Crisaborole for Treating Mild to Moderate Atopic Dermatitis in People Aged 2 Years and Older [ID 1195]: A Single Technology Appraisal – Addendum

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Declared competing interests of the authors

Carolyn Charman declared that she provides ad hoc consultancy, presentations and teaching for Galderma (hydrocortisone), GlaxoSmithKline (betamethasone valerate, clobetasone butyrate, fluticasone propionate, hydrocortisone) and Leo Laboratories (betamethasone valerate, fusidic acid, hydrocortisone, tacrolimus). None of the other authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors to this addendum

John Stevens critiqued the company's response regarding the evidence synthesis (issue 6). Edith Poku and Katy Cooper critiqued the company's response regarding the duration of treatment for TCIs. Sarah Davis and Andrew Metry critiqued the updated health economic analysis submitted by the company and conducted the ERG exploratory analyses.

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Abbreviations

AD	Atopic dermatitis
BAD	British Association of Dermatologists
CEBD	Centre for Evidence-Based Dermatology
CG	Clinical Guideline
CRTE	Company's response to technical engagement
DIC	Deviance Information Criterion
ERG	Evidence Review Group
ICD	International Congress of Dermatology
ICER	Incremental cost-effectiveness ratio
MAIC	Matching-adjusted indirect comparison
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
QALY	Quality-adjusted life year
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid

1 INTRODUCTION

1.1 Technical engagement report

The NICE technical team, in collaboration with the Committee chair and Lead Team, prepared a draft technical engagement report which was sent out for consultation with stakeholders. This report is based on their initial consideration of the company submission, consultee and commentator expert statements and the ERG report. The technical engagement report identified 6 key issues for consideration during technical engagement. These were as follows;

Issue 1: The company has included pimecrolimus as a comparator for people with mild atopic dermatitis (AD), is this appropriate?

Issue 2: The company's economic model structure does not allow sequential subsequent treatment

Issue 3: The company model does not allow for a partial response on subsequent treatment

Issue 4: The company's model does not take into account the duration of subsequent treatments

Issue 5: Drug use per application should be based on data for the anticipated population for crisaborole

Issue 6: Can the [redacted] and is it appropriate to adjust the relative effectiveness results for [redacted]?

The technical team also recognised that there were several other uncertainties in the evidence that would be unlikely to be resolved during technical engagement which were;

- The possible long-term benefits of crisaborole are unknown, as the efficacy data is based on short term trials (4 weeks).
- There are no head-to-head trials comparing crisaborole with the relevant comparators. The clinical trials compare crisaborole with vehicle ointment [redacted]
- The structure of the company's model precluded the following from being explored fully: sequential subsequent treatments, duration of treatment on subsequent therapy, the potential of atopic dermatitis progressing to severe stage.

1.2 Responses to technical engagement

In response to consultation on the technical engagement report, the company (Pfizer) provided a written response to each of the 6 issues identified and also provided a new economic model. The ERG were requested by NICE to provide a critique of the company's response to technical engagement (CRTE). In doing so, the ERG also took into account the response provided by the Centre for Evidence-Based Dermatology (CEBD). Given the limited time allowed for the ERG to provide their critique, the ERG

have focused on issues where the company has provided additional evidence or analyses or where additional evidence has been provided in the CEBD response.

2 RESPONSES TO THE SIX KEY ISSUES

2.1 Issue 1: Comparator for mild atopic dermatitis

The company provided additional evidence on this in the form of cost-effectiveness analyses comparing crisaborole to tacrolimus (0.03% in children and both 0.03% and 0.1% in adults) in patients with mild AD who have failed on topical c tosteroids (TCSs). Previously, in this population, the company had only compared crisaborole to pimecrolimus. The reason given was that pimecrolimus is the only topical calcineurin inhibitor (TCI) with a license in patients with mild AD.

The ERG notes that the submission from the CEBD states that cases of true failure of TCSs in patients with mild AD are not observed in clinical practice and that in practice clinicians would simply try an alternative mild TCS or switch to a more potent TCS. They commented that TCIs, would only be used in the rare situation that patients had genuine steroid phobia, but that 99% of patients would be happy to use TCSs when properly informed about how to use them safely. They stated that they would use either tacrolimus or pimecrolimus in this situation.

The ERG notes that the use of tacrolimus in the population with mild AD would be off-license and the use of either TCI in mild AD would be outside of NICE's recommendations in TA82. But if tacrolimus was considered to be a valid comparator, on the basis that it is preferred over pimecrolimus in current clinical practice, then the company's analysis shows that the cost savings and QALYs gains for crisaborole are smaller when comparing to tacrolimus (0.03% in children or 0.1% in adults) as it is more effective than pimecrolimus.

The company argued that it was unethical to use emollients alone in patients whose mild AD had not responded to TCSs. This was supported in the consultation response from the CEBD.

The ERG's view is that the evidence submitted by the CEBD suggests that there would be few patients with mild AD that would require an alternative to TCSs, but that in those rare cases where one is needed, clinicians would consider using either tacrolimus or pimecrolimus even though neither is recommended by NICE and tacrolimus would be off-license in this population.

