# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final appraisal document

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

## 1 Recommendations

1.1 Abrocitinib and upadacitinib are recommended as options for treating moderate to severe atopic dermatitis that is suitable for systemic treatment in adults and young people 12 years and over, only if:

- the disease has not responded to at least 1 systemic immunosuppressant, or these are not suitable.
- the companies provide abrocitinib and upadacitinib according to the commercial arrangement (see section 2).

1.2 Tralokinumab is recommended as an option, for treating moderate to severe atopic dermatitis that is suitable for systemic treatment in adults, only if:

- the disease has not responded to at least 1 systemic immunosuppressant, or these are not suitable.
- the company provides tralokinumab according to the commercial arrangement (see section 2).

1.3 Stop abrocitinib, upadacitinib or tralokinumab at 16 weeks if the atopic dermatitis has not responded adequately. An adequate response is:

- at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started and

- at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started.

1.4 Take into account how skin colour could affect the EASI score, and make any appropriate adjustments.

1.5 Take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI, and make any appropriate adjustments.

1.6 These recommendations are not intended to affect treatment with abrocitinib upadacitinib or tralokinumab 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 systemic immunosuppressants are not effective.

The clinical trial evidence shows that abrocitinib, tralokinumab and upadacitinib all reduce symptoms of atopic dermatitis compared with placebo. Abrocitinib and upadacitinib were indirectly compared with ciclosporin, but the results are highly uncertain.

Abrocitinib, upadacitinib and tralokinumab were indirectly compared with dupilumab and baricitinib for use after systemic immunosuppressants. The results are also uncertain but the most likely cost-effectiveness estimates are within the range that NICE normally considers an acceptable use of NHS resources. Therefore,

abrocitinib, upadacitinib or tralokinumab are recommended as options for use in people with moderate to severe atopic dermatitis whose disease has not responded to at least 1 systemic immunosuppressant.

# 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 (simple discount patient access scheme). This makes abrocitinib available to the NHS with a discount. The size of

the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

2.8 The list price of tralokinumab is £1,070 for a 4-pack of 150 mg per 1 ml pre-filled syringe (excluding VAT, BNF online, accessed March 2022). The company has a commercial arrangement (simple discount patient access scheme). This makes tralokinumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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 (simple discount patient access scheme). This makes upadacitinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

# 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 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. Moderate to severe atopic dermatitis in published trials is defined by an EASI score of 16 or more. Additional tools such as the investigator's global assessment (IGA) are also used to assess severity of the condition. People with an IGA score of 3 or more, or whose body surface areas are 10% or more affected are considered to have moderate to severe atopic dermatitis. 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. It recommends that clinical signs of severity are assessed using the EASI score. 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 committee understood that treatment for atopic dermatitis is variable for each patient. Initial treatment involves emollients, topical corticosteroids and topical calcineurin inhibitors. Some people may also try phototherapy, although the clinical experts explained that this treatment is not uniformly available and is used variably in the NHS. The patient experts also noted variability in practice with lack of access to phototherapy and considered that 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 their fear of systemic side effects and steroid withdrawal effects. If there is an inadequate response to topical treatments and phototherapy, systemic immunosuppressants are considered. This includes treatment with ciclosporin, methotrexate, prednisolone, azathioprine or mycophenolate mofetil. The clinical experts explained that frequent blood tests are needed during treatment with most systemic immunosuppressants and that people who take them can experience 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 people with moderate to severe atopic dermatitis.

## Positioning in the treatment pathway, comparators and sequencing

### Abrocitinib, tralokinumab or upadacitinib would likely be used after systemic immunosuppressants

3.4 The marketing authorisations for abrocitinib and upadacitinib are 'for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy'. Tralokinumab currently has a marketing authorisation only in adults with moderate to severe atopic dermatitis who are candidates for systemic therapy. The committee considered that the marketing authorisation wording is broad and could refer to first-line treatment, 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 companies also proposed that upadacitinib and abrocitinib could be used as alternatives to systemic immunosuppressants, before dupilumab and baricitinib. 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 as first-line treatment for people whose dermatitis is suitable for systemic therapy. The committee noted that all available JAK inhibitors used in inflammatory disorders (including abrocitinib, baricitinib and upadacitinib) are currently under a European Medicines Agency (EMA) safety review. This is 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 (used alone) and in combination with topical treatments (combination therapy). The clinical experts explained that all the treatments are likely to be offered alongside topical corticosteroids in clinical practice. The committee noted that monotherapy trials are used for regulatory endpoints and do not represent how these treatments would be used in clinical practice. Therefore, it 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 of sequences would be uncertain because of limited clinical data

3.6 The clinical experts explained that there is no typical patient treatment journey and there is variation in prescribing practices. Atopic dermatitis is a lifelong disease, and in practice 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 to treatment, expected differences in how they work, and potential adverse effects. 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 the clinical rationale for using various sequences of treatments would be personalised to each person. Therefore, the committee concluded that analysis of treatment sequences would be uncertain.

