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NICE National Institute for Health and Care Excellence

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

2nd Appraisal Committee meeting

Chair presentation

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ERG: Aberdeen Health Technology Assessment Group

Chair: Jane Adam

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Company: Recordati Rare Diseases/ Helsinn Healthcare SA

8th December 2020

Key issues background

- Is this a true alternative to phototherapy, or an additional therapy to be added in (i.e. more of a sequencing issues: multiple times the same decision will be made?)
- Effectiveness of phototherapy, both response and duration of response – debated
- No direct comparison with phototherapy, but all scenario analyses give chlormethine gel more QALYs than phototherapy, although very wide range (0.07 to 0.43)
- Disagreement on gel costs between company, ERG and clinical experts
- Sequencing of treatment and timing of entering systemic therapy – debated
- Incremental costs widely variable from savings of 12.5k (company) to +9k (ERG) in the original model
- New model incremental costs have a higher and wider range
- Leads to major differences in ICER, not just between company and ERG but also between 1st and 2nd model

Key clinical issues

- Is the extent of skin disease directly correlated with or separate from staging of disease?
- What is the difference between patches/plaques and tumours on the skin?
- Is systemic therapy given when disease spreads to other organs, or may it be given when skin disease alone becomes uncontrolled? i.e. does control of skin disease delay systemic treatment even though it does not alter systemic disease course?
- Who would most benefit? i.e. are there patient groups in whom it might be more cost effective?
- If phototherapy is not suitable, what is the alternative?
- How long would each 60g tube last on average?

Key cost issues

- **Model structure:**
  - Revised model structure more appropriate for decision making?
    - addition of new state ‘skin directed therapies’ for the chlormethine arm only?
    - allow repeat courses of treatment for patients who have an initial response to treatment?
- **Data used for phototherapy effectiveness parameters:**
  - Which source is preferable for phototherapy response rates and duration of response?
- **Treatment acquisition costs:**
  - What is the likely average daily dose of chlormethine gel?

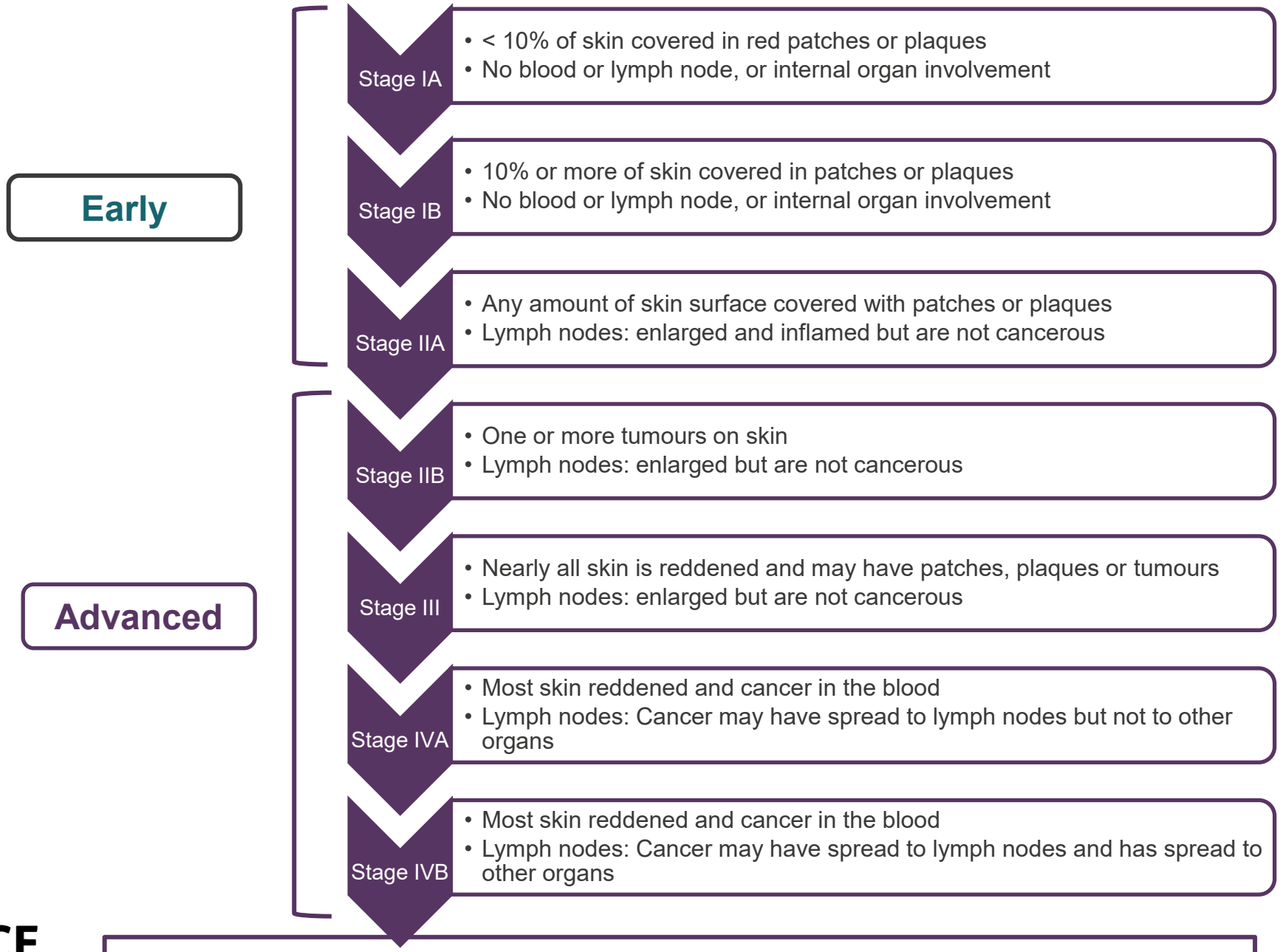
Chlormethine gel (Ledaga, Recordati Rare Diseases/ Helsinn Healthcare SA)

Mechanism	• A cytotoxic, bifunctional DNA alkylating agent which inhibits rapidly proliferating cells by disrupting DNA replication through various mechanisms such as DNA cross-linking, abnormal base pairing, or nucleic acid depurination. • Previously available as ointment (withdrawn)
Marketing authorisation received 3rd March 2017	• For the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma in adult patients.
Administration and dose	• Topical therapy applied to affected areas of skin once daily • Chlormethine gel contains chlormethine at a concentration of 0.016% (w/w) (160 micrograms/gram), equivalent to 0.02% (w/w) chlormethine hydrochloride
Indicative list price	• £1,000 per 60g tube (excluding VAT) • Patient access scheme (PAS) now in place: simple discount applies.

