NICE National Institute for Health and Care Excellence

SLIDES FOR PUBLIC - REDACTED

Crisaborole for treating mild to moderate atopic dermatitis in people aged 2 years and older

Lead team presentation

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Company: Pfizer
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Key issues

- Is 2nd line the right place for crisaborole in the treatment pathway?
- Crisaborole has a license for mild and moderate disease, but the comparators differ between mild and moderate disease.
  - For people with mild disease, are topical calcineurin inhibitors comparators?
- There are no head-to-head trials comparing crisaborole with the key comparators
- Topical crisoborole, topical calcineurin inhibitors and topical corticosteroids all require a 'vehicle' and these differ. The main trial compares crisoborole plus vehicle to vehicle alone
  - Is it appropriate to adjust a network linked for possible difference in vehicle effectiveness?
- Company's model assumes that a higher proportion of people taking crisaborole do not need subsequent therapy compared with topical calcineurin inhibitors
  - Crisaborole is dominant in most of the company analyses and dominated in most of the ERG analyses
  - Model sensitive to changes in duration and cost of subsequent therapies

Atopic dermatitis

Atopic dermatitis also called atopic eczema

- Chronic, inflammatory, relapsing or recurring, immune-mediated skin condition
- Skin may be red/inflamed, thickened/leathery, dry with scaly plaques; may bleed, ooze, crack, flake and itch
- Can start at any age, onset peaks at infancy

Epidemiology

- Around 1 in 5 children and 1 in 12 adults have atopic dermatitis
- Most cases are mild

Defining severity

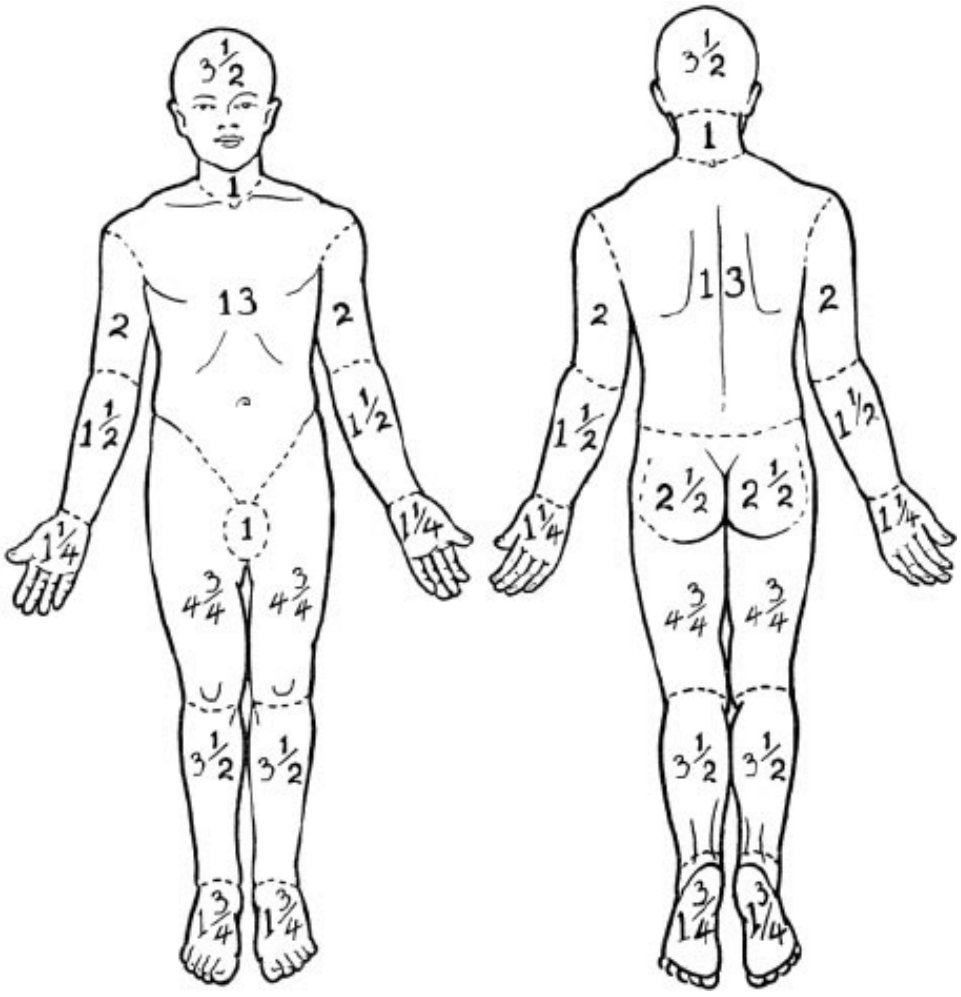
- Many instruments assess severity such as EASI, POEM, SCORAD
- No NICE clinical guideline in adults
  - CG57 Atopic eczema in under 12s recommends a holistic approach when assessing severity, taking into account severity, quality of life including everyday activities, sleep and psychosocial wellbeing
- Single measurement may over- or under-estimate severity because atopic dermatitis relapses and remits

Abbreviations: EASI, eczema and severity index; POEM, patent-oriented eczema measure; SCORAD, scoring atopic dermatitis.

Crisaborole (Staquis, Pfizer)

Marketing authorisation	'Mild to moderate atopic dermatitis in adults and paediatric patients from 2 years of age with ≤ 40% body surface area (BSA) affected'
Administration	• Topical ointment *Dosing regimen commercial in confidence, summary of product characteristics not fully endorsed until marketing authorisation received*
Mechanism	Non-steroidal small molecule, inhibits phosphodiesterase 4 (PDE4) a regulator of inflammatory cytokines. Contains boron that helps penetrate skin.
Investigations	No special monitoring
Special warnings	*Special warnings commercial in confidence, summary of product characteristics not fully endorsed until marketing authorisation received*

Example of body surface



Source: modified Lund and Browder Chart, Oslen E et al. 2007

Treatment pathway

Company positions crisaborole 2nd line where topical calcineurin inhibitors recommended for moderate, but not mild, disease

1st **Emollients and topical corticosteroids** TA81

2nd **Topical calcineurin inhibitors** TA82

Pimecrolimus		**Tacrolimus**
moderate atopic dermatitis on face and neck in children aged 2 to 16 years	**OR**	moderate to severe atopic dermatitis (not licenced for mild)

- Pimecrolimus is **NOT** recommended for mild atopic dermatitis in TA82.
- Tacrolimus is **NOT** licenced for use in mild atopic dermatitis

3rd **Phototherapy**
narrowband ultraviolet B (UVB) light

4th **Systemic immunosuppressants**
oral corticosteroids, ciclosporin (licensed), *methotrexate, azathioprine, mycophenolate mofetil*

5th **Dupilumab** TA534

Crisaborole?

