systemic therapies such as interferons and retinoids)	Phototherapy (PUVA, UVB) In patients for whom the above skin directed therapies are unsuitable: • Bexarotene • Peginterferon alfa
Outcomes	• Skin symptoms (for example erythema, scaling and pruritus) • Response rates • Duration of response • Adverse effects of treatment • Health-related quality of life • Mortality	• Skin symptoms (measured by CAILS[1]) • Response rates • Duration of response • Adverse effects of treatment • Health-related quality of life • Mortality
Subgroups to be considered	None specified	A cost-effectiveness analysis in the subgroup of patients with early stage MF-CTCL (Stage IA-IIA) only is performed, as this reflects the population of Study 201
[1] CAILS - Composite Assessment of Index Lesion Severity		

1.6 Clinical evidence: Study 201 and Study 202

Study 201 is a phase II observer-blinded randomised controlled trial (RCT) conducted in the USA. It assessed the effectiveness of 0.02% chlormethine gel in comparison with 0.02% chlormethine compounded ointment in people with stage IA-IIA MF-CTCL, and previously treated with SDTs including phototherapy. Data for two intention to treat (ITT) populations are presented: ITT including and excluding New York University (NYU) study centre, due to a protocol violation at this study centre. Patients were treated for 12 months and were then followed for an additional 12 months.

During the 12 month follow-up period, patients who had not achieved a complete response (CR) based on Composite Assessment of Index Lesion Severity (CAILS) could enrol in Study 202, an open label, 7 month trial investigating chlormethine gel (0.04%). The CAILS index is a measure to assess the burden of skin symptoms, based on an assessment of four clinical features (erythema, scaling, plaque elevation and surface area) of individual lesions. The aim of Study 202 was to evaluate the safety and efficacy of daily treatment with topical chlormethine gel (0.04%) in patients with Stage I or IIA MF-CTCL who completed 12 months of treatment with either chlormethine gel or chlormethine ointment in Study 201. Given patients received an unlicensed dose (0.04%) of chlormethine gel, study 202 only provides supportive safety data rather than safety and efficacy data.



Study 201 trial design. Source: company submission

1.7 Key trial results: Study 201, response rates

The primary endpoint of study 201 was the CAILS response rate, defined as a ≥50% improvement from the baseline CAILS index. The secondary endpoints included modified Severity Weighted Assessment Tool (mSWAT) response rate (defined as ≥50% improvement from the baseline mSWAT score), time to confirmed CAILS response, duration of confirmed CAILS response, time to progression based on CAILS score, and extent of cutaneous disease (measured as change in the percentage of total BSA involvement). The mSWAT is another tool used in the assessment of the burden of skin symptoms, and derives scores by weighting the percentage BSA (%BSA) involvement for patches, plaques and tumours, assigning a numerical value to each of these three aspects (1 for patch, 2 for plaques, 3 for tumours).

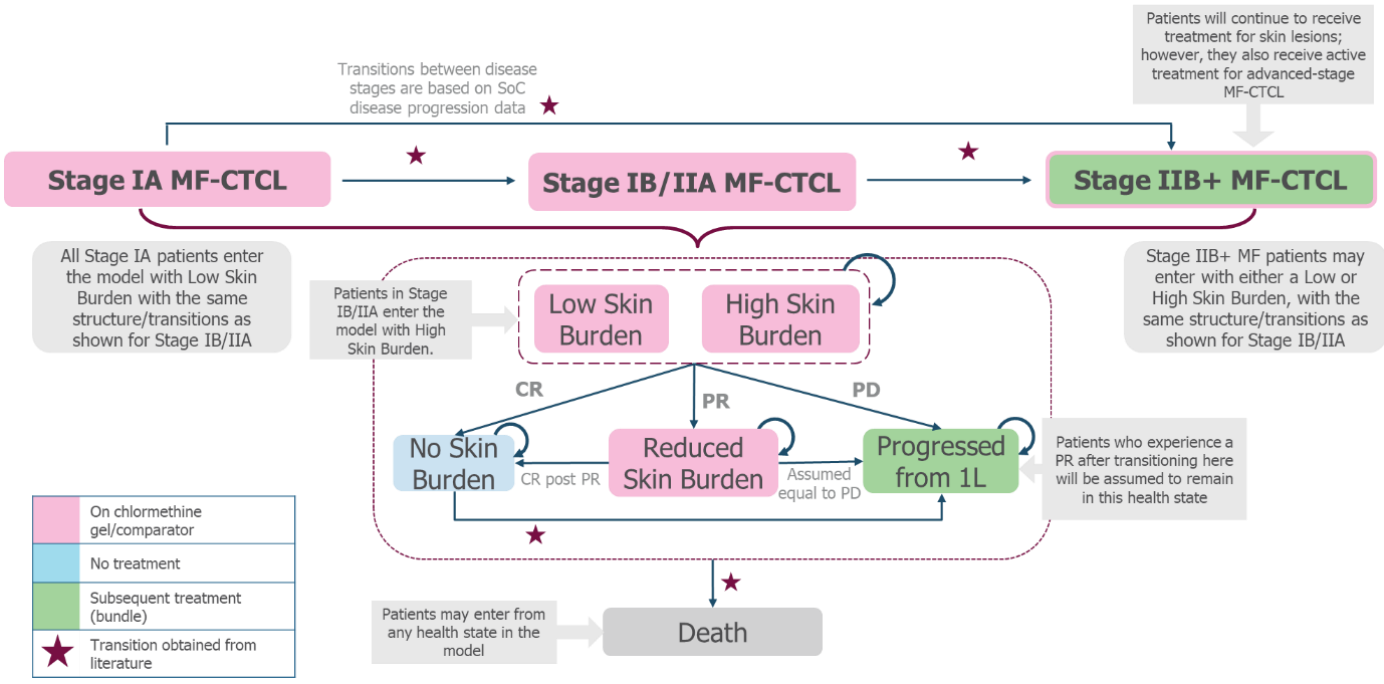
Response n (%)	Study 201			
	CAILS response		mSWAT response	
	ITT including NYU		ITT including NYU	
	Chlormethine gel (n=130)	Chlormethine ointment (n=130)	Chlormethine gel (n=130)	Chlormethine ointment (n=130)
OR	76 (58.5)	62 (47.7)	61 (46.9)	60 (46.2)
CR	18 (13.8)	15 (11.5)	[redacted]	[redacted]
PR	58 (44.6)	47 (36.2)	[redacted]	[redacted]
Non-response	54 (41.5)	68 (52.3)	[redacted]	[redacted]
SD	42 (32.3)	61 (46.9)	[redacted]	[redacted]
PD	5 (3.8)	3 (2.3)	[redacted]	[redacted]
Unevaluable	7 (5.4)	4 (3.1)	[redacted]	[redacted]
Duration of CAILS response (% maintained response) **Week 24** **Week 40**	n=76 [redacted]	n=62 [redacted]	N/A	N/A
Time to progression based on CAILS score (% who do not have ≥25% increase from Baseline CAILS score) **Week 24** **Week 52**	n=130 [redacted]	n=130 [redacted]	N/A	N/A
Abbreviations: CAILS = Composite Assessment of Index Lesion Severity, mSWAT = modified Severity Weighted Assessment Tool, ITT = intention to treat, NYU = New York University, OR = overall response, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease				

CAILS and mSWAT response rates from study 201. Source: Adapted from ERG report, tables 9 and 10

In the full ITT population, the CAILS response rate for chlormethine gel was 58.5% versus 47.7% for chlormethine ointment, with a response ratio of 1.226 (95% CI: 0.974–1.552). The company states that these data suggested that the chlormethine gel formulation was non-inferior to the compounded ointment formulation. Similar findings were reported for the secondary endpoint mSWAT.

1.8 Model structure

The cost-effectiveness model is a state transition (Markov) cohort model evaluating patients across all disease stages of MF-CTCL.



Model structure. Source: company submission.

1.9 Key model assumptions/data sources

Assumptions/data sources	Company	ERG critique and preferred assumptions
Population/ characteristics (%BSA)	PROCLIPI registry (where available); study 201 (age, gender) or the NHS Health Survey for England 2017 (height and weight)	
	Mean %BSA for low and high skin burdens from study 201	Unclear whether the %BSA from study 201 (by disease stage) is representative of what is seen in clinical practice, ICER highly sensitive to changes
Intervention: topical chlormethine gel/dosage	Median daily dosage 1.8 g	Mean daily dosage 2.8g

Assumptions/data sources	Company	ERG critique and preferred assumptions
Comparator/photo-therapy	PUVA/UVB (distribution of usage from PROCLIPI registry)	PUVA/UVB (PROCLIPI may reflect historical usage of phototherapy, clinical practice may have changed in recent years)
Underlying disease progression		
Treatment effect and underlying disease progression	Underlying disease progression is independent of treatment effect	
Transition between MF-CTCL stages	Wernham et al. 2015 (n=86, a single database study)	Company's source may have over-estimated transition between disease stages; Prefer data sourced from Agar et al. 2010 (n=1502, a larger sample of UK patients), suggested slower progression overall
CR and PR rates		
CR	**Chlormethine gel**: study 201 **Phototherapy**: weighted average of available CR and PR rates across 7 identified studies	**Chlormethine gel**: study 201 **Phototherapy**: Phan et al. 2019 for CR and PR rate, applied separately to PUVA and UVB and by MF-CTCL disease stages
PR		

Assumptions/data sources	Company	ERG critique and preferred assumptions
Skin burden transitions/time to progression & subsequent treatment post CR/PR		
Progression following CR/time to progression	Time to progression post a CR equal for chlormethine gel and phototherapy (data sourced from Whittaker et al. 2012) as patients with a CR are modelled to no longer receive treatment and there is no data from study 201 to estimate progression post CR for phototherapy; Patients with CR more likely to relapse and progress to subsequent systemic treatment than those with PR or without response.	Company's assumption may be plausible, but not evidence-based; **Chlormethine gel:** prefer company's scenario analysis using Kim et al. 2003, where progression post CR for an alternative nitrogen mustard treatment sourced, rather than assuming equal to phototherapy **Phototherapy**: prefer Phan et al. 2019, applying separate time to progression for PUVA and UVB; Whittaker et al. 2012 included more patients with advanced disease so may have overestimated the risk of progression to subsequent systemic treatment; also a small sample of patients (n=25) in the study to estimate CR.

Assumptions/data sources	Company	ERG critique and preferred assumptions
Progression following PR/time to progression	**Chlormethine gel:** Time to "progression from 1L" following PR: progression post PR equal to progression following no response, based on expert opinion **Phototherapy:** Time to "progression from 1L" following PR: assumed an equal split of progressive and stable disease based on the EORTC study, with time to progression assumed equal to the maximum treatment duration (i.e. time to initial response)	**Chlormethine gel:** accept company's assumption may be reasonable given the absence of data; note the assumption not evidence based and further uncertainty introduced; **Phototherapy**: prefer Phan et al. 2019, applying separate time to progression for PUVA and UVB
Time spent in "progressed from 1L"	No patients entering this state would observe an improvement in symptoms	A proportion of patients may respond to systemic treatment available (bexarotene or peginterferon alfa) and quality of life improves; company's assumption may have under-estimated utility values assigned; Dalal et al. 2020: suggested CR possible for some patients and return to their initial treatment, e.g. phototherapy.

Assumptions/data sources	Company	ERG critique and preferred assumptions
Distribution of post progression treatments	50% receiving bexarotene and 50% peginterferon alfa	Unclear whether the company's assumption is in line with clinical practice; varying the distribution has a substantial impact on ICER
Resource use and cost	**Phototherapy**: Fonia et al. 2010	**Phototherapy:** most recent NHS reference costs Remove costs of ECP and Methotrexate as advanced treatment, while on phototherapy and for 2 weeks after stopping treatment
Abbreviations: BSA = body surface area, CR = complete response, EORTC = European Organisation of Research and Treatment of Cancer, PR = partial response		

2. Summary of the technical report

2.1 In summary, the technical team considered the following:

Issue 1 Clinical need for chlormethine gel

The population defined in the decision problem is 'adults with mycosis fungoides-type cutaneous T-cell lymphoma'. Study 201 only enrolled patients with early-stage of MF-CTCL (IA to IIA) and assessed the clinical effectiveness of chlormethine gel in comparison with chlormethine ointment, which is no longer used in practice.

Clinical expert opinion indicates that there may be a clinical need for the use of chlormethine gel in adults with MF-CTCL in practice, given the potential side effect associated with repeated courses of phototherapy and burden of administration. Chlormethine gel would be of most use in early stage patients, but may be used in patients with advanced disease but with limited, mild skin symptoms.

Issue 2 **Phototherapy as the comparator in the model**

Study 201 compared 0.02% chlormethine gel to 0.02% chlormethine ointment, which is no longer in use and is not a comparator in the decision problem. The ERG agrees that no other randomised controlled trials relevant to the decision problem involving chlormethine gel have been missed, and concludes that the evidence base is very limited.

No connected network could be formed between study 201 and any of the comparator phototherapy studies identified by the company, as there was not a common comparator. The company used 7 phototherapy studies (3 RCTs retrieved from the systematic literature review, and 4 non-RCTs from the BAD guidelines) to inform a naïve unadjusted comparison between chlormethine gel and phototherapy. The ERG is concerned with the naïve comparison as it does not adjust for any differences in study characteristics and introduces substantial uncertainty to decision making. The technical team agrees that the true clinical effectiveness of chlormethine gel versus phototherapy is unknown.

The technical team would value expert opinion on whether there are differences between PUVA and UVB in terms of treatment effect, and whether it is appropriate to bundle them together to assess phototherapy's relative clinical effectiveness in comparison with chlormethine gel.

Issue 3 **The daily application, dosage, and costing of chlormethine gel**

Chlormethine is indicated for the topical treatment of MF-CTCL in adults, applying daily to affected areas of the skin. The company and ERG have different approaches to calculating the amount of chlormethine gel used per application. The company's preferred base-case analysis calculated treatment acquisition costs based on the median daily dosage (1.8g per day) of chlormethine gel observed and %BSA obtained from study 201. The ERG prefers the mean daily dose (2.8g per day) and considers it more appropriate for calculating chlormethine gel acquisition costs. Chlormethine gel is supplied in a 60g tube, and the amount of gel that is

used and therefore the costs of chlormethine gel are also proportional to the %BSA affected.

Given that chlormethine gel is supplied in a 60g tube with a shelf life of 60 days, a series of factors may have an impact on the amount of gel used daily, the frequency of prescribing, and consequently its costing. Currently it is uncertain how best the cost of chlormethine gel should be calculated.

The technical team seek expert opinion on:

- How long a 60g tube would be expected to last in consideration of its shelf life (60 days once thawed), and as such what would be the considerations for its prescription in practice, in terms of dosage, and potential dosing modifications.
- How much wastage of a tube of chlormethine gel there would be, and whether there are any other external factors that would affect the amount of chlormethine gel used in practice.
- Whether the %BSA for low and high skin burdens from study 201 is representative of what is seen in practice and appropriate for costing in the model.
- How best should the cost of chlormethine gel be calculated considering its package (60g tube) and the above.

Issue 4 Costing and distribution of PUVA/UVB phototherapy

The company estimates the monthly administration costs of phototherapy to be £3,458.52, as reported in Fonia et al. 2010 and inflated to 2017/18 values. The ERG prefers the use of the most recent NHS reference costs 2017/18 for phototherapy to inform the model. The ERG's preferred approach reduces the phototherapy administration cost from £3,458.52 per month to £1,093.28 per month. This leads to a substantial increase in the ICER for chlormethine gel.

The company's base-case model used data from the PROCLIPI registry to estimate the proportion of phototherapy that was PUVA or UVB: [redacted]

was PUVA and [redacted] was UVB. However, the ERG's clinical expert and the BAD guidelines suggest that the use of PUVA is more common in current clinical practice than UVB for the treatment of MF-CTCL. The technical team seek expert opinion on:

- What the monthly cost of phototherapy would be, whether the 2017/18 NHS reference costs is a more appropriate estimate of the cost of phototherapy,
- Have all relevant costs associated with the administration of phototherapy been considered by the company or ERG, and
- What proportion of patients with MF-CTCL would receive PUVA vs. UVB phototherapy in practice.

Issue 5 Underlying disease progression

The company assumes in its model that the underlying disease progression is independent of choice of treatment. The company used a single database study (Wernham et al. 2015) to inform the transition probabilities between different MF-CTCL stages. The ERG prefers a larger study, Agar et al. 2010, of UK patients with MF-CTCL to inform disease progression in the model. Agar et al. 2010 suggests slower disease progression overall (see issue 5 table in section 3 for transition probabilities).

The technical team agrees with the ERG that Agar et al. 2010, which has a larger sample size, is a more robust source to estimate underlying disease stage progression and more representative of the UK clinical setting. However due to the uncertainty in company's assumption that disease progression is independent of treatment, and the limited evidence base to inform this, the resulting ICERs are very uncertain.

Expert opinion is sought on:

- Whether the underlying disease progression is affected by either chlormethine gel or phototherapy.

- Whether the overall slower disease progression identified from Agar et al. 2010 is representative of disease progression seen in UK clinical practice.

Issue 6 **Skin burden transitions/time to progression following CR and PR**

In the chlormethine gel arm of the model, the company assumed that time to relapse following a CR is equal for chlormethine gel and phototherapy, based on data on phototherapy from Whittaker et al. 2012. This is because the transition from "No Skin Burden" (CR) to "Progressed from 1L" was assumed to be treatment independent, and patients who have a CR are assumed to no longer receive treatment. However, the ERG prefers the company's scenario analysis using data from Kim et al. 2003 which reports time to relapse following a CR for an alternative nitrogen mustard treatment to inform the transition probability from 'no skin burden' to 'progressed from 1L'. For progression following a PR, the company also assumed that progression to systemic therapy following a PR on chlormethine gel is equal to progression following no response, based on expert opinion. The ERG accepts that the company's assumption may be reasonable given the absence of data, however it is concerned that this assumption is not evidence-based and introduces further uncertainty in the changes in skin burden over time.

For the phototherapy arm of the model, the company used Whittaker et al. 2012 to inform the transition between "no skin burden" (CR) and "progressed from 1L". The ERG disagrees with the source of the company's transition probabilities, and prefers the use of Phan et al. 2019 calculating differential time to progression following CR and PR for PUVA and UVB by MF-CTCL disease stage. For the time to relapse following PR, the company assumed an equal split of progressive and stable disease based on the EORTC study, with time to progression assumed equal to the maximum treatment duration (i.e. time to initial response). The ERG considers this approach to be unclear and is unsure how these time to progression transitions can be justified. The ERG prefers Phan et

al. 2019 to calculate differential time to progression following PR for PUVA and UVB by MF-CTCL disease stage. For further information please see the table in section 3, issue 6.