2.2 Subsequent therapies

2.2.1 Sequential use of subsequent therapies

The company's updated model submitted in the CRTE assumes that all patients failing second-line treatment, with either TCIs or crisaborole, progress to receive phototherapy and only those failing to achieve a response to phototherapy progress to receive systemic therapy with immunosuppressants. This revised model is more consistent with the stepped care approach for AD management

recommended in NICE Clinical Guideline 57 (see Table 1 of the ERG report) in that phototherapy is assumed to be used prior to systemic therapies. However, the ERG also notes that phototherapy and systemic immunosuppressants are only recommended in the NICE stepped care pathway for severe AD and not for mild or moderate AD. The response from the CEBD also noted that phototherapy was not appropriate for patients with mild AD. This agrees with the ERG's previous comments that phototherapy and systematic therapies are not part of the NICE stepped care approach for mild AD.

The ERG notes the company's comment that there may be regional variation in whether subsequent therapies are used sequentially and whether there would be regional variation in treatment patterns (e.g. based on the clinician preference or for example the availability/ease of access to phototherapy). This agrees with comments by the ERG's clinical experts that uptake of phototherapy would depend on whether it was available locally as it requires frequent attendance at hospital and this would not always be acceptable to patients, particularly if they had to travel long distances.

The ERG would reiterate what it said previously which was that, *"Clinical advisors to the ERG further noted that treatment escalation to systemic immunosuppressants and phototherapy was generally restricted to patients with uncontrolled severe AD or a subgroup of moderate AD patients with severe clinical presentations. The BAD audit data show that in secondary care systemic treatments are used in a small proportion (under 2%) of children with mild to moderate AD, but they are used around 23% of children with severe AD."* In addition, the ERG note the comments from the CEBD when asked to describe treatment options for those failing to response to second line TCIs which was that, *"the range of potency of topical corticosteroids is huge and can usually control patients from very mild (1% hydrocortisone), to moderate (clobetasone) and to moderate/severe (mometasone/fluticasone)."* This suggests that clinicians would not be expecting patients with mild to moderate AD to require treatment with subsequent therapies as it should be possible to achieve a response using TCSs.

The ERG also notes that the updated model still assumes that patients will receive one of several systemic therapies and applies average parameters for cost, efficacy and duration of treatment based on the proportion assumed to receive each of the possible systemic therapies. It therefore does not capture the possibility that patients will try one systemic therapy and then try an alternative systemic therapy if the first does not work. Such an approach would be likely to increase the cumulative efficacy of subsequent therapies and avoid a large proportion of patients failing to achieve a response on subsequent therapies in the long-term as is the case in the current modelling (see section 2.4).

2.2.2 Choice of subsequent therapies

The company's updated model submitted in the CRTE assumes that a mix of possible therapies are available for systemic immunosuppressant therapy including ciclosporin, methotrexate, azathioprine

and mycophenolate mofetil. This is consistent with the approach taken in the ERG's preferred base-case analysis, although the ERG note that the company did not incorporate their corrections to the drug costs for ciclosporin and mycophenolate mofetil. The ERG have therefore reapplied these corrections in their exploratory analyses presented in section 5.

2.2.3 Progression to the severe health state

The company's updated model submitted in the CRTE assumes "*that a proportion of patients who fail TCS or TCI treatment and proceed to subsequent therapies will progress to severe disease* [redacted]*).*" To implement this, the company have assumed that this group of patients have a reduced quality of life with no change to resource use or costs. This is because any additional costs required to manage severe disease are assumed to have been captured because these patients are already receiving subsequent therapies such as immunosuppressants which are recommended for severe AD.

The utility multiplier applied in severe disease is [redacted]. The company does not explicitly state the source of this data in their response to technical engagement, however, the data in the model are consistent with the source being the same as the source for mild and moderate AD, i.e. adult EQ-5D values pooled from studies 301 and 302 (based on comparison of the data in the Excel model with data provided in Table 22 of the CS). The ERG note that the mean absolute utility value is therefore based on measurements from [redacted] adult patients with severe AD whereas the values for all other health states are based on [redacted] or more patients. Whilst this value is likely to be associated with considerable uncertainty, the fact that it is only being applied to a small minority of patients suggests that it is unlikely to significantly contribute to decision uncertainty.

Although the company claims that the inclusion of a severe disease state has a limited impact on the results and is therefore not an important area of decision uncertainty, the ERG note that in mild AD, the addition of the severe state increases the incremental QALYs three to four fold (see Table 5 and Table 7 of the CRTE). Therefore, although it does not change the broad conclusion that crisaborole dominates TCIs, when using the company's preferred NMA, it does show that the size of the QALY gains achieved are being driven by the assumptions regarding what happens to patients moving on to subsequent treatments.

2.3 Issue 3: Partial response to subsequent therapies

The company's updated model submitted in the CRTE now incorporates states to allow patients with moderate AD to experience a partial response to subsequent therapies (both phototherapy and systemic

immunosuppressants). The company states that this has a limited impact on the cost-effectiveness analysis, although the ERG notes that in patients with moderate AD, applying this change alone was found to approximately halve the incremental QALYs (see Table 6 and Table 8 of the company's response to technical engagement [CRTE]).

The ERG notes that the rate of partial response applied to phototherapies is equivalent to that applied to TCIs and crisaborole. However, the rate of partial response applied to systemic therapies (0.205) is hard coded into the spreadsheet and the source of the value is not described in either the CRTE or in the Excel file itself. Therefore, the ERG cannot confirm the validity of this probability and this introduces some uncertainty into the interpretation of the company's updated model.