Crisaborole?

- Company position for **mild** and **moderate** atopic dermatitis

Company justifies positioning crisaborole 2nd line: this is where crisaborole will be used and 1st line treatments are low cost and effective

◉ *In NHS, would crisaborole be used in mild disease? moderate disease? In primary care? Would it replace emollients/ emollients + topical corticocosteorids 1st line?*

Deviations from scope

	Scope	Company submission deviations
Population	People aged 2 years and older with mild to moderate disease	Scoped population in whom topical corticosteroids are contraindicated or not effective

Comparators	Mild atopic dermatitis:
	• Combination of emollients and mild to moderate potency topical corticosteroids
	
	Moderate atopic dermatitis:
	• High potency topical corticosteroids
	• Topical calcineurin inhibitors
		Mild atopic dermatitis:
		• Topical calcineurin inhibitor: pimecrolimus and tacrolimus
		• Emollients – scenario only not positioned 1st line
		• Mild to moderate potency TCS – scenario only not positioned 1st line
		
		For moderate atopic dermatitis:
		• Topical calcineurin inhibitors:
		  • Adults: tacrolimus 0.1%, tacrolimus 0.03%
		  • Children: tacrolimus 0.03%, pimecrolimus 1%
		  • Combination of emollients and moderate to high potency topical corticosteroids (in scenario analyses only)

Company addressed 4 subgroups

Disease severity

Age

Children mild	Children moderate
Adults mild	Adults moderate

◉ *Which of these populations are relevant?*

Scenario: assumes crisaborole is equivalent to comparators

Changing dosing changes costs

	Crisaborole	Pimecrolimus	Tacrolimus 0.03%, children	Tacrolimus 0.1% & 0.03%, adults
Summary of product characteristics (flare treatment)	*Commercial in confidence, summary of product characteristics not fully endorsed until marketing authorisation received*	**2x daily**, for as short period as possible during flare, stop after **6 weeks if no improvement**.	**2x daily, up to 3 weeks,** then reduce to 1x daily until clear.	Start with 0.1% dose **2x daily** until lesion clears. If possible reduce to 0.03% dose. **Stop after 2 weeks if no improvement**.
			If respond up to 6 weeks on tacrolimus, eligible for maintenance treatment	
1. Application frequency reduced in week 4 for tacrolimus children	2x daily for 4 weeks	2x daily for 4 weeks	2x daily for 3 weeks and 1x daily for 1 week	2x daily for 4 weeks
2. Same dosing	2x daily, 4 weeks			
3. 6 weeks therapy for TCIs	2x daily 4 weeks	6 weeks, 2x daily	3 weeks, 2x daily and 3 weeks, 1x daily	6 weeks, 2x a day*

◉ Which of the company's scenarios is most appropriate?

*the results for adults with moderate disease for this options could not be replicated so the ERG cannot verify if this was the assumption applied in adults

Relevant comparator 2nd line for people with mild disease?

Company compares crisaborole to pimecrolimus or tacrolimus, which are not recommended by NICE for mild disease

Company on people with mild disease

- Unethical to give emollients when topical corticosteroids ineffective
- Audit data indicate that a 8% receive topical calcineurin inhibitors .

Clinicians - Centre of Evidence-based Dermatology - on mild disease

- Mild atopic dermatitis can be controlled using topical corticosteroids
- We do not see resistance to topical corticosteroids
- Range of potency 'huge' from very mild (1% hydrocortisone), to moderate (clobetasone) to moderate/severe (mometasone/fluticasone) and can usually control patients
- Clinicians would offer topical calcineurin inhibitors only on sensitive sites such as the face - which are more prone to skin thinning and acne

Evidence Review Group (ERG)

- Rarely would clinicians consider using tacrolimus or pimecrolimus

◉ *Is there a group of patients (at 2nd line) with mild disease for whom corticosteroids are contraindicated or not effective?*

◉ *Are calcineurin inhibitors comparators for people with mild disease?*

Patient and carer perspectives

- Limited treatment options for eczema. Crisaborole would broaden choice
- Compliance with current topical treatments sub-optimal
- Patients have concerns about using corticosteroids
- Crisaborole reduces itch and would be more acceptable than corticosteroids for many patients
- Patients likely to accept and adhere to crisaborole treatment
- Crisaborole may be safe to use on a long-term, continuous basis.

Trial + observational evidence AD-301, AD-302, AD-303

Comparator in trial not standard care at 2nd line in NHS

AD-301 + AD-302 Double-blind, randomised USA **4 weeks**
Used in model for efficacy

- AD-301 n=763
- AD-302 n=764

Inclusion criteria

- Age ≥ 2 years
- Atopic dermatitis ≥ 5% body surface area
- ISGA score of mild (2) or moderate (3)

Crisaborole + vehicle* n=357

Vehicle* n=160

Prior therapy
43% received prior treatment for atopic dermatitis in AD-301 and AD-302

AD-303: long term, open label, single arm safety **48 weeks**
Used in model for amount of drug per application

n=517

Inclusion criteria

- Completed AD-301 or AD-302
- Clinically acceptable safety lab results
- ISGA 2 or 3

Exclusion criteria:

- Experienced a related adverse event in AD-301 or AD-302 precluding crisaborole
- Active infection

ISGA score and appropriate treatment was re-evaluated every 28 days. Stop crisaborole if no improvement after 3 cycles

All trials collected health-related quality-of-life data using the dermatology life quality index (DLQI), children's dermatology life quality index (CDLQI) and dermatitis family impact (DFI)

* Vehicle ointment: ointment that does not contain the active ingredient crisaborole