Overall, the company's model assumes that patients are more likely to relapse and progress to advanced systemic therapy following a CR, than following a PR or no response, across both arms of the model. The ERG's expert opinion was this may be plausible, but not supported by evidence. The technical team agrees with the ERG and prefers the use of Kim et al. 2003 to estimate time to relapse post CR on chlormethine gel, as this study is larger than Whittaker et al. 2012 and may be more robust. The technical team also prefers Phan et al. 2019 to calculate time to relapse following CR and PR. Phan et al. 2019 is a larger study (a systematic review of 7 studies), whereas Whittaker et al. 2012 is a single centre study that excludes stage IA disease. Phan et al. 2019 also reported time to progression data by type of phototherapy (PUVA/UVB) and by stage of MF-CTCL disease, and so it is possible to apply time to progression by type of phototherapy and by disease stage.

Expert opinion is sought on whether the company's assumptions regarding time to relapse following a CR or PR are in line with what is seen in UK clinical practice. Expert advice would also be valued on which sources of data (Whittaker et al. 2012, the EORTC study 2011 or Phan et al. 2019) for estimating transition probabilities for relapse post CR or PR on phototherapy is more appropriate and representative of UK clinical practice.

Issue 7 Time spent in 'progressed from 1L' health state

The company's model assumes that all patients who have a relapse in skin burden symptoms progress onto subsequent systemic therapy, entering the 'progressed from 1L' health state. On entering the 'progressed from 1L' health state, all patients remain on systemic

treatment (either bexarotene or peginterferon alfa) for their remaining life years.

The ERG considers that the current model structure may over-estimate the costs and QALY losses associated with entering the 'progressed from 1L' state. The ERG highlights evidence from Dalal et al. 2020 which suggests that a CR is feasible for patients with relapsed disease.

The technical team agree with the ERG that it would seem unlikely that all patients who relapse would progress to subsequent systemic treatment, and for those who progressed that they would stay in this health state for their remaining life years.

There may be a mix of "relapse" and "refractory" cases in "progressed from 1L" health state in the model. However, only a small proportion of patients whose condition becomes refractory may need to receive subsequent systemic treatment, as relapse is common for MF-CTCL and those whose skin symptoms relapse could return to their initial SDTs or switch between SDTs.

Clinical advice would be valued on what proportion of patients who have a relapse in skin burden symptoms progress to subsequent systemic therapy, how long on average patients remain on systemic therapy, and whether the subsequent estimates from the ERG on the proportion of the cohort who incur costs and quality of life decrements is representative of UK clinical practice.

Issue 8 Distribution of post progression treatments/subsequent treatment scenarios

The company's model assumes that 50% of patients requiring subsequent systemic treatment for skin burden receive bexarotene (monthly cost: £2,184) and 50% receive peginterferon alfa (monthly cost: £333), with the distribution of treatment based on expert opinion. The ERG notes that the impact of this assumption has a substantial impact on the ICER.

Clinical expert opinion is sought on what proportion of patients whose disease has progressed and requires subsequent treatment would be receiving bexarotene or peginterferon alfa respectively, in UK clinical practice.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The evidence available for assessing the relative clinical effectiveness of chlormethine gel is currently very limited; there is no evidence on head-to-head comparison between chlormethine gel and phototherapy; and the network for indirect treatment comparison could not be constructed given the lack of common comparator
- Evidence for advanced stage patients is based on non-comparative observational studies only
- Lack of evidence in support of some important model assumptions, including:
    - the underlying disease progression is independent of treatment effect
    - patients with CR are more likely to relapse and progress to subsequent systemic treatment than those with PR or without response for both arms, and progression post CR is equal for chlormethine gel and phototherapy
    - progression post PR is equal to progression following no response in the chlormethine gel arm of the model, based on expert opinion
- There is no appropriate patient-reported health-related quality of life (HRQoL) data in the literature to estimate utilities for the model.

2.3 The cost-effectiveness results do not include a commercial arrangement for chlormethine gel.

2.4 The ERG states that it is important to acknowledge that the ICER is based on small differences in QALY gains, and is highly sensitive to different plausible assumptions. The ERG is of the opinion that determining an accurate base-case ICER in light of the data limitations is problematic.

2.5 Chlormethine gel does not meet the end-of-life criteria (see other issues for information).

2.6 No equality issues were identified.

3. Key issues for consideration

Issues marked with a * represent issues which have a substantial impact on the ICER.

Issue 1 – Clinical need for chlormethine gel

Questions for engagement	a) Which MF-CTCL patient population would be offered chlormethine gel rather than phototherapy and why would chlormethine gel be chosen over phototherapy? b) Would chlormethine gel be considered a suitable adjunctive treatment option for patients with advanced stage disease? c) Is response to chlormethine gel influenced by stage of disease?
Background/description of issue	• The population defined in the decision problem is 'adults with mycosis fungoides-type cutaneous T-cell lymphoma' • It is unclear how the patient population that would be eligible for chlormethine gel would be identified in consideration of the current treatment available in the NHS, such as phototherapy, and why its use would be preferred to phototherapy. • Study 201 enrolled patients with early-stage MF-CTCL (stage IA-IIA) only. The study population is narrower than that specified in the NICE final scope and by the marketing authorisation for chlormethine gel. It does not provide evidence for the efficacy and safety of chlormethine gel for patients with advanced stage MF-CTCL. • The company suggests that in advanced MF-CTCL disease (stage IIB, III and IV), chlormethine gel can be used as an adjunct. • The only evidence that has been presented for the advanced disease stage population comes from two real-world data sources presenting efficacy data for chlormethine gel: the French ATU (Temporary Use Authorisation) single-arm study, and the PROVe study, an open-label single arm study located in the USA.
Why this issue is important	Given the current treatment (phototherapy) available for MT-CTCL in practice, it is important to understand the clinical need for chlormethine gel, for which patient population it would be used, and why its use might be preferred over the current treatments available.

	Chlormethine gel is indicated for adult patients with MF-CTCL of all stages, however study 201 only included patients with early-stage disease. The generalisability of the clinical trial evidence to UK clinical practice and whether the drug would be offered as an adjunct to patients with advanced stage disease is an important consideration for decision-making.
Technical team preliminary judgement and rationale	There may be a clinical need for the use of chlormethine gel in adults with MF-CTCL in practice, given the potential side effect associated with repeated courses of phototherapy and burden of administration. As indicated by clinical experts as well, chlormethine gel would be of most use in early stage patients, but may be used in patients with advanced disease but with limited, mild skin symptoms.

Issue 2 - Phototherapy as the comparator in the model

Questions for engagement	a) Are there differences between PUVA and UVB in terms of treatment effect? Is it appropriate to bundle them together to assess the relative clinical effectiveness of phototherapy in comparison with chlormethine gel?
Background/description of issue	• The key clinical effectiveness evidence presented by the company consists of one Phase II non-inferiority trial, study 201, conducted in the USA. It compared 0.02% chlormethine gel (n=130) with 0.02% chlormethine ointment (n=130). • However, the comparator, 0.02% chlormethine ointment, is no longer in use in UK clinical practice and is not one of the comparators specified in the decision problem. • The company identified 7 phototherapy studies to inform a naïve unadjusted comparison with chlormethine gel, including 3 RCTs from the company's SLR, and 4 non-RCTs from the BAD guidelines. The average response rate across these studies was 94% for phototherapy (CR rate 73% and PR rate 21%). • There is substantial heterogeneity across the included phototherapy studies, arising from treatment regimens, patient populations, study design, outcomes definitions and quality of reporting. The company states that the observed weighted average estimates for phototherapy may represent an optimistic assessment of its efficacy and should be taken as highly uncertain. • The company did not conduct an indirect treatment comparison because no connected network between chlormethine gel and other formulations and relevant comparators could be

	formed. A matching-adjusted indirect comparison (MAIC) was considered inappropriate as it was not possible to meet the assumption that there were no unmeasured confounders in any matching procedure, and because it was not possible to adjust for inconsistencies in terms of outcome definitions and treatment regimens. • The ERG considers that the results of the naïve comparison should be interpreted with caution as they were not adjusted for any differences in study characteristics. The ERG agrees with the company that the majority of included studies of phototherapy were poor quality, and response rate estimates are optimistic and highly uncertain. The ERG also agrees that an indirect treatment comparison (anchored or unanchored) was not feasible given the lack of evidence and the heterogeneity of the available evidence.
Why this issue is important	Clinical effectiveness of the intervention under question relative to the standard of care in practice is a key criterion for decision making. It is important to understand whether the treatment effect of PUVA and UVB differs, and whether it is appropriate to bundle them together to assess the relative clinical effectiveness of phototherapy in comparison with chlormethine gel.
Technical team preliminary judgement and rationale	The technical team agrees with the ERG that the evidence base for assessing the relative clinical effectiveness of chlormethine gel is currently very limited, and the true clinical effectiveness of chlormethine gel vs. phototherapy is unknown.

**Issue 3 – The daily application, dosage, and costing of chlormethine gel*

Questions for engagement	a) How much chlormethine gel would be used per application and therefore how long does a 60g tube of chlormethine gel last? b) Are there any limits to how often a tube of chlormethine gel can be prescribed? c) Would there be other considerations for chlormethine gel's prescription in practice, for example, in terms of dosing, dosage, and potential dosing modifications? d) Given the 2-month shelf life of a tube of chlormethine gel, would there likely be any wastage or any other external factors that would affect its use? e) How does the %BSA affected impact the amount of chlormethine gel used? Would there be any other factors that would influence the amount of chlormethine gel used? f) Is the %BSA for low and high skin burdens from study 201 representative of what is seen in clinical practice and appropriate for costing in the model?

	g) How best should the cost of chlormethine gel be calculated considering it is supplied in a 60g tube and the above?
Background/description of issue	• The company and ERG have different approaches to calculating the amount of chlormethine gel used per application. • Chlormethine gel is supplied in a 60g tube with a 60 day (once thawed) expiry date. The amount of gel that is used and therefore the costs of chlormethine gel are proportional to the %BSA affected. • The company's preferred base-case analysis calculates treatment acquisition costs based on the median daily dosage observed in Study 201 (1.8g per day) • However, the ERG considers the mean daily dosage (2.8g per day) to be more appropriate than the median for costing purposes. The ERG notes that this is obtained from the SmPC of Valchlor, chlormethine gel's US brand name, which the company assumes has been sourced from Study 201. The ERG also notes that costs are proportional to percentage body surface area (%BSA) affected, and the distribution of %BSA is likely to be right skewed. Therefore, the ERG infers that therefore the mean daily dosage is substantially higher than the median. • At clarification stage, the company retained the median daily dosage of 1.8g as their preferred base case. However, they provided three alternative methods for calculating daily chlormethine gel usage for use in the economic model. Applying a mean daily dose to costing (company scenario 1) results in doses of [redacted] and [redacted] for low and high skin burden respectively. Therefore, the ERG preferred monthly acquisition costs of chlormethine gel of [redacted] and [redacted] for low and high skin burden respectively. The result on the ICER is substantial. • Clinical expert opinion suggests that the duration of chlormethine gel use may range from a minimum of 2 months to a maximum of 3 years. Expert opinion also indicates that the average amount of chlormethine gel that is used is about 1 tube (60g) every 2 months, with a maximum amount of about 1 tube per week. In addition, clinical experts state that the mean %BSA for low and high skin burdens from study 201 may be conservative estimates, however are reasonably similar to what is observed in clinical practice.
Why this issue is important	Calculating the amount of chlormethine gel that is used per application and how long a tube of chlormethine gel lasts impacts the costs and the ICER. Using the median rather than mean daily dose has a substantial impact on the ICER.

Technical team preliminary judgement and rationale	Given that chlormethine gel is supplied in a 60g tube with a shelf life of 60 days, a series of factors as stated above may have an impact on the amount of gel used daily, the frequency of prescribing, and consequently its costing. Currently it is uncertain how best the cost of chlormethine gel should be calculated.

**Issue 4 – Costing and distribution of PUVA/UVB phototherapy*

Questions for engagement	a) Which estimate of monthly phototherapy administration cost is appropriate for decision making? b) Have all relevant costs associated with the administration of phototherapy been considered by the company or ERG? c) What proportion of patients with MF-CTCL receive PUVA vs. UVB in practice?
Background/description of issue	• The company and the ERG disagree on the cost of the comparator treatment, phototherapy. • The company estimates the monthly administration costs to be £3,458.52, as reported in Fonia et al. 2010 inflated to 2017/18 values. • On further investigation of this source, the ERG notes that the cost is based on an outpatient consultation for providing phototherapy and photo chemotherapy treatment from 2006/07 reported in Fonia et al. and inflated to 2017/18 values for use in the model (inflated costs = £294.20). However, the most recent available NHS reference cost data from 2017/18 show that the current consultant-led outpatient clinic cost for phototherapy and photo chemotherapy (HRG code: JC47Z) is £93. The ERG's clinical expert confirms that phototherapy is delivered in the outpatient setting. • The ERG therefore prefers the use of the most recent NHS reference costs 2017/18 for phototherapy to inform the model. The ERG's preferred approach reduces the phototherapy administration cost from £3,458.52 per month to £1,093.28 per month. This leads to a substantial increase in the ICER for chlormethine gel. • Furthermore, the company's base-case model used data from the PROCLIPI registry to assume [redacted] of phototherapy was PUVA and [redacted] was UVB given for a maximum of 13 weeks. The company assumed that PUVA would be administered 3 times per week and UVB 2-3 times per week, according to BAD guidelines. The company therefore assumed UVB would be delivered on average 2.5 times per week. As the cost of administration is the same

	for PUVA and UVB, the total costs associated with PUVA are higher than UVB in the company's base-case model. • The ERG's clinical expert noted that the number of doses per week for phototherapy treatment is a reasonable reflection of UK practice. However, both the ERG's clinical expert and the BAD guidelines suggest that the use of PUVA is more common in current clinical practice than UVB for the treatment of MF-CTCL. The ERG queries whether the PROCLIPI registry reflects historical usage of phototherapy and that perhaps clinical practice has changed in recent years. • The ERG conducted a scenario analysis varying the distribution of PUVA and UVB.
Why this issue is important	Accurate and reliable comparator phototherapy costs are crucial in order to accurately estimate the cost-effectiveness of chlormethine gel. The cost estimates for phototherapy and the distribution of PUVA and UVB have a substantial impact on the ICER.
Technical team preliminary judgement and rationale	The technical team considers 2017/18 NHS reference costs to be a more appropriate source of costing information if all relevant costs associated with the administration of phototherapy have been included.

Issue 5 – Underlying disease progression

Questions for engagement	a) Is the underlying disease progression affected by either chlormethine gel or phototherapy? b) Is the Agar et al. 2010 study a robust source that is representative of UK clinical practice to estimate underlying disease stage progression?
Background/description of issue	• One of the company's assumptions in their model is that the underlying disease progression is independent of treatment effect, i.e. the choice of treatment has no impact on underlying disease progression in the model. The underlying disease progression is solely informed by literature on MF-CTCL stages. However, the company and ERG prefer different sources of data from the literature to inform disease progression. • The company used a research letter, Wernham et al. 2015, which reports results from a single database study identified by a clinical expert, to inform the transition probabilities between different MF-CTCL stages in the economic model. • The ERG is concerned that the source of data was not assessed for its validity or generalisability against the rates of progression observed in UK clinical practice. • The ERG prefers a larger study, Agar et al. 2010, of UK patients with MF-CTCL to inform disease progression in the model. The ERG identified this study as a more robust source of data. It is based on a large sample of UK patients (1502 patients), it has longer follow up than Wernham et al. 2015, and it is the same source used by the company to populate overall survival by disease stage, maintaining consistency of source. Agar et al. 2010 suggests slower disease stage progression overall and this improves the cost-effectiveness of chlormethine gel compared with the company's base-case assumptions. • The ERG highlights that there is remaining uncertainty as to whether the assumption that disease progression is independent of treatment is observed in clinical practice. The ERG was also not able to alter this assumption due to the limited evidence base. Overall, this results in uncertainties in both the ERG's and the company's ICERs.

<table>
<tr><td></td><td>Alternative sources of transition probabilities for underlying disease progression. The CS used Wernham et al. 2015, and the ERG used Agar et al. 2010. Source: adapted from ERG report, table 18.
<table>
<tr><th>Stage from:</th><th colspan="3">Stage to:</th></tr>
<tr><th></th><th>IA</th><th>IB/IIA</th><th>IIB+</th></tr>
<tr><td>IA</td><td>CS: 0.9952
ERG: 0.9990</td><td>CS: 0.0032
ERG: 0.0010</td><td>CS: 0.0017
ERG: 0.0000</td></tr>
<tr><td>IB/IIA</td><td></td><td>CS: 0.9943
ERG: 0.9984</td><td>CS: 0.0057
ERG: 0.0016</td></tr>
<tr><td>IIB+</td><td></td><td></td><td>CS: 1.0000
ERG: 1.0000</td></tr>
<tr><td colspan="4">Abbreviations: CS = company submission</td></tr>
</table></td></tr>
<tr><td>Why this issue is important</td><td>A slower disease progression affects the cost-effectiveness estimates of chlormethine gel. The assumption that underlying disease progression is independent of treatment generates uncertainties in both the company’s and ERG’s ICERs.</td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>Agar et al. 2010 is a larger study and a more robust source to estimate underlying disease stage progression, and is more representative of the UK clinical setting. However due to the uncertainty in company’s assumption that disease progression is independent of treatment, and the limited evidence base to inform this, the resulting ICERs are very uncertain.</td></tr>
</table>

*Issue 6 - Skin burden transitions/time to progression following CR and PR

Questions for engagement	a) Are the following assumptions reflective of UK clinical practice: i. No matter whether a CR is obtained from chlormethine gel or phototherapy, patients who have a CR are more likely to progress to subsequent systemic therapy than those who have a PR or no response? ii. When patients do progress to systemic therapy following a CR, the time to progression is the same, regardless of whether they received chlormethine gel or phototherapy? iii. Time to progression to subsequent systemic therapy on chlormethine gel is equal following a PR or no response? b) Which sources of data (Whittaker et al. 2012, the EORTC study 2011 or Phan et al. 2019) for estimating time to progression following CR or PR on phototherapy is more appropriate and representative of UK clinical practice?
Background/description of issue	**Assumptions on time to progression across both arms of model** • In the absence of data from study 201, **the company** assumed time to progression following a CR is equal for chlormethine gel and phototherapy, based on data on phototherapy from Whittaker et al. 2012. This is because the transition from "No Skin Burden" (CR) to "Progressed from 1L" was assumed to be treatment independent, and patients who have a CR are modelled to no longer receive treatment before relapse. Therefore, those on phototherapy are more likely to progress onto systemic therapy because of the higher CR rate in this arm of the model. **The ERG's** expert opinion was this may be plausible, but there is no evidence to support the assumption. • **The ERG** also disagrees with the company's source and assumptions. The population in Whittaker et al. 2012 (stage IB-IIA MF-CTCL only) has more advanced disease compared to the PROCLIPI registry or Study 201. The ERG is concerned that this may over-estimate the risk of progression onto systemic treatments. There are also substantial differences in median relapse time across arms of the study, which may be due to the small sample size and not accounting for confounding factors.

