Upadacitinib, abrocitinib and tralokinumab for dermatitis

For committee and experts – contains ACIC information

Multiple technology appraisal – chair's presentation for ACM2

Technology appraisal committee B – 12 May 2022

Chair: Charles Crawley

Evidence review group: BMJ TAG

Technical team: Ying-Ying Wang, Adam Brooke, Henry Edwards

Companies: AbbVie, Pfizer and Leo Pharma

NICE

ACD draft recommendation

Abrocitinib, tralokinumab and upadacitinib are not recommended, within their marketing authorisations, for treating moderate to severe atopic dermatitis

Further analyses requested at ACM1	Assessment group response
Adult population to generalise to the adolescent population	✓
Fixed effect model for the network meta-analysis	✓
Pooled cost-effectiveness estimates for high- and low- doses	✓
Alternative utility value scenarios – including response-based rather than treatment-specific utility values and those used in TA534	✓
Best supportive care treatment waning over time	✓
Explore modelled time horizon	✓

Atopic dermatitis

- Chronic inflammatory skin condition
  - 1 in 5 children and 1 in 10 adults in the UK have AD
- Typically an episodic disease – periods of flare and remission
  - Red blotchy rash, dry, itchy and inflamed skin with scaly plaques, bleeding, oozing, cracking and flaking.
  - Itching is the most disruptive symptom
- There are no curative treatments for AD – treatment is based on reducing symptom burden

Committee (ACD 3.2)

- condition is life-limiting, debilitating, and isolating, and affects all aspects of life
- 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.
- unmet need for people whose dermatitis does not respond to treatment or who are unable to tolerate existing treatment

RECAP

Treatment pathways

ADULTS

Best supportive care
Emollients and topical corticosteroids (TA81)
Topical calcineurin inhibitors (tacrolimus: TA82)
Phototherapy: Narrowband UVB light

If inadequate response to topical treatments and phototherapy, add

Systemic immunosuppressants
e.g. ciclosporin, methotrexate, azathioprine, mycophenolate mofetil

Upadacitinib

Abrocitinib

If inadequate response to, inability to tolerate, or contraindication to systemic therapy, add

Dupilumab (TA534)

Baricitinib: (TA681)

Upadacitinib

Abrocitinib

Tralokinumab

ADOLESCENTS

Best supportive care
Emollients and topical corticosteroids (TA81)
Topical calcineurin inhibitors (tacrolimus: TA82)
Phototherapy: Narrowband UVB light

Systemic immunosuppressants
e.g. ciclosporin, methotrexate, azathioprine, mycophenolate mofetil

Dupilumab (TA534)

Upadacitinib

Abrocitinib

Committee (ACD 3.4, 3.5)

- systemic immunosuppressants (such as methotrexate) would normally be considered first
- likely to be used at the same time as topical treatments as ‘combination therapy’
- likely be used in sequences, but no clinical data

Technologies

RECAP

	Abrocitinib	Tralokinumab	Upadacitinib
Marketing authorisation	• Treatment of moderate-to-severe AD in adults and adolescents aged 12 years and over and who are candidates for systemic therapy.	• Treatment in adults with moderate-to-severe AD and eligible for systemic therapy	• Treatment of moderate-to-severe AD in adults and adolescents aged 12 years and over and who are candidates for systemic therapy
Mechanism of action	• Janus kinase (JAK) 1 inhibitor	• Anti-interleukin (IL)-13 human immunoglobulin- G4 monoclonal antibody	• Janus kinase (JAK) inhibitor
Administration	• 100 mg or 200 mg once daily (oral) [a lower dose recommended for those aged ≥ 65 years]	Subcutaneous injection every 2 weeks (Q2W) • Induction phase: one dose of 600 mg, then 300 mg for 16 weeks. • Maintenance: Q2W regimen or 300 mg every 4 weeks (Q4W)	• 15 mg for adolescents and 15 mg or 30 mg for adults once daily (oral)
Price	• 28-tablet pack of 100mg / 200mg – same price for each dose ([redacted]) • A patient access scheme (PAS) discount is in place.	• 4 x 150mg injection (£1,070.00) • A patient access scheme (PAS) discount is in place	• Available as 28-tablet packs of 15mg (£805.56) or 30mg doses ([redacted] • A patient access scheme (PAS) discount is in place

