# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

# Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using abrocitinib, tralokinumab and upadacitinib in the NHS in England. The appraisal committee has considered the evidence submitted by the companies and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using abrocitinib, tralokinumab and upadacitinib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 4th May 2022

Second appraisal committee meeting: 12th May 2022

Details of membership of the appraisal committee are given in section 5.

# 1 Recommendations

1.1 Abrocitinib and upadacitinib are not recommended, within their marketing authorisations, for treating moderate to severe atopic dermatitis that is suitable for systemic treatment in adults and young people 12 years and over.

1.2 Tralokinumab is not recommended, within its marketing authorisation, for treating moderate to severe atopic dermatitis that is suitable for systemic treatment in adults.

1.3 These recommendations are not intended to affect treatment with abrocitinib, tralokinumab and upadacitinib that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. In young people this decision should be made jointly by them, their clinician, and their parents or carers.

**Why the committee made these recommendations**

Standard treatment for moderate to severe atopic dermatitis (eczema) includes topical treatments such as emollients and corticosteroids. If these treatments are not effective, systemic immunosuppressants such as methotrexate and ciclosporin can be added. Dupilumab and baricitinib are used if these systemic treatments are not effective.

Clinical trial evidence shows that abrocitinib, tralokinumab and upadacitinib all reduce symptoms of atopic dermatitis compared with placebo. They have been indirectly compared with some standard treatments, but the results are highly uncertain.

The limitations in the clinical evidence mean the results from the economic model are very uncertain. Because of this it is not possible to determine a suitable cost-

effectiveness estimate for abrocitinib, tralokinumab and upadacitinib. So, they cannot be recommended.

# 2 Information about abrocitinib, tralokinumab, upadacitinib

## Marketing authorisation indication

2.1 Abrocitinib (Cibinqo, Pfizer) is 'indicated for the treatment of moderate-to severe-atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy'.

2.2 Tralokinumab (Adtralza, Leo) is 'indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy'.

2.3 Upadacitinib (Rinvoq, AbbVie) is 'indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy'.

## Dosage in the marketing authorisation

2.4 The dosage schedule for abrocitinib is available in the summary of product characteristics for abrocitinib.

2.5 The dosage schedule for tralokinumab is available in the summary of product characteristics for tralokinumab.

2.6 The dosage schedule for upadacitinib is available in the summary of product characteristics for upadacitinib.

## Price

2.7 The list price of abrocitinib is £893.76 for a 28-pack of 100 mg or 200 mg tablets (excluding VAT, BNF online, accessed March 2022). The company has a commercial arrangement, which would have applied if the technology had been recommended.

2.8 The list price of tralokinumab is £1,070 for a 4-pack of 150 mg per 1ml pre-filled syringe (excluding VAT, BNF online, accessed March 2022). The company has a commercial arrangement, which would have applied if the technology had been recommended.

2.9 The list price of upadacitinib is £805.56 for a 28-pack of 15 mg modified-release tablets or £1,611.12 for a 28-pack of 30 mg modified-release tablets (excluding VAT, BNF online, accessed March 2022). The company has a commercial arrangement, which would have applied if the technology had been recommended.

# 3 Committee discussion

The appraisal committee considered evidence from a number of sources. See the committee papers for full details of the evidence.

## Experience of people with atopic dermatitis

### Atopic dermatitis affects all aspects of a person's life

3.1 The clinical experts explained that atopic dermatitis is a chronic, recurrently flaring, generalised skin condition that often starts in childhood. People with severe atopic dermatitis may need treatment in hospital. Feedback from patient and professional organisations highlighted that the condition is life-limiting, debilitating, and isolating, and affects all aspects of life (physical, psychological, social, and financial). They emphasised that severe disease is associated with intolerable itch that disrupts sleep, and a higher risk of depression and suicide. The committee noted that having a choice of treatments that improve the condition and which are associated with few, or manageable adverse effects is important to people with atopic dermatitis.