Committee considerations at ACM1 (1)

- Chlormethine gel could be an alternative treatment option for people who cannot have phototherapy or for whom it is more convenient because there is no need for regular hospital appointments.
- Chlormethine gel addresses symptoms and improve quality of life but is not a cure.
- Chlormethine gel is likely to be used for early disease amongst a battery of skin directed treatments. People will cycle through these treatments until symptoms no longer respond. In advanced disease, it may be used in combination with systemic therapies.
- The main trial (study 201):
  - includes people with early stage disease (IA, IB, IIA) only
  - includes a comparator (chlormethine ointment) that is no longer used.
- The available evidence is not generalisable to advanced disease (stage IIB+).

Staging of cutaneous T-cell lymphoma

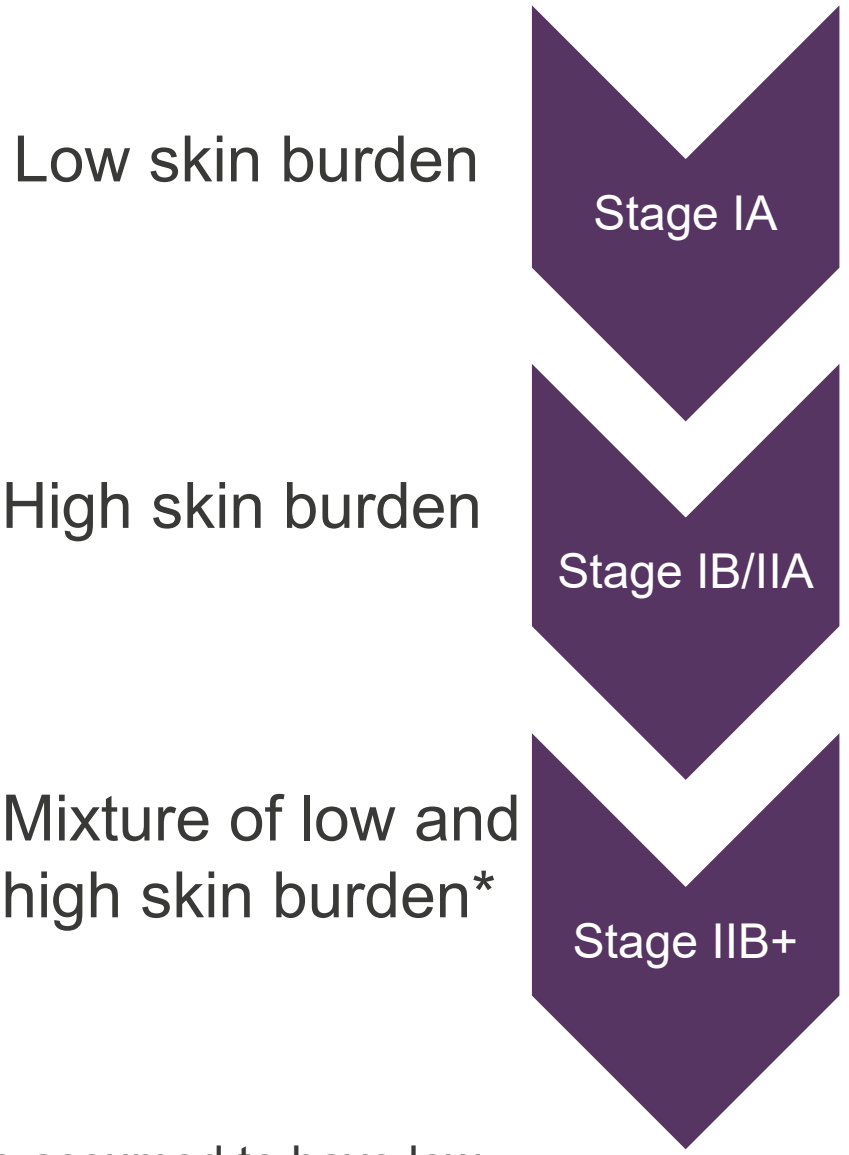


Source of information: https://www.clfoundation.org/

Relationship between skin burden and disease staging

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



Source: table 17 of ERG report

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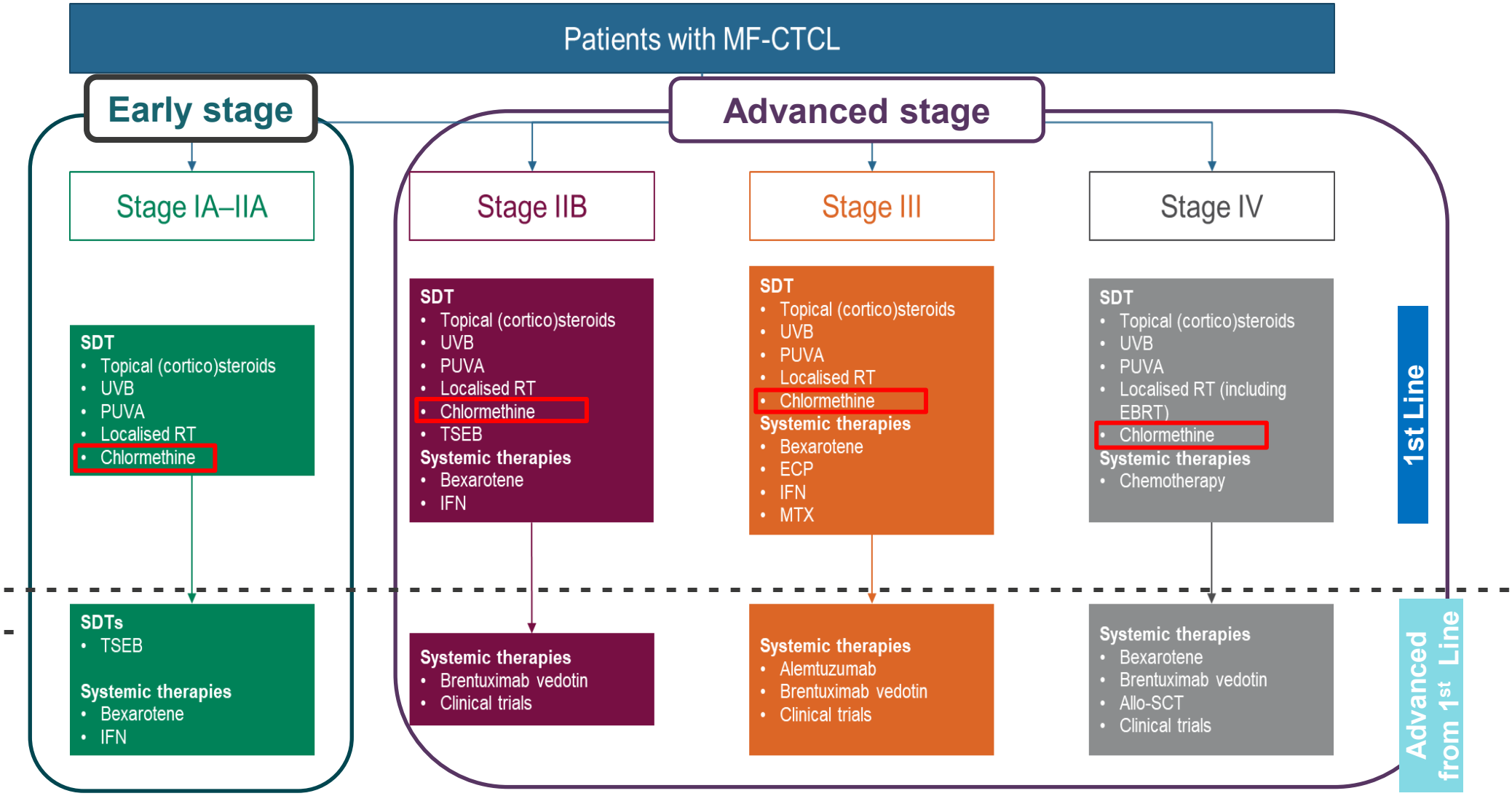
* In model those patients with stage IIB+ were assumed to have low ([redacted]) and high ([redacted]) skin burden respectively.

Treatment pathway



Early stage disease: first-line as one of a number of options patient cycle through until symptoms no longer respond; **Advanced disease**: combination with systemic therapies

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Source: adapted from Figure 2, company submission

Key trial: Study 201

Trial design	A multi-centre, randomised (1:1, observer-blind, active comparator phase II study (n=260))
Intervention	Chlormethine gel (0.02%) (n=130)
Comparator	Chlormethine ointment (0.02%) (n=130)
Population	Patients with stage IA, IB or IIA MF-CTCL, previously treated with at least one skin-directed therapy for MF-CTCL. [39% with phototherapy, 86% topical corticosteroids] Mean % body surface area affected [redacted] and [redacted] for low and high skin burden respectively*
Outcomes	• **Primary**: CAILS response rate (skin response 50% or more) • **Secondary**: mSWAT response rate (used in the model), time to confirmed CAILS response, time to progression on CAILS score, extent of cutaneous disease
Follow up	• 12 months to assess the potential for the development of secondary non-melanoma skin cancers

Abbreviations: CAILS = composite assessment of index lesion severity, mSWAT = modified severity weighted assessment tool

Advanced stage (stage IIB+) not included

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* These values were used in the model

Study 201 results: ITT including NYU population

		CAILS response	mSWAT response