	Chlormethine gel arm of model • **Time to progression following CR**: **The company** based their assumptions on Whittaker et al. 2012. **The ERG** prefers the company's scenario analysis using data from Kim et al. 2003 which reports time to progression following a CR for an alternative nitrogen mustard treatment to inform the transition probability from 'no skin burden' to 'progressed from 1L'. Using this source improves the cost effectiveness of chlormethine gel relative to the company's base-case. • **Time to progression following PR**: **The company** assumed that the progression to subsequent systemic therapy following a PR on chlormethine gel is equal to progression following no response, based on expert opinion. **The ERG** accepts that the company's assumption may be reasonable given the absence of data, however it is concerned that this assumption is not evidence-based and introduces further uncertainty in the changes in skin burden over time. • **CR/PR rates (chlormethine gel effectiveness):** **The company** used CR and PR data for chlormethine gel from mSWAT response rates from study 201. Response rates from Study 201 (Stages IA and IB/IIA) were assumed to be transferable to the proportion of the modelled cohort (sourced from the PROCLIPI registry) with Stage IIB+ disease. Whilst noting that the response may differ by disease stage, **the ERG** is unclear how this parameter could be reasonably modified given the current available data. It is also unclear in what direction any biases may affect the ICER. Overall, the ERG accepts that study 201 provides the best available evidence to populate the treatment effectiveness (i.e. response rates) of chlormethine gel. **Phototherapy arm of model** • **Time to progression following CR:** **The company** used data from Whittaker et al. 2012 to inform the transition between "no skin burden" (CR) and "progressed from 1L" in the phototherapy arm of the model. The pooled time to relapse across two arms of the trial comparing PUVA vs. PUVA + bexarotene was 6.48 months. This was based on 25 patients having a CR in the trial. **The ERG** prefers Phan et al. 2019 to calculate differential time to progression following CR

	for PUVA and UVB by MF-CTCL disease stage. This corresponds to the company's argument that time to progression following CR is shorter than following PR. • **Time to progression following PR:** **The company** assumed an equal split of progressive and stable disease based on the EORTC (European Organisation of Research and Treatment of Cancer) study, with time to progression assumed equal to the maximum treatment duration (i.e. time to initial response) **The ERG** considers this approach to be unclear and is unsure how these time to progression transitions can be justified. The ERG prefers Phan et al. 2019 to calculate differential time to progression following PR for PUVA and UVB by MF-CTCL disease stage. • **CR/PR rates (phototherapy effectiveness):** **The company** took a weighted average of available CR and PR rates across 7 different studies identified as being potentially comparable to study 201, obtained from the BAD guidelines. It is assumed that response to phototherapy is not disease stage dependent and that response rates from PUVA and UVB are equal. **The ERG** prefers Phan et al. 2019 for CR and PR rate, applied separately to PUVA and UVB and by MF-CTCL disease stages. Overall, the company's model assumes that the probability of progressing to systemic treatment would be greater in the phototherapy arm because of the higher CR rate. The impact is that the phototherapy arm accumulates greater costs and quality of life decrements compared to chlormethine gel over a lifetime horizon. The impact of the company's base case assumptions and the ERG's alternative assumptions on transition probabilities into the 'progressed from 1L' state are detailed below.

<table>
<tr><td></td><td>Transition to subsequent systemic treatment following a CR and PR on phototherapy, comparing company and ERG alternative assumptions. Source: adapted from ERG report, table 20.
<table>
<tr><th></th><th colspan="3">Relapse post CR</th><th colspan="3">Relapse post PR</th></tr>
<tr><th></th><th>Company preferred approach (Whittaker et al.)</th><th colspan="2">ERG preferred approach (Phan et al.)</th><th>Company preferred approach (Assumption)</th><th colspan="2">ERG preferred approach (Phan et al.)</th></tr>
<tr><th></th><th></th><th>PUVA</th><th>UVB</th><th></th><th>PUVA</th><th>UVB</th></tr>
<tr><td>Number of patients with response</td><td>25</td><td></td><td></td><td>N/A</td><td></td><td></td></tr>
<tr><td>Observed number of events</td><td>18</td><td></td><td></td><td>N/A</td><td></td><td></td></tr>
<tr><td>Median (months)</td><td>6.48</td><td>28.86</td><td>12.87</td><td>N/A</td><td>35.98</td><td>16.05</td></tr>
<tr><td>Rate</td><td>0.107</td><td>0.0240</td><td>0.0538</td><td>N/A</td><td>0.0193</td><td>0.0432</td></tr>
<tr><td>Estimated mean (months)</td><td>9.351</td><td>N/A</td><td></td><td>N/A</td><td>N/A</td><td></td></tr>
<tr><td>Monthly TP</td><td>0.127</td><td>0.0237</td><td>0.0524</td><td>0.01</td><td>0.0191</td><td>0.0423</td></tr>
</table></td></tr>
<tr><td>Why this issue is important</td><td>Time to progression following a response is an important driver of cost-effectiveness and has a substantial impact on the ICER.</td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>The technical team agrees with the ERG and prefers use of Kim et al. 2003 to estimate time to progression post CR on chlormethine gel, as this study is larger than Whittaker et al. 2012 and may be more robust. The technical team also prefers Phan et al. 2019 to calculate time to progression following CR and PR. Phan et al. 2019 is a larger study (a systematic review of 7 studies), whereas Whittaker et al. 2012 is a single centre study with a smaller sample size with patients of stage IA disease excluded. Phan et al. 2019 is also reports time to progression data by type of phototherapy (PUVA/UVB) and by stage of MF-CTCL disease, and so it is possible to apply time to progression by type of phototherapy and by disease stage.</td></tr>
</table>

*Issue 7 – Time spent in 'progressed from 1L' health state

Questions for engagement	a) Is it possible that for patients whose condition relapsed, the relapse would respond to the same initial treatment and patients could switch between skin-directed therapies (SDTs)? And that only in a small proportion of patients the condition would become refractory, therefore requiring subsequent systemic treatments? b) Do all patients who have a relapse in skin burden symptoms progress to subsequent systemic treatment as assumed by the company? If not, what proportion of them would progress to systemic treatment? c) For those who progress to subsequent systemic treatment, how long on average do they remain on it? d) Are the subsequent estimates from the ERG of the proportion of the cohort who incur costs and quality of life decrements representative of UK clinical practice?
Background/description of issue	• The company's model assumes that all patients who have a relapse in skin burden symptoms progress onto subsequent systemic therapy, entering the 'progressed from 1L' health state. Once entering the 'progressed from 1L' health state, all patients remain on the subsequent systemic treatment (either bexarotene or peginterferon alfa) for their remaining life years. • The ERG disagrees with these modelling assumptions. The ERG's clinical expert is of the opinion that some patients who achieve a complete and sufficiently long response to initial treatment may revert to their initial successful treatment should their skin burden relapse. • The ERG also notes that the costs of the subsequent systemic therapies and the quality of life decrements associated with progressive skin burden are incurred for the remainder of the patient's life years in the 'progressed from 1L' health state, regardless of whether there is a response to the subsequent systemic treatment or not. The ERG's clinical expert considers that an adequate response or a complete response would be seen in some patients after receiving the subsequent systemic treatment. • The ERG also highlights evidence from a review (Dalal et al. 2020) that suggests that a complete response is feasible for patients with relapsed disease. Dalal et al. 2020 suggested an average CR of 21% (6 studies) and 64% (4 studies) for bexarotene and peginterferon alfa respectively. The average duration of response was approximately 9 months (data reported

	for bexarotene only). Those who have a CR, mostly those with Stage IA disease, would then have their subsequent treatment discontinued and have an improvement in QoL. • The ERG explored this assumption in a scenario analysis surrounding the company's base-case. Using data from Dalal et al. 2020, the ERG estimates that approximately 97.8% and 98.1% in the chlormethine gel and phototherapy cohorts respectively incur costs and quality of life decrements of progressed disease.
Why this issue is important	The proportion of patients who may relapse and progress into the "progressed from 1L" health state, and the length of time staying in this state have a substantial impact on costs incurred and consequently on the ICER. The company's model structure may over-estimate the proportion of the cohort who progress to systemic treatment, as well as under-estimating the average time to progression. The current model structure may also over-estimate the costs and QALY losses associated with entering the 'progressed from 1L' state. This generates a bias in favour of chlormethine gel due to the greater proportion of the cohort who enter this state in the phototherapy arm of the model under the company's base case assumptions.
Technical team preliminary judgement and rationale	The technical team agree with the ERG that it would seem unlikely that all patients who relapse would progress to subsequent systemic treatment, and for those who progressed that they would stay in this health state for their remaining life years. There may be a mix of "relapse" and "refractory" cases in "progressed from 1L" health state in the model. However, only a small proportion of patients whose condition becomes refractory may need to receive subsequent systemic treatment, as relapse is common for MF-CTCL and those whose skin symptoms relapse could return to their initial SDTs or switch between SDTs.

**Issue 8 – Distribution of post progression treatments/subsequent treatment scenarios*

Questions for engagement	a) For patients whose condition has progressed and systemic treatment is needed, what proportion of them would be receiving bexarotene or peginterferon alfa respectively, in UK clinical practice? b) What proportion of patients would be able to return to their initial treatment or other SDTs after responding to systemic treatment?

	c) What proportion of patients would receive further treatment following a PR on phototherapy or, choose not to receive further treatment immediately once their course of phototherapy finished? d) What other factors relating to treatment switching between SDTs or between systemic treatment and initial SDTs following PR or CR on the two arms should be accounted for in the model?
Background/description of issue	• The company's model assumes that 50% of patients requiring subsequent systemic treatment for skin burden receive bexarotene (monthly cost: £2,184) and 50% receive pegylated peginterferon alfa (monthly cost: £333), with the distribution of treatment based on expert opinion. • The ERG's clinical expert agrees that this is a reasonable assumption. However, the ERG notes that increasing the proportion of patients assumed to receive bexarotene would increase the total cost of progressive disease substantially and improve the cost-effectiveness case for chlormethine gel in the model. • The cost of subsequent systemic treatment in the company's model is applied to the full proportion of the modelled cohort that progress from first line treatment for the remainder of their lives. • The ERG considers this an important limitation of the model structure as it is unreasonable to assume that all patients would be treated with bexarotene or peginterferon alfa for the rest of their lives as some patients would achieve a CR and thus no longer require treatment. Similarly, ineffective treatments would not be continued indefinitely. • The costs of subsequent systemic treatment are also applied in the company's model for the full proportion of the phototherapy cohort who achieve no response or PR. • The ERG's clinical expert noted that when PR is achieved on phototherapy, a systemic treatment would often but not always be considered as an additional treatment. Some patients who have a PR on phototherapy would be satisfied with that progress and would not immediately progress onto further treatment once their course of phototherapy finished. Additionally, it is feasible that some patients achieving only a PR on chlormethine gel would change treatment and consider moving to systemic treatments, rather than remaining on chlormethine gel indefinitely. The net impact of these uncertainties on incremental costs is unclear.

Why this issue is important	The distribution of post progression treatments and the length of time patients remain on treatment is uncertain and have a substantial impact on the ICER.
Technical team preliminary judgement and rationale	The technical team agree with the ERG that, based on clinical expert opinion, a 50:50 split of bexarotene and IFN-a for patients requiring subsequent systemic treatment seems a fair representation of UK clinical practice. However, uncertainties still remain regarding the choice and distribution of subsequent systemic treatment, the switching between SDTs following a PR or relapse, and switching from systemic treatment to SDTs if a CR is achieved.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: ERG's preferred assumptions surrounding company's base case and cumulative impact on the cost-effectiveness estimate

Alteration	ERG's justification	Incremental cost	Incremental QALY	ICER	Cumulative impact of ERG preferred assumptions on the ICER
Company					
Original company base case	–	-£7,000	-0.16	£44,915^	
Updated company base case (post clarification)	Correction of error over-estimating QALY losses associated with adverse events in the chlormethine gel arm of the model.	-£7,005	+0.03	Phototherapy dominated	
^Chlormethine gel vs. phototherapy, ICER in the southwest quadrant of the cost-effectiveness plane (chlormethine gel is less costly and less effective compared with phototherapy)					

Alteration	ERG's justification	Incremental cost	Incremental QALY	ICER	Cumulative impact of ERG preferred assumptions on the ICER
ERG					
Company base case (following ERG correction of minor errors)		-£7,005	+0.0282	Phototherapy dominated	
ERG preferred base case analysis (deterministic)		+£16,372	+0.0089	£1,830,197	
ERG preferred base case analysis (probabilistic)		+£16,160	+0.0062	£2,613,493	
ERG's preferred assumptions: exploratory analyses surrounding company's base case and cumulative					
The use of data from Agar et al. 2010 to determine the progression between CTCL stages in the model	This is more appropriate than data from Wernham et al. 2015 as in the company base-case.	-£8,415	+0.0385	Phototherapy dominated	Phototherapy dominated
Apply general population mortality to those patients with Stage IA	Sourced from Agar et al. 2010 which is large study of UK patients with MF-CTCL. This is more appropriate than applying general population mortality as in the company's base-case.	-£7,449	+0.0289	Phototherapy dominated	Phototherapy dominated

Alteration	ERG's justification	Incremental cost	Incremental QALY	ICER	Cumulative impact of ERG preferred assumptions on the ICER
CR and PR rate for phototherapy: Use data from Phan et al. 2019 applied separately to PUVA and UVB and by CTCL disease stages	The technical team agreed with the ERG amendments. Phan et al. 2019 allows an estimation of response data by phototherapy type and across MF-CTCL disease stages.	-£7,611	+0.0285	Phototherapy dominated	Phototherapy dominated
Time to progression post CR and PR for phototherapy: Apply separate time to progression for PUVA and UVB (Phan et al. 2019) for those on phototherapy	The technical team agreed with the ERG amendments. Phan et al. 2019 allows an estimation of differential time to progression following CR and PR for PUVA and UVB by MF-CTCL disease stage.	-£657	-0.0497	£13,217	£154,249
Time to progression post CR for chlormethine gel: Use data from Kim et al. 2003	The technical team agreed with the ERG amendments and using a study of an alternative nitrogen mustard treatment to estimate time to progression post CR for chlormethine gel.	-£16,413	+0.1413	Phototherapy dominated	Phototherapy dominated

Alteration	ERG's justification	Incremental cost	Incremental QALY	ICER	Cumulative impact of ERG preferred assumptions on the ICER
Chlormethine gel treatment acquisition costs based on mean daily gel usage	Costs should be based on mean rather than median daily dosage.	+£10,711	+0.0282	£380,444	£1,075,201
Use of most up to date NHS reference costs 2017/18 to inform the treatment administration costs associated with phototherapy	Up to date reference costs are more appropriate than the company's approach which used reference costs from 2006/7 as reported in Fonia et al. 2010 inflated to 2017/18 values.	-£2,934	+0.0282	Phototherapy dominated	£1,484,862
Removal of ECP and methotrexate from the advanced treatment bundle while the cohort is receiving phototherapy	The ERG's clinical expert opinion is that these treatments cannot be provided together.	-£7,135	+0.0282	Phototherapy dominated	£1,473,167

Alteration	ERG's justification	Incremental cost	Incremental QALY	ICER	Cumulative impact of ERG preferred assumptions on the ICER
Inclusion of an outpatient consultation with a dermatologist for the management of all grade 3 and 4 adverse events included in the model	The ERG's clinical expert is of the opinion that patients with grade 3 or 4 adverse events would require treatment review prior to recommending discontinuation, which would require an additional outpatient appointment with a dermatologist. This is instead of simply receiving corticosteroid treatment as per the company's base-case.	-£6,938	+0.0282	Phototherapy dominated	£1,480,109
Proportion of cohort in 'progressed from 1L' health state that incur costs of bexarotene and peginterferon alfa and QoL decrements of progressed disease (approximated from CR and duration of response reported in Dalal et al. 2020).	Dalal et al. 2020 provide reasonable estimates rather than the company's base-case assumptions that 100% incur cost and get reduced QoL for all remaining life years.	-£6,679	+0.0273	Phototherapy dominated	£1,830,197

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
The true relative clinical effectiveness of chlormethine gel vs. phototherapy is unknown as only an unadjusted naïve comparison was conducted	Comparative clinical effectiveness of the treatment under question is a key criterion for decision-making.	Substantial uncertainties may be introduced in the model and the likely impact is unknown.
Lack of evidence in support of the assumption that the underlying disease is independent of treatment effect in the economic model	Disease stage transitions in the model are non-treatment specific, and overall disease progression probabilities are obtained from the literature. Alternative assumption may have an impact on not only the modelling of underlying disease progression but also the transition of skin burdens.	Unknown
Utility values generated by the vignette study	The company submission relies on a vignette study for its quality of life outcomes. This is not a preferred NICE methodology. The responses are from clinicians rather than patients, and therefore the accuracy of the responses is uncertain.	Unknown. Clinician proxy responses to the EQ-5D may have led to under or over estimation of the impact of the vignette on quality of life, and therefore the direction and magnitude of bias is unclear.

Table 3: Other issues for information

Issue	Comments
Implementation of company model	The ERG highlighted an error in the company model (relating to application of adverse event disutility) which substantially over-estimated the QALY losses associated with adverse events for chlormethine gel. Correction of these errors changed the ICER so that phototherapy was dominated.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.
End-of-life criteria	Chlormethine gel is not likely to meet the end-of-life criteria which are the following: The treatment provides an extension to life of more than an average of three months compared to current NHS treatment and; The treatment is indicated for patients with short life expectancy, normally a mean life expectancy of less than 24 months; The company has not made a case for end of life.
Stopping rule	The marketing authorisation for chlormethine gel states that treatment should be stopped for any grade of skin ulceration or blistering, or moderately severe or severe dermatitis (e.g. marked skin redness with oedema). The company states that their base-case assumes that dosing and efficacy data are included in the model to account for any treatment discontinuation, temporary pausing of treatment and dose frequency modification due to adverse events, as dosing and efficacy data is derived from study 201.