Overview of clinical evidence

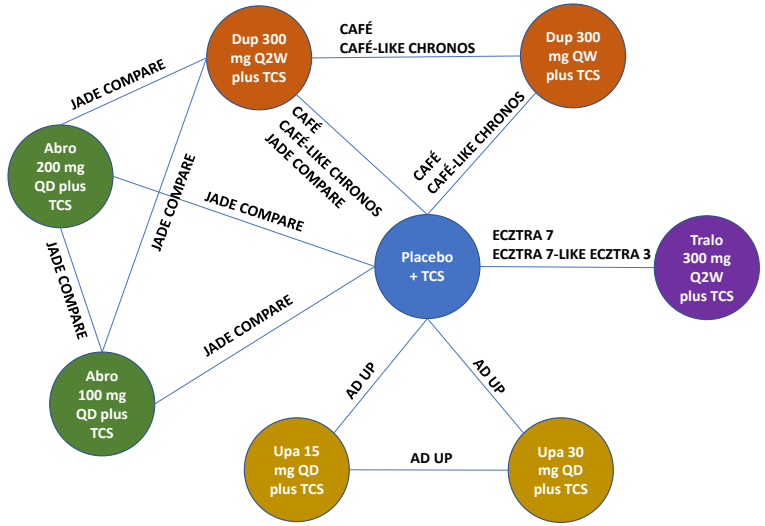
RECAP

	Abrocitinib (oral 100mg or 200mg)	Tralokinumab (subcutaneous injection 300mg or 600mg)	Upadacitinib (oral 15mg or 30mg)
No. of RCTs	6 including one ongoing (JADE-DARE)	6	6
Population	Adolescents/adults with moderate-to-severe AD	Adults with moderate-to-severe AD	Adolescents/adults with moderate-to-severe AD
Intervention	• Monotherapy (Phase IIb, JADE MONO1 and 2) • Combination therapy (JADE-TEEN, **JADE-COMPARE**)	• Monotherapy (ECZTRA 1, 2, 5) • Combination therapy (phase IIb, **ECZTRA 3, 7**)	• Monotherapy (Phase IIb, HEADS-UP, MEASURE-UP1, 2) • Combination therapy (**AD-UP**, RISING UP)
Comparator(s)	• Placebo • Dupilumab (JADE DARE)	Placebo	• Placebo • Dupilumab (HEADS-UP)
Duration	• 12 weeks • 20 weeks (JADE COMPARE)	• 16 weeks • 26 weeks (ECZTRA 7)	• 16 weeks • 24 weeks (HEADS-UP)
Primary outcome	EASI 50 + ΔDLQI ≥4	EASI 50 + ΔDLQI ≥4	EASI 50 + ΔDLQI ≥4
Included in network meta-analyses	MONO 1 and 2; JADE-TEEN JADE-COMPARE	ECZTRA 1,2,3, 7	All except RISING UP (data not available)
Location	UK sites were included in all trials except Phase II study	UK sites were included in ECZTRA 2, 3 and 7	UK sites were included in HEADS UP, MEASURE UP 1 and 2; AD-UP

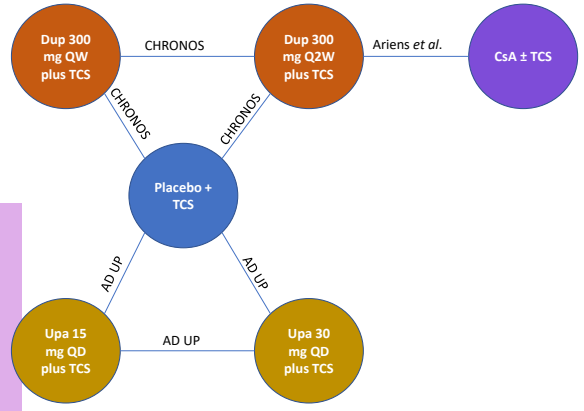
Clinical effectiveness

- Evidence came from a series of RCTs for each intervention, creating a placebo centric network
- Comparative effectiveness was estimated in a NMA using random effect model with informed prior for between-trial heterogeneity