Response n (%)		Chlormethine gel n=130	Chlormethine gel n=130
OR		76 (58.5)	61 (46.9)
CR		18 (13.8)	[redacted]
PR		58 (44.6)	[redacted]
Response rate (CR+PR) ratio		1.226 (95% CI 0.974-1.552, [redacted])	1.017 (95% CI 0.783-1.321, [redacted])
CAILS response rates (CR+PR) by MF-CTCL stage	**Stage IA**	45 (59.2)	N/A
	Stage IB/IIA	31 (57.4)	
Response rate ratio	**Stage IA**	1.48 (95% CI 1.05-2.14)	
	Stage IB/IIA	1.04 (95% CI 0.75-1.43)	

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

Source: p.5 and tables 9 and 10 ERG report, p.54 to 56 company submission

Study 201 is **a non-inferiority study** comparing chlormethine gel with a treatment not in use (ointment), however, data from it has been used to inform the following parameters in the model:

- the extent of skin involvement
- dosage of chlormethine gel per application
- transition probabilities for chlormethine gel

For modelling, mSWAT has been used (**not** CAILS)

Committee considerations at ACM1 (2)

- Phototherapy: comparator in the company submission but the **relative effectiveness is not known** no head-to-head evidence or a connected network for an indirect comparison.
- The economic model **does not reflect the treatment pathway** in clinical practice related to:
  - the use of multiple skin-directed treatments, treatment length or what happens to people when the disease progresses (including after an initial response – complete or partial – to treatment).
- Mean daily dose of chlormethine gel is unclear (ERG used 2.8g from SPC but company used a smaller value, [redacted]) but has a significant impact on the ICER.
- Model: remaining on bexarotene or peginterferon alfa for life not likely to reflect clinical practice. ERG's scenario analyses with shorter time horizon gave much higher ICERs demonstrating uncertainty with the company's base case.

Cost-Effectiveness results (ACM1)

	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's revised base case post-technical engagement (based on [redacted] dosage)	-£12,510	+0.23	Phototherapy dominated
ERG's preferred base case analysis (based on 2.8g dosage)	+£9,028	+0.14	£62,457

Source: ERG critique, table 2

PAS for subsequent treatment not included in results presented on this slide.

ERG assumptions in preferred base-case:

- 0%/50%/50% chlormethine gel/bexarotene/pegylated IFN-α
- Source Phan et al. 2019 for time to progression post CR and PR for phototherapy (applied separately to progression for PUVA and UVB), and adjusted duration of CR on phototherapy downwards by dividing the mean CR duration by 1.66
- Chlormethine gel treatment acquisition costs based on mean daily gel usage (2.8g)

Preliminary ACD recommendation: Chlormethine gel is not recommended, within its marketing authorisation, for treating mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) in adults.

