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

Lead team presentation

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Company: Recordati Rare Diseases/ Helsinn Healthcare SA

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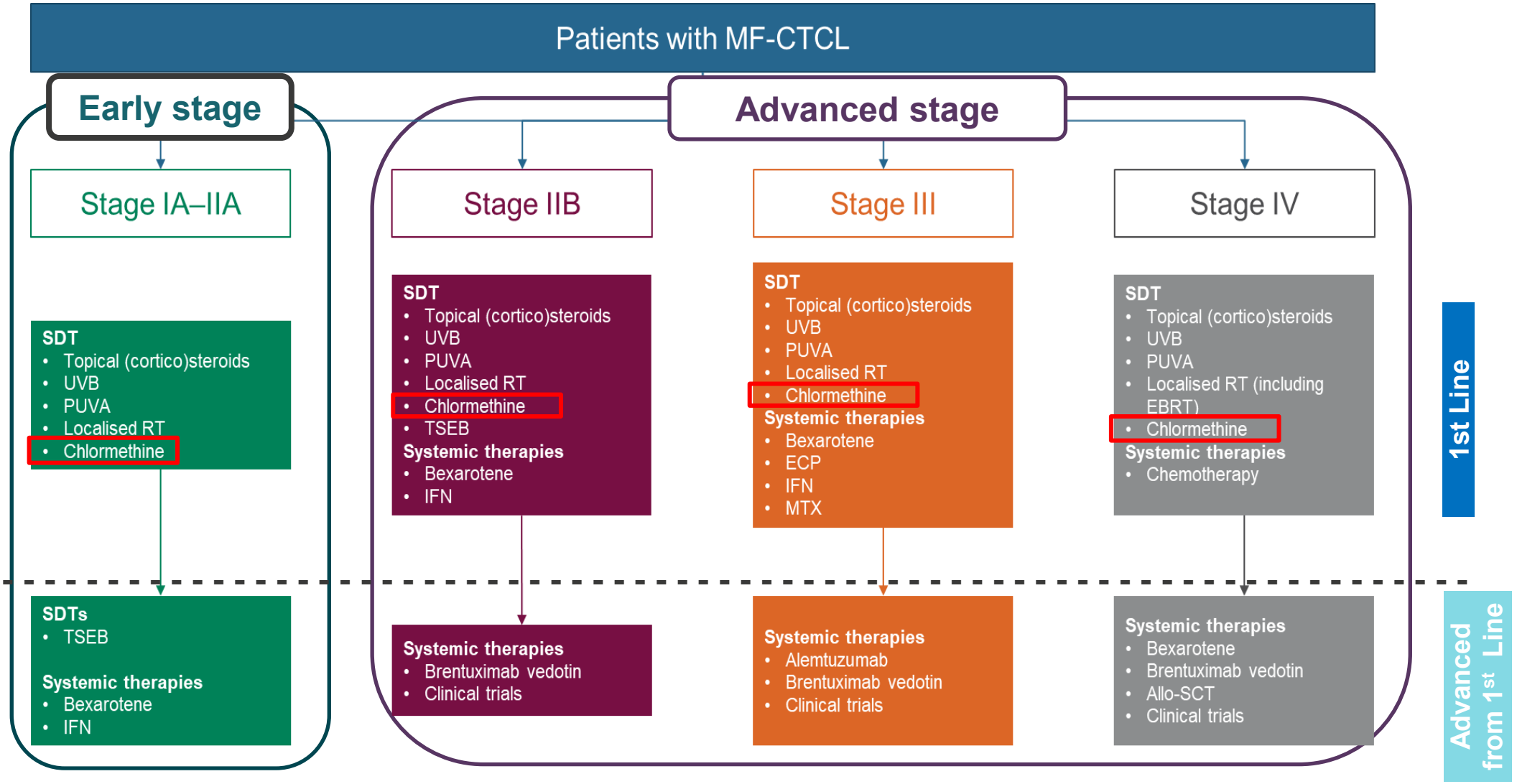
Key issues: clinical-effectiveness

- **Underlying disease progression (issue 5)**
  - Does treatment of the skin lesions stop progression to advanced disease or affect mortality? Is the committee minded to accept that topical treatments do not affect disease progression?
- **Use for patients with advanced stage disease (issue 1, 2nd part)**
  - Does the committee consider the clinical effectiveness evidence available for chlormethine gel to be generalisable to the advanced disease stage population?
  - Is the mean %BSA for low (xxx) and high skin burdens (xxxx) from study 201 representative of UK practice?
- **The true clinical effectiveness of chlormethine gel vs. phototherapy (issue 2, 2nd part)**
  - Is phototherapy the most appropriate 1st line comparator? If skin gets worse again what would be used?
  - What would be used in case of treatment failure of phototherapy or chlormethine gel? Could phototherapy or chlormethine gel be used more than once in practice?
  - What is the committee's view on the naïve unadjusted comparison?