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Issue date: May 2020

NICE National Institute for Health and Care Excellence

Technical engagement response form

Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

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: **Friday 12th 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	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Recordati Rare Diseases; Helsinn Healthcare SA (Recordati/Helsinn; collectively 'the company')
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Questions for engagement

Responses to the technical engagement questions are presented in the table below. The key assumptions/data sources and results of a revised base case are presented in an Appendix to this document. An updated cost-effectiveness model (which incorporates updated dosing data from Study 201) has also been provided as part of this response. Please note that all new components that have been added to cost-effectiveness model have had their headings highlighted in light pink in the model. Further, one minor error on the "Monitoring & Resource Use" tab has been amended as part of this response. A note has been added next to the two cells affected in red text.

Issue 1: Clinical need for chlormethine gel	
Which MF-CTCL patient population would be offered chlormethine gel rather than phototherapy and why would chlormethine gel be chosen over phototherapy?	As described in the company submission, based on clinical expert opinion, chlormethine gel is anticipated to be used as a treatment option at first line in the treatment of the skin symptoms (patches and plaques) of MF-CTCL across both early (Stage IA–IIA) and advanced stage disease (Stage IIB+).[1] Phototherapy requires patients to attend multiple hospital appointments each week, which is incompatible with an active daily life, and may cause inconvenience and loss of productivity for patients. Further, following phototherapy, patients may be required to cover up for long periods of time to avoid sunlight due to the potential adverse effects of sensitisation with psoralen.[1-3] In contrast, chlormethine gel is suitable for self-application at home, and therefore would reduce the need to attend regular hospital appointments. This would have a substantial benefit for patients in terms of increasing the ability of patients to attend work rather than needing to regularly travel to and wait for hospital appointments, and could also reduce any potential infection risk of attending hospital. Notably, recent recommendations from the European Organisation for Research and Treatment of Cancer (EORTC) state that during the COVID-19 outbreak, phototherapy units have been closed in several centres, and therefore, chlormethine gel is a suitable alternative for patients for whom phototherapy is not available at the current time given the need to avoid hospital visits to reduce the risk of viral transmission.[4] Patients would also not be required to cover up and reduce exposure to sunlight following treatment with chlormethine gel, resolving this inconvenient feature of phototherapy. Chlormethine gel may therefore be chosen over phototherapy when taking into account patient lifestyle factors and ability/willingness to attend multiple hospital appointments. Phototherapy is also known to be associated with secondary malignancies which limit the number of treatments that patients can receive in a lifetime. This secondary malignancy risk precludes phototherapy as a maintenance treatment, and leads to a proportion patients (~5% supported by clinical expert opinion) being contraindicated due to prior melanoma.[1] Further, when considering treatment options. clinicians may need to weigh up the risk to benefit ratio when treating patients with phototherapy as to whether the benefit

	to skin symptoms outweighs the risk of these severe adverse effects.[1, 2, 5, 6] On the other hand, treatment with chlormethine gel is well-tolerated, with no evidence to suggest an increased risk of secondary malignancies, based on evidence from clinical studies (Study 201 and Study 202; as described in Document B of the company submission).[2, 7, 8] Overall, chlormethine gel represents a new additional first line treatment option for the skin symptoms of MF-CTCL in patients across disease stages. Given that MF-CTCL treatment is often based on patient and clinician choice, chlormethine gel would be particularly valuable in patients for whom phototherapy is not a convenient or preferred treatment option, or those for whom phototherapy is not suitable due to a contraindication. Specifically, the former would include patients who cannot or do not wish to regularly attend hospital to receive phototherapy treatment, those who do not wish to experience inconvenience such as covering their body when in sunlight or those for whom the potential benefit of phototherapy may not outweigh the risk of developing secondary malignancies.
Would chlormethine gel be considered a suitable adjunctive treatment option for patients with advanced stage disease?	Chlormethine gel is a skin-directed therapy (SDT) for the treatment of the skin symptoms (patches and plaques) associated with MF-CTCL. Patients can be affected by patches and plaques across both early and advanced stage disease, and clinical expert opinion has suggested that chlormethine gel would be suitable to for use in both early and advanced stage patients (with the exception of erythrodermic disease where >80% BSA is affected), even though Study 201 focusses on patients with Stage IA and Stage IB/IIA patients only.[1, 7] Furthermore, current MF-CTCL treatment guidelines recommend the use of SDTs, including chlormethine, at first line across disease stages.[2] In addition, evidence from the real-world usage of chlormethine gel in the French early-access programme and the PROVe study demonstrates that chlormethine gel is prescribed to patients with advanced stage disease in clinical practice.[9, 10] In early stages of disease, it is anticipated that chlormethine gel would be used as a monotherapy for the treatment of MF-CTCL, with the concomitant use of (cortico)steroids used alongside the gel to manage skin toxicities should these develop. As there is not currently evidence to support the effectiveness of chlormethine gel in delaying or preventing progression of underlying disease, when used in advanced disease stages it is likely that chlormethine gel would be used in combination with systemic therapies that aim to treat the underlying cancer, thereby providing dual treatment of both skin symptoms and underlying disease. As discussed in the company submission, clinical evidence suggests that chlormethine gel is not absorbed systemically, which makes it a suitable option for combination therapy with systemic MF-CTCL treatments, or with other concomitant medicines patients may require.[11, 12]
Is response to chlormethine gel influenced by stage of disease?	Study 201 included patients with Stage IA–IIA disease and subgroup analyses were conducted by stratum (considering Stage IA and Stage IB/IIA patients separately) for the primary endpoint: a ≥50% improvement (i.e. a complete or partial response) in the Composite Assessment of Index Lesion Severity (CAILS) score. In the chlormethine gel arm, in the intention-treat (ITT) population including New York University (NYU), the response rates by CAILS were similar in Stage IA (59.2%) and Stage IB/IIA ([redacted] patients. The same

	pattern was observed in the ITT excluding NYU population, where the CAILS response rates were [redacted] and [redacted] for Stage IA and Stage IB/IIA, respectively.[11] In addition to the data available from Study 201, there are some available data on response rates across disease stages (including for advanced stage patients) receiving chlormethine gel in real-world clinical practice in France. Favourable responses to chlormethine gel (stable disease or a complete or partial response) were achieved in [redacted] of [redacted] Stage IA/IB patients and [redacted] of [redacted] advanced stage patients, demonstrating that response rates were consistent between early and advanced disease.[10, 13] Additional data were also available on the use of chlormethine gel in advanced stage patients from the US based PROVe study, where a response was defined as a ≥50% reduction in pre-enrolment baseline %BSA coverage of lesions.[14] In Stage IA and IB patients at 12 months, [redacted] had responded to treatment with chlormethine gel; in the whole (Stage IA–IV) evaluable patient population at 12 months, the response rate was [redacted] ([redacted]. [14] Overall, available data from Study 201 and real-world practice does not appear to suggest considerable differences in efficacy or effectiveness of chlormethine gel across disease stages, however, it should be noted that use of concomitant therapies was permitted in these real-world settings, with 48% and [redacted] of patients prescribed concomitant therapies in the PROVe study and French ATU programme, respectively. Moreover, the aspect of MF-CTCL disease targeted by chlormethine gel is the skin lesions. However, differential disease stage classification according to the tumour, nodes, metastasis and blood (TNMB) system is not wholly dependent upon differences in skin lesion severity and BSA coverage. Lesion severity and BSA coverage are the 'T' part of the classification (i.e. %BSA coverage and types of lesions; see Tables 3 and 4 in Document B of the company submission); however, lymph node involvement ('N'), metastasis ('M') and blood involvement ('B') also inform disease stage definitions for MF-CTCL. In other words, a patient may be classified as having advanced stage disease due to the presence of clinically abnormal lymph nodes, visceral metastases and/or blood tumour burden, but have the same or similar skin burden ('T' level) to those with early stage disease. Therefore, given that the action of chlormethine gel is targeted at the skin lesion severity ('T') and not the other underlying aspects of the disease that form part of the definitions of disease stages ('N', 'M' or 'B'), skin response to chlormethine gel is expected to be independent of overall disease stage. In the absence of data suggesting otherwise, Recordati/Helsinn therefore considers it reasonable to assume that chlormethine gel would be no less effective in treating the skin symptoms of an advanced stage patient as it would in treating an equivalent burden of skin symptoms in an early stage patient.
Issue 2: Phototherapy as the comparator in the model	
Are there differences between PUVA and UVB in terms of treatment effect? Is it appropriate to bundle them together	As described in the company submission, an SLR was carried out to identify any RCTs of relevance to the decision problem, and a targeted review of studies cited in the BAD guidelines was additionally performed to

to assess the relative clinical effectiveness of phototherapy in comparison with chlormethine gel?	capture any relevant non-RCT evidence. The SLR identified no RCTs that compared PUVA to UVB directly; therefore, there is no robust, head-to-head data on the relative treatment effect of PUVA versus UVB in MF-CTCL. Four RCTs were identified in the SLR that investigated PUVA (none were identified for UVB).[15-18] Further, a number of studies exploring the efficacy of either PUVA or UVB were also identified through a review of the BAD guidelines. However, across the entire evidence base, the majority of studies were judged to be of poor quality, particularly in relation to the factors such as their historical nature, small sample size, study design (e.g. retrospective studies) and limited reporting of patient characteristics; this conclusion is coherent with the overall rating of evidence for phototherapy in the BAD guidelines (ranging from 2- to 2+).[2] As such, there is a paucity of robust data available on the treatment effects of PUVA and UVB individually, or in comparison to one another. Of the studies that were captured in the economic SLR and deemed relevant to the submission, Xia *et al.* (2019) reported individual baseline probabilities of complete remission of 65% (in 7.2 months), and 78% (in 12.3 months) with life year gains of 15.07 and 15.17 for PUVA and narrow band-UVB (NB-UVB), respectively.[19] An additional source of data for the treatment effect of UVB versus PUVA is the Phan *et al*. (2019) systematic review, which was identified by the ERG during the appraisal process for this submission. Phan *et al.* reported complete response (CR) rates of 73.8% and 62.2% for PUVA and NB-UVB, respectively. It is important to note, however, that the studies included in Phan *et al.* were retrospective observational studies – they were not randomised controlled trials and therefore are subject to selection bias in the comparison of PUVA and UVB. Furthermore, the Phan *et al.* (2019) review only included patients with early stage disease only and only included studies in which both PUVA and UVB were administered (in separate cohorts of patients).[20] Therefore, the Phan *et al.* (2019) review represents a restricted selection of the evidence available for these therapies, ignoring all studies on the efficacy of these therapies individually. As highlighted above, Xia *et al.* (2019) modelled UVB to be more effective than PUVA, but Phan *et al.* (2019) finds precisely the opposite; this serves to highlight the uncertainty over the true relative effectiveness of PUVA and UVB. The BAD guidelines support that an assumption of equivalent efficacy of PUVA and UVB is reasonable, stating “There have been no prospective RCTs of narrowband UVB, but a retrospective case series showed it to be as effective as PUVA for treatment of early-stage disease, with no difference in time to relapse”.[2] Given the above, there is considerable uncertainty in the relative efficacy of PUVA versus UVB. Therefore, these treatments were not considered separately in the cost-effectiveness model informing the company submission (although treatment acquisition and administration costs associated with UVB and PUVA individually were taken into account in the cost-effectiveness model and weighted accordingly in order to represent each of these interventions within the data constraints).

	However, Recordati/Helsinn acknowledge the advantages of the Phan *et al.* (2019) study in providing a meta-analysis of response rates across multiple systematically identified evidence sources. The company revised base case included in the appendix of this response does therefore consider the efficacy of UVB and PUVA separately, given the data available from Phan *et al.* (2019), as identified by the ERG.
Issue 3: The daily application, dosage, and costing of chlormethine gel	
How much chlormethine gel would be used per application and therefore how long does a 60g tube of chlormethine gel last?	Recordati/Helsinn would like to note that the amount of chlormethine gel used, and thereby how long a tube will last, will depend not only on the amount used per application, but also the frequency at which the gel is applied. Recordati/Helsinn are aware that whilst the summary of product characteristics (SmPC) for Ledaga® states that once daily dosing is recommended,[21] in real-world clinical practice dosing frequency may deviate from this, with evidence from real-word evidence studies to suggest that a lower frequency of application may likely occur.[9, 22] In the company submission, the median daily dose from the Ledaga® SmPC (and assumed to derive from Study 201) of 1.80 g was used to estimate the amount of gel used in patients with either Low or High skin burden.[23] For updated analyses provided in the clarification response that incorporated a mean rather than a median dose, a mean daily dose of 2.80 g, as reported in the Valchlor® SmPC, was used. This value was also assumed to be based on data from Study 201, though this could not be confirmed at the time of the clarification response.[24] However, during the technical engagement process, further evidence has become available from Study 201 to allow usage to be calculated using direct study individual patient data (IPD) on the number of used tubes returned per follow-up visit, based on the ITT population ([redacted]) – aligning with the efficacy source used in the cost-effectiveness analyses. [redacted]. The IPD has been provided to the ERG and NICE Technical Team as part of this response. Recordati/Helsinn note that the mean/median doses calculated from the IPD differ to that reported in the Valchlor® and Ledaga® SmPCs (respectively);[21, 24] however, as detail on how these values in the SmPCs

	were calculated is unfortunately not available (as this was carried out prior to the transfer of the license for chlormethine gel to Helsinn), the reason for this difference cannot be confirmed at the current time. It appears that the doses presented in the SmPCs were not based on the ITT population but might have been based on the safety set (n=128) and made further adjustments to the included patients.[21, 24] However, as the company's revised mean daily dosage is based on IPD from Study 201 and its derivation is transparent and repeatable, Recordati/Helsinn considers this updated mean daily dosage figure to be the most reliable. Updated dosing figures from the latest data available (i.e. an overall mean daily dose of [redacted] for Low Skin Burden and [redacted] for High Skin Burden]) have been incorporated into the company's revised base case included in the appendix of these responses.
Are there any limits to how often a tube of chlormethine gel can be prescribed?	Recordati/Helsinn is not aware of any limits to the frequency of chlormethine gel prescription and no information regarding this is reported within the SmPC. Further, no overdoses have been reported in the SmPC for chlormethine gel.[21]
Would there be other considerations for chlormethine gel's prescription in practice, for example, in terms of dosing, dosage, and potential dosing modifications?	As discussed above, the frequency of dosing will be an important factor in determining the dosage of chlormethine gel. In real-world practice the dosing frequency of chlormethine gel has been shown to be lower than the daily dosing specified in the Study 201 protocol.[9] For example, in the PROVe study, chlormethine gel was applied once daily in 74.5% of patients, every two days in 37.6% patients, every three days in 16.4% patients, once weekly in 8.7% patients, and daily Monday through Friday in 10.1% of patients (percentages exceed 100% because patients may have had more than one dosing regimen over the course of the study, or may have used different numbers of tubes each month, or both).[9] In a real-world study of usage of chlormethine gel in France the prescribed dosage was variable; however, a once daily dosage was utilised in [redacted] patients, with the majority of patients [redacted] applying chlormethine gel three times weekly.[22] Furthermore, adverse events (AEs), hypersensitivity and pregnancy may also be important considerations. Treatment with chlormethine would be stopped due to AEs including skin ulceration or blistering, or moderately severe or severe dermatitis, or may additionally be stopped due to hypersensitivity to chlormethine or any excipients, or in pregnancy.[21] The use of mean dose data from Study 201 should reflect any impact on usage arising from temporary or permanent discontinuation of chlormethine gel due to AEs. Additionally, as there is a relationship between dosage and BSA coverage of lesions, it is likely that the dosage would decrease as patients' %BSA coverage decreased following response to treatment.
Given the 2-month shelf life of a tube of chlormethine gel, would there likely be any wastage or any other external factors that would affect its use?	Clinical expert feedback sought for the company submission indicated that a Stage IA patient would use a minimum of 6 tubes per year (as a tube of chlormethine gel has a shelf life of 60 days once defrosted). Therefore, the cost-effectiveness model used this consumption as a minimum value for all patients, even if a patient was calculated as needing fewer than 6 tubes worth of gel annually (note: in practice, this adjustment was only required to be implemented when applying the median dosing approach described

	above in the company original base case submitted in Document B). This approach implicitly takes wastage into account. Other external factors that may influence the use of chlormethine gel are its storage, as the gel should be refrigerated and used within 30 minutes once taken out of the refrigerator.[21] Therefore, if patients do not comply to these storage requirements, the shelf life of chlormethine gel may be affected and therefore patients may require more than the predicted amount of tubes in a given year.
How does the %BSA affected impact the amount of chlormethine gel used? Would there be any other factors that would influence the amount of chlormethine gel used?	As chlormethine gel is a topical treatment that should only be applied to affected areas of the skin, the usage of chlormethine gel would be correlated to the overall BSA coverage of lesions. Based on data from Study 201 (see earlier response to Issue 3), there is a general linear trend between %BSA affected and the mean dose per application, with an increase in %BSA affected accompanied by an increase in daily dose. Chlormethine gel usage would therefore also be expected to decrease as a patient's %BSA lesion coverage decreased in response to successful treatment. The relationship between %BSA and dosing of chlormethine gel has been accounted for in the economic model by assuming a different daily dose for Low and High Skin Burden patients. Furthermore, applying a mean dose calculated based on treatment usage across the Study 201 duration should incorporate any impact of treatment response on dose utilised by patients over the course of the study. Recordati/Helsinn is not aware of further factors that would influence the amount of gel used, other than those discussed above.
Is the %BSA for low and high skin burdens from study 201 representative of what is seen in clinical practice and appropriate for costing in the model?	Individual baseline patient %BSA coverage from the PROCLIPI registry are not currently available for use in the model, hence there is a lack of data on the %BSA that is seen in UK clinical practice. In the company submission, patients were defined as either Low or High Skin Burden within each disease stage category in the model, based on the TNMB classification guidelines and proportions from the PROCLIPI registry. The Low/High distinction was based on the %BSA affected: Low = <10%; High = 10–80% BSA. Patients with >80% BSA would be classed as erythrodermic and are excluded from the model based on clinical feedback which indicates that erythrodermic patients would not be considered for treatment with chlormethine gel.[25, 26] Skin burden category at model entry by disease stage was based on the TNMB classification system, according to which Stage IA patients have <10% BSA affected (and hence were assumed to have Low Skin Burden at model entry), Stage IB patients have at least 10% BSA affected, and patients in Stage IIB+ can have either <10% or at least 10% BSA affected. Based on data from PROCLIPI, the majority of Stage IIA patients ([redacted]) have at least 10% BSA affected, and therefore Stage IB/IIA patients were all assumed to have High Skin Burden at model entry given that this reflects the skin burden of all Stage IB and a majority of Stage IIA patients.[27] This is also a conservative assumption with respect to the assumed skin burden of patients, as the proportion patients with Stage IB/IIA disease assumed to have High Skin Burden (and therefore the cost of chlormethine gel in this group) is therefore