2.4 Issue 4: Duration of subsequent therapies

The company's updated model submitted in the CRTE now incorporates rates of response that are adjusted to reflect the ERG's preferred assumptions regarding the duration of time required to achieve a response for each of the subsequent therapies (see Table 32 of the ERG report). However, in the ERG's previous scenario analysis addressing this issue (scenarios 7 and 14 in the ERG's exploratory analyses presented in the ERG report), the ERG also limited the costs of treatment to the duration of treatment to prevent patients accruing costs for unsuccessful subsequent treatments indefinitely. This was done by applying the costs for the whole duration of subsequent treatment at the time of initiation of subsequent treatment. In contrast, in the company's updated model, patients continue to receive the cost of subsequent treatment in each cycle that they remain non-responsive. This results in around 42% of adults remaining on systemic treatment long-term and accruing costs for those systemic treatments without achieving an adequate response. The proportion in children is lower due to the assumption that disease resolves in a proportion of children, but the model still predicts that 21% of children end up on long-term systemic treatment. This does not appear to have clinical face validity given that the data from the BAD audit suggest that in secondary care systemic treatments are used in a small proportion (under 2%) of children with mild to moderate AD. Therefore, the model appears to be over estimating the proportion of patients accruing costs for systemic therapy without achieving a response.

Although the company states that the changes to adjust response times to reflect duration of treatment show no impact on overall conclusions, the ERG notes that the QALY gains approximately double when incorporating both the broader range of subsequent therapies and the appropriate duration of time to response for these subsequent therapies (see Tables 6 to Table 8 of the CRTE). Therefore, although it does not change the broad conclusion that crisaborole dominates TCIs, when using the company's preferred NMA, it does show that the size of the QALY gains achieved are being driven by the assumptions regarding the effectiveness of subsequent therapies.

2.5 Issue 5: Drug use per application

The ERG agrees with the company's decision to use data on drug use per application which is based on data for the indicated population for crisaborole despite the fact that this has a small impact on the incremental costs.

2.6 Issue 6: Network meta-analysis (NMA)

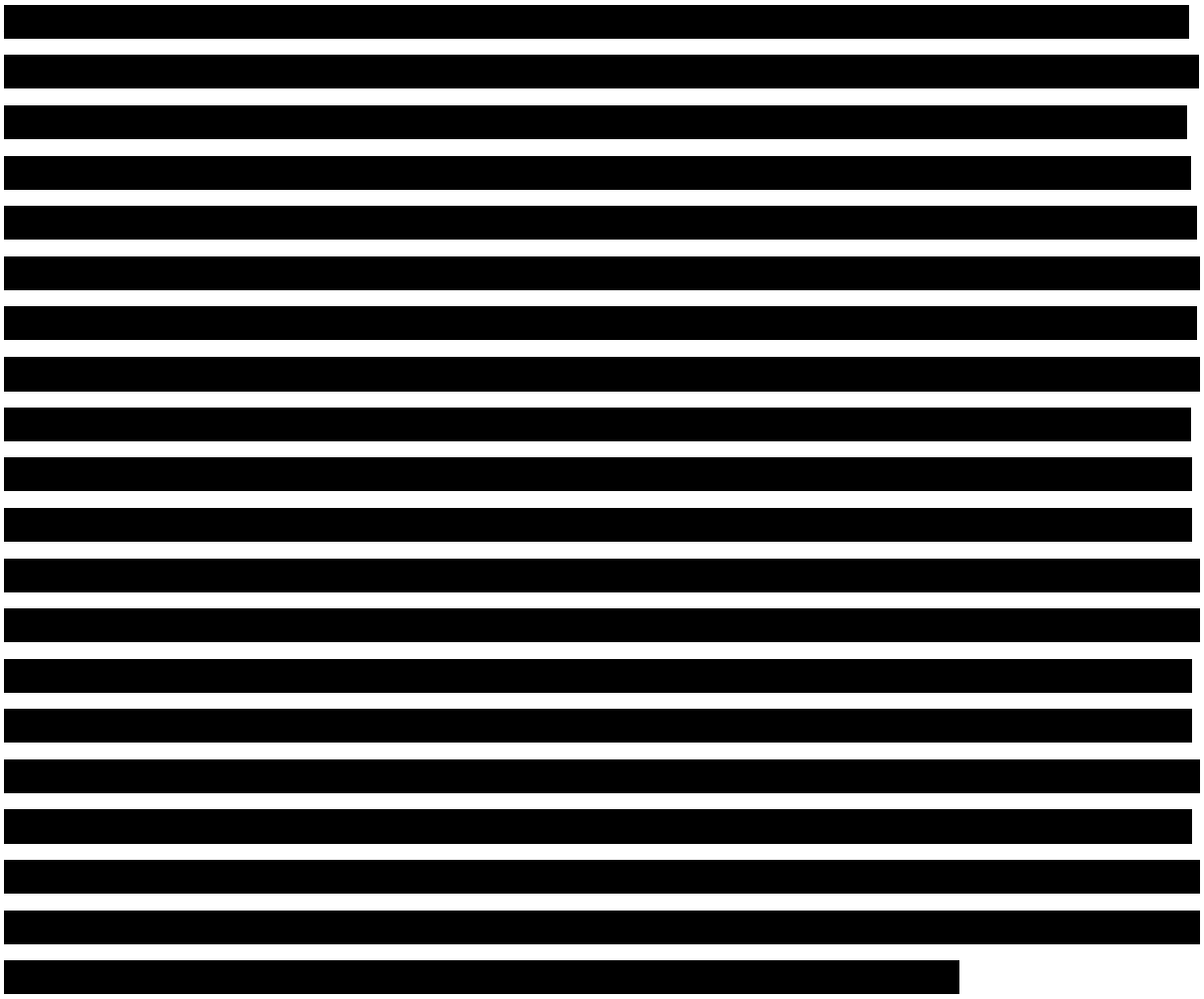
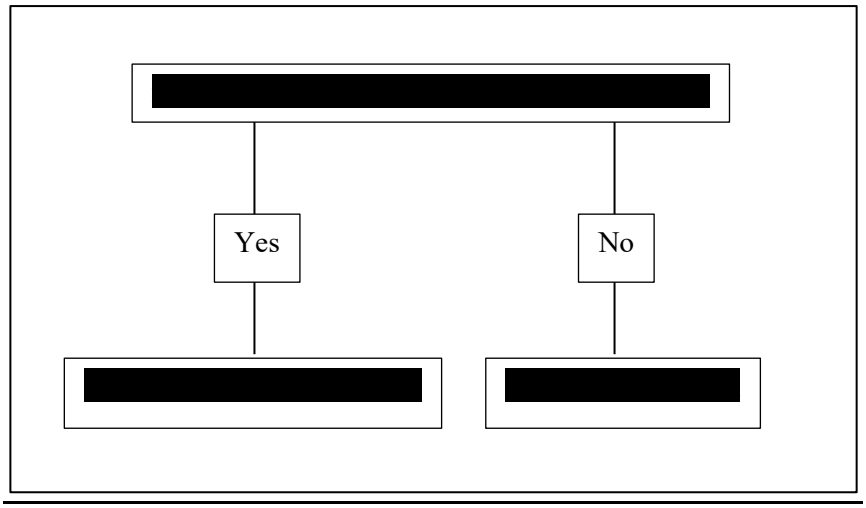