Disease background: Mycosis Fungoides-type Cutaneous T-cell Lymphoma

- Primary cutaneous lymphomas are extra-nodal Non-Hodgkin lymphomas (NHLs) that affect the lymphatic cells in the skin. CTCLs account for approximately 75 to 80% of all cases. Mycosis fungoides-type CTCL (MF-CTCL) is one of the sub-types of CTCL
- **Incidence:** about 182 new diagnoses on average in England each year (*source: company submission*)
- **Skin symptoms:** patches and/or plaques, can be painful and itchy. 25% will eventually die of widespread disease, some remain with skin disease only, and have repeated topical treatments over time.
- **Stage categorisation:** based on the number and type of skin lesions, lymph node or peripheral blood involvement and metastasis
  - *Early*: stages IA to IIA
  - *Advanced*: stages IIB to IVB
- **Treatment options:** skin-directed therapies (SDTs), are 1st choice in early stage disease for local treatment of skin lesions, and may be combined with systemic therapies in advanced stage disease. Stem cell transplant the only potentially curative option.

Treatment pathway



- **Company**: chlormethine gel is expected to be used as first-line in early stage disease and in combination with systemic therapies in advanced disease

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Source: adapted from Figure 2, company submission

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	• 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 & Carer Perspectives (*Lymphoma Action)*

- People live with MF-CTCL and experience flare ups for many years.
- Distressing symptoms - itching, pain, fatigue, anxiety, depression, fever & hypothermia.
- Psychological and social wellbeing are significantly affected, impacting on patients' and carers' employment, leisure activities, relationships and day-to-day living.
- Current treatments (multiple cycles of existing topical treatments, radiotherapy, phototherapy, systemic chemotherapy and stem cell transplants) may require travel for repeated hospital appointments and can significantly affect patients' quality of life.
- "Existing treatments do not keep symptoms under control for long."
- 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.

Clinical expert statements and discussion

Aims of treatment

- Reduce extent of skin involvement in **early stages** of disease, stop progression, and improve symptoms and quality of life. Would only be used in advanced stage disease for those with **limited mild skin disease.** It is for symptomatic control of disease and is **not a cure.**

Current treatment options

- **3 modalities of skin-directed therapies for early stage disease: topical therapies, phototherapy, localised radiotherapy. None are curative**.
- Lack of durable complete remissions in early stage disease – **most relapse** and cycle between topical treatments/phototherapy/radiotherapy.
- Phototherapy is standard of care for early stage disease but has drawbacks: reach cumulative UV dose, risks of skin cancer and expensive treatment (twice weekly therapy for 12 to 14 weeks, could be given 3-4 times over a decade).
- PUVA more powerful than NB-UVB and has more adverse effects. PUVA used for thick, bulky skin disease (BSA>10% or thickened plaques), NB-UVB used for less bulky early stage disease (BSA<10%). NB-UVB would be best comparator to chlormethine gel.

Clinical need

- Currently patients have to come in to hospital for **phototherapy – inconvenient, time-consuming.**
- Historical experience of chlormethine/nitrogen mustard so know the value of it.
- **No active chemotherapy creams/gels currently available.**

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. Mean % body surface area affected XXXX and XXXX 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

Study 201 results: ITT including NYU population

		CAILS response		mSWAT response	
Response n (%)		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)	XXXX	XXXX
PR		58 (44.6)	47 (36.2)	XXXX	XXXX
Response rate (CR+PR) ratio		1.226 (95% CI 0.974-1.552, XXXX)		1.017 (95% CI 0.783-1.321, XXXX)	
CAILS response rates (CR+PR) by MF-CTCL stage	**Stage IA**	45 (59.2)	26 (40.0)	N/A	
	Stage IB/IIA	31 (57.4)	36 (55.4)		
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 have 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)