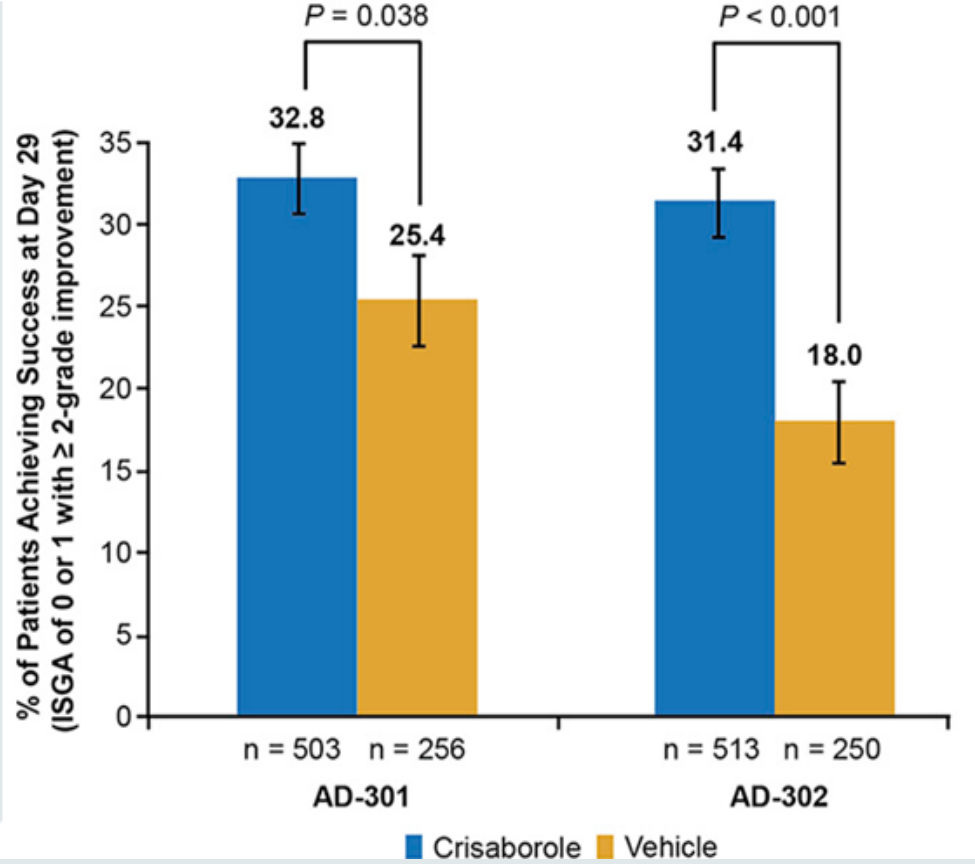
ISGA, Investigator's Static Global Assessment score; a subjective evaluation of disease severity, 5-point scale ranging from clear to severe.

Trial results

Results do not inform effectiveness vs. treatments used 2nd line in NHS

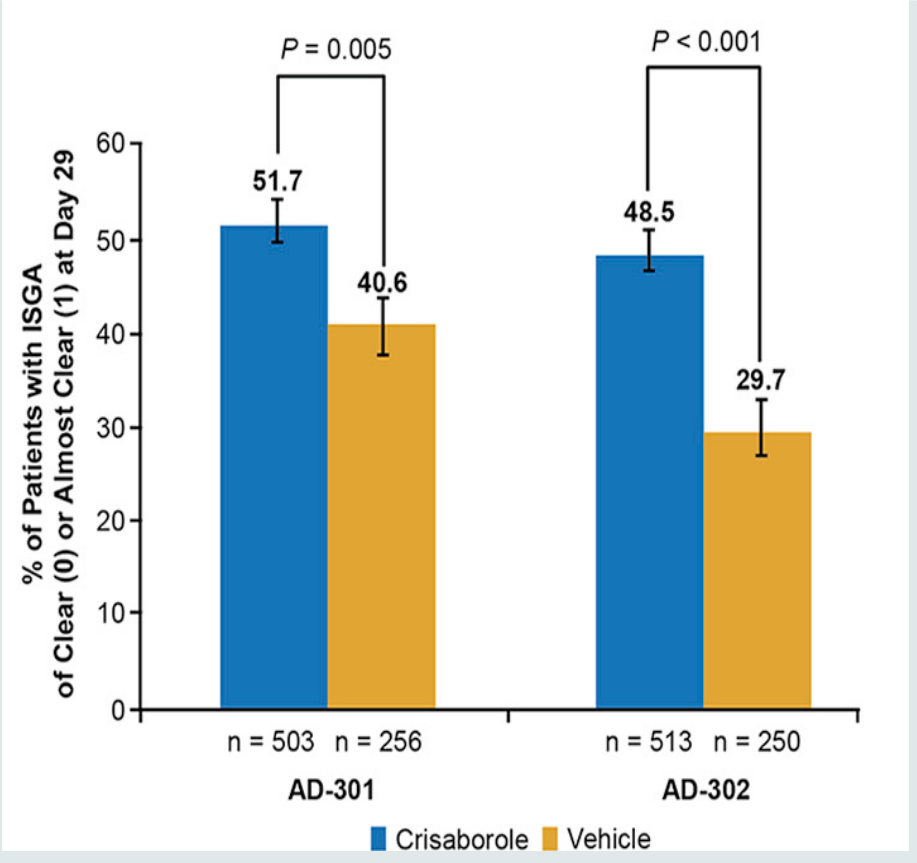
1º outcome: Not used in model

% of patients achieving Investigator's Static Global Assessment ISGA success at Day 29: ISGA clear/ almost clear and at least a 2-grade improvement from baseline



2º outcome: Used in model

Proportion of patients achieving ISGA score of Clear or Almost Clear at Day 29



◉ *Is ISGA 'success' at Day 29 a reasonable endpoint? Is the drug effective? Is it appropriate to model the 2 º outcome not 1 º outcome?*

Adverse events

Company chose not to include adverse events rates in model as they were low

- No comparative safety data presented, results from long-term safety study AD-303 pooled with pivotal trials AD-301, AD-302, not reported by mild/ moderate subgroup
- Most frequently reported treatment-related adverse events: atopic dermatitis worsening, exacerbation, flare or flare-up; 3.1%, application-site pain: burning and/or stinging 2.3%, and application-site infection 1.2%

Treatment-emergent adverse events(≥5% of patients) for AD-301 -302 and -303

Cohort	2-11 yrs N = 308	12-17 yrs N = 146	≥ 18 yrs N = 63	Total N = 517
Treatment-emergent adverse event for crisaborole, n (%)				
General disorders and administration site conditions	41 (13.3)	12 (8.0)	12 (8.0)	58 (11.2)
Pyrexia	27 (8.8)	2(1.4)	0 (0.0)	29 (5.6)
Infections and infestations	157 (51.0)	56 (38.4)	14 (22.2)	227 (43.9)
Nasopharyngitis	21 (6.8)	15 (10.3)	4 (6.3)	40 (7.7)
Upper respiratory tract infection	38 (12.3)	12 (8.2)	3 (4.8)	53 (10.3)
Respiratory, thoracic, and mediastinal disorders	55 (17.9)	26 (17.8)	5 (7.9)	86 (16.6)
Cough	27 (8.8)	6 (4.1)	2 (3.2)	35 (6.8)
Skin and subcutaneous tissue disorders	65 (21.1)	35 (24.0)	9 (14.3)	109 (21.1)
Dermatitis atopic	37 (12.0)	16 (11.0)	5 (7.9)	58 (11.2)