Figure 1: Process for deciding which modelling approach to use



[redacted]

[redacted]

3 OTHER CHANGES TO THE COMPANY MODEL

The company made several other changes to their model in addition to the changes made to the company model in response to the six key issues already described in section 2.

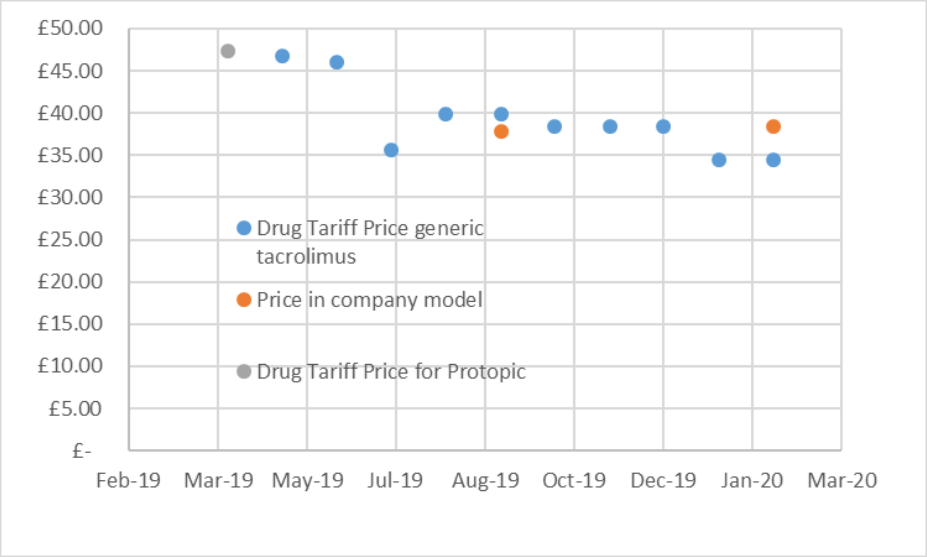
3.1 Adjusting clinician visits

Patients are now assumed to receive one consultant visits per on-treatment cycle in subsequent therapy (phototherapy or systemic therapy) instead of 6 per year, although these costs are now only applied to those who have uncontrolled disease as per the ERG's preferred assumption. The ERG notes that this single change approximately halves the incremental cost savings in the company's analyses (see Table 5 to 8 of the CRTE). This further highlights the importance of correctly estimating downstream costs in order to accurately quantify the size of any cost savings or QALY gains from avoiding patients progressing to subsequent therapies which are managed mostly in secondary care.

3.2 Updating the cost of tacrolimus

The company's updated model uses an acquisition cost for generic 0.1% tacrolimus of £38.46. Although this matches the drug tariff price reported in the current BNF online (accessed 17th Feb 2020), the ERG notes that there is lag between updates to the drug tariff and updates to the BNF online and the drug tariff price for February 2020 is £34.52. The ERG notes that the price of generic 0.1% tacrolimus has varied several times over the course of this appraisal and the costs may continue to fluctuate in future. Figure 2 shows how the price of tacrolimus has varied since a price was listed for the generic version in May 2019. The ERG have applied the latest price from the February 2020 for generic 0.1% tacrolimus (£34.52) in their analyses presented in Section 5.

Figure 2: Drug tariff prices for 0.1% tacrolimus over time and prices applied in the company's models submitted in Sept 2019 and Feb 2020



3.3 Phototherapy costs

Phototherapy costs are now applied once when patients initiate phototherapy. The cost applied is £93 which is based on the reference cost for phototherapy. Therefore, the company appears to be assuming that £93 is the cost of a whole course of phototherapy. The ERG notes that in the appraisal of dupilumab, the reference cost for phototherapy was £86.85 per session (2016/17 prices), and the number of session over 3 months was assumed to be 22 giving a cost per course of £1,910.70 (TA534: Sanofi response to ACD, Appendix C). Therefore, the ERG does not believe that the company has properly estimated the costs of phototherapy. The impact of this is that the cost savings from avoiding patients progressing to subsequent therapy will have been underestimated. This will obviously favour crisaborole in the company's base-case but would favour TCIs when using the ERG's preferred simple random effects NMA. This failure by the company to properly estimate the cost of phototherapy adds further to the uncertainty regarding the cost savings and QALY gains attributable in the model to avoiding treatment with subsequent therapies.