Post TE: ERG subgroup by stage analysis applied to ERG's preferred base case (2.8g dose) (discussed at ACM1)

	Inc. cost	Inc. QALY	Deterministic ICER
ERG preferred base case	£9,028	0.14	£62,457
Model population: early stage MF-CTCL (Stage IA, IB, IIA)	£3,103	0.15	£21,355
Model population: later stage MF-CTCL (Stage IIB+ only)	£32,318	0.14	£227,954

Source: ERG critique, table 3

ACD consultation responses

Professional organisations / groups	• British Association of Dermatologists (BAD), Therapy & Guidelines sub-committee • Royal College of Physicians • UK Cutaneous Lymphoma Group (UKCLG)
Clinical experts	• 2 individuals
Patient organisations	• Lymphoma Action
Company	• Recordati Rare Diseases/ Helsinn Healthcare SA
Public (web) comments	• Member of the public (n=1)

General disagreement (1)

- Clinical trial and real-world experience dismissed.
- Unfairly dismissed on the ‘grounds that there is “no robust evidence of its effectiveness compared to phototherapy’, “concerns regarding its cost-effectiveness due to the patient pathway being oversimplified” and “uncertainty regarding dose per application of gel”.
- Rejection on the basis of cost efficacy data is withholding an important therapy against expert advice.
- Unfair to dismiss evidence on the basis that the comparator is no longer available in the UK. Study 201 shows it is effective as an ointment but gel is more convenient to prescribe and administer.
- Failure to approve, limits patient and clinician choice; alternative options of topical steroids, phototherapy or radiotherapy are either less effective, more expensive to deliver or less convenient for patients and carers.

General disagreement (2)

- Use in 80s and 90s (as nitrogen mustard) as accepted effective treatment but then deemed unacceptable health risk due to chemotherapy spillage. Usage in Manchester, UK continued until recently. It is being used internationally.
  - After it was discontinued, there was as waiting list of patients who wished to restart, indicating patient acceptance or preference over other therapies.
- NICE has not taken into account that the novel gel (vs the previous preparations) does not require specialised compounding in hospital departments and is cosmetically acceptable to use by patients.
- Small patient group due to rare condition – resulting in few people to advocate for treatment options and difficulty conducting trials.
- No blanket treatment for this disease as each responds uniquely so data gathering problematic.

Addresses unmet need in early stage (1)

- Simpler treatment for stage 1A than phototherapy which may be considered unsuitable.
- Patients with early stage disease often have multiple courses of topical treatments, phototherapy or localised radiotherapy before moving to systemic therapy. Having an additional effective, well tolerated and convenient topical treatment has the potential to delay the need for systemic treatments – an option that would be welcomed by patients and would also reduce the burden on the NHS.
- Topical corticosteroids are cheap and may improve symptoms so should be given prior to chlormethine gel. It is often used during diagnostic delay in early stage. Chlormethine gel does not cause skin damage with atrophy with long term use. Can lead to complete remission in a cohort of patients with stage IA disease.
- No available curative treatments for early disease so unfair and unreasonable to exclude on the basis of a 20% complete response and 50-60% partial response which compares favourable to other anti cutaneous T-cell lymphoma therapy.
- Patients with stage IA to IIA disease in trials heterogenous. Unmet need for effective topical therapies for stage IA patients (other than topical steroids) which chlormethine gel could provide.

Addresses unmet need: impact on QoL (2)

- Improving skin tumour burden will improve quality of life (QoL) which is affected by symptoms (pruritus, pain, burning), emotional distress from visible disfigurement, poor function preventing daily activity
- Too much emphasis on chlormethine not being curative; while acknowledging it is about the impact on symptoms not cure, there is not enough appreciation of the impact of symptoms on day-to-day lives and the potential to significantly improve QoL.
- Long-term and often debilitating condition so priority should be given to consideration of the quality of life of these patients.

Addresses unmet need: advantages over phototherapy (3)

- Phototherapy requires travel to hospital 3x per week for 6-10 weeks. Chlormethine gel is safer, more practical, and has additional economic benefits beyond NHS costs:
  - less travel time/time off work
  - no increase risk of skin cancer from UV light (issue with this lifelong disease)
  - targeted not whole body treatment so unaffected skin is being spared treatment
  - requires space, specialised equipment and staff; unpractical for rural patients
  - no need for blood test monitoring.
- Can be used in the long-term (up to 12 months in study 201 or longer in clinical practice); 2 or more courses of phototherapy may be offered in that time.
- Important during COVID as can be used at home to protect vulnerable group from hospital attendance and reduce hospital footfall. Phototherapy units were closed during COVID-19 as non-essential; chlormethine gel reduced pressure on hospital departments and reduced hospital visits for vulnerable.
- Missed phototherapy treatment can push back treatment timings, it is time consuming and not suitable for all patients due to skin cancer risk.

Key clinical issues

- Is the extent of skin disease directly correlated with or separate from staging of disease?
- What is the difference between patches/plaques and tumours on the skin?
- Is systemic therapy given when disease spreads to other organs, or may it be given when skin disease alone becomes uncontrolled? i.e. does control of skin disease delay systemic treatment even though it does not alter systemic disease course?
- Who would most benefit? i.e. are there patient groups in whom it might be more cost effective?
- If phototherapy is not suitable, what is the alternative?
- How long would each 60g tube last on average?