## Assessing the severity of atopic dermatitis

### Symptom burden and quality of life are used to determine the severity of atopic dermatitis

3.2 The clinical experts explained that there is variability in how clinicians assess the severity of atopic dermatitis. They assess severity based on clinical assessment of signs of the disease and the areas of the body that are affected. They also assess patient-reported symptoms including their effect on sleep and work, and how much patients need to use topical corticosteroids or systemic therapy. The committee understood that clinical trials in this disease area routinely use the Eczema Area and Severity Index (EASI) to assess clinical signs (for example, skin lesions) and the Dermatology Life Quality Index (DLQI) to assess quality of life. The consensus-based Harmonising Outcome Measures for Eczema (HOME) initiative also recommends using the Patient Oriented Eczema Measure (POEM) to assess symptoms (for example, itch) in clinical practice, but recommends that clinical signs of severity are assessed using the EASI score. In most published trials, moderate to severe atopic dermatitis is defined using an EASI score of 16 or more, an investigator global assessment (IGA) score of 3 or more, pruritus (itching) numerical rating score (NRS) greater than 4 and whose body surface areas had 10% or more affected by atopic dermatitis. The committee did not consider there to be substantial variation in classification of moderate to severe severity.

## Clinical management

### There is an unmet need for people whose dermatitis does not respond to treatment or who are unable to tolerate existing treatment

3.3 The clinical experts explained that treatment for atopic dermatitis is variable for each patient. Initial treatment involves emollients, topical corticosteroids and topical calcineurin inhibitors (immunosuppressants). Some people may also try phototherapy, although the clinical expert explained that this treatment is not widely available in the NHS and is

used variably. The patient experts also noted variability in practice with lack of access to phototherapy and considered there is insufficient guidance on topical corticosteroids. They also explained that many people prefer not to use topical corticosteroids because of their potential to sting, the increased burden of administration and fear of steroid systemic and withdrawal side effects. If there is an inadequate response to topical treatments and phototherapy, systemic immunotherapies are considered. This includes treatment with ciclosporin, methotrexate, azathioprine or mycophenolate mofetil. The clinical experts explained that frequent blood tests are needed during treatment with some systemic immunosuppressants and patients can have serious adverse effects. Although ciclosporin is the only licensed treatment, it is used for only short periods because of toxicity concerns and many clinicians now prefer to consider methotrexate first. If there is inadequate response, intolerance, or contraindication to at least 1 systemic treatment, dupilumab and baricitinib are recommended as alternative options for moderate to severe atopic dermatitis that has not responded to at least 1 other systemic therapy. Exacerbations (flares) in atopic dermatitis are managed using short-term high-potency topical corticosteroids, oral corticosteroids and other systemic treatments. The committee concluded that there is an unmet need for well-tolerated treatments for patients with moderate to severe atopic dermatitis.

## Positioning in the treatment pathway, comparators and sequencing

### Abrocitinib, tralokinumab or upadacitinib would likely be used in similar positions in the treatment pathway but the companies' additional positioning of upadacitinib and abrocitinib is less appropriate

3.4 The marketing authorisations for abrocitinib and upadacitinib are 'for the treatment of moderate to severe atopic dermatitis in adults and adolescents who are candidates for systemic therapy'. Tralokinumab currently has a marketing authorisation only in adults with moderate to severe atopic dermatitis. The committee considered that the marketing authorisation wording could be generally broad but all the companies