4 COST COMPARISONS ASSUMING EQUIVALENT EFFICACY

In the technical report conclusions on issue 6, the NICE technical team requested that the company provide some analyses assuming that crisaborole has the same efficacy as comparator treatments. The company has provided results tables for these comparison but no spreadsheet model has been provided therefore the ERG had to determine what assumptions had been used in these analyses by trial and error.

The ERG were able to replicate the results for patients with mild AD (i.e. Table 9 for children with mild AD and Table 12 for adults for mild AD) by setting the response probability for crisaborole equal to that for pimecrolimus. No change was made to the duration of treatment for pimecrolimus which remained twice daily for four weeks.

The ERG were able to replicate the results in Table 11 for patients with children moderate AD when assuming 3 weeks of twice daily treatment followed by 3 weeks of once daily treatment for tacrolimus 0.03% and setting the efficacy of crisaborole equal to that of pimecrolimus, but again no change was made to the duration of treatment for pimecrolimus.

The ERG were unable to replicate the results in Table 10 by then setting the efficacy of crisaborole equal to that of tacrolimus 0.03%. The results presented in Table 10 by the company lack face validity because the QALY gains are not equivalent between crisaborole and tacrolimus 0.03% suggesting that there is an error in these results. The ERG believe that the results in Table 10 of the CRTE were obtained in error by setting crisaborole to have equivalent efficacy to tacrolimus 0.1% instead of tacrolimus 0.03%. The ERG has produced corrected results for this scenario in Table 1 below.

Table 1: Children with moderate disease: Crisaborole efficacy equivalent to tacrolimus 0.03% and assuming 6 weeks of treatment tacrolimus 0.03%†

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER vs. baseline	ICER incremental
Crisaborole	[redacted]	[redacted]	[redacted]	[redacted]	-	Dominant
Tacrolimus 0.03%	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Pimecrolimus	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

† ERG correction to Table 10 of the CRTE in which efficacy was mistakenly set equal to tacrolimus 0.1%

The ERG was able to replicate the results for adults in Tables 12 to 14 by setting the duration of treatment for tacrolimus 0.03% and tacrolimus 0.1% to 6 weeks and setting the efficacy of crisaborole to the appropriate TCI option.

The ERG notes that the results presented in Tables 9 to 14 of the CRTE do not apply a 6 week duration for pimecrolimus but they do assume a 6 week duration for both tacrolimus 0.03% and tacrolimus 0.1%. This is despite the company stating on page 12 that they assumed *"up to 6 weeks of therapy per treatment cycle for TCIs*" and not just tacrolimus. The ERG notes that results assuming 6 weeks of treatment with pimecrolimus are presented in the bottom row in Tables 15 and 16 of the CRTE and in these scenarios crisaborole dominates due to the additional costs incurred over these additional two weeks.

The ERG was able to validate the results in Tables 15 to 17 of the CRTE. It is noted that in Tables 17 and 18 which present results for moderate AD where there is more than one comparator treatment, the efficacy of treatment for all three options has been set to the same value. This is in contrast to Tables 10, 11, 13 and 14, where the efficacy of crisaborole was set to match one comparator but the efficacy of the other comparator was left at its original value. The cost assumptions applied for the three options in Tables 15 to 17 are summarised in Table 2. These are based on the description provided by the company on page 7 to 8 of the CRTE and the ERG's attempts to replicate the results in Tables 15 to 18. However, it should be noted that the ERG were unable to replicate the costs presented in the final row of Table 18 of the CRTE, although it believes that the costs in this row should match those in Table 14 so these results are still provided in the CRTE.

Despite the ERG being unable to replicate some results, it is clear that when assuming equivalent efficacy, and equivalent treatment duration, crisaborole is never cost saving. In contrast, when assuming that TCIs are used for 6 weeks instead of 4 weeks, the treatment with the lowest cost is always crisaborole. Therefore, the key decision uncertainty is whether the cost of TCIs should be assumed to apply for 6 weeks or 4 weeks.

Table 2 : Cost assumptions applied in the equivalence scenarios (Tables 15 to 18 of the CRTE)

Company's description of scenario	Crisaborole dosing	Pimecrolimus dosing	Tacrolimus 0.03% in children	Tacrolimus 0.03% in adults	Tacrolimus 0.1%
Equivalent efficacy	4 weeks of twice daily	4 weeks of twice daily	3 weeks of twice daily and 1 week of once daily	4 weeks of twice daily	4 weeks of twice daily
Equivalent efficacy and dosing	4 weeks of twice daily	4 weeks of twice daily	4 weeks of twice daily	4 weeks of twice daily	4 weeks of twice daily
Equivalent efficacy and 6 weeks of therapy for TCIs	4 weeks of twice daily	6 weeks of twice daily	3 weeks of twice daily and 3 weeks of once daily	6 weeks of twice daily*	6 weeks of twice daily*