◉ *Company excludes adverse events from its model – is this appropriate?*

Effectiveness of crisaborole vs comparators

no head-to-head studies comparing crisaborole with comparators

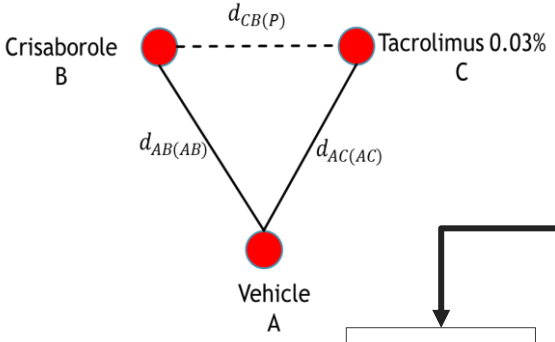
- Company use 'vehicle adjusted network meta-analysis' for crisaborole vs
  - 1. tacrolimus (0.03% [children] and 0.1% [adults]),
  - 2. pimecrolimus (1%)
- Networks require a 'common comparator'
  - 'Vehicle' may be active and vehicles between studies differ
  - [redacted]
  - [redacted]
- Company believes that differences in composition and effectiveness of treatment-specific vehicles justifies using a network meta-analysis adjusted for baseline risk
- ERG disagrees with company
  - If vehicles differ, network disconnected, so company should use a matching adjusted indirect comparison (MAIC)
  - ERG provides cost-effectiveness analysis using MAIC and simple random effects NMA for the committees consideration

Vehicle treatment ingredients

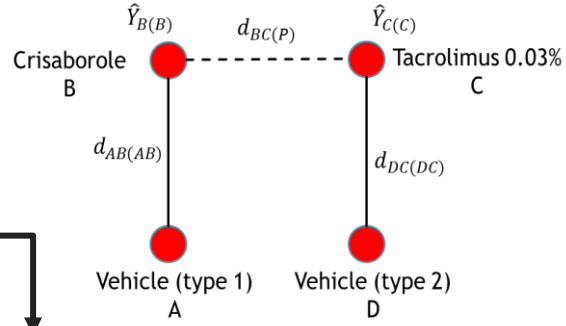
Comparison of vehicle ingredients from the company submission.

Base Components	Crisaborole Ointment	Tacrolimus Ointment	Pimecrolimus Cream
White petrolatum	Commercial in confidence	[redacted]	[redacted]
Paraffin/white wax		[redacted]	[redacted]
Mineral oil		[redacted]	[redacted]
Propylene glycol		[redacted]	[redacted]
Propylene carbonate		[redacted]	[redacted]
Mono-di-glycerides		[redacted]	[redacted]
Triglycerides		[redacted]	[redacted]
Citric acid		[redacted]	[redacted]
Oleyl alcohol		[redacted]	[redacted]
Benzyl alcohol		[redacted]	[redacted]
Cetyl alcohol		[redacted]	[redacted]
Stearyl alcohol		[redacted]	[redacted]
Sodium cetostearyl sulphate		[redacted]	[redacted]
Butylated hydroxytoluene		[redacted]	[redacted]
Edetate calcium disodium		[redacted]	[redacted]
Sodium Hydroxide		[redacted]	[redacted]

◉ *Is it reasonable to assume that vehicles have different effectiveness?*



Are the [redacted] ?



Yes

Simple random effects NMA

- A network meta-analysis is only valid if the treatments represented by each node are the same treatments

Adjust for relevant treatment effect modifiers if possible and/or report predictive treatment effects

No

Unanchored MAIC

- Limitation of matching adjusted indirect comparison: Not possible to tell if all relevant prognostic factors and treatment effect modifiers adjusted for
- Company adjusts based on regression analysis, literature search and clinical opinion for:
  - [redacted]

◉ What is the most appropriate method to determine relative effectiveness?

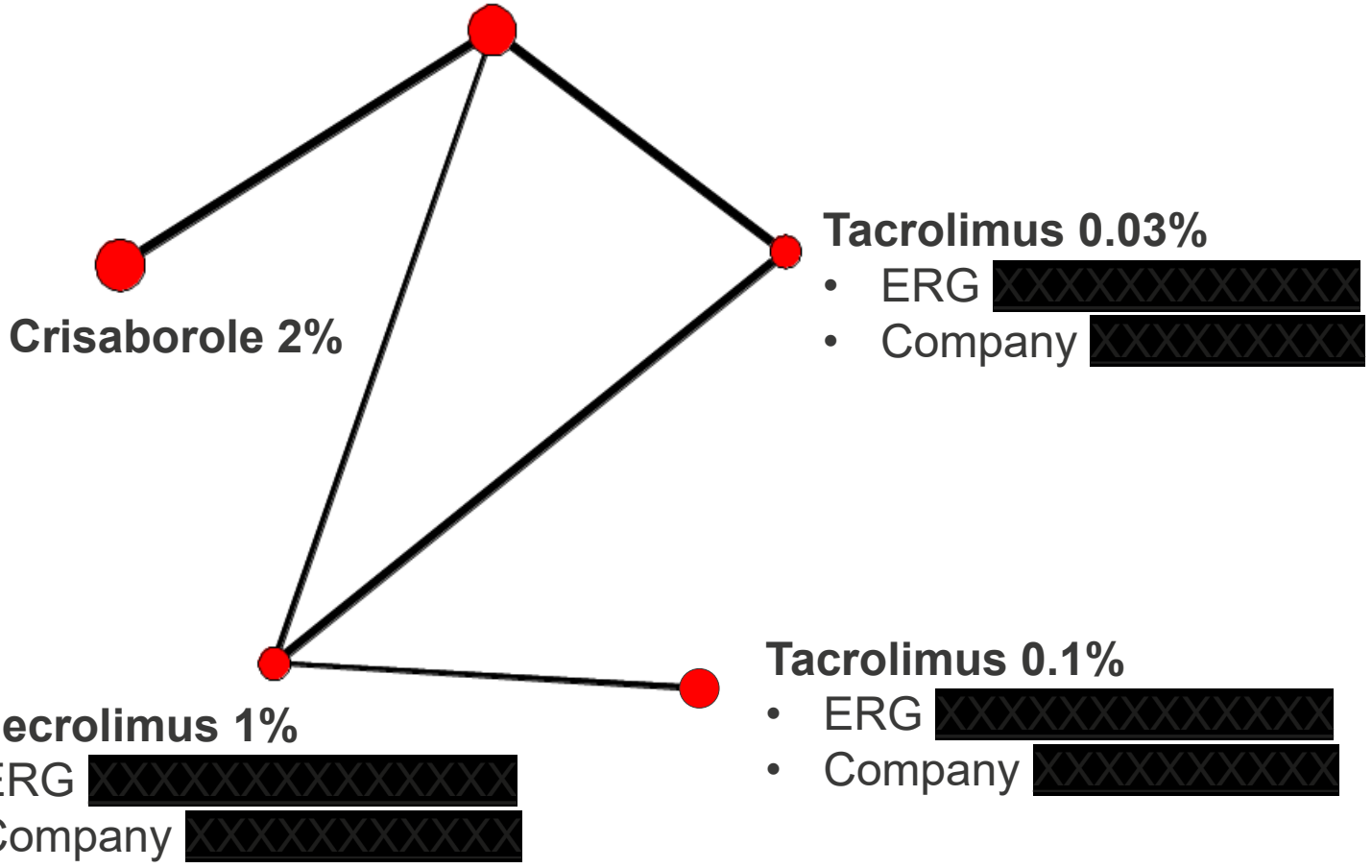
Comparative effectiveness of crisaborole: NMA