positioned their treatments after at least 1 systemic immunosuppressant, as alternatives to dupilumab and baricitinib. One of the clinical experts considered this positioning to be appropriate. The company for upadacitinib also positioned it in the same place treatment line as systemic immunosuppressants, or before dupilumab and baricitinib. After consultation, the company for, abrocitinib also considered it had a similar clinical effectiveness profile to upadacitinib and could be considered in the same position. One of the clinical experts considered that this positioning was less appropriate. They explained that methotrexate and other systemic immunosuppressants are clinically effective and well tolerated, although there is limited randomised trial evidence to show this effect. They also have substantially lower costs and are therefore likely to be more cost-effective to try first-line for patients whose dermatitis is suitable for systemic therapy. The committee noted that all available JAK inhibitors used in inflammatory disorders (including abrocitinib, baricitinib and upadacitinib) used in inflammatory disorders are currently under a European Medicines Agency (EMA) safety review because of a potential class effect of increased risk of major cardiovascular events and higher risk of developing cancer. The committee concluded that in clinical practice, systemic immunosuppressants (such as methotrexate) would normally be considered first, so the companies' additional positioning of upadacitinib and abrocitinib is less appropriate.

## Abrocitinib, tralokinumab or upadacitinib are likely to be used at the same time as topical treatments as 'combination therapy'

3.5 All the companies provided evidence for their treatments both as monotherapy and in combination with topical treatments. The clinical experts explained that all the treatments are likely to be offered alongside topical corticosteroids in clinical practice. The committee therefore agreed to focus on the evidence for 'combination therapy' as the most relevant evidence for decision-making.

### Treatments would likely be used in sequences, but cost-effectiveness analysis in sequence would be uncertain because of no clinical data

3.6 The clinical experts explained that there is no typical patient treatment journey and there is high variation in prescribing practices. In clinical practice, because atopic dermatitis is a lifelong disease, people who receive treatment, such as dupilumab, may have an inadequate response and switch to baricitinib or retry other systemic immunotherapies. The treatment choice would likely be based on previous responses, differences in drug class and mechanism of action, and adverse event profiles. New treatment options are therefore also likely to be used in sequence with existing treatments but there would likely be no 'standard' sequence. The committee considered that cost-effectiveness analyses for sequences should ideally be taken into account in decision-making. But, it acknowledged that there is no clinical data on sequential effectiveness and treatment various sequences offered would vary substantially in clinical practice. Therefore, the committee concluded that analysis of treatment sequences may be uncertain.

## Clinical evidence

### The JADE-COMPARE trial provides the key clinical evidence for abrocitinib

3.7 The evidence for abrocitinib came from 6 trials, including 2 trials (JADE-DARE, JADE-COMPARE) that compared abrocitinib plus background topical corticosteroids to dupilumab in adults. JADE-COMPARE was a randomised double-blind trial that included 837 adults who had moderate to severe atopic dermatitis for at least 12 months, had inadequately responded to medicated topical treatment or systemic treatment. Participants were allowed to use more than one topical treatment. The trial compared two doses abrocitinib with different comparators: 200 mg once daily with dupilumab (300 mg every 2 weeks) or 100 mg once daily with placebo. The primary endpoints were assessed at the end of the ‘induction period’ (that is, 12 weeks after starting treatment):

- at least a 75% reduction in the EASI score from when treatment started (EASI 75)
- a rating of ‘clear’ (score of 0) or ‘almost clear’ (score of 1) on the investigator’s global assessment (IGA), and at least a 2-point improvement from baseline.

Results for JADE-DARE were not available at the time of analysis so were not included, but have since become available. The committee considered it would be appropriate to include these results in future analysis. The committee considered that the JADE-COMPARE trial provides the key clinical evidence for abrocitinib. A subgroup of patients who were eligible for systemic therapy in UK clinical practice were identified and included in the main analysis.

The JADE-TEEN trial also compared abrocitinib against placebo in combination with topical corticosteroids in young people aged 12 to18.