*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

The ERG wishes to point out that the company's assumption that patients receive 6 weeks of initial treatment because the summary of product characteristics (SmPCs) for TCIs specify that they can be used for up to 6 weeks, is at odds with their modelling of partial responders who would receive 6 weeks of treatment cost during the first model cycle and then 6 weeks of treatment costs in the second model cycle. Given that the company claims that TCI treatment should be given for up to 6 weeks based on the SmPCs for TCIs, it seems unreasonable for the model to include costs for up to 12 weeks for the proportion who have a partial response. In the company's original base-case model, patients received 4 weeks of treatment in the initial 4 week cycle, and partial responders received a second cycle of 4 weeks treatment allowing them to receive up to 8 weeks of treatment with TCIs, which already is longer than the 6 weeks that the company claims is the maximum duration of treatment for TCIs based on the SmPCs for TCIs. The ERG would also point out that the draft SmPC for crisaborole (as described in Table 2 of the company submission) states, *"Staquis can be used for up 4 weeks per treatment course. If any signs/and or symptoms persist, or new areas affected with atopic dermatitis appear, further treatment courses can be used. Staquis should be discontinued if signs and/or symptoms on treated areas persist after 3 consecutive treatment courses of 4 weeks each or if the signs and/or symptoms worsen during treatment."* Therefore, the draft SmPC for crisaborole suggests that it can be used for up to 12 weeks, but cost for 12 weeks of crisaborole are not explored in any of the company's scenario analyses.

The company's rationale for assuming 6 weeks of TCI treatment is that they had previously assumed that the costs for tacrolimus reflected 4 weeks usage, even though, the efficacy data for tacrolimus used in the NMA, captured outcomes for up to 6 weeks tacrolimus treatment. The ERG noted that whilst three of the TCI trials included in the efficacy NMA reported outcomes at 6 weeks,[2-4] two studies reported outcomes at four weeks [5, 6] and two studies reported outcomes at both 4 weeks and 6 weeks,[7, 8] but the 4 week data was included in the NMA as this was closer to the duration of the crisaborole studies. In addition, all of the 5 studies that had a duration longer than 4 weeks,[2-4, 7, 8] mentioned that patients could stop TCIs early if symptoms cleared. Therefore, whilst treatment was allowed to be continued up to 6 weeks in some of the TCI studies included in the NMA, it is not clear that all patients required 6 weeks of treatment to achieve the response rates incorporated in the NMA, and outcomes in the NMA were based on data from 4 weeks in 4 of the 7 studies.

The ERG also notes that all of the comparisons assuming equivalence of efficacy are heavily dependent on the fact that it assumed that the same amount of treatment is needed per application for crisaborole and all TCIs and that there is no wastage due to a mismatch between the tube size and the total amount needed to treat a single flare. In practice, the costs could be quite different if one intervention needed just under 2 tubes of treatment and the other needed just over 2 tubes. The bottom line is that these interventions have [redacted]

5 IMPACT ON THE ICER OF ADDITIONAL ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG ran all exploratory analyses deterministically using the latest cost for tacrolimus 0.1% (£34.52 per tube). A summary of the exploratory analyses undertaken by the ERG is presented in Table 3 for children with mild AD, Table 4 for children with moderate AD, Table 5 for adults with mild AD, and Table 6 for adults with moderate AD. It can be seen from these results that when using the simple random effects NMA, crisaborole is dominated by TCIs in all four populations. Conversely when using the MAIC, TCIs are dominated by crisaborole in all populations except adults with moderate AD. Therefore, the key area of decision uncertainty relates to whether the [redacted] as this determines whether the results from the simple random effects NMA or MAIC should be preferred.

There is only one scenario using the MAIC where TCIs are not dominated by crisaborole, and this is the comparison between tacrolimus 0.1% and crisaborole in adult patients with moderate AD. In this case crisaborole is associated with a small additional cost and a small QALY gain with an ICER of [redacted] per QALY gained for crisaborole versus tacrolimus 0.1%. For comparison, the ICER for crisaborole versus tacrolimus 0.1% in adults with moderate AD was [redacted] per QALY gained in the company's revised model when selecting the MAIC and using the latest cost for tacrolimus 0.1%.

It should be noted that only pair-wise cost-effectiveness analyses can be presented when using the MAIC as the rate of response for crisaborole is estimated based on the MAIC specific to the individual comparator. Therefore, the rate of response for crisaborole when comparing against tacrolimus 0.03% will be different to the rate of response for crisaborole when comparing against tacrolimus 0.1%. For this reason, incremental analysis cannot be conducted when using the MAIC if there are two or more comparators.

Additionally, the ERG highlights that the small decrement in tacrolimus 0.1% price (from £38.46 to £34.52 per tube) had a considerable impact on the analyses for the adult moderate population, and crisaborole does not dominate tacrolimus 0.1% anymore, even in the company's base case. This illustrates that the cost differences between comparators are minimal, and the conclusion that one or another treatment dominates would be sensitive to any price changes that could happen in the future.