Hazard ratios above 1 favour crisaborole

Outcome: Proportion of patients achieving ISGA score of Clear (0) or Almost Clear (1) at Day 29

Company: Adjusted network meta-analysis :
- fixed treatment effect
- random class effects
- Adjusted for vehicle

ERG: Simple random effects network meta-analysis:
- random treatment effect
- no class effect
- no adjusting for vehicle



	ERG	Company
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Diagram source: company submission
Key: Hazard ratio (95% credible interval)

Comparative effectiveness of crisaborole: MAIC

Odds ratios above 1 favour crisaborole

Outcome: Proportion of patients achieving ISGA score of Clear (0) or Almost Clear (1) at Day 29

Company's unanchored matching adjusted indirect comparison. Adjusted to the comparator population:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

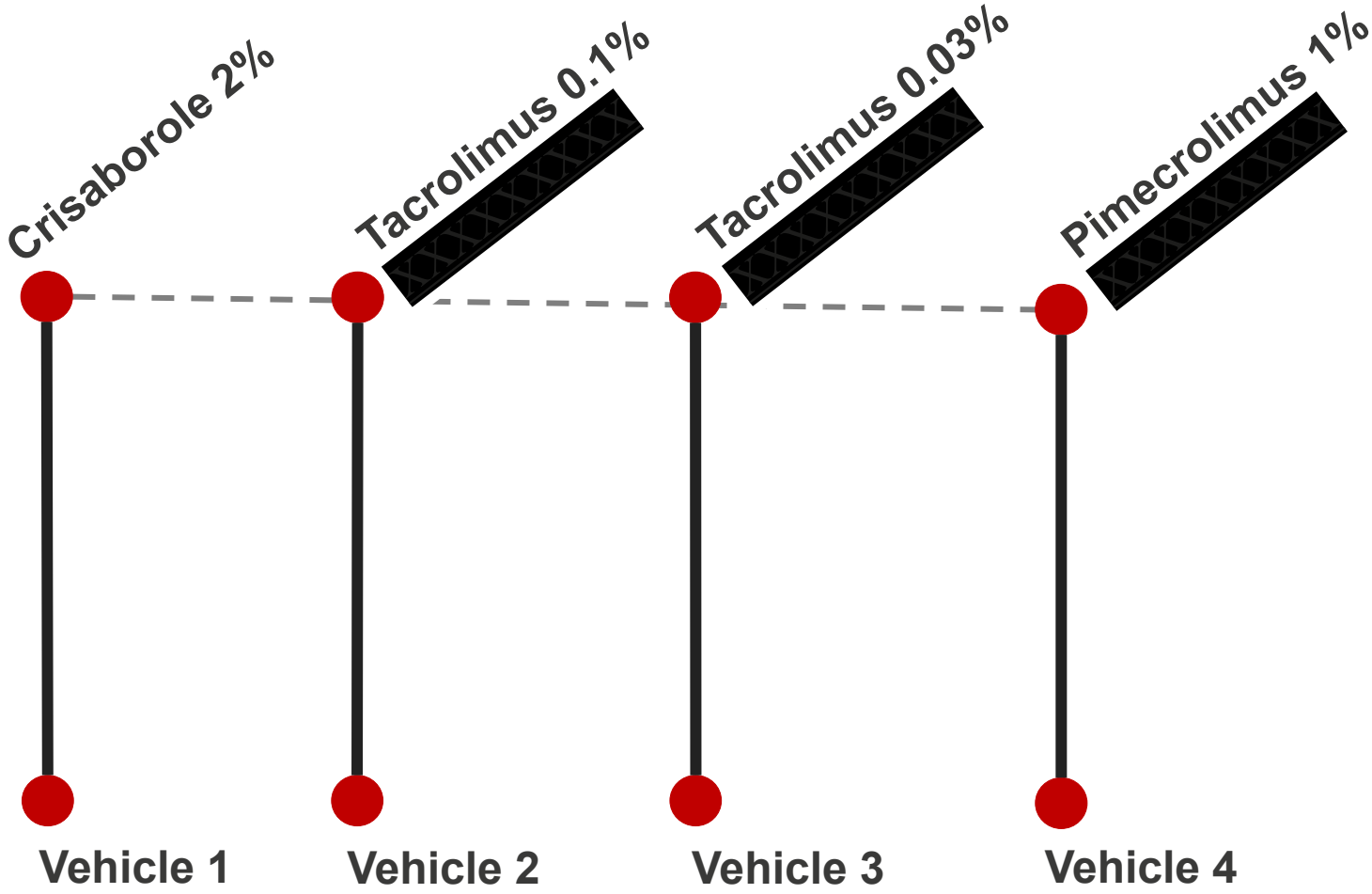
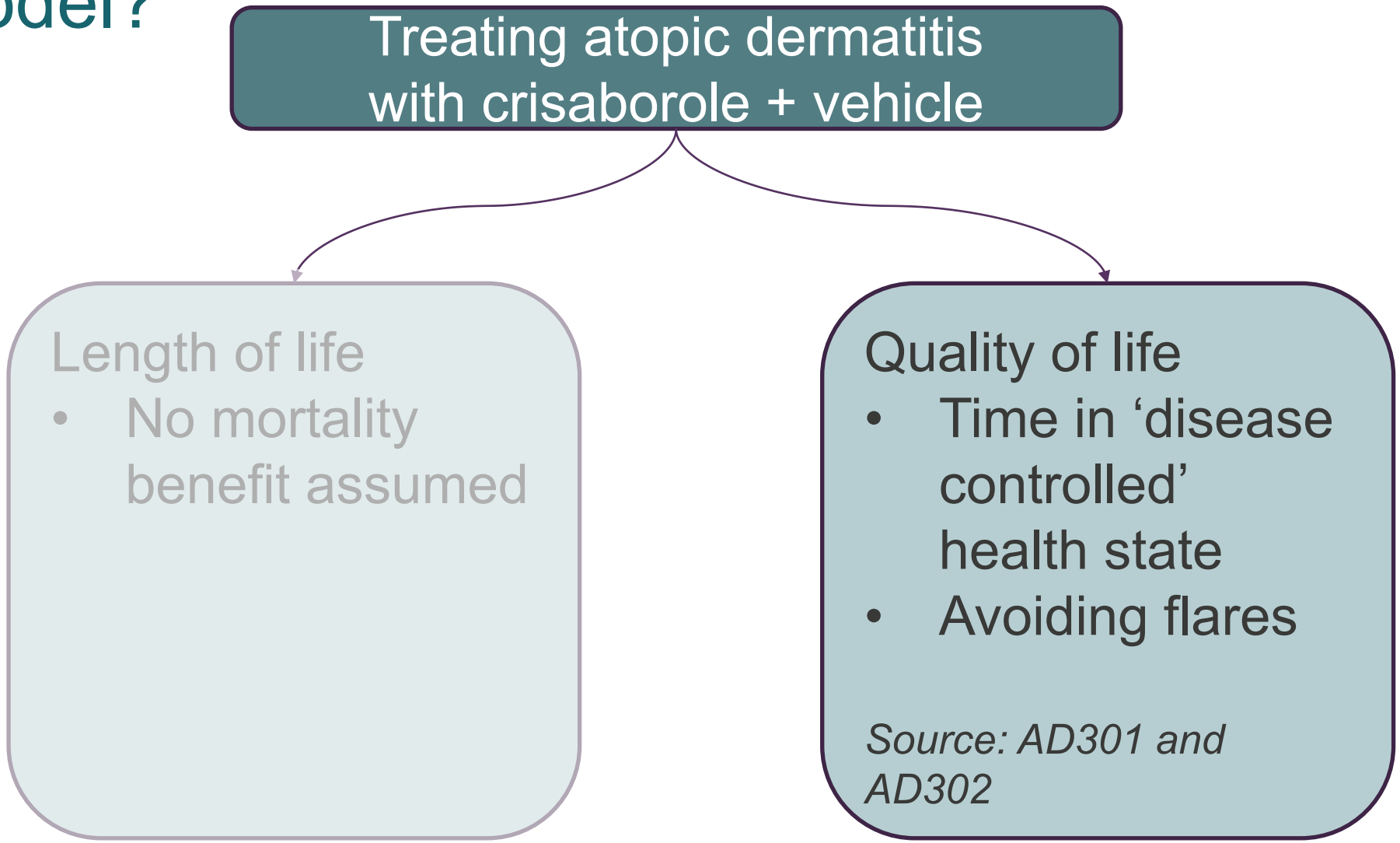