### The AD-UP trial provides the key clinical evidence for upadacitinib

3.8 The evidence for upadacitinib came from 6 trials including 2 trials on upadacitinib plus background topical corticosteroids (AD-UP and RISING-UP). RISING-UP was a randomised controlled trial carried out in Japan but data is not yet available. The results from the RISING-UP trial were and it was not included in the analysis. AD-UP was a randomised double-blind trial that included 901 people (aged 12 to 75) who had moderate to severe atopic dermatitis and had an inadequate response to medicated topical therapy or systemic therapies. The trial compared 2 doses of upadacitinib (15 mg or 30 mg once daily) with a placebo. The primary endpoints were assessed at 16 weeks after the 'induction' period:

- AD-UP: at least a 75% reduction in the EASI score from when treatment started (EASI 75)
- AD-UP: a rating of ‘clear’ (score of 0) or ‘almost clear’ (score of 1) on the IGA, and at least a 2-point improvement from baseline.

Patients in AD-UP had an additional 120-week blinded extension period that was not included in the analysis. A subgroup of patients who were eligible for systemic therapy in UK clinical practice were identified and included in the main analysis.

## The ECZTRA 3 and ECZTRA 7 trials provide the key clinical evidence for tralokinumab

3.9 The evidence for tralokinumab came from 6 trials including 2 trials on tralokinumab plus background topical corticosteroids (ECZTRA 3 and ECZTRA 7). Both were randomised double-blind trials that included adults who had moderate to severe atopic dermatitis for at least 12 months and had inadequately responded to medicated topical treatment or systemic treatment. The trials compared tralokinumab (200 mg every 2 weeks) with a placebo. The primary endpoints were assessed at 16 weeks after the 'induction' period:

- ECZTRA 3 and ECZTRA 7: at least a 75% reduction in the EASI score from when treatment started (EASI 75)
- ECZTRA 3: a rating of ‘clear’ (score of 0) or ‘almost clear’ (score of 1) on the IGA, and at least a 2-point improvement from baseline.

## Abrocitinib, tralokinumab and upadacitinib are clinically effective treatments compared with placebo

3.10 For all people that received treatment in the key clinical evidence studies (see sections 3.7 to section 3.9), the results showed a greater chance of reaching a 50% reduction in EASI score plus an improvement of at least 4 in the DLQI score at week 12 or 16, than patients who had a placebo. These results were statistically significant for abrocitinib and upadacitinib. More people who had tralokinumab also achieved EASI 50 than those who had placebo treatment, but the results were not statistically significant. Significantly more people treated with tralokinumab achieved EASI 75 compared with people who used placebo However, the committee noted substantial heterogeneity in trial design and placebo response rates may have contributed to these results and affected the

comparison of these studies (see section 3.13 for discussion of the network meta-analysis). The committee concluded that abrocitinib, tralokinumab or upadacitinib are clinically effective treatments compared with placebo.

### A composite endpoint of EASI 50 plus an improvement in the DLQI of at least 4 is most relevant endpoint for decision-making

3.11 Common outcomes in clinical trials are relative reductions in EASI scores from baseline by 50% and 75% (EASI 50 and EASI 75). The clinical experts considered that these outcomes were appropriate for measuring response to treatment, but ideal outcomes would be an absolute reduction to none or mild symptoms. One of the clinical experts noted that EASI 75 was commonly used in clinical trials for assessing improvement in atopic dermatitis. The committee understood that using EASI 75 alone is not adequate to capture a quality-of-life improvement and it may not capture clinically meaningful improvements. The committee agreed to use a composite endpoint of EASI 50 plus an improvement in the DLQI of at least 4 in the analysis. It included patient-reported quality of life and was consistent with NICE's technology appraisal guidance on dupilumab for treating moderate to severe atopic dermatitis (TA534) and baricitinib for treating moderate to severe atopic dermatitis (TA681). Therefore, the committee considered that the EASI 50 combined with DLQI of at least 4 is the most relevant endpoint for decision-making and should be used to define treatment response. The external assessment group (EAG) used this composite outcome as the basis for assessing relative response, but also considered the EASI 75 outcome when data was not available for the composite outcome.