Table 3: ERG exploratory model results for mild child patients

Analysis	Discounted costs		Discounted QALYS		ICER (crisaborole versus pimecrolimus)
	Crisaborole	Pimecrolimus	Crisaborole	Pimecrolimus	
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	**Crisaborole dominates** [redacted]
1) Correcting acquisition costs of subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	Crisaborole dominates [redacted]
2) Assuming non responders receive 4 weeks of treatment	[redacted]	[redacted]	[redacted]	[redacted]	Crisaborole dominates [redacted]
ERG base case (scenarios 1 – 2) using the company's preferred NMA	[redacted]	[redacted]	[redacted]	[redacted]	**Crisaborole dominates** [redacted]
3) Adjusting costs of subsequent therapy to reflect the whole time on treatment†	[redacted]	[redacted]	[redacted]	[redacted]	Crisaborole dominates [redacted]
ERG base case (scenarios 1 – 2) using the company's MAIC results	[redacted]	[redacted]	[redacted]	[redacted]	**Crisaborole dominates** [redacted]
Company base case using the ERG's simple random effects NMA results	[redacted]	[redacted]	[redacted]	[redacted]	**Pimecrolimus dominates** [redacted]
4) Correcting acquisition costs of subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	Pimecrolimus dominates [redacted]
5) Assuming non responders receive 4 weeks of treatment	[redacted]	[redacted]	[redacted]	[redacted]	Pimecrolimus dominates [redacted]
ERG base case (scenarios 4 – 5) using the ERG's simple random effects NMA results	[redacted]	[redacted]	[redacted]	[redacted]	**Pimecrolimus dominates** [redacted]
6) Adjusting costs of subsequent therapy to reflect the whole time on treatment†	[redacted]	[redacted]	[redacted]	[redacted]	Pimecrolimus dominates [redacted]

†In conjunction with the ERG base case mentioned above

ΔC, difference in costs, ΔQ, difference in QALYs; ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; QALY, quality adjusted life year

Table 4: ERG exploratory model results for moderate child patients

Analysis	Discounted costs			Discounted QALYS			ICER (crisaborole versus tacrolimus 0.03%†)
	Crisaborole	Tacrolimus 0.03%	Pimecrolimus	Crisaborole	Tacrolimus 0.03%	Pimecrolimus	
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Crisaborole dominates tacrolimus 0.03%†** [redacted]
1) Correcting acquisition costs of subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Crisaborole dominates tacrolimus 0.03%† [redacted]
2) Assuming non responders receive 4 weeks of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Crisaborole dominates tacrolimus 0.03%† [redacted]
ERG base case (scenarios 1 – 2) using the company's preferred NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Crisaborole dominates tacrolimus 0.03%†** [redacted]
3) Adjusting costs of subsequent therapy to reflect the whole time on treatment†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Crisaborole dominates tacrolimus 0.03%† [redacted]
ERG base case (scenarios 1 – 2) using the company's MAIC results (Crisaborole vs tacrolimus 0.03%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Crisaborole dominates tacrolimus 0.03%†** [redacted]
ERG base case (scenarios 1 – 2) using the company's MAIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Crisaborole dominates pimecrolimus**

Analysis	Discounted costs			Discounted QALYS			ICER (crisaborole versus tacrolimus 0.03%†)
	Crisaborole	Tacrolimus 0.03%	Pimecrolimus	Crisaborole	Tacrolimus 0.03%	Pimecrolimus	
results (Crisaborole vs pimecrolimus)							[redacted]
Company base case using the ERG's simple random effects NMA results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Tacrolimus 0.03%† dominates crisaborole** [redacted]
4) Correcting acquisition costs of subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Tacrolimus 0.03%† dominates crisaborole [redacted]
5) Assuming non responders receive 4 weeks of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Tacrolimus 0.03%† dominates crisaborole [redacted]
ERG base case (scenarios 4 – 5) using the ERG's simple random effects NMA results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Tacrolimus 0.03%† dominates crisaborole** [redacted]
6) Adjusting costs of subsequent therapy to reflect the whole time on treatment†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Tacrolimus 0.03%† dominates crisaborole [redacted]

†Tacrolimus 0.03% always dominates pimecrolimus in all scenarios
†In conjunction with the ERG base case mentioned above
ΔC, difference in costs, ΔQ, difference in QALYs; ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; QALY, quality adjusted life year
NR = not reportable – the analyses based on the MAIC can only be used to conduct pairwise comparisons as the MAIC estimates different response rates for crisaborole when different comparators are selected

Table 5: ERG exploratory model results for mild adult patients

Analysis	Discounted costs		Discounted QALYS		ICER (crisaborole versus pimecrolimus)
	Crisaborole	Pimecrolimus	Crisaborole	Pimecrolimus	
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	**Crisaborole dominates** [redacted]
1) Correcting acquisition costs of subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	Crisaborole dominates [redacted]
2) Assuming non responders receive 4 weeks of treatment	[redacted]	[redacted]	[redacted]	[redacted]	Crisaborole dominates [redacted]
ERG base case (scenarios 1 – 2) using the company's preferred NMA	[redacted]	[redacted]	[redacted]	[redacted]	**Crisaborole dominates** [redacted]
3) Adjusting costs of subsequent therapy to reflect the whole time on treatment†	[redacted]	[redacted]	[redacted]	[redacted]	Crisaborole dominates [redacted]
ERG base case (scenarios 1 – 2) using the company's MAIC results	[redacted]	[redacted]	[redacted]	[redacted]	**Crisaborole dominates** [redacted]
Company base case using the ERG's simple random effects NMA results	[redacted]	[redacted]	[redacted]	[redacted]	**Pimecrolimus dominates** [redacted]
4) Correcting acquisition costs of subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	Pimecrolimus dominates [redacted]
5) Assuming non responders receive 4 weeks of treatment	[redacted]	[redacted]	[redacted]	[redacted]	Pimecrolimus dominates [redacted]
ERG base case (scenarios 4 – 5) using the ERG's	[redacted]	[redacted]	[redacted]	[redacted]	**Pimecrolimus dominates** [redacted]