adults second-line treatment, EASI 50 + DLQI>4



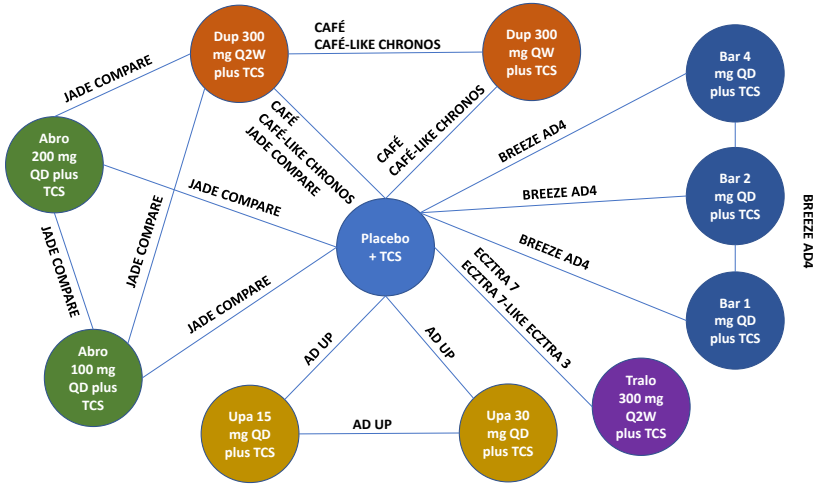
adults first-line treatment, EASI 75



Committee

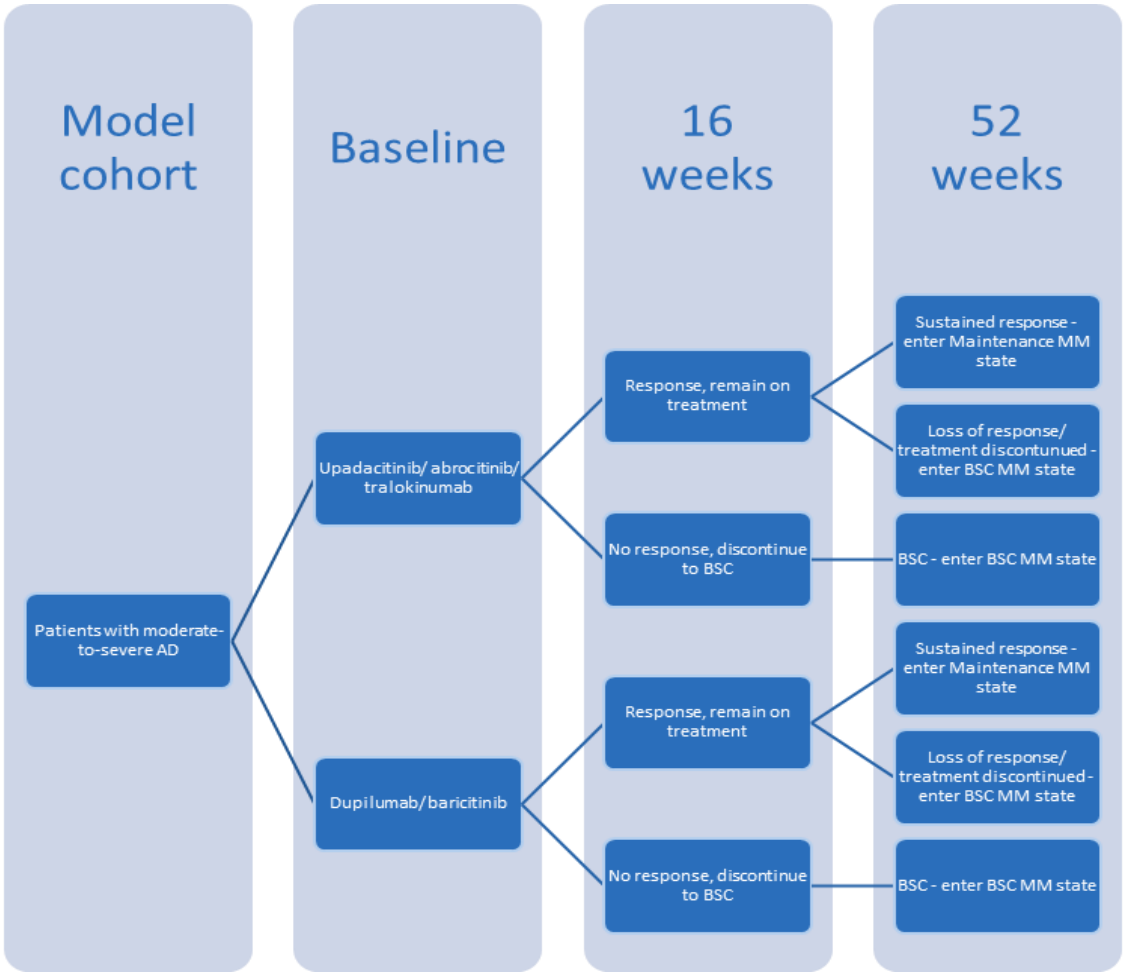
- Treatments are clinically effective compared with placebo
- 1st line comparisons with ciclosporin are highly uncertain
- Random effect models may not be appropriate because of the small number of trials for each treatment arm