	overestimated. Patients in Stage IIB–IV were assumed to consist of a combination of patients with Low Skin Burden ([redacted] low, [redacted] high based on data from the PROCLIPI registry).[27] These skin burden category assumptions were validated by clinical expert opinion, and were based on robust sources of data which are relevant to UK clinical practice, including the BAD guidelines and the PROCLIPI registry.[2, 26, 28] In summary, in the absence of data from real-life clinical practice regarding baseline BSA for patients with MF-CTCL, Recordati/Helsinn feels that the approach taken with regards to skin burden is appropriate as it utilises objective definitions specified in UK-specific treatment guidelines and makes use of UK PROCLIPI data where these are available.
How best should the cost of chlormethine gel be calculated considering it is supplied in a 60g tube and the above?	Overall, Recordati/Helsinn believes that the approach taken within the revised base case is the most appropriate for estimating the cost of chlormethine gel, given the available data to inform these estimates. In summary, this approach involves utilising individual patient dosing data from Study 201 to calculate a mean daily dose for chlormethine gel for patients with Low Skin Burden ([redacted]) and High Skin Burden ([redacted] respectively. This aligns with the ERGs preference to use the mean over the median in dosing calculations and takes into account that chlormethine gel, as a topical treatment, would likely be associated with higher consumption in patients with High Skin Burden and lower consumption in patients with Low Skin Burden. Further, the proportion of patients with Low and High Skin Burden (by Stage) was informed by definitions in published guidelines and data from the PROCLIPI registry, therefore reflecting UK clinical practice.[28] In addition, use of the mean dosing data from Study 201 ensures that the impact of treatment response and adverse events on the amount of chlormethine gel used (e.g. patients using less gel if their skin symptoms improve over time or they discontinue due to AEs) is also considered. In the revised base case, as per the original base case, chlormethine gel is assumed to be applied once daily as per the SmPC and Study 201, though real-world evidence sources suggesting that application frequency may be less often in clinical practice.[7, 9, 10, 21] Lastly, given that a tube of chlormethine gel has a shelf life of 60 days (and clinical expert opinion indicated that a minimum of 6 tubes per year would therefore be used), the dosing calculations ensure that patients are never considered to have a consumption of less than 6 tubes per year i.e. wastage is implicitly included.[1, 21, 29]
Issue 4: Costing and distribution of PUVA/UVB phototherapy	
Which estimate of monthly phototherapy administration cost is appropriate for decision making?	Recordati/Helsinn acknowledge that there is uncertainty regarding the most appropriate cost to use for phototherapy in the cost-effectiveness model, given a lack of transparency in the constituent costs included in the costs utilised in the company base case, and that chosen by the ERG. Namely, in the company submission, Fonia *et al.* (2010) was used and inflated to the current cost year from 2010, resulting in a cost of £294.20. This source was considered appropriate as it has been used in several

	NICE technology appraisals for psoriasis (TA475, TA511, TA575 and TA442) as the source of phototherapy costs (alongside other supportive care treatments for psoriasis).[30-33] This cost was assumed to include the cost of psoralen and the administration of the phototherapy procedure itself although this is not explicitly stated as being the case in the previous appraisals or Fonia *et al.* publication.[34] The ERG preferred the use of the NHS reference cost from 2017/18 for a consultant led outpatient clinic cost for phototherapy and photo chemotherapy (HRG code: JC47Z; £93). The ERG commented that the Fonia *et al.* (2010) source also used NHS reference costs for phototherapy, and that inflating an old reference cost is less appropriate than using recent NHS reference costs. Whilst Recordati/Helsinn agrees with this, it is nevertheless still unclear whether the NHS reference costs for phototherapy includes both the administration of phototherapy and the cost of psoralen. Recordati/Helsinn agrees that the use of NHS reference costs aligns with the NICE reference case, and that using recent NHS reference costs is preferable to inflating old reference costs. We have therefore updated the cost of phototherapy in the revised base case. Given that MF-CTCL is a cutaneous malignancy, Recordati/Helsinn have taken the approach of deriving the cost of phototherapy from the mean of the dermatology and oncology costs for a consultant led outpatient clinic cost for phototherapy and photo chemotherapy (HRG codes: JC47Z, service code 300 [dermatology] and 800 [clinical oncology]; £97.63), in contrast to the ERG's value that related to a dermatology clinic cost only. As it is unclear whether the NHS reference costs include the cost of psoralen, Recordati/Helsinn notes that this may still represent an underestimate of the cost of phototherapy.
Have all relevant costs associated with the administration of phototherapy been considered by the company or ERG?	As per the response above, there is uncertainty as to the costs included in the NHS reference costs, particularly with regards to whether the cost of psoralen is included or not. Without further insight into the constituent costs contributing to the total reported in the NHS reference costs, this uncertainty cannot be fully resolved. However, in response to this question specifically, Recordati/Helsinn considers that all costs relevant to the *administration* of phototherapy have been captured. Clinical feedback sought by the ERG supports the fact that phototherapy is an outpatient procedure, and therefore the use of the NHS reference cost for a consultant led outpatient clinic cost for phototherapy and photo chemotherapy would capture the relevant administration costs to be considered. As above, Recordati/Helsinn considers that the outpatient clinic cost should reflect an average of dermatology and oncology clinics, rather than dermatology alone.
What proportion of patients with MF-CTCL receive PUVA vs. UVB in practice?	The phototherapy comparator in the model was assumed to comprise a proportion of patients ([redacted]) receiving PUVA and a proportion of patients ([redacted]) receiving UVB, with the proportional split based on data from the PROCLIPI registry (across all disease stages), a recent source of data which is based on UK clinical practice.[28] The ERG highlighted concerns in the ERG report as to the relevance and appropriateness of the PROCLIPI registry data to support this, stating, 'The ERG queries whether the PROCLIPI registry reflects historical usage of phototherapy and note that perhaps clinical practice has

	changed in recent years' (page 65 of the ERG report). However, the PROCLIPI registry consists of data from 2015 until October 2019. Therefore, Recordati/Helsinn considers that the PROCLIPI data reflects current clinical practice, given the recency of the data from this registry, and therefore does not agree that the registry may only reflect historical usage. On the contrary, as a formal registry that includes six UK centres, Recordati/Helsinn consider the PROCLIPI registry to be the best available source and that derivation of the proportions from the PROCLIPI registry represents the most evidence-based, accurate and appropriate approach to sourcing these proportions for use in the cost-effectiveness model.
Issue 5: Underlying disease progression	
Is the underlying disease progression affected by either chlormethine gel or phototherapy?	Chlormethine gel and phototherapy are used to treat local disease (i.e. skin patches and plaques) rather than targeting cancer cell dissemination. The evidence base is therefore focused on outcomes relating to skin response rather than impact on disease stage progression. Study 201 did not evaluate the impact of chlormethine gel on disease stage progression. Whilst further research may elucidate a role for treatment of skin symptoms in delaying or preventing progression of the underlying cancer to more advanced disease stages, there is currently a lack of evidence to support such benefits. Clinical expert feedback sought by Recordati/Helsinn indicated that, in practice, patients would not be considered to have achieved regressed disease stage even if their skin symptoms improved.[1]
Is the Agar et al. 2010 study a robust source that is representative of UK clinical practice to estimate underlying disease stage progression?	Data from Agar *et al.* (2010) were not originally considered for the company cost-effectiveness model because the data on progression only provides data on what disease stage patients are progressing from but does not provide data on what disease stage patients are progressing to.[35] Therefore, the use of these data requires the assumption that all Stage IA patients are progressing to Stage IB/IIA and all Stage IB/IIA patients are progressing to Stage IIB+.[35] However, this may not be the case (e.g. patients progressing from Stage IA to Stage IIB+, or patients at Stage IB progressing to Stage IIA, rather than to advanced stages, which is a transition that is seen in the original company source: Wernham *et al.* [2015]).[36] However, Recordati/Helsinn accept that progressions beyond the subsequent disease stage would be unlikely in a 1-month time frame. Further, Recordati/Helsinn agrees that Agar *et al.* may be a more appropriate source than Wernham *et al.* due to its larger sample size, longer follow-up and the fact that utilising these data mean that the source for progression and disease-specific mortality would be consistent in the cost-effectiveness model.[35, 36] Given the above, the company's revised base case presented in the appendix to this response uses Agar *et al.* (2010) for underlying disease stage progression rather than Wernham *et al.* (2015).[35, 36]
Issue 6: Skin burden transitions/time to progression following CR and PR	
Are the following assumptions reflective of UK clinical practice:	**Response to question on whether the stated assumptions are reflective of UK clinical practice**

- *No matter whether a CR is obtained from chlormethine gel or phototherapy, patients who have a CR are more likely to progress to subsequent systemic therapy than those who have a PR or no response?* - *When patients do progress to systemic therapy following a CR, the time to progression is the same, regardless of whether they received chlormethine gel or phototherapy?* - *Time to progression to subsequent systemic therapy on chlormethine gel is equal following a PR or no response?*	No matter whether a CR is obtained from chlormethine gel or phototherapy, patients who have a CR are more likely to progress to subsequent systemic therapy than those who have a PR or no response. Patients who achieve a CR would stop active treatment with their SDT. In contrast, patients who achieve PR or have not yet achieved a response would continue treatment with their SDT. Given this context, patients may be more likely to relapse following a CR than a PR or no response. However, this relapse may not necessarily lead to a progression to a subsequent systemic therapy as patient may instead return to treatment with their SDT where this is possible. Please see the response to Issue 8 for further discussion of subsequent treatments following relapse. **When patients do progress to systemic therapy following a CR, the time to progression is the same, regardless of whether they received chlormethine gel or phototherapy** There are no head-to-head RCTs that provide a robust evidence base for comparing relative duration of CR to chlormethine gel and phototherapy. In addition, analysis of reported durations of CR for phototherapy from the literature is complicated by the fact that a number of studies apply maintenance phototherapy, resulting in continued treatment with phototherapy beyond that recommended in the BAD guidelines and used in UK clinical practice. **Time to progression to subsequent systemic therapy on chlormethine gel is equal following a PR or no response** As a clarification, Recordati/Helsinn would like to highlight that the original assumption in the company cost-effectiveness model was that time to progression to systemic therapy on chlormethine gel post-PR is equal to the time to progression for patients for whom a response has not yet been achieved (as opposed to those who have been actively determined to have had “no response”). Patients in the initial skin burden health state represent patients for whom a response has not yet been achieved (but may potentially still be achieved in time), which is a slight distinction from obtaining a result of “no response”. There is a paucity of data to confirm this assumption. On balance, given that both patients in the initial skin burden health states and patients who have achieved PR would continue to receive chlormethine gel, we consider it likely that time to relapse for patients who have had a level of response to this therapy (i.e. achieved PR) might be expected be longer than for patients who have not yet achieved a response. As such, the assumption that time to progression post-PR is equal to time to progression for patients who have not yet had a response is likely not fully reflective of clinical practice; it represents a conservative assumption that potentially overestimates the rate of relapse post-PR for chlormethine gel. **Updated approach to modelling of relapse rates for the revised base case**

	In considering these questions alongside the content of the Technical Engagement Report, including the ERG's preferred assumptions, Recordati/Helsinn has provided a revised base case (see Appendix). Explanation for the revisions to data sources and assumptions regarding relapse rates in the revised base case is provided below, categorised by the relevant transitions considered in the cost-effectiveness model. Chlormethine gel - relapse post-CR (CR to Progressed from 1L) In the company submission, the transition from No Skin Burden to Progressed from 1L was treatment independent, as patients are no longer receiving treatment in this health state (this assumption was validated by clinical expert opinion). Data from Study 201 were not used to inform this transition due to the fact that, by definition of the trial outcome, patients with progressive disease in Study 201 could not have had a previous confirmed CR i.e. patients could not go from having No Skin Burden to progressive disease. Therefore, data from Whittaker *et al.* (an RCT of PUVA alone versus PUVA plus bexarotene in Stage IB/IIA MF-CTCL patients) were used to inform this transition in the model. Data from both treatment arms was used due to the treatment-independent nature of this transition and to therefore maximise sample size. Furthermore, data were pooled across disease stages. However, the ERG preferred approach for this transition was to use separate sources for chlormethine gel and phototherapy, choosing Kim *et al.* (2003) as the source for this transition for chlormethine gel. This was a trial investigating topical nitrogen mustard (chlormethine) largely in early stage patients. As per the approach in the company submission, data were pooled across disease stages. Recordati/Helsinn have adopted this approach in the revised base case. However, IPD from Study 201 used in the calculation of relapse post-PR for the revised base case (see below) indicate that no patients experienced PD following CR during the 12-month follow-up, suggesting that use of Kim *et al.* (2003) may overestimate rate of relapse following a CR with chlormethine gel. Chlormethine gel - relapse post-PR (PR to Progressed from 1L) In the company submission, this transition probability for chlormethine gel was assumed to be the same as the transition to Progressed from 1L from the Low/High Skin Burden health states respectively, based on expert clinical opinion. The reason these data were not available from Study 201 was due to the fact that, by the definition of the progressive disease outcome in Study 201, patients with progressive disease could not have had a previous confirmed CR or PR. Hence, external data were sought. This was a conservative assumption with regards to relapse rates as it would be expected that patients who had previously had a PR would be less likely to relapse compared to those who have never had a PR. With regards to the technical engagement question regarding whether time to progression to subsequent systemic therapy on chlormethine gel is equal following a PR or no response, please see the above response. There is a paucity of data to confirm this assumption; however, on balance, given that both patients in the initial skin burden health states and patients who have achieved PR would continue to

	receive chlormethine gel, we consider it likely that time to relapse for patients who have had a level of response to this therapy (i.e. achieved PR) might be expected be longer than for patients who have not yet achieved a response. As such, the assumption is likely not fully reflective of clinical practice; it represents a conservative assumption that potentially overestimates the rate of relapse post-PR for chlormethine gel. Given this, Recordati/Helsinn have revisited this transition within the cost-effectiveness model to determine whether a data-based approach to inform this transition probability is possible. In the revised base case, IPD from Study 201 (assuming an alternative definition for progressive disease) have been utilised. Specifically, this transition is now informed by patients from Study 201 who had a single PD post-PR (two patients; the time to relapse for these patients was [redacted], respectively). Data were pooled across disease stages due to the small sample size. This approach was not taken originally because the definition of PD within Study 201 trial outcomes precluded the assignment of PD to a patient who had previously achieved PR (i.e. PD was only defined if it occurred prior to CR or PR). However, having revisited the IPD from Study 201 the revised approach has been identified as a way to use data to avoid this assumption (albeit we acknowledge the small number of patients informing the transition probability). The revised approach utilising data from Study 201 has the advantage of alignment with the source used for the majority of the transitions for chlormethine gel in the cost-effectiveness model, and removes the need to assume that this transition is equal to the initial transition to PD, which was associated with uncertainty, is likely not fully reflective of clinical practice and represented a simplification in the cost-effectiveness model associated with the company submission. In response to the technical engagement question relating to whether patients who obtain a CR are more likely to relapse than patients who obtain a PR or do not have a response, we consider that for patients receiving chlormethine gel this is plausible. Patients who have achieved CR are no longer receiving treatment with chlormethine gel, whereas patients who have achieved PR or have not had a response continue to receive treatment. The revised base case using Kim *et al.* (2003) for the relapse post-CR and Study 201 for relapse post-PR remains consistent with this, with patients in CR relapsing at a higher rate than patients in PR. <u>Phototherapy – initial PR and CR (Low Skin Burden/High Skin Burden to CR/PR)</u> In the company submission, these transitions were informed via a weighted average (weighted by sample size) of response rates from trials identified in the BAD guidelines and for which CR and PR were reported. These rates were assumed to be equal across disease stages.[16-18, 37-40] The ERG preferred the use of data from Phan *et al.* (2019), a systematic review of trials investigating NB-UVB and PUVA for patients with early stage MF-CTCL. Separate efficacy was used for UVB and PUVA, and data were stratified by disease stage (Stage IA and Stage IB); the PUVA and UVB efficacy was

	weighted according to the proportion of patients assumed to receive each form of phototherapy in the model to produce a weighted average efficacy for phototherapy.[20] When considering this transition, Recordati/Helsinn have further investigated the Phan *et al.* (2019) source.[20] Whilst this publication was based on a systematic review, the searches identified studies only if they included both PUVA and UVB and therefore would not have identified studies only investigating PUVA or only UVB (for example, Whittaker *et al.* [2012], an RCT of PUVA versus PUVA plus bexarotene was not identified).[17] Furthermore, Phan *et al.* (2019) identified studies that were retrospective and observational only. However, Phan *et al.* does have some advantages, including the fact that CR and PR rates are provided for PUVA and UVB separately (the reason cited in the ERG report as to why Phan was preferred) and that data are separated by disease stage. Ultimately, Recordati/Helsinn have therefore adopted Phan *et al.* (2019) for these transitions in the revised base case, including modelling PUVA and UVB separately and splitting out efficacy by disease stage (i.e. weighted for PUVA/UVB and applied separately to Stage IA and Stage IB/IIA).[20] <u>Phototherapy – initial PD (Low Skin Burden/High Skin Burden to Progressed from 1L)</u> In the company submission, in the absence of consistent reporting of rates of progressive disease and SD across studies from the BAD guidelines (used to generate CR and PR rates), it was assumed that the remainder of patients not achieving CR or PR were split equally between progressive disease and SD. This was consistent with the EORTC 21011 study, in which an equal proportion of patients were classified as having SD and having progressive disease.[17] The ERG assumed that this transition was equal to the probability of relapse post-PR, the inverse of the assumption taken by Recordati/Helsinn in the base case where it was assumed that post-PR relapse was assumed to be equal to initial progression. Arguably, the ERG assumption is not conservative and is likely to underestimate the rate of transition from initial Low/High Skin Burden to Progressed from 1L, as, in practice, patients who have achieved a level of response to therapy (i.e. PR) are less likely to relapse than patients who have not achieved a response. As such, Recordati/Helsinn considers that this assumption is likely not fully reflective of clinical practice. During a review of the Phan *et al.* (2019) source as part of this Technical Engagement response, Recordati/Helsinn has identified 'failed response' data. The definition for failed response is not provided in the Phan *et al.* (2019) publication; however, when referring to the source publications (some of which reported the definition), it appears that the definition is either a <50% response or disease progression equating to a response of either PD or SD.[20] Use of Phan *et al.* (2019) to model transition of patients from initial Low/High Skin Burden states to Progressed from 1L offers consistency with the use of this source to model transition of patients from initial Low/High Skin Burden states to either CR or PR, as preferred by the ERG and incorporated into the company revised base case. Recordati/Helsinn revised base case therefore