Overview of issues

Issues	Summary
Underlying disease progression (issue 5)	**Provisionally agreed**
• *The clinical need for chlormethine gel (issue 1, 1st part);* • **Use for patients with advanced stage disease (issue 1, 2nd part)**	*1st part resolved;* **2nd part for discussion**
• *Phototherapy (bundled) as the comparator in the model (issue 2, 1st part);* • **The true clinical effectiveness of chlormethine gel vs. phototherapy (issue 2, 2nd part)**	*1st part resolved;* **2nd part for discussion**
The daily application, dosage, and costing of chlormethine gel (issue 3)	**For discussion**
Costing and distribution of PUVA/UVB phototherapy (issue 4)	*Resolved*
• *Time to progression following CR and PR on chlormethine gel arm; CR and PR rates (issue 6, 1st part)* • **Skin burden transitions/time to progression following CR and PR on phototherapy arm; use of Phan 2019 vs. Whittaker 2012 data for modelling (issue 6, 2nd part)**	*1st part: uncertainty remained or resolved* **2nd part for discussion;**
Progression from 1L and post progression treatments (issues 7&8)	**For discussion**

Underlying disease progression (issue 5)

Question for committee

- **Does treatment of the skin lesions stop progression to advanced disease or affect mortality? Is the committee minded to accept that topical treatments do not affect disease progression?**

Assumption also has an impact on the model

Background

- Company assumes underlying disease progression is independent of treatment effect on the skin lesions and uses **Wernham et al. 2015** (a single database study) to inform transition probabilities between MF-CTCL stages
- ERG prefers larger study **Agar et al. 2010** of UK patients with MF-CTCL
- Uncertainty remains at to whether disease progression is independent of treatment effect

Post TE

- ERG and company agree **Agar et al. 2010** is most appropriate source to inform disease stage progression
- **Insufficient evidence to suggest that treatment of skin symptoms may delay or prevent disease stage progression of MF-CTCL**

Provisionally Agreed

Use for patients with advanced stage disease (issue 1, 2nd part)

Background

- Study 201 included early-stage MF-CTCL (stage IA-IIA) only
- No evidence for advanced stage MF-CTCL
- Company suggests that it can be used as an adjunct in advanced MF-CTCL disease (stage IIB, III and IV)

Stakeholder comments

- Relevant population: early stage disease with limited skin involvement
- Less effective for patients with severe skin disease (stages IIB and III)
- May be used as adjunct in advanced disease but only for patients with **limited mild skin disease**
- May be used instead of phototherapy for the following reasons:
  - more convenient for patients (fewer hospital visits)
  - already reached cumulative UV dose
  - alternative to avoid adverse events of phototherapy (UV linked as a mutagen in CTCL and risk of non-melanoma skin cancers)

Use for patients with advanced stage disease (issue 1, 2nd part)

Company post TE

- Expected to be used as first line treatment of skin symptoms for early (Stage IA–IIA) & advanced disease (Stage IIB+)
- Chlormethine gel works on skin lesions, not disease in lymph nodes or elsewhere, therefore skin response expected to be independent of overall disease stage.

ERG

- **Does not consider the clinical or cost-effectiveness evidence adequate to support the use of chlormethine gel in patients with advanced disease**
  - Study 201 only included Stage IA and Stage IB/IIA disease and is not generalisable to the proposed use in early and advanced disease
  - Company assumes effectiveness of chlormethine gel is transferable from early stage disease (as per Study 201) to the proportion of the modelled cohort with more advanced (Stage IIB+) disease. This extrapolation is not evidence-based.
  - There is currently no evidence to rule out differences in effectiveness of chlormethine gel across disease stages.

Use for patients with advanced stage disease (issue 1, 2nd part)

Question for committee

There is a lack of evidence on chlormethine gel's effectiveness on patients with advanced stage disease, and whether the response to the technology is affected by stage of disease.

- **Does the committee consider the clinical effectiveness evidence available for chlormethine gel to be generalisable to the advanced disease stage population?**
- **Is the mean %BSA for low and high skin burdens from study 201 representative of UK practice?**

The true clinical effectiveness of chlormethine gel vs. phototherapy (issue 2, 2nd part)

Background

- No connected network could be formed between study 201 and any of comparator phototherapy studies because no common comparator
- Company used 7 phototherapy studies to inform **naïve unadjusted comparison** of chlormethine gel vs. phototherapy: 3 RCTs from systematic literature review, 4 non-RCTs from BAD guidelines.
- Observed weighted average estimates for phototherapy: **CR rate 73%, PR rate 21%, ORR 94%**

ERG: the true relative clinical effectiveness of chlormethine gel vs. phototherapy is unknown

- Naïve comparisons prone to bias and unadjusted comparisons represent very limited level of evidence.
- Majority of phototherapy studies poor quality and heterogeneity across studies (study population, disease stage, and definition of response)
- Observed weighted average estimates for phototherapy may represent an optimistic assessment of its efficacy and should be taken as highly uncertain
- Results not adjusted for any difference in study characteristics and therefore are highly uncertain