### Results for adults that who have tried systemic immunotherapy are likely to be generalisable to young people

3.12 Both the abrocitinib and upadacitinib marketing authorisations include young people aged 12 to 18 with atopic dermatitis. The clinical experts explained that the current treatment pathways for adults and adolescents

with atopic dermatitis are similar. However, baricitinib is currently licensed for adults only. The EAG performed a separate analysis for the adolescent population, using data on adolescent patient subgroups from the relevant key trials. The only data available for the full indirect comparison analysis was in monotherapy (without topical corticosteroids) using the EASI 75 outcome as the basis for comparison. The EAG also noted very small patient numbers for some of the treatment arms. The committee considered that because of the limited available evidence and likely similarity between adolescents and adults, it had not seen sufficient justification for considering adolescents as a separate subgroup, and this approach would increase uncertainty around treatment effect. It concluded that the results of the 'combination therapy' analysis for adults who had tried systemic immunotherapy would likely be generalisable to the adolescent population.

## Indirect treatment comparisons

### The network meta-analysis with dupilumab or baricitinib is appropriate for decision-making

3.13 There was no direct evidence comparing tralokinumab or upadacitinib used in combination with topical treatments ('combination therapy') with dupilumab or baricitinib for atopic dermatitis in adults, so the data from the relevant trials were analysed to compare treatments indirectly through a network meta-analysis:

- abrocitinib: a subgroup of the JADE-COMPARE trial who would be eligible for systemic therapy in UK practice
- tralokinumab: ECZTRA 7 plus the ECZTRA 7-like subgroup from ECZTRA 3
- upadacitinib: a subgroup of the AD-UP trial who would be eligible for systemic therapy in UK practice
- dupilumab: the CAFÉ trial and a subgroup of patients from the CHRONOS trial for whom ciclosporin was contraindicated or not

tolerated, or whose disease was uncontrolled on ciclosporin (the 'CAFÉ-like' subgroup)

- baricitinib: BREEZE-AD4 and BREEZE-AD7.

All trials included a placebo arm, so the trials were compared through this node in a 'star-shaped' network. The EAG explained that one head-to-head trial comparing abrocitinib doses with dupilumab was included in the network of indirect comparisons to improve consistency. The EAG considered that only patients whose dermatitis had not responded to systemic treatments were included in the analysis, but noted that:

- ECZTRA 7 and CAFÉ specified that people either had not been exposed to ciclosporin and were not a candidate for ciclosporin treatment, or had previous exposure to it and had an inadequate response.
- Baseline characteristics for the full trial populations are comparable, but ECZTRA 7 and CAFÉ included a blended population and clinical data to inform the comparisons were from post-hoc subgroups.

The committee concluded that, despite its limitations, the indirect treatment comparisons with dupilumab or baricitinib for patients whose dermatitis had not responded to or tolerated systemic immunosuppressants used the most appropriate clinical evidence.

## The indirect comparisons of treatments with ciclosporin are highly uncertain

3.14 For the systemic-naïve population, the EAG presented results for first-line treatments from a network using results from the AD-UP trial for upadacitinib. The clinical experts explained that randomised evidence for currently used systemic treatments is limited because of the off-label use of systemic immunosuppressants (see section 3.3). The EAG considered the most appropriate evidence to include in the network was an observational study (Ariens et al.) that compared individual patient data from a clinical trial for dupilumab against individual patient data from

ciclosporin use in daily clinical practice in a treatment centre in the Netherlands. The clinical experts considered this was the most appropriate source of data because there is limited randomised clinical data for systemic treatments at this line of therapy. However, they noted that methotrexate is now the most commonly used treatment in people who have not had systemic immunotherapies before (see section 3.4) and that there could soon be data available for methotrexate. The committee noted that, in order to compare ciclosporin with upadacitinib, the comparison had to be done indirectly through both dupilumab and placebo, which increased uncertainty of the comparison. The committee considered the observational study to be of limited use because it had a small sample size (n=57) and had not adjusted for many confounders of treatment effect. It also noted that there are likely to be substantial differences between daily clinical practice and clinical trial evidence in this disease area, including adherence to topical treatments. It also considered that upadacitinib would be used for longer periods of time in clinical practice than ciclosporin, which is only indicated for a short time frame. The committee concluded that the indirect comparison with ciclosporin was highly uncertain. The committee considered that this uncertainty for the this comparison further questioned the appropriateness of analysis considering a systemic-naive population.