	uses the 'failed response' data from Phan *et al.* (2019) as the combined transitions to SD and PD, and assumes that these patients are split equally between SD and PD as per the company original base case, consistent with the relative split between SD and PD in the EORTC 21011 study. [20] Phototherapy – relapse post-CR (CR to Progressed from 1L) As for chlormethine gel above, in the company submission, the transition from No Skin Burden to Progressed from 1L was treatment independent, as patients are no longer receiving treatment in this health state (this assumption was validated by clinical expert opinion). Data from Whittaker *et al.* were used to inform this transition in the model. Data from both treatment arms was used as no significant difference was found between treatment arms (PUVA and PUVA+bexarotene) for the proportion of patients relapsing post-CR, and to therefore maximise sample size. Furthermore, data were pooled across disease stages. The ERG preferred the use of Phan *et al.* (2019), whereby the reported duration of overall response (CR and PR combined) was used alongside data from Whittaker *et al.* (2012) to calculate the relative relationship between CR and PR. This transition was applied for PUVA and UVB separately but pooled across disease stages.[17, 20] Recordati/Helsinn is concerned that the use of Phan *et al.* (2019) to inform these transitions is inappropriate. Firstly, Recordati/Helsinn has been unable to replicate the median time to relapse post-CR cited in Phan *et al.* (2019) from the original sources. Secondly, Phan *et al.* (2019) cites the median and range of the time to relapse estimates from across the source studies, which highlights a very large range of reported time to relapse data.[20]Whilst taking the median of the estimates (as opposed to the mean) is less subject to skew by outlier data, Recordati/Helsinn is concerned that the wide reported range indicates that the studies are not measuring like-for-like and are subject to considerable sources of heterogeneity between studies. As such, adopting the median of the reported values is a simplification that doesn't account for the uncertainty associated with this estimate. It should also be noted that whilst Phan *et al.* (2019) took the median of the reported time to relapse estimates, the individual study estimates were a mix of median and mean time to relapse.[20] Finally, and most importantly, there are reasons to consider that some of the studies informing the median estimate from Phan *et al.* (2019) are not appropriate. Multiple studies used maintenance phototherapy, which would likely help to prolong time to relapse post-CR but is not representative of UK clinical practice where maintenance phototherapy is not used due to the risk of associated malignancies.[1] In addition, some studies use considerably more phototherapy sessions than the 12.5 weeks at two sessions/week (i.e. total of approximately 25 sessions) recommended in the UK, as per the BAD guidelines. Ultimately, the data from Phan *et al.* (2019) may be overly optimistic for duration of CR. Therefore, Recordati/Helsinn proposes using the Whittaker *et al.* (2012) source for this transition, and has kept this source in its revised base case.[17, 20] The Whittaker *et al.* (2012) study design stopped treatment once a CR had been achieved, and limited to treatment with phototherapy to a maximum of 16 weeks of treatment (at 3

	times per week), which is more aligned to UK clinical practice than some of the studies informing the Phan *et al.* (2019) estimates. Phototherapy – relapse post-PR (PR to Progressed from 1L) In the company submission, this transition probability was assumed to be the same as the transition to Progressed from 1L from the Low/High Skin Burden health states respectively due to a lack of relevant data for phototherapy. The same assumption has been maintained in the revised base case.
Which sources of data (Whittaker et al. 2012, the EORTC study 2011 or Phan et al. 2019) for estimating time to progression following CR or PR on phototherapy is more appropriate and representative of UK clinical practice?	Please see response above – Recordati/Helsinn considers Whittaker *et al.* (2012) a more appropriate source for estimating progression following CR on phototherapy.[17]
Issue 7: Time spent in 'progressed from 1L' health state	
Is it possible that for patients whose condition relapsed, the relapse would respond to the same initial treatment and patients could switch between skin-directed therapies (SDTs)? And that only in a small proportion of patients the condition would become refractory, therefore requiring subsequent systemic treatments?	Recordati/Helsinn first wish to highlight that the only SDTs considered within the cost-effectiveness model are chlormethine gel and phototherapy (PUVA and UVB). Based on the BAD guidelines, there is a maximum duration of phototherapy that patients are permitted to receive in the UK (12–14 weeks); therefore, patients would not receive a course of phototherapy more than once (i.e. patients cannot receive phototherapy and then receive phototherapy again at a later date).[2] This is also supported by clinical expert opinion sought for the company submission.[1] Therefore, it is not possible that patients treated with phototherapy initially would be re-treated with this same initial treatment. Recordati/Helsinn consider that it would also be inappropriate to model phototherapy patients to receive chlormethine gel after a course of phototherapy, as including the chlormethine gel intervention in the comparator arm would 'contaminate' the comparison and mean that the model is not comparing the introduction of chlormethine gel to current practice (i.e. a world in which chlormethine gel is not yet available). Therefore, it is appropriate to consider that following a course of phototherapy patients who relapsed would receive systemic therapy. However, there is the possibility that patients receiving chlormethine gel would be able to receive chlormethine gel again following a relapse in the skin symptoms of MF-CTCL. Therefore, in the company's revised base case, a proportion of patients who receive chlormethine gel and achieve a response, but then relapse, are assumed to receive chlormethine gel again as part of the Progressed from 1L treatment basket i.e. 33% patients receive chlormethine gel, 33% receive bexarotene and 33% receive pegylated IFN-α. Varying these proportions is explored in a scenario analysis on the revised base case (see Appendix). As noted below, the ERG amended the modelling of Progressed from 1L treatment basket to estimate that a proportion of patients in this cohort would be in CR as a result of their received therapy, with associated quality of life improvements and avoided treatment costs. In order to reflect this approach, the company revised base case needed to consider what proportion of time spent in

	the Progressed from 1L health state would be spent in CR for the proportion of patients receiving chlormethine gel. In order to estimate this, Recordati/Helsinn has used the estimates of time spent in CR for chlormethine gel from the cost-effectiveness (Markov) model to estimate proportion of time spent in CR. This does, however, rely on the assumption that the chlormethine gel is as efficacious when used for the second time as for the first.
Do all patients who have a relapse in skin burden symptoms progress to subsequent systemic treatment as assumed by the company? If not, what proportion of them would progress to systemic treatment?	In the company submission, all patients were assumed to receive either bexarotene or pegylated IFN-α in a 50:50 split following skin symptom progression. This was based on clinical expert opinion that patients would receive either bexarotene or pegylated IFN-α following phototherapy, and was assumed to also be appropriate for patients receiving chlormethine gel given that both bexarotene and pegylated IFN-α are second line treatment options following first-line SDTs (including chlormethine) in the BAD guidelines (for Stage IA–IIA patients).[1, 2] However, as per the response above, the revised base case now includes a proportion of patients receiving chlormethine gel to receive this treatment for a second time following a relapse (after an initial response). This was not considered to be an appropriate assumption for phototherapy given the maximum treatment duration for this as per the BAD guidelines.[2]
For those who progress to subsequent systemic treatment, how long on average do they remain on it?	Please see below response.
Are the subsequent estimates from the ERG of the proportion of the cohort who incur costs and quality of life decrements representative of UK clinical practice?	In the company submission, patients entered the Progressed from 1L health state and were assigned to receive bexarotene or pegylated IFN-α (based on clinical expert opinion) for their remaining time in that health state.[1] However, the ERG included the option for patients to re-achieve CR and therefore discontinue treatment and have an associated improvement in quality of life upon treatment with systemic therapies. Specifically, based on CR rates and duration of response data for bexarotene and IFN-α from Dalal *et al*. (2020), the ERG estimated that 97.8% patients receiving chlormethine gel and 98.1% patients receiving phototherapy incur the costs and quality of life decrements of progressed disease, rather than the 100% assumed in the company base case.[41] Recordati/Helsinn agree that patients may achieve a CR on subsequent therapies, and therefore accept that the ERG approach is reasonable and have incorporated this approach in the revised base case. However, whilst Recordati/Helsinn accepts the need to incorporate the fact that some of the time in the Progressed from 1L state is spent in CR and hence have ultimately used data from Dalal *et al.* (2020) to inform this, Recordati/Helsinn considers that the assumption made by the ERG that the duration/efficacy of CR with IFN is the same as bexarotene is not necessary. This assumption was made on the basis that the Dalal *et al.* (2020) study did not report a duration of CR for IFN, which appears to be because three of the four reported sources informing efficacy (CR) of IFN do not report CR duration.[41] However, one of the studies, Roberge *et al.* (2007), does report these data. Therefore, the company revised base case uses the

	duration of CR data from Roberge *et al.* (2007) for the calculation of time spent in CR for IFN, rather than assuming that this is the same as for bexarotene.[42] This approach reduces the duration of CR with IFN versus the ERG's assumption, but Recordati/Helsinn considers that it is likely still an overestimate of the efficacy of IFN (and therefore may result in overestimation of the time spent in CR following IFN) given that in this study IFN was used in combination with total skin electron irradiation. However, this is still considered more appropriate than assuming the same efficacy for IFN and bexarotene.
Issue 8: Distribution of post progression treatments/subsequent treatment scenarios	
For patients whose condition has progressed and systemic treatment is needed, what proportion of them would be receiving bexarotene or IFN-α respectively, in UK clinical practice?	As per the responses to Issue 7 above, in the company submission, patients were assumed to receive either bexarotene or pegylated IFN-α in a 50:50 split following skin symptom progression. This was based on clinical expert opinion that patients would receive either bexarotene or pegylated IFN-α following phototherapy, and was assumed to also be appropriate for patients receiving chlormethine gel given that both bexarotene and pegylated IFN-α are second line treatment options following first-line SDTs (including chlormethine) in the BAD guidelines (for Stage IA–IIA patients).[1, 2] Whilst Recordati/Helsinn acknowledge that there are no data to inform the proportional split, it is understood that some clinicians may prefer to prescribe bexarotene and some may prefer to prescribe pegylated IFN-α. Therefore,the 50:50 split is considered to a reasonable assumption to accurately reflect the fact that these treatments are provided in similar proportions in UK clinical practice, in line with clinical expert opinion.[1] Data from the PROCLIPI registry (albeit not specifically related to the Progressed from 1L setting) indicated that generally usage of these two treatments in MF-CTCL is not dissimilar, and therefore does not suggest that a 50:50 split is unreasonable.[28]
What proportion of patients would be able to return to their initial treatment or other SDTs after responding to systemic treatment?	Data are not available to support specific estimates of the proportion of patients returning to their initial treatment or other SDTs after responding to systemic treatment. Therefore, in the absence of robust data to reliably inform this transition into the cost-effectiveness model, the company's revised base case (which adopts the same approach as the ERG) does not explicitly make an assumption in this regard. The ERG approach adopted by Recordati/Helsinn does not explicitly preclude that a proportion of patients are returning to SDTs after response to systemic therapy, as it simply models that a proportion of patient time in that health state is spent on the various therapies.
What proportion of patients would receive further treatment following a PR on phototherapy or, choose not to receive further treatment immediately once their course of phototherapy finished?	Clinical expert opinion sought for the company submission concluded that all patients would go on to subsequent treatment following phototherapy (bexarotene and pegylated IFN-α in a 50:50 ratio), as PR and even a CR would not be considered a cure, and the response duration may be short.[43] Therefore, given that the BAD guidelines cite PUVA and narrow band UVB regimens as being 12–14 weeks and that clinical expert opinion confirmed that in clinical practice phototherapy would be limited to a single treatment course to limit the risk of secondary malignancies, all patients receiving phototherapy in the cost-effectiveness model were assumed to receive treatment for 13 weeks and then receive subsequent treatment with either bexarotene or pegylated IFN-α.[2, 5, 6, 26]

What other factors relating to treatment switching between SDTs or between systemic treatment and initial SDTs following PR or CR on the two arms should be accounted for in the model?	Recordati/Helsinn are not aware of any additional factors relating to treatment switching between SDTs or between systemic treatments and initial SDTs following PR or CR on the two arms that should be accounted for in the cost-effectiveness model.

Appendix

As noted above, in response to the Technical Engagement and following consideration of the ERG's preferred assumptions and additional data sources identified by the ERG (notably Phan *et al.* (2019), Recordati/Helsinn has provided a revised base case.

The updates in the revised base case are discussed *in situ* in the relevant parts of the responses to specific issues raised for Technical Engagement above, and outlined in Table 1. In addition to the changes incorporated into the revised base case as specified in the responses above, Recordati/Helsinn has also revised the treatments included for advanced disease patients in the cost-effectiveness model as outlined below, based on the ERG preferred approach.

In the company submission, a single advanced treatment basket (containing bexarotene, ECP [UVADEX], gemcitabine, methotrexate or pegylated IFN-α) was applied for all patients irrespective of health state or initial treatment. However, the ERG proposed an alternative treatment basket for patients receiving phototherapy given that patients receiving phototherapy would be contraindicated to receiving methotrexate and ECP. The ERG also mentioned that it may not be appropriate to have pegylated IFN-α and bexarotene in the subsequent treatment basket when patients are in the Progressed from 1L health state. Therefore, in the revised base case, advanced disease treatment baskets are varied based on the treatment a patient is receiving and the health state in which they reside:

- Chlormethine gel – two types of advanced disease treatment baskets are modelled. One basket is applied to patients in the progressed from 1L health state (this advanced disease treatment basket does not include pegylated IFN-α/bexarotene to avoid double-counting with the Progressed from 1L treatment basket) and the other basket (containing bexarotene, ECP [UVADEX], gemcitabine, methotrexate or pegylated IFN-α) is applied to all other health states in advanced disease
- Phototherapy – three types of advanced disease treatment baskets are modelled. One basket is applied to patients in the progressed from 1L health state (this advanced disease treatment basket does not include pegylated IFN-α/bexarotene to avoid double-counting with the Progressed from 1L treatment basket), as per chlormethine gel. The other two baskets cover the other health states and depend on whether the patient is actively receiving phototherapy or not. If the patient is not receiving phototherapy (e.g. No skin burden, or after maximum treatment duration) they receive the original treatment basket (containing bexarotene, ECP [UVADEX], gemcitabine, methotrexate or pegylated IFN-α). If the patient is on phototherapy, they receive the basket without methotrexate and ECP, to reflect the contraindication to these therapies for patients receiving phototherapy

In addition to this above update, it should be noted that a minor error relating to monitoring costs that was not noted in the ERG report was identified by the company and corrected in the revised base case. Cell M74:75 were corrected to refer to Q47 on the 'HCRU Mapping' tab, rather than Q48 and Q49 respectively. These cells now equal 18.65 rather than 0.00.

Other than the adjustment to the advanced treatment baskets outlined above and the specific points of difference with the ERG preferred approach as discussed in response to the specific issues and outlined in Table 1, the revised base case mirrors the ERG preferred approach. All ERG-identified technical corrections have been incorporated. Furthermore, the following points that are not presented as issues for technical engagement but represented points of difference between the company original base case and the ERG preferred approach have been incorporated into the revised base case.

- Mortality for Stage IA patients has been updated to be based on general population mortality rather than Agar *et al.* (2010), in line with the ERG preferred approach
- The cost of treating adverse events has been updated to the ERG-preferred cost of £115

A summary of the key model assumptions and data sources utilised in the revised base case is presented in Table 1, with a comparison to the approach preferred by the ERG and that from the original company submission.

Table 1: Comparison of key model assumptions/data sources

Assumptions/data sources	Approach in company submission	Approach/comments of ERG	Approach in company revised base case
Population/characteristics (%BSA)	PROCLIPI registry (where available); Study 201 (age, gender) or the NHS Health Survey for England 2017 (height and weight)		
	Mean %BSA for Low and High Skin Burdens from Study 201	Unclear whether the %BSA from Study 201 (by disease stage) is representative of what is seen in clinical practice, ICER highly sensitive to changes	Mean %BSA for Low and High Skin Burdens from Study 201 *[see response to Issue 1]*
Intervention: topical chlormethine gel/dosage	Median daily dosage 1.8 g	Mean daily dosage 2.8 g	Mean daily dosage [redacted] ([redacted] for Low Skin Burden and [redacted] for High Skin Burden), based on updated dosing data available from Study 201 *[See response to Issue 3]*
Comparator/phototherapy	PUVA/UVB (distribution of usage from PROCLIPI registry)	PUVA/UVB (PROCLIPI may reflect historical usage of phototherapy, clinical practice may have changed in recent years)	PUVA/UVB (distribution of usage from PROCLIPI registry) *Recordati/Helsinn considers that PROCLIPI is not 'historical' data, as the registry consists of data from UK clinical practice from 2015–2019* *[see response to Issue 4]*
Underlying disease progression			
Treatment effect and underlying disease progression	Underlying disease progression is independent of treatment effect		
Transition between MF-CTCL stages	Wernham *et al.* (2015; n=86, a single database study)	Company's source may have over-estimated transition between disease stages; prefer data sourced from Agar *et al.* (2010; n=1502, a larger sample of UK patients), suggested slower progression overall	Agar *et al.* (2010) *[see response to Issue 5]*