# Clinical evidence

## The JADE-COMPARE and JADE-DARE trials provide 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 with 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 and had an inadequate response to medicated topical treatment or systemic treatment. People in the trial were allowed to use more than one topical treatment. The trial compared 2 doses abrocitinib with different comparators: abrocitinib 200 mg once daily with dupilumab 300 mg every 2 weeks or abrocitinib 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 IGA, and at least a 2-point improvement from baseline.

JADE-DARE is an ongoing trial. It compared abrocitinib with dupilumab, each used with topical corticosteroids. Initial response data for JADE-DARE was provided by the company and included in the analysis after consultation. The committee considered that these trials provided the key clinical evidence for abrocitinib.

The JADE-TEEN trial also compared abrocitinib with placebo in combination with topical corticosteroids in young people aged 12 to 18.

## 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, and its results were 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 an inadequate response to medicated topical treatment or systemic treatment. The trials compared tralokinumab (300 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 had 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 (EASI 50) plus an improvement of at least 4 in the DLQI score at week 12 or 16, than people 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, but the results were not statistically significant. Significantly more people treated with tralokinumab achieved EASI 75 compared with people who had placebo However, the committee noted that substantial heterogeneity in trial design and placebo response rates may have contributed to these results. This may have 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 end point of EASI 50 plus an improvement in the DLQI score of at least 4 is the most relevant end point 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 no symptoms or mild symptoms. A consultee also commented that the use of EASI 50 may not capture additional benefits measured by EASI 75 or above. 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 end point 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 end point 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 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. At the first committee meeting the clinical experts explained that the current treatment pathways for adults and young people with atopic dermatitis are similar. The feedback from consultees agreed that young people were treated the same as adults and the results of the trials for adults would be generalisable to young people. However, baricitinib is currently licensed for adults only. For young people, the only data available that allowed for indirect comparison with other treatments was using EASI 75 outcome measurements. The EAG also noted the very small numbers of people in the treatment arms, leading to high uncertainty. The EAG initially did separate analyses for the adult and young people populations, but after the first committee meeting an updated analysis was done for the adult population. The committee considered that because of the likely similarity in treatment for young people and adults, and limited available evidence for young people, it had not seen sufficient justification for considering young people as a separate subgroup. The committee concluded that the results of the ‘combination therapy’ analysis for adults who had tried systemic immunotherapy would likely be generalisable to young people.

## 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 data from the relevant trials was 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 placebo was the common comparator for all trials in the network analysis. The EAG explained that 1 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 only included people who had either not received ciclosporin and were not a candidate for it, or who had previous exposure to ciclosporin but 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 was from post-hoc subgroups.

The committee concluded that, despite their limitations, the indirect treatment comparisons with dupilumab or baricitinib used the most appropriate clinical evidence.

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

3.14 For people who have not previously had systemic treatment, the EAG presented results for first-line treatments from a network analysis using results from the trials for upadacitinib and abrocitinib. The clinical experts explained that randomised trial evidence for currently used systemic treatments is limited because of the off-label use of systemic immunosuppressants (see section 3.4). The EAG considered the most appropriate evidence to include in the network was a small observational study (Ariens et al, 2019). The study compared individual person 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 (n=57). The clinical experts considered this appropriate although noted that methotrexate is now the most commonly used treatment in people who have not had systemic immunotherapies before (see section 3.4). One consultee noted the TREAT trial which compared ciclosporin with methotrexate in young people, but its results have not been published yet. There is also additional published evidence regarding methotrexate compared with ciclosporin in adults. The committee considered that including the comparison of ciclosporin and methotrexate in the network analysis would introduce uncertainties because of ciclosporin's limited evidence base. The committee also noted that, in order to compare ciclosporin with upadacitinib and abrocitinib, the comparison had to be done indirectly through both dupilumab and placebo, which increased uncertainty of the comparison. 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.

## Results of fixed-effects and random-effects network meta-analysis are comparable

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

- use of post-hoc subgroups to define patients who were eligible for systemic therapy, and 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 and 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 random-effects model 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. After consultation, the EAG also presented a fixed-effects model. The committee considered that the results were very similar but the random-effects model had slightly wider credibility intervals. It considered that the wide credibility intervals indicated substantial uncertainty around the point estimates of the results used in the deterministic base case analysis. However, the results of the analyses were comparable when fixed-effects or random-effects models were applied.