### Random effect models with uninformed priors may not be appropriate because of the small number of trials for each treatment arm

3.15 The results of the network meta-analyses were highly uncertain with very wide credibility intervals. The committee considered that there was substantial clinical heterogeneity in the trial design that may have contributed to these differences. The EAG considered that these included:

- use of post-hoc subgroups to define patients that are eligible for systemic therapy, that would break randomisation
- methodological heterogeneity across studies in the washout period before starting the treatment in the trial

- the type and potency of concomitant topical corticosteroids and other relevant optimisation of baseline care used in the trial
- heterogeneity in how rescue therapy was implemented or allowed in the trial.

The EAG considered that this substantial between-trial heterogeneity would best be accounted for using a random effects model with an informed prior for the between-trial heterogeneity. This would otherwise be ignored using a fixed effect model that assumes all placebo arms are estimating the same treatment effect. The EAG explained that adjusting the placebo effect for each trial was not possible for some analyses or may have overfitted the data in other analyses. The committee noted the substantial heterogeneity in the treatment arms but also noted the very wide confidence intervals. It considered that the approach taken by the EAG may not be appropriate because the small number of trials for each treatment arm of the analyses may be inflating the heterogeneity in the network. It concluded it would like to consider the results of the fixed effects analysis, which may reduce the width of the credibility intervals and also may plausibly affect the point estimates of the results used in the deterministic base case analysis.

## Adverse events

### Trial evidence shows low adverse event rates but more safety data on JAK inhibitors would be valuable

3.16 The number of adverse events reported in the trials was generally small. Upper respiratory tract infections (URTIs) were one of the most frequent adverse events in the abrocitinib trials. URTI, conjunctivitis (allergic and infectious), and injection-site reactions were commonly reported in people using tralokinumab. Upadacitinib was associated with slightly higher rates of acne, oral herpes, and URTI compared with placebo. The committee understood that the EMA has started a safety review of JAK inhibitors including baricitinib, abrocitinib and upadacitinib. Preliminary findings suggest that using JAK inhibitors may be associated with an increased

risk of cardiovascular problems such as heart attack and developing cancer. The clinical experts considered it was too early to conclude the impact of JAK inhibitors on developing cardiovascular problems or cancer because of limited available safety data. The committee noted that the increased cancer risk would be a particularly important outcome for people with atopic dermatitis, because of an already increased risk of some skin cancers. The committee agreed that more safety data on JAK inhibitors would be valuable.

## The economic model

### The structure of the economic model is appropriate for decision-making

3.17 The economic model for this appraisal was produced by the EAG. The model structure was informed by a systematic literature review, the companies' submissions, and previous technology appraisals in the disease area. The economic model is a short-term (52 week) decision tree model that feeds into a long-term Markov model for the rest of the lifetime horizon. People in the economic model start in the baseline health state and are assigned to active treatment. At 16 weeks, people are assigned to health states based on response to treatment informed by the results of the network meta-analysis (see section 3.13). People whose dermatitis does not respond discontinue treatment, and progress to the best supportive care health state. People whose dermatitis does respond continue treatment in the responder health state. People enter the Markov model in different maintenance health states depending on initial response to treatment and discontinuation up until week 52. People then transition to the best supportive care health state based on annual discontinuation and treatment effect waning assumptions agreed upon in previous appraisals (TA534). The committee noted that this represented a simplification of clinical practice, in which further sequential treatments would be trialled (see section 3.6). However, it considered this was a problem that appropriately simplified a chronic recurrent disease over a lifetime horizon. The committee concluded that the model structure was

similar to models previously seen in atopic dermatitis appraisals and was appropriate for decision-making.