adults second-line treatment, EASI 75

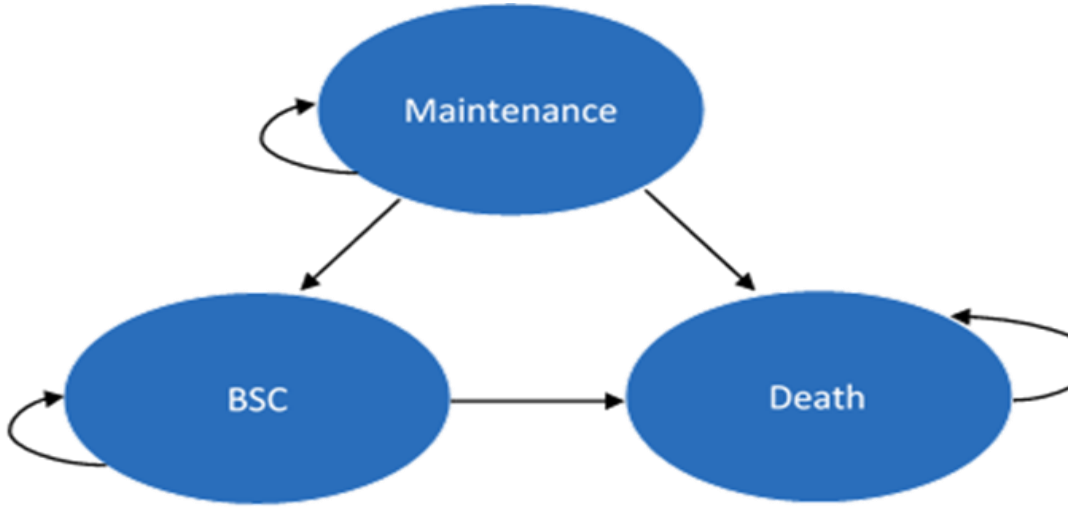


EAG 's model structure

Short-term decision tree model (until week 52, based on 16-week response)



Long-term Markov model for lifetime horizon beyond year 1



Committee (ACD 3.17)

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

Summary committee conclusions – clinical evidence

Topic	Conclusion	ACD
Positioning in the treatment pathway	All technologies are positioned as a treatment option after at least 1 systemic immunosuppressant, as alternatives to dupilumab and baricitinib.	3.3
Combination therapy	All the treatments are likely to be offered alongside topical corticosteroids in clinical practice. The committee agreed to focus on the evidence for 'combination therapy' as the most relevant evidence for decision-making.	3.5
Efficacy	Abrocitinib, tralokinumab or upadacitinib are clinically effective treatments compared with placebo.	3.10
Population	No evidence on the full indirect comparison analysis in combination therapy in adolescents. The clinical experts explained that the current treatment pathways for adults and adolescents with atopic dermatitis are similar.	3.12
First line treatment comparator evidence	A small observational study informed the in the network analysis that used ciclosporin as a comparator. The indirect comparison with ciclosporin was highly uncertain.	3.14
Random effect models	The EAG used random effect models in the base case analysis. The approach 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.	3.15
Safety	Trial evidence shows low adverse event rates. Limited safety data is available on the impact of JAK inhibitors on developing cardiovascular problems or cancer.	3.16

Summary committee conclusions – economic model

Assumption at ACM1	Committee conclusion	ACD
Treatment dose options	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. Treatment dose options should not be modelled separately.	3.18
Model structure	All patients that discontinue or lose response transition to the best supportive care state over time. Active treatment waning as per TA534 should be explored.	3.17
Utility values	Utility values used in the economic model are derived from the clinical trial data	3.19
Treatment-specific utility values	Using different baseline utility values introduced unnecessary complexity, making it difficult to interpret the results. Treatment-specific utility values are uncertain and alternative utility value scenarios should be explored.	3.20
Best supportive care utility values	The utility values for the best supportive care health state are highly uncertain and have a large impact on the cost-effectiveness.	3.21
Best supportive care waning effect	Inconsistency with previous appraisals creates uncertain model drivers for the response health state	3.22

ACD consultation responses

Responses from:

- Companies:
  - AbbVie (Upadacitinib)
  - Pfizer (Abrocitinib)
  - Leo Pharma (Tralokinumab)

- British Association of Dermatologists (BAD)
- Eczema Outreach Support (EOS)
- EAG