Diagram is for illustrative purposes, source: NICE

Key: Odds ratio (95% confidence interval)

Cost effectiveness

Where do QALY gains come from in company's model?



- Treatment has no impact on probability of disease resolving for children
- Subsequent treatment costs are key driver of the model

NICE

QALY, quality-adjusted life year

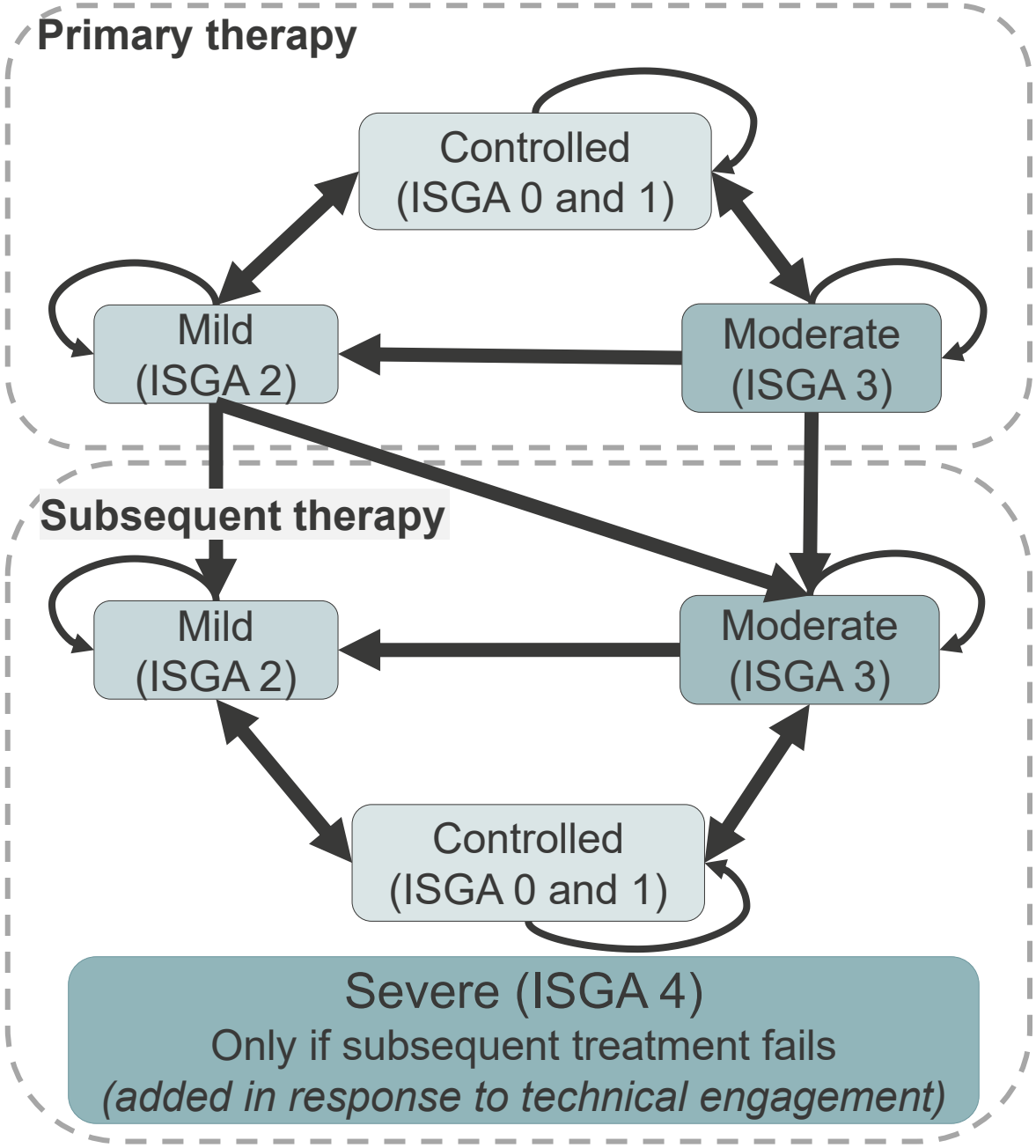
Background – economic

Model	Markov model 4 health states: mild flare, moderate flare, disease controlled, dead *Disease can 'resolve' in a proportion of children*
Therapies	Compared with topical calcineurin inhibitors People go on to receive therapies 3rd line and beyond
Company cost effectiveness results	Crisaborole dominates (better, cheaper) for all 4 subgroups
ICER ranges across plausible scenarios	• Very small changes in costs and QALYs, • Results of model very sensitive to changing £/QALY • Results heavily driven by whether model uses network meta-analysis, or matching adjusted indirect comparison • ERG scenarios: topical calcineurin inhibitors dominates crisaborole