## Assumptions in the economic model

### Treatment dose options should not be modelled separately

3.18 Abrocitinib and upadacitinib each have daily 2 treatment doses (low dose treatment and or a high dose treatment.) depending on individual patient presentation and response. The clinical evidence was assessed as individual daily doses in the network meta-analysis and this was maintained in the economic model, as different treatment options. This approach was informed by the companies' submissions. The committee considered that in clinical practice, the decision to start treatment would be based on the overall effectiveness of the drug and not on efficacy evidence of individual doses. Therefore, they considered that this approach added difficulties to the decision-making process and would not represent use in clinical practice. It noted that for both abrocitinib and upadacitinib, there was some potential observed benefit from using higher dose treatments, and therefore many patients would consider using higher doses if tolerated. The committee considered that, ideally, separate populations could be modelled to receive the doses that are indicated for them using the characteristics and natural history of disease in each population. However, in the absence of this evidence, the committee requested sensitivity analysis that pools the results of the high and low doses, using a proportional weighting of each treatments' expected dose distribution in clinical practice.

## Utility values in the economic model

### Utility values used in the economic model are derived from the clinical trial data

3.19 Health-related quality of life data were collected in all the key clinical trials using the 5-level EQ-5D (EQ-5D-5L) and the data was then mapped to the 3-level EQ-5D (EQ-5D-3L), using the van Hout crosswalk method. The

treatments were separated into 3 groups: high dose JAK inhibitors (abrocitinib 200 mg, upadacitinib 30 mg, and baricitinib), low dose JAK inhibitors (abrocitinib 100 mg, upadacitinib 15 mg, and baricitinib), and monoclonal antibodies (dupilumab and tralokinumab). The EAG presented analyses with both high and low dose utility values for baricitinib. For adult second-line 'combination therapy' analysis, the JAK inhibitor low dose and high dose utility values were derived from the AD-UP trial and the monoclonal antibody utility values were derived from ECZTRA 7 and the ECZTRA 7-like subgroup in ECZTRA 3.

## Treatment-specific utility values are uncertain and alternative utility value scenarios should be explored

3.20 The EAG explained that the baseline utility values were elicited after a 'washout' period in the trials, where previous treatment with standard care was stopped. The clinical experts noted that the 'washout' period does not reflect clinical practice in the NHS because patients would always be receiving some treatment. The responder utility values were also treatment-specific and based on response at 16 weeks. The EAG explained that treatment-specific utility values were used to better represent potential treatment-specific differences. The committee noted the differences between baseline utility values and considered that these represented heterogeneities between the trials. It considered that using different baseline utility values introduced unnecessary complexity, making it difficult to interpret the results. It also considered that it lacked face validity by assuming that patients had different baseline utility based on values at 16 weeks after starting treatments that their dermatitis had not yet responded to, lacked face validity. The treatment-specific response state utility values also added additional complexity to the analysis that the committee considered may be inappropriate. The committee considered it plausible that there may be some differences in utility values based on responses to treatment. However, it considered the size of the differences between treatments could also include differences between trial design and reporting methodology. The committee proposed

that an alternative way to explore treatment-specific response utilities would be to use a single baseline value and apply changes in utility based on the degree of change observed in the trials. Ideally, this would include a single synthesis of the utility evidence linked via the common comparator of placebo, similar to the network meta-analysis approach used for the effectiveness data. The committee also considered that it would like to see analysis that used health-state utility values, in order to more clearly see the effect of using treatment-specific utility values. This would consist of utility values based on a response health state representing an EASI 50 and DLQI of at least 4 (as per section 3.11) which as a response to treatment should have an absolute value if assuming the same baseline characteristics. It also considered that reconsidering the utility values used in TA534 would also be appropriate to explore consistency (see section 3.22). The committee, therefore, concluded that it would like to see further analyses that used alternative utility value assumptions.