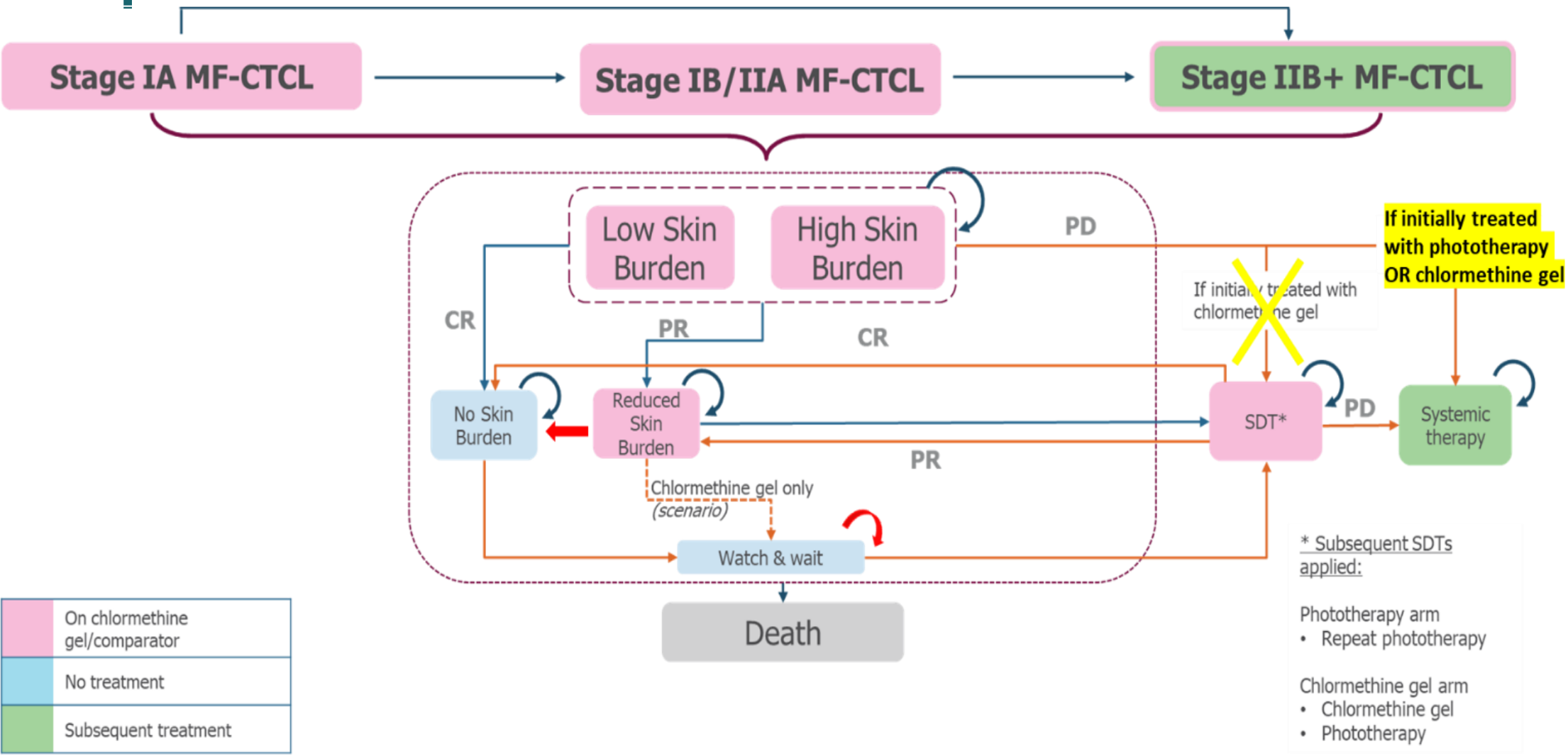
Specific comments about evidence and economic analyses

- Concern with ERG estimate of a ‘typical patient’ use of chlormethine gel per month rather than lower estimates provided by clinical experts or the studies provided by the company. Unclear why committee chose ERG estimate without evidence to show it is correct.
- In study 201 many patients would have used the gel on the whole skin surface; reported 1.8g daily usage would still be an overestimate compared to likely usage in the UK, where whole body application has never been advocated.
- Historical response rates (~2003) of topical chlormethine gel are similar to those from phototherapy considered in the appraisal – all based on retrospective studies. Lower response rates in study 201 may be because of relapse from prior treatment. So may not be comparable to the phototherapy trials, particularly in European studies where phototherapy was first line.
- Three phototherapy studies preferred by the ERG (Phan et al) did not use comparable definitions for complete response (CR) using ‘clearance’ of between 80-95% instead which negates the comparability of CR with Chlormethine gel in the 201 trial.
- Many of the retrospective and non-RCTs included in Phan et al will have allowed concomitant use of topical corticosteroids for symptom control and phototherapy; study 201 (chlormethine) did not.

Company Response – summary

- Little consideration this is a rare disease, therefore problems conducting research in this area. This has lead to a lack of treatment options which create high unmet need. This has created difficulty comparing to phototherapy which has limited and poor quality evidence.
- While issues with quality for most of the evidence on phototherapy, the phototherapy effectiveness has been overstated.
- Amended model structure and shortened time horizon
  - 20 year time horizon
  - new states ‘watch and wait’ and ‘skin directed therapy’ (SDT); ‘progressed from 1L’ renamed to systemic therapy
  - those who do not respond to treatment (considered ‘progressed skin disease’ or PD) in enter SDT rather than going straight to systemic therapy (chlormethine arm only).
- Amended effectiveness parameters for phototherapy used in the model (complete response (CR) rate, partial response (PR) rate, and duration of response).
- Disagreement about dosage used for chlormethine gel.
- Commercial arrangement submitted and accepted by NHSE.

Updated model structure and ERG amendments



CR: complete response; MF-CTCL: mycosis fungoides cutaneous T-cell lymphoma; PD: progressive disease; PR: partial response; SDT: skin-directed therapy. (arrows: blue - old transitions, orange - new transitions, red - added by the ERG to represent model)

Source: Figure 1, ERG critique (adapted from company response – amendments in yellow)

When do you receive systemic therapy, only when you have systemic disease or when skin disease is uncontrollable?

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Issue: model structure - addition of new state 'skin directed therapies' for chlormethine arm only

- For chlormethine arm only, those with progressed disease enter a new 'skin directed therapy' state where they receive subsequent treatments.
- This state includes patients who achieve an initial response to chlormethine gel, but subsequently relapse and those who do not achieve a CR or PR (those with progressed disease).

ERG response

- Addition of new state reasonable but phototherapy arm excluded and provides unfair advantage for chlormethine gel.
- Suggest that some with initial progressed disease in both arms can transition directly to systemic therapy. Allows for phototherapy arm to be treated with interferon or bexarotene but includes 13-week course of phototherapy for those progressing from chlormethine.
  - Results in a treatment distribution of bexarotene (44.65%), IFN-a (44.65%) and phototherapy (10.71%) (rather than 50:50 for systemic therapies).
  - Ensures 'SDT' state includes only patients who have previously responded to therapy; supported by ERG's clinical expert which suggests those with progressed disease may have more treatment resistant disease and cannot be considered equal to previous responders.

Does committee prefer the revisions suggested by the ERG to the company's proposed new model structure?