Phototherapy effectiveness data: Phan vs. 7 studies

	Phototherapy		Chlormethine gel (for comparison)
	7 phototherapy studies (company submission)	**Phan et al**. 2019 (meta-analysed outcomes, weighted by type of phototherapy (PUVA/UVB) applied by stage)	**Study 201**
CR	73.2%	Stage IA: XXXX Stage IB/IIA: XXXX	XXXX*
PR	20.8%	Stage IA: XXXX Stage IB/IIA: XXXX	XXXX*

ERG:

- Little difference in probability of CR/PR comparing Phan 2019 vs. 7 phototherapy studies
  - Company and ERG agree to use **Phan et al. 2019** for CR/PR due to additional granularity of data (by type of phototherapy and stage of disease)
- However, substantial difference noted between phototherapy and chlormethine gel
  - differences in how CR/PR measured across studies, difficult to draw robust comparisons
  - **Cannot accurately determine the relative clinical benefit of chlormethine gel vs. phototherapy**

Source: ERG additional information document post-TE
*** based on mSWAT definitions and individual patient data from study 201**

The true clinical effectiveness of chlormethine gel vs. phototherapy (issue 2, 2nd part)

Questions for committee

- Is phototherapy the most appropriate 1st line comparator? If skin gets worse again what would be used?
- What would be used in case of treatment failure of phototherapy or chlormethine gel? Could phototherapy or chlormethine gel be used more than once in practice?
- What is the committee's view on the naïve unadjusted comparison?

Key issues: clinical-effectiveness

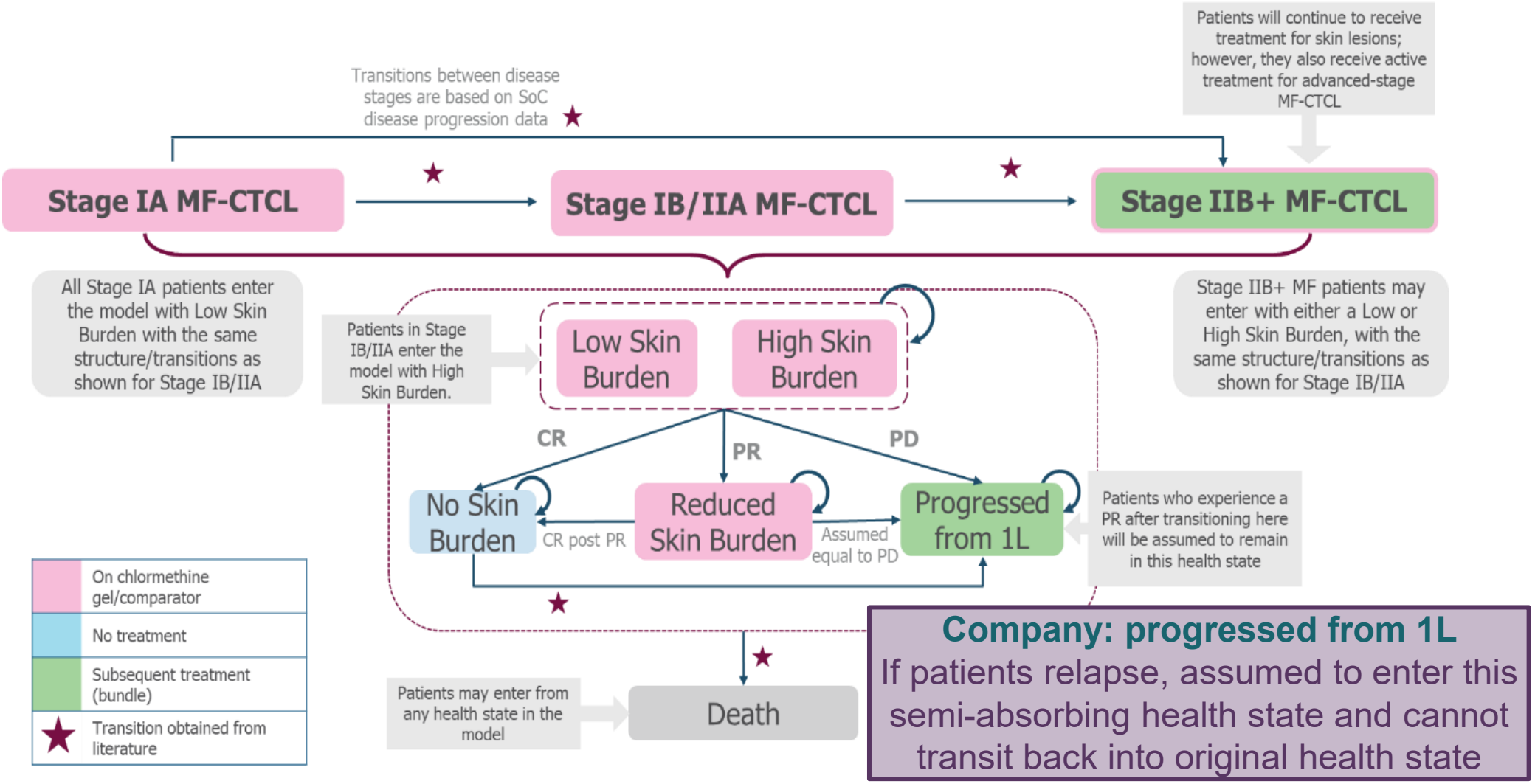
- **Underlying disease progression (issue 5)**
  - Does treatment of the skin lesions stop progression to advanced disease or affect mortality? Is the committee minded to accept that topical treatments do not affect disease progression?
- **Use for patients with advanced stage disease (issue 1, 2nd part)**
  - Does the committee consider the clinical effectiveness evidence available for chlormethine gel to be generalisable to the advanced disease stage population?
  - Is the mean %BSA for low (xxxx) and high skin burdens (xxx) from study 201 representative of UK practice?
- **The true clinical effectiveness of chlormethine gel vs. phototherapy (issue 2, 2nd part)**
  - Is phototherapy the most appropriate 1st line comparator? If skin gets worse again what would be used?
  - What would be used in case of treatment failure of phototherapy or chlormethine gel? Could phototherapy or chlormethine gel be used more than once in practice?
  - What is the committee's view on the naïve unadjusted comparison?