CR and PR rates			
CR PR	Chlormethine gel: Study 201 Phototherapy: weighted average of available CR and PR rates across 7 identified studies from the BAD guidelines	Chlormethine gel: Study 201 Phototherapy: Phan *et al.* (2019) for CR and PR rate, applied separately to PUVA and UVB and by MF-CTCL disease stages	Chlormethine gel: Study 201 Phototherapy: Phan *et al.* (2019) for CR and PR rate, applied separately to PUVA and UVB and by MF-CTCL disease stages *[see response to Issue 6]*
PD and SD	Chlormethine gel and phototherapy: Proportion of patients not achieving CR or PR split 50:50 between PD and SD based on the relative proportions of patients achieving SD and PD in the EORTC 21011 study	Chlormethine gel: as per company base case Phototherapy PD transition assumed equal to the ERG's preferred transition probability for relapse post-PR	Chlormethine gel: as per company base case Phototherapy: Proportion obtaining "failed response" (equated to either SD or PD following investigation of the sources) in Phan *et al.* (2019) split 50:50 between PD and SD based on the relative proportions of patients achieving SD and PD in the EORTC 21011 study *[see response to Issue 6]*
Skin burden transitions/time to progression & subsequent treatment post CR/PR			
Progression following CR/time to progression	Time to progression post a CR equal for chlormethine gel and phototherapy (data sourced from Whittaker *et al.* [2012]) as patients with a CR are modelled to no longer receive treatment and there is no data from study 201 to estimate progression post CR for phototherapy Patients with CR more likely to relapse and progress to subsequent systemic treatment than those with PR or without response	Company's assumption may be plausible, but not evidence-based Chlormethine gel: prefer company's scenario analysis using Kim *et al.* (2003), where progression post CR for an alternative nitrogen mustard treatment sourced, rather than assuming equal to phototherapy Phototherapy: prefer calculated transition probability based on proportion of patients achieving OR from Phan *et al.* (2019) and proportional split between CR and PR from Whittaker *et al.* (2012), applying	Chlormethine gel: Kim *et al.* (2003) Phototherapy: Whittaker *et al.* (2012), due to concerns with the appropriateness of Phan *et al.* (2019) as a source of relapse rates given the difficulty in replicating the Phan *et al.* (2019) estimate from source studies and concerns over generalisability to UK practice of the application of phototherapy in the source studies (e.g. application of maintenance phototherapy), where such differences may be expected to influence time to progression

		separate time to progression for PUVA and UVB; Whittaker *et al.* (2012) included more patients with advanced disease so may have overestimated the risk of progression to subsequent systemic treatment; also, a small sample of patients (n=25) in the study to estimate CR	*[see response to Issue 6]*
Progression following PR/time to progression	Chlormethine gel: Transition to "progression from 1L" following PR: progression post PR equal to initial probability of progression, based on expert opinion (conservative) Phototherapy: Transition to "progression from 1L" following PR: as per chlormethine gel, progression post PR equal to initial probability of progression, based on expert opinion (conservative)	Chlormethine gel: accept company's assumption may be reasonable given the absence of data; note the assumption not evidence based, and further uncertainty introduced Phototherapy: prefer calculated transition probability based on proportion of patients achieving OR from Phan *et al.* (2019) and proportional split between CR and PR from Whittaker *et al.* (2012), applying separate time to progression for PUVA and UVB	Chlormethine gel: Study 201 (based on revisiting the IPD) Phototherapy: Assumed the same as the probability of progression to "Progressed from 1L" from the initial skin burden health states (the same assumption as per the original company base case) *[see response to Issue 6]*
Time spent in "Progressed from 1L"	No patients entering this state would observe an improvement in symptoms	A proportion of patients may respond to systemic treatment available (bexarotene or pegylated IFN-α) and quality of life improves; company's assumption may have under-estimated utility values assigned; Dalal *et al.* (2020): suggested CR possible for some patients and return to their initial treatment, e.g. phototherapy	Adopted ERG-preferred approach in terms of using CR rates and duration of CR for basket therapies to adjust costs/QALYs in "Progressed from 1L" state. However, chlormethine gel additionally incorporated into the basket of therapies for the chlormethine gel arm of the model Duration of CR for IFN from Roberge *et al.* (2007), rather than assumed equal to bexarotene *[see response to Issue 7]*

Distribution of post progression treatments	50% receiving bexarotene and 50% pegylated IFN-α	Unclear whether the company's assumption is in line with clinical practice; varying the distribution has a substantial impact on ICER	Bexarotene and pegylated IFN-α in a 50:50 ratio *(not always 50% bexarotene and 50% pegylated IFN-α as chlormethine gel also included in the treatment basket in the chlormethine gel arm to reflect that patients now have the option to receive chlormethine gel more than once)* *[see response to Issue 7 and Issue 8]*
Resource use and cost	Phototherapy: Fonia *et al.* (2010)	Phototherapy: most recent (2017/18) NHS reference costs Remove costs of ECP and methotrexate as advanced treatment, while on phototherapy and for 2 weeks after stopping treatment	2017/18 NHS reference costs (mean of the dermatology and oncology costs for a consultant led outpatient clinic cost for phototherapy and photo chemotherapy) Costs of ECP and methotrexate as advanced treatment whilst on phototherapy removed *[see response to Issue 4]*

Abbreviations: BSA: body surface area; CR: complete response; ECP: extracorporeal photopheresis; ICER: incremental cost-effectiveness ratio; IFN: interferon; MF-CTCL: mycosis fungoides-type cutaneous T-cell lymphoma; NHS: National Health Service; PR: partial response; PUVA: psoralen ultraviolet A; UVB: ultraviolet B.

The results of the revised base case are presented below in addition to a scenario varying the proportions patients receiving chlormethine gel, pegylated IFN-α and bexarotene in the second line SDTs basket for chlormethine gel.

Revised base case results (discounted)

	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Chlormethine gel ICER (£/QALY)	NMB
Chlormethine gel	£238,582	12.63	9.07	-	-	-	-	-
Phototherapy (PUVA/UVB)	£251,092	12.63	8.84	-£12,510	0.00	0.23	Phototherapy dominated	£19,422

Abbreviations: ICER: incremental cost effectiveness ratio; LY: life year; NMB: net monetary benefit; PUVA: psoralen-ultraviolet A; QALY: quality adjusted life year; UVB: ultraviolet B.

Revised base case results – altering second line SDTs basket for chlormethine gel

	Incremental costs	Incremental LYs	Incremental QALYs	Chlormethine gel ICER (£/QALY)	NMB
Revised Base Case (33%/33%/33%)	-£12,510	0.00	0.23	Phototherapy dominated	£19,422
Revised Base Case + (0%/50%/50% chlormethine gel/bexarotene/pegylated IFN-α, as per phototherapy)	-£11,258	0.00	0.24	Phototherapy dominated	£18,333
Revised Base Case + 50% chlormethine gel, 25%/25% bexarotene/pegylated IFN-α	-£13,141	0.00	0.23	Phototherapy dominated	£19,971

Abbreviations: ICER: incremental cost effectiveness ratio; IFN: interferon; LY: life year; NMB: net monetary benefit; PUVA: psoralen-ultraviolet A; QALY: quality adjusted life year; SDT: skin-directed therapy; UVB: ultraviolet B.

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Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

ERG critique of company response to Technical Engagement

Produced by Aberdeen HTA Group

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This report provides the ERG's brief commentary and critique of additional economic evidence and modelling submitted by the company Recordati Rare Diseases/Helsinn Healthcare SA received by the ERG on June 15th, 2020 in response to the Technical Engagement and in advance of the first AC meeting for this appraisal. The commentary/critique provided below should be read in conjunction with the company's submitted technical engagement response, NICE's technical engagement report and the ERG report. This commentary covers the main headings used by NICE in their technical engagement document, identifying 8 issues for engagement. It also provides the results of further scenario analyses conducted by the ERG.

Issue 1: Clinical need for Chlormethine gel

The ERG acknowledge that chlormethine gel may offer an alternative treatment option for patients who are contra-indicated to phototherapy and some patients may prefer chlormethine gel because patients can apply it in their own homes, negating the need for regular hospital phototherapy appointments. The ERG accept that chlormethine gel would most feasibly be used as a stand-alone skin directed treatment (SDT) for patients with early stage disease (Stage IA and IB/IIA) and as an adjunctive therapy alongside systemic therapies for patients with advanced stage disease.

However, the ERG consider it important to acknowledge that the main source of clinical-effectiveness data (Study 201) only recruited patients with Stage IA and Stage IB/IIA disease and therefore not generelisable to the proposed positioning of chlormethine gel. The study did not include patients with advanced Stage IIB+ disease. However, [redacted] of the cohort in the economic model are assumed to receive chlormethine gel for Stage IIB+ disease, based on the distribution of disease severity sourced from the PROCLIPI registry. The company have assumed that the effectiveness of chlormethine gel in terms of response is transferable from those with early stage disease (as per Study 201) to the proportion of the modelled cohort with more advanced (Stage IIB+) disease. The ERG note that this extrapolation is not evidence based and introduces additional uncertainty into the assessment of cost-effectiveness. In particular, there is currently no randomised evidence to indicate that there is no considerable differences in efficacy or effectiveness of chlormethine gel across disease stages.

Furthermore, the ERG note that patients with more advanced disease typically have a greater skin burden and greater proportion of body surface area (BSA) affected compared to earlier (Stage IA) stage disease. This has important implications for the treatment acquisition costs of chlormethine gel. Under the company's revised preferred assumptions, considering a cohort of patients with early stage disease only (Stage IA: [redacted]; Stage IB/IIA: [redacted]) leads to a chlormethine gel treatment acquisition cost of [redacted] per person and incremental costs of -£18,504. Restricting the cohort to later stage disease (Stage IIB+ only) results in Chlormethine gel acquisition costs of [redacted] and incremental costs of +£10,951.

For these reasons, the ERG does not consider the clinical or cost-effectiveness evidence adequate to support the use of chlormethine gel in patients with advanced disease.

Issue 2: Phototherapy as the comparator in the model

The ERG considers it important to emphasize to the committee that the true relative effectiveness of chlormethine gel compared to phototherapy, in terms of response rates, or duration of response cannot be robustly determined, as no randomised evidence exists. Similarly, the company did not identify any studies that would enable a network of evidence to be generated to allow an indirect comparison. Additionally, due to the heterogeneity observed across phototherapy studies and Study 201 any form of matched adjusted indirect comparison (MAIC) proved unfeasible. For this reason, the company have relied on a naïve comparison.

The ERG acknowledges the limitations of the evidence base, and accepts that there are advantages and disadvantages of both the 7 studies identified by the company through their own systematic literature review (SLR) and among those cited in the British Association of Dermatologists (BAD) guidelines and the studies included in the Phan et al. systematic review identified by the ERG. The seven studies identified by the company (4 RCTs and 3 non-randomised, non-comparative studies) assessed either PUVA or UVB and none compared PUVA with UVB[1]. The Phan et al. review included 6 retrospective and 1 prospective observational studies that compared PUVA with narrowband UV-B (NBUBV) in patients with early stage disease.[1] The company states that the Phan et al. review represents a restricted selection of the evidence available for these therapies. While acknowledging the limitations of the studies included in the Phan et al. review, the ERG does not consider the evidence on the effects of phototherapy submitted by the company stronger than that provided by the Phan et al. review. The ERG therefore accept the company's decision to include the response data from Phan et al. in their revised base case analysis due to the fact that it uses systematically identified sources, meta-analysed outcomes, and provides a granularity of data that enables application of response rates by type of phototherapy (PUVA / UVB) and by stage of MF-CTCL disease. The ERG consider an additional advantage of Phan et al. is that it provides information to inform both phototherapy response and time to progression following a response. The ERG considers it important, given the significant

heterogeneity across studies to use consistent sources of evidence to populate different economic model parameters wherever it is possible and appropriate to do so.

The ERG note that the pooled response data meta-analysed by Phan et al. and applied separately by disease stage in the economic model are broadly similar to those initially considered by the company's review of studies included in the BAD guidelines lending some reassurance to the face validity of the phototherapy response rates used in the economic model. Nevertheless, the uncertainties surrounding the relative effectiveness of phototherapy compared to chlormethine gel remain.

Issue 3: The daily application, dosage, and costing of chlormethine gel

The amount of chlormethine gel used, and by extension the treatment acquisition cost will depend upon the frequency with which the gel is applied and the amount of the gel used per application (primarily determined by the proportion of BSA affected).

With regards to frequency, the company note that real world evidence suggests the frequency of gel application is less than the once daily application from Study 201. Whilst this may be true, any consideration of this evidence in the economic model would generate a substantial bias in favour of chlormethine gel because it would fail to consider the highly likely scenario that less frequent application of the gel would result in poorer response rates than observed in Study 201. For this reason, the ERG agrees with the company's decision not to use this evidence to inform their preferred base case cost-effectiveness analysis.

With regards to the amount of gel used per application, the company have updated the treatment acquisition costs to include a revised analysis based on individual patient data (IPD) from Study 201 (ITT population, [redacted]), with a mean daily dosage of chlormethine gel calculated according to the number of returned empty tubes per follow up visit. This generates a mean daily dosage of [redacted] ([redacted] for low skin burden and [redacted] for high skin burden). Whilst the ERG agrees that the calculations are accurate, they are based on several assumptions that likely underestimate the true treatment acquisition costs. For example, the calculation approach does not account for a patient forgetting to return an empty tube at their follow-up appointment, a patient retaining unfinished tubes at the final study visit, or patients not turning up to the follow-up appointments. Furthermore, the wastage associated with the use of a 60g tube as used in clinical practice may be substantially greater

than the wastage associated with a [redacted] tube as used in Study 201 due to the 60-day shelf life.

The ERG notes that the company have been unable to gain direct access to the mean daily dosage of study drug from the trial. However, the ERG is unaware of any evidence from any formal regulatory documentation for either Ledaga®, or the US version (Valchlor™) to support the company's claim that the data used to generate a mean study drug usage of 2.8g per day might relate to an analysis of the safety data set rather than the intention to treat (ITT) data set.[2,3] The ERG's understanding of the publicly available prescribing information on the Valchlor™ product website (See Section 14) for chlormethine gel's US branding (Valchlor™) is that the mean of 2.8g is actually derived from the ITT sample ([redacted]), excluding the New York University (NYU) site, who were excluded from the primary efficacy analysis due to a violation of the Study 201 protocol[4]. Similar prescribing information is also hosted on the FDA website.[5] For all of these reasons, the ERG considers 2.8g to be the most appropriate daily dosage of chlormethine gel to inform the treatment acquisition costs in the economic model.

The mean daily dosage, and hence treatment acquisition costs that would be observed in real-world clinical practice is directly related to the proportion of BSA that would be affected. The ERG remains concerned that the proportion BSA affected in Study 201 may not be reflective of the proportion BSA affected in real-world clinical practice, particularly given that Study 201 was restricted to patients with Stage 1A and Stage IB/IIA disease. However, the company positioned chlormethine gel to also be used to treat patients with Stage IIB+ disease. It is plausible that this would lead to a higher average proportion BSA affected in real-world practice than observed in the trial. Indeed, the economic model includes a proportion of patients with Stage IIB+ disease, where the mean daily dosage applied is derived from Study 201, which included only Stage IA and IB/IIA disease. On this basis, it is plausible that the estimate of 2.8g of gel per day may be an underestimate of the true usage of the drug. The ERG acknowledges that the company do not have access to proportion BSA data from the PROCLIPI registry at the time of submission. However, if these data could subsequently be obtained they would provide much greater reassurance about the likely proportion BSA affected in real world clinical practice and would likely provide the most realistic data by which to calculate the likely treatment acquisition costs of chlormethine gel.

Issue 4: Costing and distribution of PUVA/UVB phototherapy

Distribution of PUVA / UVB

The original company submission noted that the phototherapy comparator comprised a proportion of patients receiving PUVA ([redacted]) and a proportion receiving UVB ([redacted]) based on data from the PROCLIPI registry. As the original company submission was unclear about the dates from which these data were obtained, the ERG report questioned whether the split of treatments was an accurate reflection of current usage of phototherapy in UK clinical practice. The company provided additional information at the Factual Accuracy Check stage to clarify that data from the PROCLIPI registry were obtained from 2015 to October 2019, a point raised again in the company's response to technical engagement. The ERG accepts the additional clarification provided by the company and agrees that the PROCLIPI registry is the most appropriate source of evidence to derive the proportions of phototherapy patients that receive PUVA / UVB respectively.

Costing of phototherapy

The ERG accept that the revised company submission now uses NHS reference costs 2017/18 which is in line with the ERG's preferred approach to determining phototherapy administration costs. The ERG note that the company prefer the use of a slightly different outpatient tariff to that used in the ERG report. The company's preferred cost is calculated as the mean of dermatology and oncology costs for a consultant led outpatient clinic cost for phototherapy and photo chemotherapy (HRG codes: JC47Z, service code 300 [dermatology] and 800 [clinical oncology]; £97.63). In contrast, the ERG reported included an outpatient tariff from service code 300 [dermatology], which resulted in a cost of £93.23. The ERG note that the unit costs are very similar, and that the impact on the ICER is minimal. The ERG consider the company's rationale plausible and are content with the revised unit cost of phototherapy administration.

The company raise an additional point about the uncertainty regarding whether the cost of psoralen is included within the cost of the outpatient tariff for phototherapy administration. The ERG's understanding is that drugs typically used to enable an outpatient procedure to take place, such as psoralen, are usually absorbed within the unit cost, but accept that there is some uncertainty surrounding this. Therefore, the ERG have sourced the cost of psoralen and provided a scenario analysis including the additional cost of psoralen, 5-methoxypsoralen

20mg tablets (pack of 50), £271.52 per pack (including VAT), to be taken daily, leading to a psoralen cost of £12.67 per PUVA session (=(7/3)*(271.52/50)), administered 3 times per week over a maximum course of 13 weeks. The inclusion of psoralen therefore increases the total phototherapy administration costs under the company's revised preferred costing approach from £180,113 to £180,240 (i.e. an additional £127). The resultant impact on the ICER is minimal (See Table 2).

Issue 5: Underlying disease progression

The ERG's clinical expert agrees with the company's claim that there is currently insufficient evidence to suggest that treatment of skin symptoms may delay or prevent progression of underlying MG-CTCL. The ERG agrees that the use of Agar et al. (2010) is the most appropriate source to inform both MF-CTCL disease progression and disease stage specific mortality in the economic model[6].

Issue 6: Skin burden transitions/time to progression following complete response (CR) and partial response (PR)

Chlormethine gel:

The ERG and company originally preferred assumption for use in the economic model was that the time to progression following a partial response on chlormethine gel was equal to the time to progression following initial progressive disease (i.e. from the initial skin burden health state).

The ERG notes that the company have subsequently conducted a further analysis using Study 201 data to calculate the time to relapse post a partial response on chlormethine gel. The revised approach is based on a sample of only 2 patients from Study 201 and is therefore considered highly uncertain by the ERG. Whilst the ERG accepts that where possible it is preferable to use available data to populate the model, these data should be considered cautiously due to small numbers. The ERG notes that the company's revised approach reduces the proportion of patients on chlormethine gel moving to the 'Progressed from 1L' health state and thus leads to a moderate reduction in the original preferred ICER by both the company and the ERG (see additional scenario analysis at the end of Table 2).

Phototherapy:

The structure of the company's economic model assumes that once a patient experiences a CR, they are more likely to progress to second line therapy as they are removed from their initial SDT, that is, chlormethine gel or phototherapy [up to week13] + bexarotene/IFN-a [post week 13]. The proportion of the cohort that experiences a relapse, and progresses then enter the semi-absorbing "progressed from 1L" health state where they remain for the duration of their life years, and can only exit to the death state. The ERG note that the use of this semi-absorbing state, where patients remain or die, was a simplifying assumption of the economic model. Whilst a model structure that allowed a proportion of the cohort to return to their initial skin burden health state following a relapse and receive re-treatment with the chlormethine gel would have been preferable, the ERG accepts that there is little data to robustly inform such transitions. Nonetheless, because the proportion of the cohort who enter the "progressed from 1L" state incur substantial long terms costs of 2nd line treatment and quality of life decrements, the time to progression into this state is a key driver of cost-effectiveness results. The longer the time to progression for any treatment, the more cost-effective that treatment option becomes.