Issue: model structure - allow repeat courses of treatment for patients who have an initial response to treatment (1)

- 'Watch and wait' uses utility equal to 'reduced skin burden' state; 'SDT' uses utility equal to the 'initial skin burden' health state.
- SDT state allows for repeat courses of chlormethine gel or phototherapy:
  - patients treated with phototherapy are treated with a repeat course of phototherapy
  - patients treated with chlormethine gel treated are treated with second round of chlormethine gel treatment (80%) or switch to phototherapy (20%) for subsequent lines of treatment (based on study 201).

  (health state costs and efficacy of treatment depend on proportion treated with either treatment)

ERG response

- Agree with assumptions re: utility in absence of robust data.
- Assumption that phototherapy patients cannot receive chlormethine gel may be appropriate but may not reflect clinical practice if chlormethine gel was available.
- Prefer if 100% of chlormethine gel patients are retreated with chlormethine gel.

Issue: model structure - allow repeat courses of treatment for patients who have an initial response to treatment (2)

- Effectiveness of second line treatments in SDT state (CR, PR, duration of response) is equal to initial treatment.

ERG response

- Similar effectiveness in first and second line is not plausible (ERG's clinical expert) – additional rounds of treatment have decreasing effectiveness in clinical practice.
- No evidence on effectiveness of subsequent treatment lines but prefer ERG clinical expert opinion that CR and PR for both treatments might be 75% of response achieved 1st line. Duration of response might be 50% of 1st line.
  - ERG have created an additional state 'no skin burden 2+' to allow for differential effectiveness for both model arms and for first and subsequent lines – different percentage reductions could be explored in scenario analyses
- The new model structure submitted by the company with ERG modifications to allow differential treatment effectiveness for subsequent lines of treatment better reflects clinical practice.

Does committee agree that similar effectiveness in first and second line is not plausible for chlormethine gel and phototherapy?

Issue: phototherapy effectiveness (1)

From ACD : *The clinical experts said that the reason the response rates in Study 201 appeared lower than the phototherapy trials is that Study 201 used clear criteria for assessing response (CAILS and mSWAT), whereas most of the phototherapy trials were based on less reliable assessments by clinicians.*
AND
…the true clinical effectiveness of chlormethine gel compared with phototherapy is not known, given the high uncertainty associated with the unadjusted naive comparison.

Company response to ACD:

- Poor quality phototherapy evidence was considered but efficacy is overstated. Concerns apply to all phototherapy studies, both in company submission and in the Phan et al study preferred by the ERG, but Whittaker is controlled, prospective and uses an objective scoring system.
- [redacted]
- Studies in Phan et al are from non-UK settings so maybe less generalisable to the real-world efficacy of phototherapy in the UK.
- Updated submission used Phan et al for CR, PR and PD rates but PROCLIPI in scenario analyses. (company prefers the later)

Issue: phototherapy effectiveness (2)

ERG response:

- Whittaker et al uses different response measurement tool than study 201 but it also has a small sample size and excludes stage 1A disease.
- Consistency of outcome measures helps to minimise uncertainty but no data provided on duration of response from PROCLIPI registry so it can not be used to derive all phototherapy effectiveness parameters.
- Response rate from Phan et al are not unreasonable or inconsistent with study 201. Rates are consistent with:
  - NCT01686594 RCT which measured CR and PR using mSWAT as Study 201 did (CR=70% and PR=30% compared with Phan et al: CR: Stage IA-IIA: 70.24%, Stage IB: 61.79%, and PR: Stage IA-IIA: 22.56%, Stage IB: 19.83%).
  - seven studies originally identified by the company from the BAD guidelines.
- Prefer Phan et al because of consistency in the source of data for response rate and duration (reducing some potential bias). It also separates outcomes by type of phototherapy and stage of disease not available from other studies.
- ERG agree that adjustment of phototherapy response duration is appropriate to account for maintenance phototherapy in some Phan et al. studies. Likely conservative estimate as not all studies included maintenance phototherapy.

Issue: phototherapy effectiveness (3)

- The sources of the CR, PR and PD/failed response are the same for both the ERG and company base case (from Phan et al 2019)

	ERG			Company		
	Value		Source	Value		Source
	Stage IA (low skin burden)	Stage IB (high skin burden)		Stage IA (low skin burden)	Stage IB (high skin burden)	
Duration of CR (months)	PUVA:17.40 UVB:7.76		Phan et al. 2019	6.48*		Whittaker et al. 2012
Duration of PR (months)	PUVA:21.70 UVB:9.68		Phan et al. 2019	N/A†		Phan et al. 2019

Source: Table 1, ERG critique

* While Whittaker et al 2012 excluded stage IA patients, this value was applied to both stages in the model.
†The transition *probability for failure following a PR* used in the company's preferred base case is assumed to be equal to the *probability of initial progressive disease* (obtained as failed response from Phan et al.), and as such is not derived from any direct information on duration of PR.

Which source is preferable for phototherapy duration of response?

Issue: chlormethine gel treatment acquisition costs (1)

Committee conclusion at CM1: *The committee concluded that the average daily dose of chlormethine gel, and therefore the costs, were uncertain*.

Company response to ACD:

- It is not uncertain as the company have proven this from individual patient data (IPD) from Study 201, using transparent analyses: [redacted]g provided by the company's derivation and analysis (which the ERG confirmed in response to TE is accurate).
- Not able to reproduce the mean dose specified in the SmPC for Valchlor® (2.81g; also preferred by the ERG) despite this being derived from the same patients in Study 201 (this value was generated before Helsinn acquired chlormethine gel).
- If ERG wish to use SmPC, they should also use the consumption by low and high skin burden estimates there ([redacted]g and [redacted]g respectively, as opposed to 1.14g and 5.10g).

Issue: chlormethine gel treatment acquisition costs (2)

ERG response:

- ERG have been able to replicate [redacted]g (using calculation 'average daily dose per patient = [total number of returned tubes*25g/365.25]/[redacted]') but think it underestimates mean daily dose. Should account for time on treatment, rather than assuming a full year.
- Concerned the use of complete responders in the company's calculation of daily usage underestimates daily usage for patients on treatment.
- Duration of study treatment needed to more accurately estimate mean dosage.
- The 60-day shelf life suggests a minimum of 6-tubes per year (0.99g/day). However, the company calculation of [redacted]g includes some participants from Study 201 where <0.99g/day was used. This likely underestimates the mean.
- ERG's preferred estimate of 2.81g from Valchlor® SmPC:
  - incorporates individual patients' total days on study drug – company have not provided this at patient level but ERG feels it would enable replication of this figure.
  - is from safety set which only excludes one patient who did not receive treatment (minimal – 0.05 g – impact on mean).
  - is conservative.
- Agree with usage of consumption rates of split by low and high skin burden and have used ([redacted]g and [redacted]g) from Valchlor® SmPC in updated analyses in their base case.