Abbreviations: ICER, incremental cost-effectiveness ratio

Markov model structure

◉ *Is the model structure appropriate?*



Resolved for children: From any point in model

Death From any point in the model

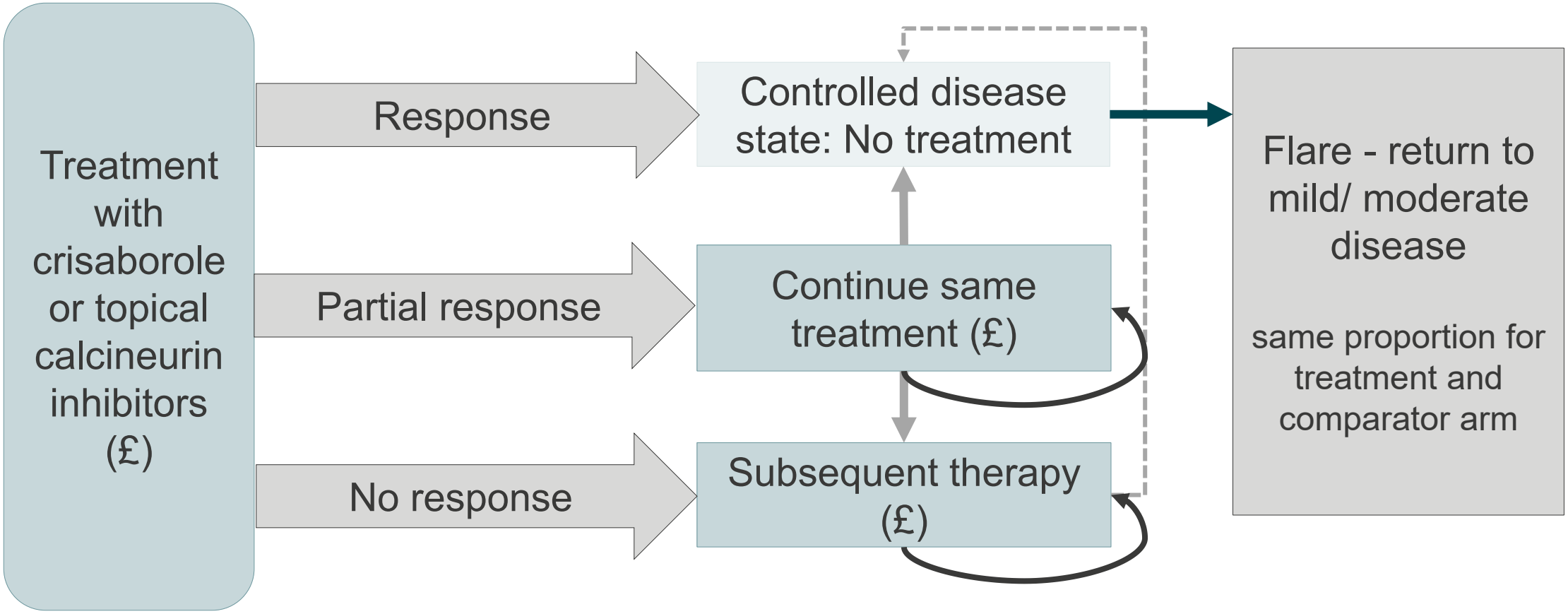
Subsequent therapy sequence: phototherapy → systemic therapies

ERG comments:

- Company does not model subsequent therapies adequately
- Subsequent therapy drives incremental costs and QALYs
- Patients cannot experience a flare of different severity to baseline severity
- Time horizon: not lifetime for children, disease progression stops at 18

Incremental costs

Therapies 3rd line and beyond drive costs; fewer therapies, lower cost



- If respond to treatment, no further treatment and avoid cost of subsequent therapy
- More people who take crisaborole than other drugs respond in company base case
- If no difference in clinical effectiveness, then drug cost drives cost-effectiveness results

Costs: clinician visits

Costs from doctor visits, increasing with disease severity

	GP visits per 28 days	Dermatologist visits per year
Controlled	none	
Mild	• Crisaborole or topical calcineurin inhibitors: 2 • Subsequent therapy: [redacted] children, [redacted] adults	• Crisaborole or topical calcineurin inhibitors: 0 • Non-responders: 1 visit on treatment failure • Subsequent therapy, non-responders: 13
Moderate	• Crisaborole or topical calcineurin inhibitors: 3 • Subsequent therapy: [redacted] children, [redacted] adults	• Crisaborole or topical calcineurin inhibitors: 0 • Non-responders: 1 visit on treatment failure • Subsequent therapy, non-responders: 13
Severe (Only if subsequent treatment fails)	• Same cost as subsequent therapy. No change to resource use or cost. • Company assumes additional costs for severe disease are captured because patients in severe state are already receiving subsequent therapies such as immunosuppressants	
Impact	Company deterministic sensitivity analysis: increasing/ decreasing GP visits by 25% while on subsequent therapy has a small impact.	**Decreasing the dermatology visits per year** from 6 per year (in all referred to subsequent therapy) to 13 per year (in people with uncontrolled disease) **halves the incremental cost savings in the company analysis**

◉ *Does this reflect clinical practice?*

Cost – topical calcineurin inhibitors

Drug	Applications per flare	Pack size (g)	Cost per pack	Cost per gram
Crisaborole	56	60	CiC	CiC
Tacrolimus 0.03% (children)	56	60	£42.55	£0.71
Tacrolimus 0.1% (adults)	56	60	£34.52*	£0.67
Pimecrolimus	56	100	£59.07	£0.59
*the price of tacrolimus fluctuates: Company submission; £37.82 September 2019, Company factual accuracy check £39.90 November 2019, ERG analyses February 2020 £34.52				

- **Company's base case assumes no difference in amount needed (g) per application**: for crisaborole, tacrolimus (adults) and pimecrolimus – 4 weeks treatment, applied twice daily, 56 applications. Tacrolimus for children: 3 weeks treatment, applied twice daily, followed by once daily for 1 week, 49 applications.
- Assumes no wastage.
- Company provides scenarios with different assumptions for application and duration of treatment (slide 31-32)

Other issues raised in technical engagement (1)

'No major impact on results'