Key issues: cost-effectiveness

- **The daily application, dosage, and costing of chlormethine gel (issue 3)**
  - What is the most appropriate daily dose of chlormethine gel to include in the model?
  - Is the mean %BSA for low and high skin burdens from study 201 representative of UK practice? *(discussed under clinical section, impact on costing too)*
- **Skin burden transitions/time to progression following CR and PR on phototherapy arm; use of Phan et al. 2019 vs. Whittaker et al. 2012 data for modelling (issue 6, 2nd part)**
  - Does the committee consider the ERG's data source (Phan et al. 2019) or the company's data sources (Whittaker et al. 2012 and expert opinion) more appropriate to estimate time to progression following CR and PR in the phototherapy arm of the model?
- **Progression from 1L and post progression treatments (issues 7 & 8)**
  - The 'progressed from 1L' treatment baskets assumed by the company and ERG differ. Which is likely to be seen in clinical practice and is more appropriate for decision making?
  - Is the assumption that patients entering 'progressed from 1L' stay there for remaining life years clinically plausible? What is the committee's view on the ERG's scenario analyses with altered time horizons?

Model structure

- The cost-effectiveness model is a state transition (Markov) cohort model evaluating patients across all disease stages of MF-CTCL



Source: Figure 12, company submission

The daily application, dosage, and costing of chlormethine gel (issue 3): Major effect on ICER

Background: the larger the area affected % of body surface area, the more gel will be used

- Company used **median** daily dose (1.8g) of chlormethine gel from study 201
- ERG preferred **mean** daily dose (2.8g) of chlormethine gel, from the SmPC of chlormethine gel

Company post TE

- Additional IPD data (ITT population, XXXX) from study 201 obtained, based on the number of used tubes returned per follow-up visit in ITT population
- Updated preferred **mean** daily dose of XXXX
  - XXXX for low skin burden (<10% %BSA)
  - XXXX for high skin burden (10-80% %BSA)
- Frequency of dosing may be less than once daily and will likely decrease as %BSA decreases, however the base-case assumes once daily application
- Wastage is factored in to calculations by assuming a minimum of 6 tubes per year would be used per patient (based on a shelf-life of 60 days)

The daily application, dosage, and costing of chlormethine gel (issue 3)

ERG

- Company's estimate based on 201 underestimates costs e.g. patients retaining unfinished tubes at final study visit, not attending follow up, greater wastage with 60g tube vs. XXXX tube (in study 201) due to 60 day shelf life
- ERG: mean of 2.8g derived from the ITT excluding NYU population (XXXX) (not safety set as suggested by company)
- Unclear if the mean %BSA within each disease stage from study 201 (XXXX and XXXX for low and high skin burden respectively) corresponds with mean % BSA for patients in the PROCLIPI registry.
- PROCLIPI registry would better reflect %BSA in real world clinical practice to calculate costs (company did not have access at time of submission) rather than study 201 (did not include advanced stage)
- **ERG prefers mean daily dose of 2.8g in absence of PROCLIPI data, however it is likely an underestimate of true usage. This is because the company assumed that chlormethine gel can be used for advanced stage patients in the model.**