## 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, will stop 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 a previous appraisal (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 that 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

### Comparison with systemic immunosuppressants does not represent clinical practice

3.18 The EAG explained that for the first-line treatment comparison with ciclosporin in the economic model, it was assumed that people would only have ciclosporin for 1 year and then have best supportive care for the rest

of the modelled time horizon. The committee considered that this did not represent clinical practice because it would involve sequential treatment. It also did not represent ciclosporin's marketing authorisation indication, nor how methotrexate or other systemic immunosuppressants would be used as a first-line treatment. The committee also recalled the substantial limitations of the comparative efficacy evidence (see section 3.14). Therefore, the committee concluded that the analysis comparing treatments with first-line systemic immunosuppressants was limited in value and further evidence is needed for this comparison.

## Cost-effectiveness of different dosing options are explored through pooling

3.19 Abrocitinib and upadacitinib each have 2 daily dose options (low dose treatment or high dose treatment). The choice of dose would depend 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, it considered that modelling individual doses in the economic model would not represent expected use in clinical practice and that it added difficulties to the decision-making process. After consultation, the EAG provided a scenario analysis which pooled the cost-effectiveness results of the high and low doses, assuming an equal split of high and low dose distribution. This was because there was no robust data on which to base this distribution. An alternative dose distribution for abrocitinib was provided by the company, based on its use in an early access programme. The company consider this distribution to be confidential. The clinical experts considered this dose distribution was likely to reflect expected use in clinical practice of abrocitinib and upadacitinib. The committee concluded that in the absence

of further evidence, it was appropriate to pool the doses using the distribution provided for abrocitinib.

### It is appropriate to consider tralokinumab's alternative dosing schedule but its use in clinical practice is uncertain

3.20 The committee noted an alternative dosing schedule for tralokinumab which allowed for dosing every 4 weeks for people whose dermatitis is clear or almost clear after 16 weeks of treatment. The EAG included an option in the economic model for a proportion of people taking tralokinumab to switch to the less frequent dosing schedule, based on evidence from ECZTRA 3. The committee considered that some people would switch to less frequent dosing, but others may stay on the more frequent dose if they tolerate the treatment and respond well to it. However, the committee considered that the proportion of those who would switch to the 4-weekly dosing is uncertain outside of a clinical trial context. The committee therefore considered a range of results. These ranged from assuming the same number of people use the alternative dosing schedule as in the ECZTRA 3 trial, to assuming all people continue on the 2-weekly dosing schedule.

## Utility values in the economic model

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

3.21 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. At the first committee meeting, the EAG separated the treatments into 3 treatment-specific 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. The monoclonal antibody utility values were derived from ECZTRA 7 and the ECZTRA 7-like subgroup in ECZTRA 3. After the first committee meeting, the EAG provided a scenario using data from the AD-UP trial to create a response-based health-state utility value, that was applied to all treatments regardless of drug class.

### Response-based utility values are more appropriate than treatment-specific utility values

3.22 At the first committee meeting, the EAG explained that treatment-specific utility values were used to better represent potential treatment-specific differences. This included differences in baseline utility values for people that respond to treatment at 16 weeks. The committee considered that there is no rationale for differences in baseline utility values, and this would likely only represent heterogeneity between the clinical trials. It considered it plausible that there may be some differences in utility values based on response to treatment. But the size of the difference between the different treatments was likely to be because of trial design and reporting methodology, rather than true differences in quality of life. It considered that the use of different baseline utility values and treatment-specific utility values introduced unnecessary complexity to the economic model. The committee preferred a single response-based utility value for baseline and response, or ideally a single synthesis of relative difference in utility, similar to the network meta-analysis. After the first committee meeting, the EAG provided a scenario using health-state utility values based on data from the AD-UP trial only. One consultee considered that removal of treatment-specific utility values would not capture all the benefits of treatment. Therefore they proposed an alternative approach of applying a common baseline utility value and a responder utility value associated with being a EASI 50 plus DLQI 4 or more responder, to all treatments. Additional utility benefits were applied based on the proportion of people achieving EASI 75 and EASI 90 within the trials. The EAG considered this approach may not be appropriate because it bases

longer-term utility increments on trials measured at a single time point after a few months. The EAG also considered that larger reductions in EASI score may not be maintained outside of a trial setting for longer time periods, but this is unclear. The committee also noted that the largest gains in quality of life came from achieving good response on the DLQI's measure of health-related quality of life. It considered the proposed approach could increase uncertainty and also highlight further heterogeneity between trials. Therefore, it concluded that there was not enough evidence to justify changing the specified composite outcome of interest in regards to utility data, because it may introduce additional uncertainties.