### The utility values for the best supportive care health state are highly uncertain and have a large impact on the cost-effectiveness results'

3.21 The EAG explained that the utility values for the best supportive care health state were derived using a weighted average of the utility values for responders and non-responders at week 16. This method was used to capture the waxing and waning nature of response to best supportive care and was also used in NICE's technology appraisal guidance for baricitinib for treating moderate to severe atopic dermatitis (TA681). The EAG explained that the utility value for non-responders was significantly higher than the baseline health state utility values because it included people whose dermatitis had partially responded to treatment but did not reach the EASI 50 or DLQI of at least 4 threshold, or who later lost response but still maintained some residual effect. Previous appraisals have also modelled best supportive care waning effect, where response to treatment wanes towards that seen in the baseline of the trial over time. The clinical expert considered this waning effect to plausibly represent a reduction

over time for those that do not have further treatment and reduced benefit from topical corticosteroids. The committee noted that this was having a large impact on the cost-effectiveness of the treatments because most people stay in the best supportive care health state for most of the time horizon. The committee considered that the best supportive care health state may wane to some extent over time, but in clinical practice, people would receive further treatments as part of a sequence (see section 3.6) and some could improve over time. The committee considered that it would like to see sensitivity analysis that included best supportive care treatment effect waning, to explore high levels of uncertainty around this modelling assumption. It noted that this would require changes to the model structure and tunnel states would need to be included in the long-term Markov model.

### Inconsistency with previous appraisals creates uncertain model drivers for the response health state

3.22 The committee noted that changes to the best supportive care waning (see section 3.21) and treatment-specific utility values (see section 3.20) meant that the utility value for the best supportive care health state was associated with a relatively high quality of life compared with previous appraisals, and the benefit from responding to treatment was relatively low, particularly for dupilumab. The costs associated with the best supportive care health state were also low. This meant that previously recommended treatments no longer represented effective use of NHS resources. Comparing the new treatments against previously recommended treatments favoured treatments that most quickly result in patients entering the low cost, high utility best supportive care health state, through lower response or faster discontinuation of more costly treatments. The committee questioned the plausibility that a worse response to treatment would positively impact the cost-effectiveness results. The committee agreed that investigating scenarios with best supportive care waning and alternative utility values may lessen the effect of this interaction. It also considered that sensitivity analysis varying the

time horizon may also be valuable, in order to characterise the uncertainty associated with modelling a chronic recurrent disease over a lifetime horizon, especially given that the model did not attempt to model the treatment sequences that would be used over a lifetime in clinical practice. The committee concluded it wanted further analysis of consistency with previous appraisals that could explain why this uncertainty drove the model results.

### Cost-effectiveness estimates

#### Because of the issues with the model inputs, it is not currently possible to assess the cost-effectiveness of the treatments

3.23 Because of the issues with the model inputs, the committee did not consider that it had seen analysis that represented its preferred assumptions so it was unable to assess the cost-effectiveness of the treatments in the appraisal or recommend their use. The committee requests analysis that uses:

- data from the adult population to generalise to the adolescent population (see section 3.12)
- a fixed effect model for the network meta-analysis (see section 3.15)
- a pooled cost-effectiveness estimate for each of the treatment options that have high and low doses (see section 3.18)
- additional utility values scenarios based on degree of change observed in the trials, health-state specific values rather than treatment-specific utility values and utility values used in TA534 (see section 3.20)
- analysis that represents best supportive care treatment waning over time and sensitivity around the modelled time horizon (see section 3.21)

## 4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review 3 years after publication of the guidance. NICE welcomes comment on this proposed date. NICE will decide whether the technology

should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Charles Crawley
Chair, appraisal committee
April 2022

# 5 Appraisal committee members and NICE project team

## Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Ying-Ying Wang**
Technical lead

**Adam Brooke**
Technical adviser

**Jeremy Powell**
Project manager

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