As with the response rate discussion under issue 2, there is no evidence to robustly compare Chlormethine gel with phototherapy in terms of time to progression onto second line therapy. This necessitates a naïve comparison of studies form the literature. The ERG prefers the use of data from Phan et al. and the company prefers the use of Whitaker et al. to inform the time to progression following a phototherapy response.[1,7] Table 1 summarises the characteristics of each source to aide a comparison of the different sources.

Table 1: Comparison of ERG and company preferred sources of time to progression following phototherapy response parameters

Issue	Company preferred approach (Whittaker et al.[7])	ERG preferred approach (Phan et al.[1])
Study design	Prospective phase III RCT	Systematic review and meta-analysis of N=7 studies (6 retrospective cohort, 1 prospective cohort)
Sample size	Total N = 93 OR N=69 CR N=25	Total N=778 OR N=699 CR N=545
Setting	Europe	7 studies in 7 different countries (Ireland, Canada, Netherlands, Egypt, Greece, Portugal, Turkey)
Population	Gender: NR Age: mean=57	Gender: 55% male; Age: mean=52
Disease Stage	Stage IA: 0/93 (0%) Stage IB/IIA: 93/93 (100%) Stage IIB+: 0/93 (0%)	Stage IA: 375/777(48%) Stage IB/IIA: 402/777 (52%) Stage IIB+: 0/777 (0%)
Treatments included	PUVA; PUVA + Bexarotene	PUVA; UVB
Treatment duration of phototherapy (including any maintenance therapy)	PUVA – median (range): 12 weeks (1-17) PUVA + Bexarotene: 10.5 weeks (1-16)	2/7 studies report mean duration (14 months; 15.6 months)
Total number of phototherapy sessions (including maintenance therapy if applicable)	Unclear (assume 36 (12x3)) *(median of 22 and 27.5 sessions required to achieve complete response across arms)*	6/7 studies report median total number of sessions (19;50;42;22;34;64), Cross study median: 38 Cross study average: 38.5
Maintenance therapy after response?	No	5/7 studies include maintenance phototherapy, not currently used in UK clinical practice

The ERG prefers the use of data from the Phan et al. systematic review because Phan et al. is a larger sample of patients, identified through systematic review with meta-analysed outcomes data.[1] The larger sample is particularly important in informing the most robust and generalisable duration of complete response to inform the economic model. Additionally, the distribution of disease stage severity in Phan et al. (48% Stage IA, 52% Stage IB/IIA) is more

comparable with Study 201 ITT including NYU sample (59% Stage IA, 42% Stage IB/IIA) than Whittaker et al.[1,7] where there were no patients with Stage IA disease. Finally, the use of data from Phan et al. are advantageous in that they allow the application of a consistent source of data to all phototherapy effectiveness parameters in the economic model. The ERG consider it appropriate, where possible to use the same source of data for response rates and duration of response. The ERG notes that the company consider the use of Phan et al. to be appropriate for the sourcing of response rates to inform the model.

The ERG notes that, the total number of phototherapy sessions reported in studies included in the Phan et al. review is similar to the likely number of sessions used in Whittaker et al (assuming a high degree of compliance with the number of treatments specified in the protocol).[1,7] However, the ERG also acknowledges the company's concerns about the use of data from Phan et al., in particular in relation to the impact of maintenance phototherapy on duration of complete response in particular. The ERG notes that 5 of the 7 studies included in Phan et al. report at least some use of maintenance phototherapy or a tapered reduction of phototherapy following a response. The ERG's clinical expert confirms that maintenance phototherapy is not usually used in UK clinical practice due to concerns about the potential for secondary malignancies. One of the studies included in the Phan review, Nikolaou et al. compared the duration of complete response for patients receiving vs. those not receiving maintenance phototherapy, with a similar number of sessions for those with / without maintenance.[8] The group receiving maintenance phototherapy had similar OR/CR/PR to those that did not, but the mean duration to relapse was longer for those receiving maintenance phototherapy (mean 32.27 vs. 19.46 months, p=0.002; N=227). On the basis of this evidence, the ERG accepts that the preferred source in the ERG report may have over-estimated the overall time to relapse following a phototherapy CR. To accommodate the company's legitimate concerns, and to retain the advantages of Phan et al., the ERG considers an appropriate analysis would be to adjust the duration of complete response from Phan et al. downwards by dividing the mean CR duration by 1.66 (i.e. 32.27/19.46) to approximate the likely duration in patients who do not receive maintenance phototherapy. The ERG accepts that this approach will still under-estimate the duration of CR as it will also adjust the duration of CR downwards from two studies included in the Phan et al. review where maintenance therapy was not used. Given that the company economic model assumes patients having a partial response to phototherapy treatment remain on bexarotene / IFN-a treatment, the ERG do not consider it appropriate to adjust the time to progression following

a partial response from Phan et al. The ERG considers the proposed solution to be a fair compromise that uses the most appropriate evidence available whilst also addressing the company's concerns. The cost-effectiveness results applying this assumption are presented in Table 2.

Issue 7: Time spent in 'progressed from 1L' health state

The ERG agree with the company's assessment that it would be inappropriate to include chlormethine gel in the phototherapy comparator arm of the model. As the company points out, this would 'contaminate' the comparison between chlormethine gel and phototherapy, which would no longer be a comparison between the introduction of chlormethine gel compared to current practice. The ERG also agrees that patients who relapse following a complete response to chlormethine gel may receive a second dose of treatment.

The company's revised approach attempts to accommodate this by assuming that a proportion of patients who relapse following a complete response to chlormethine gel will receive chlormethine gel again as part of the second line bundle of treatment. The company's revised preferred analysis is to assume that patients relapsing following a CR on phototherapy will continue to be treated with 50% bexarotene / 50% IFN-a, but those who relapse following a CR in the chlormethine gel arm will receive a treatment distribution of 33% bexarotene, 33% chlormethine gel and 33% IFN-a. The ERG raise two concerns with the approach taken by the company. First, the ERG consider that it would have been more appropriate to model a reversion back to the initial skin burden state for people who relapse following the first round of treatment than to assume they enter the 'Progressed from 1L' state where they incur extensive costs for the remainder of their life years. Secondly, the company's approach makes the implausible assumption that chlormethine gel has the same efficacy and duration of response each subsequent time it is used. The ERG's clinical expert notes that a useful rule of thumb is that each time a treatment is re-used, its effectiveness might be expected to drop by approximately half. Therefore, the company's approach is likely an over-estimate of the effectiveness of chlormethine gel used as a second line of therapy. On balance, the ERG considers the company's revised approach to be highly uncertain and prefers the exclusion of chlormethine gel from the 'progressed from 1L' treatment bundle.

The company have adopted the ERG's preferred approach to weighting the life years in which the costs of the subsequent treatment bundle and quality of life decrements are incurred in the 'progressed from 1L' state, with one amendment to use available data from IFN-a from a single study in the Dalal et al. review to inform the duration / efficacy of CR with IFN-a.[9] The ERG considers the company's calculation amendment to be reasonable.

Issue 8: Distribution of post progression treatments/subsequent treatment scenarios

The ERG has no further comments in relation to this point. All the relevant issues have been discussed in response to issue 7 above.

Summary:

In summary the ERG have reviewed the company's response to technical engagement and inspected the submitted economic model. The ERG note that substantial uncertainties in the evidence relating to the relative effectiveness of chlormethine gel vs. phototherapy remain and these uncertainties feed through to decisions about the most appropriate selection of parameters to populate the economic model. The ERG have attempted to re-create the original base case results provided in the original ERG report, but have been unable to calibrate the models in time for submission of this critique. This is because several changes made by the company have not been implemented using switches within the model.

The ERG accept several of the company's proposed amendments to the base case assumptions as reasonable. However, there remain three areas of disagreement between the company and the ERG. The ERG prefers the following assumptions applied to the company's revised base case analysis:

A) the use of the mean daily dose of chlormethine gel to calculate treatment acquisition costs;
B) the use of phan et al data (with appropriate adjustment for the effect of maintenance phototherapy) as the source of time to relapse following phototherapy response;
C) the removal of chlormethine gel from the 'Progressed from 1L' treatment basket.

Applying all of ERGs preferred assumptions and including the adjustment of the progression post CR on phototherapy (reducing the time to progression by about half) results in an ICER of £62,457. Table 2 describes these results and Table 3 illustrates the impact of subgroup analyses on the ICER.

Table 2 Cumulative impact of ERG preferred assumptions on the company revised ICER

	Chlormethine gel		Phototherapy					
Analysis	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. cost**	**Inc. QALY**	**Deterministic ICER**	**NMB**
Company revised base case	£238,582	9.07	£251,092	8.84	-£12,510	0.23	Phototherapy dominated	£19,422
+ (0%/50%/50% chlormethine gel/bexarotene/pegylated IFN-α, as per phototherapy)	£239,834	9.07	£251,092	8.84	-£11,258	0.24	Phototherapy dominated	£18,333
+ Source Phan et al. 2019 for the time to progression post CR and PR for phototherapy (applied separately to progression for PUVA and UVB), and adjust the duration of complete response on phototherapy downwards by dividing the mean CR duration by 1.66	£239,834	9.07	£244,181	8.93	-£4,346	0.14	Phototherapy dominated	£8,683

	Chlormethine gel		Phototherapy					
Analysis	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. cost**	**Inc. QALY**	**Deterministic ICER**	**NMB**
+ Chlormethine gel treatment acquisition costs based on mean daily gel usage (2.8g)	£253,335	9.07	£244,181	8.93	£9,155	0.14	£63,335	-£4,818
+ Cost of psoralen when on phototherapy	£253,335	9.07	£244,307	8.93	£9,028	0.14	£62,457	-£4,692
ERGs preferred base case analysis	**£253,335**	**9.07**	**£244,307**	**8.93**	**£9,028**	**0.14**	**£62,457**	**-£4,692**
Additional scenario analysis applied to ERG preferred base case								
Assume that relapse post PR = relapse post initial PD for chlormethine gel (see Issue 6 above)	£253,027	9.04	£244,307	8.93	£8,719	0.11	£78,640	-£5,393

Table 3 ERGs subgroup analysis on ERGs preferred base case

	Chlormethine gel		Phototherapy					
Analysis	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. cost**	**Inc. QALY**	**Deterministic ICER**	**NMB**
ERGs preferred base case	£253,335	9.07	£244,307	8.93	£9,028	0.14	£62,457	-£4,692
Model population: early stage MF-CTCL (Stage IA / IIA)	£250,329	10.71	£247,226	10.57	£3,103	0.15	£21,355	£1,256
Model population: later stage MF-CTCL (Stage IIB+ only)	£264,489	2.71	£232,171	2.56	£32,318	0.14	£227,954	-£28,065

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Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma [ID1589]

Additional information and scenario analyses provided in advance of 1st AC meeting

Produced by Aberdeen HTA Group

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The ERG have provided the following additional information to help address queries raised at the PMB (dated: 07/07/2020).

Point 1: Please provide additional information on efficacy data of Phan et al. vs. 7 studies identified by the company on BAD guidelines – what difference does it tell us regarding the effectiveness of phototherapy

Parameter	7 phototherapy studies from CS	Meta-analysed outcomes from Phan et al., weighted by type of phototherapy (PUVA / UVB) applied by stage	Study 201 (Chlormethine gel for comparison)
CR	73.2%	Stage IA: [redacted] Stage IB/IIA: [redacted]	[redacted]
PR	20.8%	Stage IA: [redacted] Stage IB/IIA: [redacted]	[redacted]

ERG notes:

1) The choice of Phan et al. or the 7 phototherapy studies in the original CS, sourced from the BAD guidelines has little impact on the probability of achieving a CR or PR on phototherapy. The company and ERG are in agreement regarding the use of Phan et al. as the preferred data source for CR / PR due to the additional granularity of data (by type of phototherapy and stage of disease) that Phan et al. provides.
2) Of importance to note however is the substantial difference between phototherapy and chlormethine gel (differences in how CR and PR are measured across different studies mean that it is incredibly difficult to draw any robust comparisons between phototherapy and chlormethine gel) – note the key point remains that we cannot accurately determine the incremental clinical benefit of chlormethine gel vs. phototherapy.
3) Lower CR actually favours chlormethine gel, because time to progression into the 2nd line skin therapy (i.e. 'Progressed from 1L') is shorter after CR than PR (assumption is that patients removed from treatment following CR relapse more quickly) – validity of this assumption requires clinical expert input. The impact of this can be seen on the traces below (see Point 2).

Point 2: Scenario analyses with respect to time horizon:

Model traces provided below:

ERG preferred base case

	Chlormethine gel						Phototherapy					
Year	Initial health state (low skin burden)	Initial health state (high skin burden)	No skin burden (CR)	Reduced skin burden (PR)	Progressed from 1L	Dead	Initial health state (low skin burden)	Initial health state (high skin burden)	No skin burden (CR)	Reduced skin burden (PR)	Progressed from 1L	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.001	0.001	0.421	0.117	0.416	0.044
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.000	0.000	0.187	0.059	0.666	0.088
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.000	0.000	0.017	0.008	0.777	0.198
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.000	0.000	0.000	0.000	0.665	0.335

Company revised base case

	Chlormethine gel						Phototherapy					
Year	Initial health state (low skin burden)	Initial health state (high skin burden)	No skin burden (CR)	Reduced skin burden (PR)	Progressed from 1L	Dead	Initial health state (low skin burden)	Initial health state (high skin burden)	No skin burden (CR)	Reduced skin burden (PR)	Progressed from 1L	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.001	0.001	0.243	0.090	0.621	0.044
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.000	0.000	0.051	0.037	0.824	0.088
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.000	0.000	0.001	0.004	0.796	0.198
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.000	0.000	0.000	0.000	0.665	0.335

ERG Notes:

1) Phototherapy arm progresses more quickly into 'Progressed from 1L' state because CR is higher on phototherapy and progression time post CR is shorter than progression time post PR.

Table 1 Scenario analyses exploring impact of different time horizons on ERG preferred ICER

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
FULL cohort population					
ERG preferred base case					
Chlormethine gel	£253,335	9.07	-	-	-
Phototherapy (PUVA/UVB)	£244,307	8.93	£9,028	0.14	£62,457
5 year time horizon					
Chlormethine gel	£92,359	3.20	-	-	-
Phototherapy (PUVA/UVB)	£75,749	3.15	£16,611	0.05	£365,666
10 year time horizon					
Chlormethine gel	£146,496	5.32	-	-	-
Phototherapy (PUVA/UVB)	£135,453	5.20	£11,044	0.13	£86,705
20 year time horizon					
Chlormethine gel	£212,236	7.73	-	-	-
Phototherapy (PUVA/UVB)	£203,132	7.59	£9,104	0.14	£62,957
Early Stage (Stage IA/IIA) only					
ERG preferred base case					
Chlormethine gel	£250,329	10.71	-	-	-
Phototherapy (PUVA/UVB)	£247,226	10.57	£3,103	0.15	£21,355
5 year time horizon					
Chlormethine gel	£70,304	3.53	-	-	-
Phototherapy (PUVA/UVB)	£58,087	3.49	£12,217	0.05	£259,682
10 year time horizon					
Chlormethine gel	£124,024	6.06	-	-	-
Phototherapy (PUVA/UVB)	£118,465	5.94	£5,559	0.13	£44,005
20 year time horizon					
Chlormethine gel	£199,749	9.04	-	-	-
Phototherapy (PUVA/UVB)	£196,549	8.89	£3,200	0.15	£22,002

ERG notes:

1) The ICER is substantially lower for early stage disease, primarily due to less gel usage for lower % BSA affected on average

2) The model results are heavily influenced by the time the cohort spends in the semi-absorbing 'progressed from 1L' health state. Treatment which delay entry to the state and / or reduce the proportion of the cohort entering the state are more likely to be cost-effective as long term costs of 2nd line skin treatments and QALY losses are incurred for remaining life years. As per the traces above, phototherapy cohort enter this state earlier and thus spend longer in the state (due to higher CR on phototherapy, and shorter time to progression following CR than PR).

Point 3: Data from Phan et al. vs. Whittaker et al. used in the model

Parameter	Company preferred Whittaker et al.	ERG preferred Phan et al. (adjusted for maintenance phototherapy)
Median time to progression following CR	6.48 months	11.69 months (weighted average of PUVA and UVB)

ERG notes:

1) ERG approach to remove the effect of maintenance phototherapy likely over adjusts as only 5/7 included studies in Phan et al. included maintenance; time to relapse post CR is likely longer; true ICER may be higher than reported.

2) See the ERG critique of company's response to TE for a full comparison of the characteristics of Phan et al. vs. Whittaker et al.

Point 4: Summary of Issue 6 as a whole:

ERG summary of issue six provided in two tables below:

Issue 6 –Time to progression of skin burden following CR & PR – Chlormethine gel

Parameter	Company submission	ERG Critique	Company post TE	ERG post TE critique
Progression post CR	Assume equal to phototherapy (sourced from Whittaker et al)	Prefers Kim et al. as provides data for similar treatment (topical nitrogen mustard)	Company agrees with use of Kim et al.	Agree
Progression post PR	Due to lack of data, assume equal to progression from initial skin burden state (data from Study 201)	Assumption is not evidence based, raises uncertainty	Re-analysis of Study 201, using data from 2 patients to inform parameter	Agree, but notes substantial uncertainty remains due to N=2

Issue 6 –Time to progression of skin burden following CR & PR – Phototherapy

Parameter	Company submission	ERG Critique	Company post TE	ERG post TE critique
Progression post CR	Whittaker et al.	Prefer Phan et al. - larger sample - Meta-analysis - Reports data by type of phototherapy (PUVA / UVB) - Consistent parameter source	Retains Whittaker et al. - Phan et al. over-estimates duration of CR - Includes effect of maintenance phototherapy (not used in UK)	- Company's concerns about maintenance phototherapy are legitimate - Retain Phan et al. as preferred source but adjust CR duration down to remove the effect of maintenance
Progression post PR	Equal to progression from initial skin burden (assumed equal to phototherapy treatment duration)	Assumption not evidence based; Prefer Phan et al. weighted by proportion with CR/PR (obtained from Whittaker et al.)	Critique of Phan et al. as per above	- Prefers Phan et al. (no maintenance adjustment) - PR on phototherapy are modelled to receive bexarotene / IFN-a so additional treatment is modelled