Question for committee:

- **What is the most appropriate daily dose of chlormethine gel to include in the model?**
- **Is the mean %BSA for low and high skin burdens from study 201 representative of UK practice?** *(discussed under clinical section, impact on costing too)*

Skin burden transitions/time to progression following CR and PR on phototherapy arm; use of Phan et al. 2019 vs. Whittaker et al. 2012 data for modelling (issue 6, 2nd part)

- Time to progression is key driver of ICER in the model
- Various assumptions that could affect cost-effectiveness some of which remain uncertain *(see slide on additional uncertainty under issue 6, 1st part).*
- One area of disagreement between company and ERG and their modelling is their use of **Phan vs Whittaker**

Parameter: phototherapy arm	Post TE: Company	ERG
Time to relapse of skin disease following CR (median)	**Whittaker et al. 2012:** 6.48 months	**Phan et al. 2019:** 11.69 months (weighted average of PUVA and UVB), adjusted for maintenance phototherapy
Time to relapse of skin disease following PR	**Expert opinion**: progression post PR equal to initial probability of progression (assumed equal to phototherapy treatment duration) based on expert opinion	• Prefers **Phan et al. 2019** (no maintenance adjustment) • PR on phototherapy are modelled to receive bexarotene / IFN-a so additional treatment is modelled

Skin burden transitions/time to progression following CR and PR on phototherapy arm; use of Phan et al. 2019 vs. Whittaker et al. 2012 data for modelling (issue 6, 2nd part)

ERG

- Prefers **Phan et al. 2019** due to:
  - larger sample size, and meta-analysed outcomes data
  - reports data by type of phototherapy (PUVA/UVB)
  - distribution of disease severity more comparable with study 201
  - consistent data source across all phototherapy effectiveness parameters in model
- However, acknowledges company concerns that 5 out of 7 studies used maintenance phototherapy, with longer mean duration to relapse (32.27 vs.19.46 months, p=0.002, n=227).
- To account for this, ERG reduced duration of CR on phototherapy by dividing mean CR duration by 1.66 (32.27/19.46). This will still be an underestimate of duration of CR, ICER may be higher than reported.

Question for committee:

Does the committee consider the ERG's data source (Phan et al. 2019) or the company's data sources (Whittaker et al. 2012 and expert opinion) more appropriate to estimate time to progression following CR and PR in the phototherapy arm of the model?

Progression from 1L and post progression treatments (issues 7 & 8)

Background

- The company's model assumes:
  - all patient who relapse in skin burden symptoms progress onto subsequent skin-directed therapy **(bexarotene or peginterferon-alfa) entering 'progressed from 1L' health state**
  - patients remain on subsequent skin-directed therapy **(50:50 bexarotene or peginterferon alfa)** for remaining life years
- The ERG disagrees, as some patients who achieve a CR may revert to initial SDT should symptoms relapse
- The ERG uses estimates of CR and duration of CR from Dalal et al. 2020, suggesting an average CR of 21% and 64% for bexarotene and peginterferon alfa respectively, and average duration of response for bexarotene of 9 months

Company post TE

- Patients cannot receive more than 1 course of phototherapy
- Therefore, patients who relapse after phototherapy can be assumed to progress onto systemic therapy
- Patients may be able to receive chlormethine gel again following relapse

Progression from 1L and post progression treatments (issues 7 & 8)

Company revised base-case

- Progressed from 1L treatment basket in the **chlormethine gel** arm:
  - 33% chlormethine gel (assuming has equal efficacy 2nd time round)
  - 33% bexarotene
  - 33% peginterferon alfa
- Progressed from 1L treatment basket in the **phototherapy** arm:
  - 50% bexarotene
  - 50% peginterferon alfa

- Used estimates of time spent in CR for chlormethine gel from the CE model
- Agrees with ERG to use **Dalal et al. 2020** to calculate time spent in CR for bexarotene
- However, uses data from **Roberge et al. 2007** to calculate time spent in CR for peginterferon alfa (rather than assuming they are the same as per Dalal et al. 2020)

Progression from 1L and post progression treatments (issues 7 & 8)