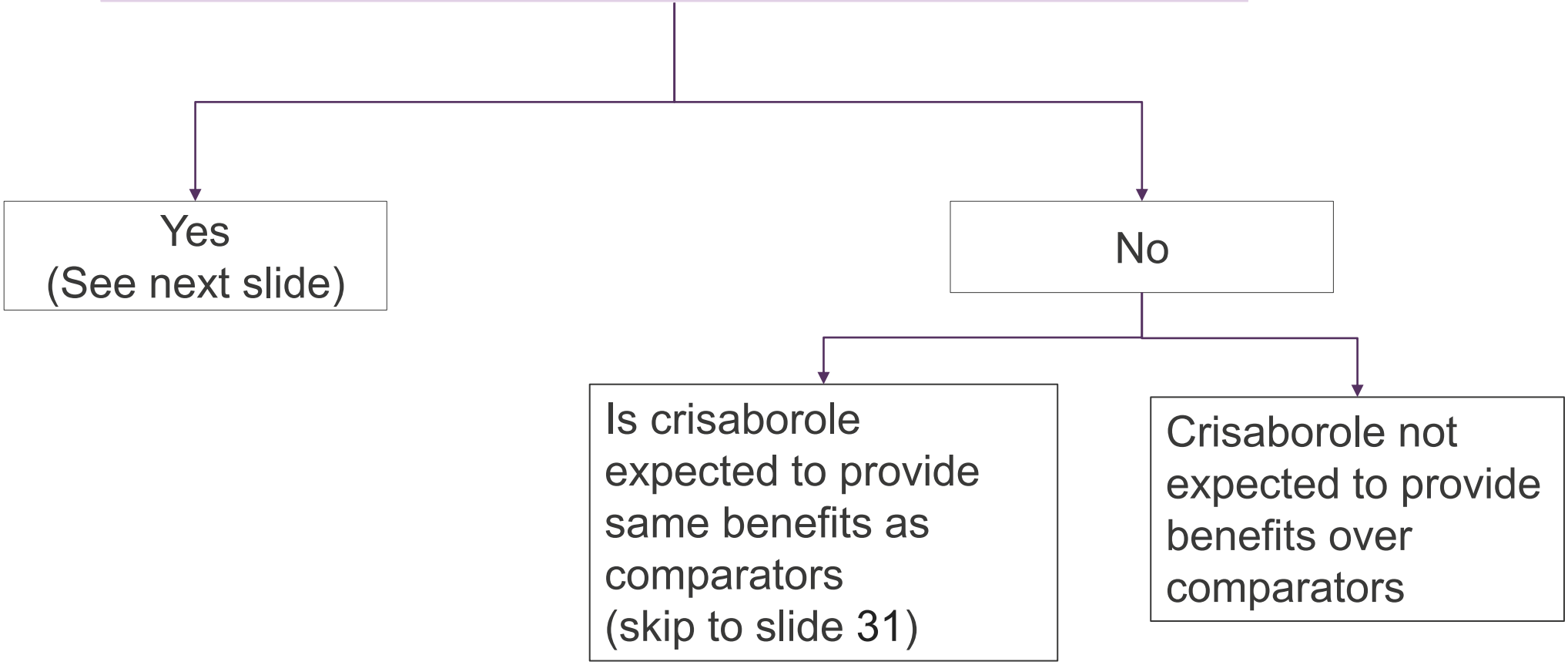
Issue re company base case	In company's updated base case?	ERG comment
Does not include sequential modelling of subsequent therapies	?- Included: phototherapy used before systemic therapy, consistent with NICE guidelines **No major impact on results**	Consistent with NICE guidelines, but model allows mild and moderate patients to receive phototherapy and systemic therapy
Subsequent therapy: company included only phototherapy and ciclosporin	✓ - Updated to include other relevant subsequent therapies: methotrexate, azathioprine and mycophenolate. **No major impact on results**	Error in company model for costing ciclosporin and mycophenolate mofetil – ERG corrected this
Partial response on subsequent therapy: company did not allow partial response to subsequent therapy.	? - Included **No major impact on results**	Rate of response applied to systemic therapies (0.205) differs to to topical corticosteroids and crisaborole (0.505). Company have not provided source for systemic therapy partial response – ERG cannot validate

Other issues raised in technical engagement (2)

'No major impact on results'

Issue	In company's updated base case?	ERG comment
Company's time on subsequent therapy did not reflect average time to response	? - Included. **No impact on results**	Company reduced time on subsequent therapy but not costs. 42% adults and 21% children incur costs for subsequent therapy with no benefit **Overestimates costs**
Company does not model progression to 'severe' health state	✓ - Assumes some patients who receive subsequent therapy progress to severe disease [redacted].	Company assume same costs and lower quality of life in severe state as with moderate state. Utility based on pooled adult EQ-5D values from AD-301 and AD-302. **Impact: increases incremental QALYs 3-4 fold (crisaborole more dominant).**
Drug use per application should be based on data for the body surface area affected ≤40%	✓ - updated. Reduces costs in all arms as model assumes same amount of treatment applied in all arms	ERG agrees

◉ *Does the model generate plausible results? If no, what needs to change?*



Cost effectiveness results

- ICERs not robust: differences in incremental costs and QALYs are small
- Model results driven by most effective comparator, depending on efficacy data source
- Cost-effectiveness analyses results presented for 4 subgroups: Adult/ Child, mild/ moderate
- ICERs, incremental costs and incremental QALYs are commercial in confidence and not presented here

Source	Result
Company base case using vehicle adjusted NMA	Crisaborole dominates
ERG base case using simple random effects NMA	Crisaborole is dominated
ERG base case using MAIC	Crisaborole dominates except in adults with moderate AD.
ERG base case using vehicle adjusted NMA	Crisaborole dominates except in adults with moderate atopic dermatitis

Abbreviations: AD, atopic dermatitis; Inc, incremental; MAIC, matching adjusted indirect comparison; NMA, network meta-analysis

Scenario: assumes crisaborole is equivalent to comparators

Changing dosing changes costs

	Crisaborole	Pimecrolimus	Tacrolimus 0.03%, children	Tacrolimus 0.1% & 0.03% adults
1. Application frequency reduced in week 4 for tacrolimus children	2x daily for 4 weeks	2x daily for 4 weeks	2x daily for 3 weeks and 1x daily for 1 week	2x daily for 4 weeks
2. Same dosing	2x daily, 4 weeks			
3. 6 weeks therapy for TCIs	2x daily 4 weeks	6 weeks, 2x daily	3 weeks, 2x daily and 3 weeks, 1x daily	6 weeks, 2x a day*

*the results for adults with moderate disease for this options could not be replicated so the ERG cannot verify if this was the assumption applied in adults

Innovation

Company makes a case for innovation

Company:

- Crisaborole has a unique mechanism of action, it is a non-steroidal compound and first-in-class topical PDE4 inhibitor
- A topical ointment
- Not associated with the serious adverse events reported with oral PDE4 inhibitors, such as nausea, vomiting, emesis, and headache
- Trials show that crisaborole improves in pruritus, a symptom of AD responsible for a significant proportion of disease burden but is not adequately captured by the EQ-5D

Equality and diversity

- None identified