Analysis	Discounted costs		Discounted QALYS		ICER (crisaborole versus pimecrolimus)
	Crisaborole	Pimecrolimus	Crisaborole	Pimecrolimus	
simple random effects NMA results					
6) Adjusting costs of subsequent therapy to reflect the whole time on treatment†	[redacted]	[redacted]	[redacted]	[redacted]	Pimecrolimus dominates [redacted]

†In conjunction with the ERG base case mentioned above
ΔC, difference in costs, ΔQ, difference in QALYs; ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; QALY, quality adjusted life year

Table 6: ERG exploratory model results for moderate adult patients (using £34.52 as the cost per tube of tacrolimus 0.1%)

Analysis	Discounted costs			Discounted QALYS			ICER (crisaborole versus tacrolimus 0.1%†)
	Crisaborole	Tacrolimus 0.1%	Tacrolimus 0.03%	Crisaborole	Tacrolimus 0.1%	Tacrolimus 0.03%	
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] **per QALY versus tacrolimus 0.1%†** [redacted]
1) Correcting acquisition costs of subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Crisaborole dominates tacrolimus 0.1%† [redacted]
2) Assuming non responders receive 4 weeks of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] per QALY tacrolimus 0.1%† [redacted]
ERG base case (scenarios 1 – 2) using the company's preferred NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] **per QALY versus tacrolimus 0.1%†** [redacted]
3) Adjusting costs of subsequent therapy to reflect the whole time on treatment†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] per QALY tacrolimus 0.1%†

Analysis	Discounted costs			Discounted QALYS			ICER (crisaborole versus tacrolimus 0.1%†)
	Crisaborole	Tacrolimus 0.1%	Tacrolimus 0.03%	Crisaborole	Tacrolimus 0.1%	Tacrolimus 0.03%	
							[redacted]
ERG base case (scenarios 1 – 2) using the company's MAIC results (Crisaborole vs tacrolimus 0.1%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] **per QALY versus tacrolimus 0.1%** [redacted]
ERG base case (scenarios 1 – 2) using the company's MAIC results (Crisaborole vs tacrolimus 0.03%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Crisaborole dominates tacrolimus 0.03%** [redacted]
Company base case using the ERG's simple random effects NMA results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Tacrolimus 0.1% dominates crisaborole** [redacted]
4) Correcting acquisition costs of subsequent systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Tacrolimus 0.1% dominates crisaborole [redacted]
5) Assuming non responders receive 4 weeks of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Tacrolimus 0.1% dominates crisaborole [redacted]
ERG base case (scenarios 4 – 5) using the ERG's simple random effects NMA results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Tacrolimus 0.1% dominates crisaborole** [redacted]
6) Adjusting costs of subsequent therapy to reflect the whole time on treatment†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Tacrolimus 0.1% dominates crisaborole [redacted]

†Tacrolimus 0.1% always dominates Tacrolimus 0.03% in all scenarios
†In conjunction with the ERG base case mentioned above
ΔC, difference in costs, ΔQ, difference in QALYs; ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; QALY, quality adjusted life year

Analysis	Discounted costs			Discounted QALYS			ICER (crisaborole versus tacrolimus 0.1%†)
	Crisaborole	Tacrolimus 0.1%	Tacrolimus 0.03%	Crisaborole	Tacrolimus 0.1%	Tacrolimus 0.03%	

NR = not reportable – the analyses based on the MAIC can only be used to conduct pairwise comparisons as the MAIC estimates different response rates for crisaborole when different comparators are selected

6 OVERALL CONCLUSIONS

The company has not provided any updated analyses using either the MAIC or the simple random effects NMA. However, the ERG's exploratory analyses using these show that they provide very different results with crisaborole being dominated by TCIs when using the simple random effects NMA and crisaborole dominating TCIs when using the MAIC in all except one population (adults with moderate AD). Therefore, the key area of decision uncertainty relates to whether the [redacted] as this determines whether the results from the simple random effects NMA or MAIC should be preferred. The ERG notes that double blind placebo controlled trials comparing crisaborole head-to-head against TCIs would be the best way to determine the relative effectiveness of crisaborole and TCIs and details of ongoing studies including some that compare against TCIs are provided in section 4.2.9 of the ERG report.

In the CRTE it is argued that crisaborole should be compared to [redacted]. However, the ERG would argue that a full incremental analysis should always be conducted to determine whether crisaborole is cost-effective compared to the comparator which reflects the most cost-effective use of NHS resources, [redacted]
The ERG does not accept that crisaborole is cost-saving relative to TCIs on the basis that it will be used for 4 weeks instead of 6 weeks as the draft SmPC for crisaborole suggests that it may be used [redacted] and the company has not presented any comparison assuming longer than 4 weeks treatment with crisaborole. The ERG would argue that head-to-head studies of crisaborole versus TCIs would be needed to determine whether one treatment or the other required a longer duration to achieve an adequate response.

The company repeatedly claims in their response to technical engagement that each of the changes made to the model indicate that the issues raised in the technical engagement report are not significant areas of decision uncertainty. The ERG would agree with this, in so much that the key area of decision uncertainty remains whether crisaborole is more, less or equally as effective as TCIs in achieving a response in mild to moderate AD. The other areas of uncertainty are only relevant in determining the likely size of cost savings or QALY gains for the more effective therapy, but it is still important to determine these accurately. In addition, the ERG believes that there remains considerable uncertainty regarding whether having any additional treatment option for managing a mild to moderate AD flare is likely to result in fewer patients receiving subsequent treatments such as phototherapy or systemic therapies further down the treatment pathway given that these subsequent treatments are usually reserved for patients with severe AD.

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