ERG

- Progressed from 1L treatment basket
  - Would be more appropriate to model patients going back to initial skin burden state on relapse, rather than entering 'progressed from 1L' health state
  - Implausible to assume chlormethine gel has same efficacy and duration of response each subsequent time it is used; company's revised approach is highly uncertain
  - **ERG prefers exclusion of chlormethine gel from 'progressed from 1L' treatment bundle**
- Costs and quality of life decrements in 'progressed from 1L' state
  - **Considers the company's calculation to use Roberge et al. 2007 to inform duration of CR with peginterferon-alfa to be reasonable**

- In company's model, phototherapy arm progresses more quickly into 'Progressed from 1L' state than chlormethine gel arm (CR higher on phototherapy, time to progression post CR shorter than time to progression post PR)
- Treatment which delays entry / reduces proportion of cohort entering state more likely to be cost-effective as 2nd line skin treatments costs and QALY losses incurred for remaining life years.
- **Assumption of patients entering the semi-absorbing 'progressed from 1L' health state staying there for remaining life years highly uncertain; model results heavily influenced by the time the cohort spends in the health state**
- **Conducted additional scenario analyses exploring the impact of varying the time horizon (see slides 33 to 34)**

Progression from 1L and post progression treatments (issues 7 & 8)

Questions for committee

- The ‘progressed from 1L’ treatment baskets assumed by the company and ERG differ. Which is likely to be seen in clinical practice and is more appropriate for decision making?
- Is the assumption that patients entering ‘progressed from 1L’ stay there for remaining life years clinically plausible? What is the committee’s view on the ERG’s scenario analyses with altered time horizons?

Additional uncertainty: utility values

Company	ERG
• Utility values generated by de novo vignette study • 12 vignettes 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) • Clinician EQ-5D-5L responses as a proxy for patient responses • Responses cross-walked to EQ-5D-3L and valued using UK general population time-trade off tariffs.	• Accepts there is a lack of data • Would have preferred patient-completed responses • Vignettes inconsistent with domains of EQ-5D, which may have been difficult for respondents to assign an EQ-5D response and may have led to under or over-estimation of impact of vignette on quality of life. Direction and magnitude of bias unclear. • Substantial differences in elicited utility scores across states with differential skin burden • Unknown impact on ICER estimate

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	XXXX	XXXX	XXXX	XXXX
Stage IB/IIA	XXXX	XXXX	XXXX	XXXX
Stage IIB+ (Low)	XXXX	XXXX	XXXX	XXXX
Stage IIB+ (High)	XXXX	XXXX	XXXX	XXXX

Source: ERG report, table 21

Additional uncertainty: time to progression following PR on chlormethine gel (issue 6, 1st part)

Chlormethine gel arm of model	Post TE: Company	ERG
Time to relapse of skin disease following PR	**Study 201 IPD data** (n=2; 2 patients who had progressive disease post PR pooled across disease stages)	• Agrees with company but notes that IPD data from study 201 based on sample of 2 patients and therefore highly uncertain and should be approached with caution

Time to progression is a key driver of ICER in the model but there is no robust evidence comparing chlormethine gel with phototherapy in terms of time to progression from 1L post PR

Post TE: Cumulative impact of ERG preferred assumptions on the company revised ICER

	Inc. Cost	Inc. QALY	Deterministic ICER
Company revised base case (based on XXXX)	**-£12,510**	**+0.23**	**Phototherapy dominated**
+ (0%/50%/50% chlormethine gel/bexarotene/pegylated IFN-α, as per phototherapy) **(based on XXXX)**	-£11,258	+0.24	Phototherapy dominated
+ 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 **(based on XXXX)**	-£4,346	+0.14	Phototherapy dominated
+ Chlormethine gel treatment acquisition costs based on mean daily gel usage **(based on 2.8g)**	+£9,155	+0.14	£63,335
+ Cost of psoralen when on phototherapy **(based on 2.8g)**	+£9,028	+0.14	£62,457
ERGs preferred base case analysis (based on 2.8g)	**+£9,028**	**+0.14**	**£62,457**

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Source: ERG critique, table 2

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

	Inc. cost	Inc. QALY	Deterministic ICER
ERG preferred base case	£9,028	0.14	£62,457
Model population: early stage MF-CTCL (Stage IA / 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

ERG scenario analysis: time horizon with full cohort

		Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG preferred base-case	Chlormethine gel	-	-	-
	Phototherapy (PUVA/UVB)	£9,028	0.14	£62,457
5 year time horizon	Chlormethine gel	-	-	-
	Phototherapy (PUVA/UVB)	£16,611	0.05	£365,666
10 year time horizon	Chlormethine gel	-	-	-
	Phototherapy (PUVA/UVB)	£11,044	0.13	£86,705
20 year time horizon	Chlormethine gel	-	-	-
	Phototherapy (PUVA/UVB)	£9,104	0.14	£62,957