Issue: chlormethine gel treatment acquisition costs (3)

From ACD: …*The clinical experts explained that in stage 1B most people have limited skin disease, and that people with advanced disease do not necessarily need more gel…. estimated that people would use 1 tube every 1 to 2 months, which is 6 to 12 tubes a year with a mean daily dose of approximately 1g to 2g and lower than what was estimated by both the company and the ERG.*

Company response:

- Shows the company's IPD analysis may be conservative compared with expert opinion.
- IPD from PROVe trial (submitted with ACD response) also shows mean daily dosage maybe lower in a real-world than a trial setting.
  - [redacted]g and [redacted]g mean daily dose for low and high skin burden patients, respectively (compared with [redacted]g and [redacted]g)
  - Note PROVe trial included use of concomitant medication (not permitted in study 201), and only a small proportion of all patients could contribute to dosing calculations (because lack of data on body surface area for patients that data on number of tubes dispensed and duration of treatment were available).

ERG response:

- Accept some heterogeneity in practice exists, but important same data which is used to derive effectiveness parameters are used to derive treatment acquisition costs. (Unclear how any changes in dosage to study 201 may modify treatment effectiveness).
- Agree with company study 201 should inform treatment acquisition costs but disagree on the value chosen (prefer 2.81g to [redacted]g).

Issue: chlormethine gel treatment acquisition costs (4)

From ACD: *…"the company's model did not account for people keeping unfinished tubes, or not attending follow-up appointments".*

Company response:

- Study 201 Clinical Study Report outlines the procedure for handling containers including labelling, recording numbers of dispensed containers, reminders for returning all containers and unused contents at each visit.
- Only [redacted] patients ([redacted]) in the chlormethine gel arm were lost to follow-up in Study 201, suggesting that the vast majority of patients are accounted for and thus would not have discontinued without returning tubes at subsequent visits

ERG response:

- Number of dispensed rather than returned tubes more accurate.
- FDA documentation shows at least [redacted] patients did not return containers; feasible to assume there may be discrepancy between dispensed and returned tubes for other patients.
- Accept the proportion lost to follow-up is small but note that any bias caused from loss of follow-up would increase treatment acquisition costs.
- Consider the ERG estimate to be accurate, justified and conservative

What is the likely average daily dose of chlormethine gel?

Cost-Effectiveness results (ACM1)

	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's revised base case post-technical engagement (based on [redacted] dosage)	-£12,510	+0.23	Phototherapy dominated
ERG's preferred base case analysis (based on 2.8g dosage)	+£9,028	+0.14	£62,457

Source: ERG critique, table 2

PAS for subsequent treatment not included in results presented on this slide.

ERG assumptions in preferred base-case:

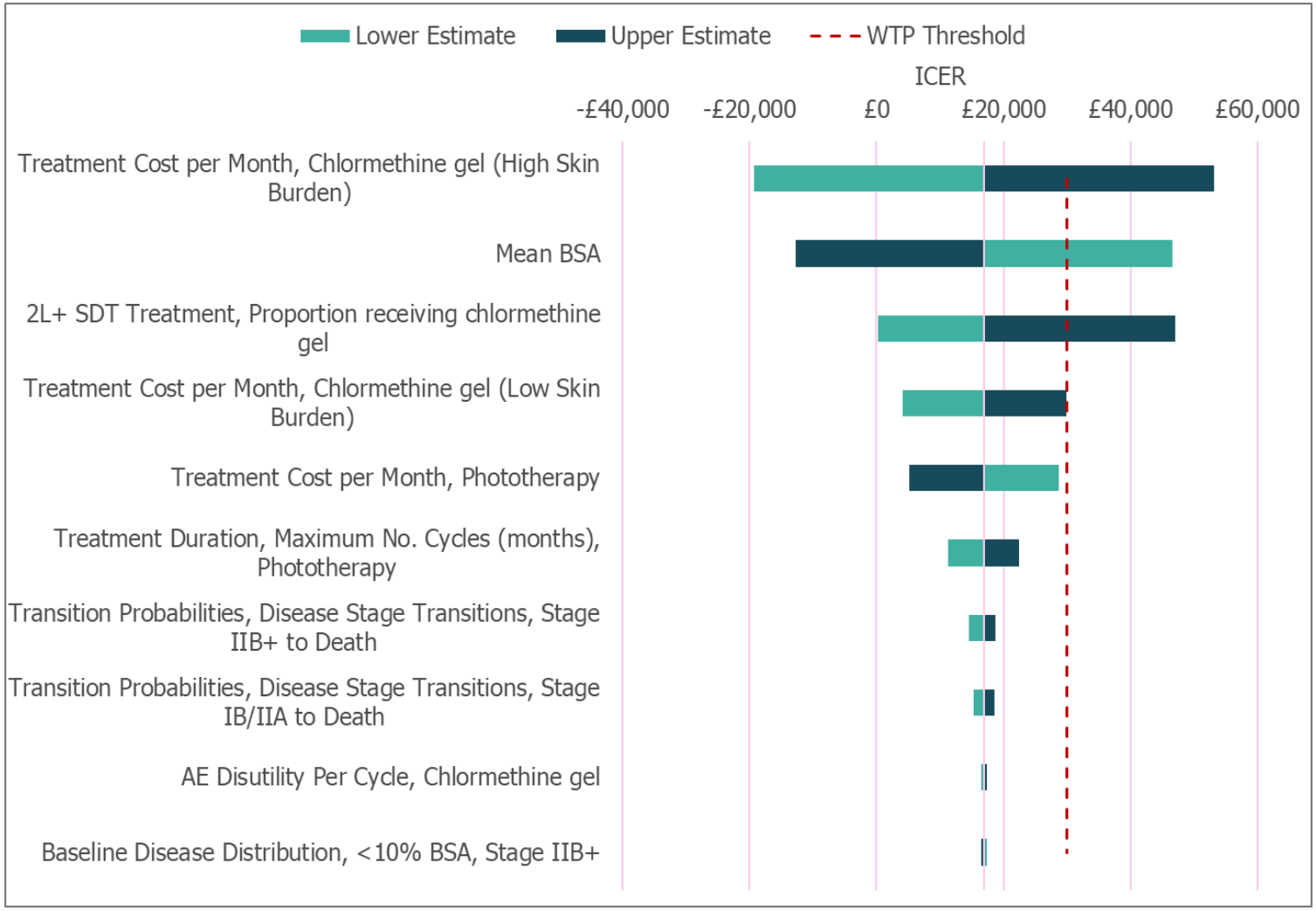
- 0%/50%/50% chlormethine gel/bexarotene/pegylated IFN-α
- Source Phan et al. 2019 for time to progression post CR and PR for phototherapy (applied separately to progression for PUVA and UVB), and adjusted duration of CR on phototherapy downwards by dividing the mean CR duration by 1.66
- Chlormethine gel treatment acquisition costs based on mean daily gel usage (2.8g)