## Best supportive care assumptions

### The utility values for the best supportive care health state are highly uncertain, and have a large impact on the modelled benefit

3.23 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. In addition, the baseline utility values were elicited after a 'washout' period in the trials, when previous treatment with standard care was stopped. This included stopping use of topical corticosteroids in the AD-UP trial. 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 committee considered that the utility values for best supportive care are highly uncertain using this approach because they represent most of the

modelled time over a lifetime horizon. After the first committee meeting, the committee requested further exploration of best supportive care utility through time using a best supportive care waning assumption.

### Best supportive care waning assumptions are highly uncertain

3.24 Previous appraisals have also modelled best supportive care waning effects, when response to treatment wanes towards that seen in the baseline of the trial over time. The clinical experts considered this waning effect to plausibly represent a reduction over time for those who do not have further treatment and who have reduced benefit from topical corticosteroids. 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. After the first committee meeting consultation, the EAG updated the analyses and included a scenario with best supportive care waning. The analysis applied the accepted best supportive care waning assumptions for dupilumab from TA534. The scenario assumed that by year 5, 97% of people had returned to baseline utility, and none of them had topical corticosteroids. The committee acknowledged that the EAG's approach represented different people in the model moving in and out of disease control over time. The committee considered this may simplify the effect of people having best supportive care because their quality of life could vary because of other factors such as treatment sequence. The committee concluded that there was significant uncertainty with attempting to model best supportive care waning without evidence of the natural history of the disease, or use of further sequential treatments.

## Cost-effectiveness estimates

### Abrocitinib, tralokinumab and upadacitinib are cost effective compared with dupilumab or baricitinib based on the ICERs for the committee's preferred scenarios

3.25 The committee considered that the cost-effectiveness estimates for abrocitinib and upadacitinib for first-line treatment compared with ciclosporin were highly uncertain and did not represent clinical practice. Therefore the committee concluded that it was inappropriate to consider the economic model outputs for these comparisons and could not make a recommendation for first-line treatment.

The committee considered second-line treatment, for use in people whose disease has not responded to at least 1 systemic immunosuppressant, or when systemic immunosuppressants are not suitable. For second-line treatment, the incremental cost-effectiveness ratios (ICERs) were calculated for abrocitinib, tralokinumab and upadacitinib plus topical corticosteroids compared with dupilumab or baricitinib. The exact ICERs are confidential and cannot be reported here.

The committee noted their preferred assumptions to:

- consider clinical effectiveness data from adults to be generalisable to young people (see section 3.12)
- use specific dose and dose scheduling assumptions for each treatment (see section 3.19 and section 3.20)
- use utility values derived from a single baseline and response to treatment data (see section 3.22)

The committee noted substantial uncertainty with the relative clinical effectiveness of each treatment in the network meta-analysis and effectiveness of sequential treatments and best supportive care over the full time horizon. It considered that taking into account these uncertainties, the ICERs for each treatment suggested that abrocitinib,

upadacitinib and tralokinumab are likely to be an effective use of NHS resources compared with current treatments.

## Other factors

### Head-to-head trials and real-world data may help future decision-making

3.26 The EAG noted that there are limited head-to-head comparative studies which evaluate the efficacy of treatment options for atopic dermatitis. Feedback from consultees highlighted that real-world data such as the A-STAR registry (UK-Irish Atopic Eczema Systemic Therapy Register) could potentially improve the current evidence base. The registry is an independent research data platform and collects both clinical and cost data to help treatment decisions for people with atopic eczema. The committee understood that real-world evidence could improve the current evidence base and help inform decision-making, and may also help inform understanding of sequential treatments in NHS clinical practice.

### EASI and DLQI may not be appropriate for all people with atopic dermatitis

3.27 The committee noted the following potential equality issues:

- the EASI might underestimate the severity of atopic dermatitis in people with brown or black skin
- the DLQI may not account for anxiety and depression.

The committee concluded that, when using the EASI, healthcare professionals should take into account skin colour and how this could affect the EASI score. Also, it concluded that when using the DLQI, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or difficulties in communication that could affect a person's response to the DLQI.

# 4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations for tralokinumab and upadacitinib in this appraisal within 3 months of its date of publication. Because abrocitinib has been available through the early access to medicines scheme, NHS England and commissioning groups have agreed to provide funding to implement the recommendation for abrocitinib in this guidance within 30 days after publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has moderate to severe atopic dermatitis and the doctor responsible for their care thinks that abrocitinib, tralokinumab or upadacitinib, is the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. 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

# 6 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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