Source: ERG additional information document post-TE, table 1

Question for committee

- **Is the assumption that patients entering 'progressed from 1L' stay there for remaining life years clinically plausible? What is the committee's view on the ERG's scenario analyses with altered time horizons?**

ERG scenario analysis: time horizon with early stage (stage IA/IIA) disease only

		Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG preferred base-case	Chlormethine gel	-	-	-
	Phototherapy (PUVA/UVB)	£3,103	0.15	£21,355
5 year time horizon	Chlormethine gel	-	-	-
	Phototherapy (PUVA/UVB)	£12,217	0.05	£259,682
10 year time horizon	Chlormethine gel	-	-	-
	Phototherapy (PUVA/UVB)	£5,559	0.13	£44,005
20 year time horizon	Chlormethine gel	-	-	-
	Phototherapy (PUVA/UVB)	£3,200	0.15	£22,002

Source: ERG additional information document post-TE, table 1

Question for committee

- **Is the assumption that patients entering 'progressed from 1L' stay there for remaining life years clinically plausible? What is the committee's view on the ERG's scenario analyses with altered time horizons?**

Clinical issues resolved at technical engagement

Issue	Agreement between ERG and company post TE
The clinical need for chlormethine gel (issue 1, 1st part)	• The ERG and clinical experts 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.
Phototherapy (bundled) as the comparator in the model (issue 2, 1st part)	• The company and ERG acknowledge that 1 prospective observational study from Phan et al. 2019 compares PUVA vs. UVB in patients with early stage disease • There remains considerable uncertainty in the relative efficacy of PUVA vs. UVB • The company revised base-case considers the efficacy of UVB and PUVA separately given data from Phan et al. 2019

NICE

Resolved

Cost-effectiveness issues resolved at TE: Costing and distribution of PUVA/UVB phototherapy (issue 4)

	Company post TE	ERG
Phototherapy administration costs	£97.63 • Source: mean of dermatology and oncology costs for consultant-led outpatient clinic cost of phototherapy and photochemotherapy (NHS reference costs 2017/18) • Unclear if includes cost of psoralen so may underestimate cost	• **ERG accepts the company's revised cost of £97.63** • Scenario analysis including cost of psoralen increases total costs with minimal impact on ICER
Distribution of PUVA/UVB phototherapy	XXXX receiving PUVA, XXXX receiving UVB • Source: PROCLIPI registry • Considers PROCLIPI registry reflects current clinical practice (data is from 2015 to October 2019)	• **Agrees that the PROCLIPI registry is most appropriate source of evidence to derive proportions of PUVA and UVB phototherapy**

Resolved

Cost-effectiveness issues resolved at TE:
Time to progression following CR on chlormethine gel; and CR and PR rates (issue 6, 1st part)

Time to relapse of skin disease following CR	Post TE: Company	ERG
Chlormethine gel	**Kim et al. 2003 -** agrees with ERG	**Kim et al. 2003 –** provides data for similar treatment (topical nitrogen mustard)

CR/PR rates	Post TE: Company	ERG
Chlormethine gel	mSWAT response rates Source: **Study 201**	Accepts **study 201** provides best available evidence
Phototherapy	**Phan et al. 2019**	**Phan et al. 2019**

NICE

Resolved

Key issues: cost-effectiveness

- **The daily application, dosage, and costing of chlormethine gel (issue 3)**
  - What is the most appropriate daily dose of chlormethine gel to include in the model?
  - Is the mean %BSA for low and high skin burdens from study 201 representative of UK practice? *(discussed under clinical section, impact on costing too)*
- **Skin burden transitions/time to progression following CR and PR on phototherapy arm; use of Phan et al. 2019 vs. Whittaker et al. 2012 data for modelling (issue 6, 2nd part)**
  - Does the committee consider the ERG's data source (Phan et al. 2019) or the company's data sources (Whittaker et al. 2012 and expert opinion) more appropriate to estimate time to progression following CR and PR in the phototherapy arm of the model?
- **Progression from 1L and post progression treatments (issues 7 & 8)**
  - The 'progressed from 1L' treatment baskets assumed by the company and ERG differ. Which is likely to be seen in clinical practice and is more appropriate for decision making?
  - Is the assumption that patients entering 'progressed from 1L' stay there for remaining life years clinically plausible? What is the committee's view on the ERG's scenario analyses with altered time horizons?