Company's updated base case (chlormethine gel PAS)

- Summary of assumptions in company's updated base case:
  - time horizon reduced to 20 years
  - new states 'watch and wait' and 'skin-directed therapy' (progressed from 1L renamed to systemic therapy) [SDT state allows patients to use other treatments, better reflecting clinical practice]
  - Patients with initial response are able to repeat courses of treatment

Treatment	Incremental costs	Incremental QALYs	ICER (£/QALYS)
Company revised base-case (deterministic)			
Chlormethine gel	-	-	-
Phototherapy (PUVA/UVB)	[redacted]	0.33	[redacted]

Company deterministic sensitivity analysis – 10 most influential parameters (list price)



ERG comment: The ERG note that the tornado diagrams do not include uncertainty surrounding transition probabilities between skin burden states in the model.

Source: company ACD response, figure 4

Company's updated scenario analyses (1/3)

	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	0.33	[redacted]
1) 20% discount for bexarotene	[redacted]	0.33	[redacted]
2) 30% discount for bexarotene	[redacted]	0.33	[redacted]
3) ERG preferred source for relapse after CR or PR	[redacted]	0.14	[redacted]
4) Early population only*	[redacted]	0.35	[redacted]
5) PROCLIPI for CR and PR	[redacted]	0.43	[redacted]
6) No adverse events for chlormethine gel	[redacted]	0.36	[redacted]

* Note that there was an error in the company submission which had this also numbered as 3. This has been corrected here, resulting in the subsequent numbers being different from the company submission.

Company's updated scenario analyses (2/3)

	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	0.33	[redacted]
7) Stopping rule: Study 201 efficacy after 12 months	[redacted]	0.34	[redacted]
8) Stopping rule as #7 above + early population only	[redacted]	0.37	[redacted]
9) Stopping rule as #8 above + ERG preferred source for relapse after CR or PR + 20% discount for bexarotene	[redacted]	0.19	[redacted]
10) Stopping rule as #8 above + ERG preferred source for relapse after CR or PR + 30% discount for bexarotene	[redacted]	0.19	[redacted]
11) Stopping rule: watch and wait efficacy after 12 months	[redacted]	0.28	[redacted]

Company's updated scenario analyses (3/3)

	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	0.33	[redacted]
12) 100% of patients receiving chlormethine gel in SDT health state	[redacted]	0.28	[redacted]
13) 0% of patients receiving chlormethine gel in SDT health state	[redacted]	0.38	[redacted]
14) Dosing as per Valchlor® summary of product characteristics by disease stage	[redacted]	0.33	[redacted]

Cost-Effectiveness results (ACM1)

	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's revised base case post-technical engagement (based on [redacted] dosage)	-£12,510	+0.23	Phototherapy dominated
ERG's preferred base case analysis (based on 2.8g dosage)	+£9,028	+0.14	£62,457

Source: ERG critique, table 2

PAS for subsequent treatment not included in results presented on this slide.

ERG assumptions in preferred base-case:

- 0%/50%/50% chlormethine gel/bexarotene/pegylated IFN-α
- Source Phan et al. 2019 for time to progression post CR and PR for phototherapy (applied separately to progression for PUVA and UVB), and adjusted duration of CR on phototherapy downwards by dividing the mean CR duration by 1.66
- Chlormethine gel treatment acquisition costs based on mean daily gel usage (2.8g)

Cumulative impact of ERG preferred assumptions on the ICER (with PAS)

	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company revised base case	[redacted]	0.33	[redacted]
1) Phan et al used for phototherapy effectiveness data (duration of CR & PR)	[redacted]	0.14	[redacted]
2) Allow chlormethine patients to progress straight into systemic therapy	[redacted]	0.07	[redacted]
3) Reduced effectiveness for 2nd and further rounds of skin directed therapy for patients who respond but relapse	[redacted]	0.22	[redacted]
4) Reduced effectiveness of phototherapy for patients with progressed disease after chlormethine in the systemic therapy state	[redacted]	0.21	[redacted]
5) ERG preferred base case*	[redacted]	0.21	[redacted]

Source: table 1, ERG critique

*used mean daily chlormethine gel dose from Valchlor® SmPC by disease stage ([redacted] for stage I and [redacted] for stage IB/IIA)

ERG's additional scenario analyses (with PAS)

	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG preferred base case	[redacted]	0.21	[redacted]
Model population early stage (IA, IB, IIA)	[redacted]	0.24	[redacted]
Model population later stage (stage IIB+)	[redacted]	0.10	[redacted]
10-year time horizon	[redacted]	0.06	[redacted]
Lifetime horizon	[redacted]	0.29	[redacted]
Whittaker 2012 for phototherapy response rates and duration of response	[redacted]	0.13	[redacted]
Stopping rule for chlormethine gel: watch and wait after 12 months	[redacted]	0.13	[redacted]

Source: table 2, ERG critique

Key cost issues

- **Model structure:**
  - Revised model structure more appropriate for decision making?
    - addition of new state ‘skin directed therapies’ for the chlormethine arm only?
    - allow repeat courses of treatment for patients who have an initial response to treatment?
- **Data used for phototherapy effectiveness parameters:**
  - Which source is preferable for phototherapy response rates and duration of response?
- **Treatment acquisition costs:**
  - What is the likely average daily dose of chlormethine gel?