NICE National Institute for Health and Care Excellence

Assessment groups updated model

Further analyses	Assessment group response	For discussion
Adult population to generalise to the adolescent population	Included – assumption that adult results generalisable for adolescents	No
Fixed effect model for the network meta-analysis	Provided scenarios with both EAG base case of random effects and fixed effect NMAs	Yes
Pooled cost-effectiveness estimate for high & low doses	Provide a 50:50 pooled dose in absence of evidence	Yes
Alternative utility values scenarios	Provide health-state specific utility values and TA534 utility value scenario. No analysis based on change in utility from trial	Yes
Best supportive care treatment waning over time	Provide a scenario as in TA534	Yes
Explore modelled time horizon	Provide a scenario with 5 year time horizon	No

Adult population generalised to the adolescent population

***ACD committee conclusions**:*

- *'the results of the 'combination therapy' analysis for adults who had tried systemic immunotherapy would likely be generalisable to the adolescent population'*

EAG update:

- An updated separate analysis for the adolescent population is therefore not provided.

Consultation comments:

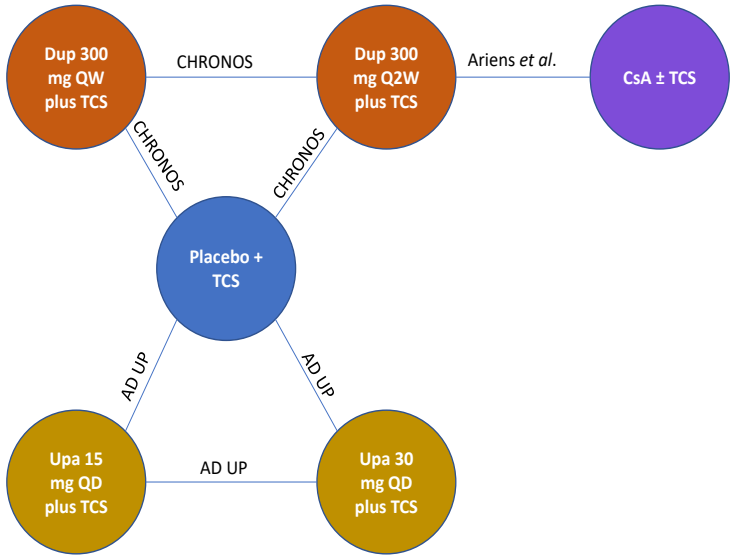
- **Abbvie**: the results (of upadacitinib compared with dupilumab) based on adolescent clinical trial participants should not be ignored for decision making.
- **Leo Pharma** : no comment.
- **Pfizer**: we agree with the approach proposed by the committee to assume that the results from the 'combination therapy' analysis for adults who were previously exposed to a systemic immunotherapy (and based on EASI 50 + DLQI≥4) would be generalisable to the adolescent population. Only the comparison with dupilumab would be relevant given that baricitinib is licensed for adults only.

First-line (systemic-naïve) treatment uncertainty

***ACD committee conclusions**:*

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 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

- ***Ariens et al. (2019)***
  - Patient-level data on dupilumab (CHRONOS RCT) and ciclosporin treatment of AD obtained from observational data in clinical practice (University Medical Center Utrecht).
  - Different baseline characteristics (i.e treatment history)
  - Small sample size (n=57 ciclopsporin)
  - there was no granularity in the exact timing of its assessment (EASI) in patients treated with ciclosporin
- **In the economic model, people are assumed to revert to the BSC state after 1 year of ciclosporin treatment**



- **BAD**: The committee may wish to consider the results of the TREAT trial (ciclosporin vs. methotrexate in adolescents). There is also additional published evidence regarding methotrexate in adults which would ideally be considered because methotrexate is the most commonly used first-line treatment for eczema and is much cheaper than ciclosporin or the new drugs

Network meta-analysis: Fixed effect vs random effect models

***ACD committee conclusions**:*

- *Using random effect model 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. …would like to consider the results of the fixed effects analysis, which may affect the point estimates of the results used in the deterministic base case analysis*

EAG update:

- Results are provided both using a fixed effect model and using a random effects model, with the latter using an informed prior for the between-trial heterogeneity.

Consultation comments:

- **Abbvie**: the use of a random effects model is often preferred in a Bayesian indirect comparison, as it allows for between-studies heterogeneity in the estimates of treatment effect. …in this situation the **fixed effects model is the appropriate** network meta-analysis model for base case analysis due to the low number of trials used to estimate between study variability.
- **LEO Pharma**: we consider the **random effects approach** to the NMA as more appropriate.
- **Pfizer**: …in our original submission, the overall conclusions are **largely comparable regardless of approach** (fixed or random effects). It is important to ensure that both fixed effects and random effects-are explored in the EAG NMA.

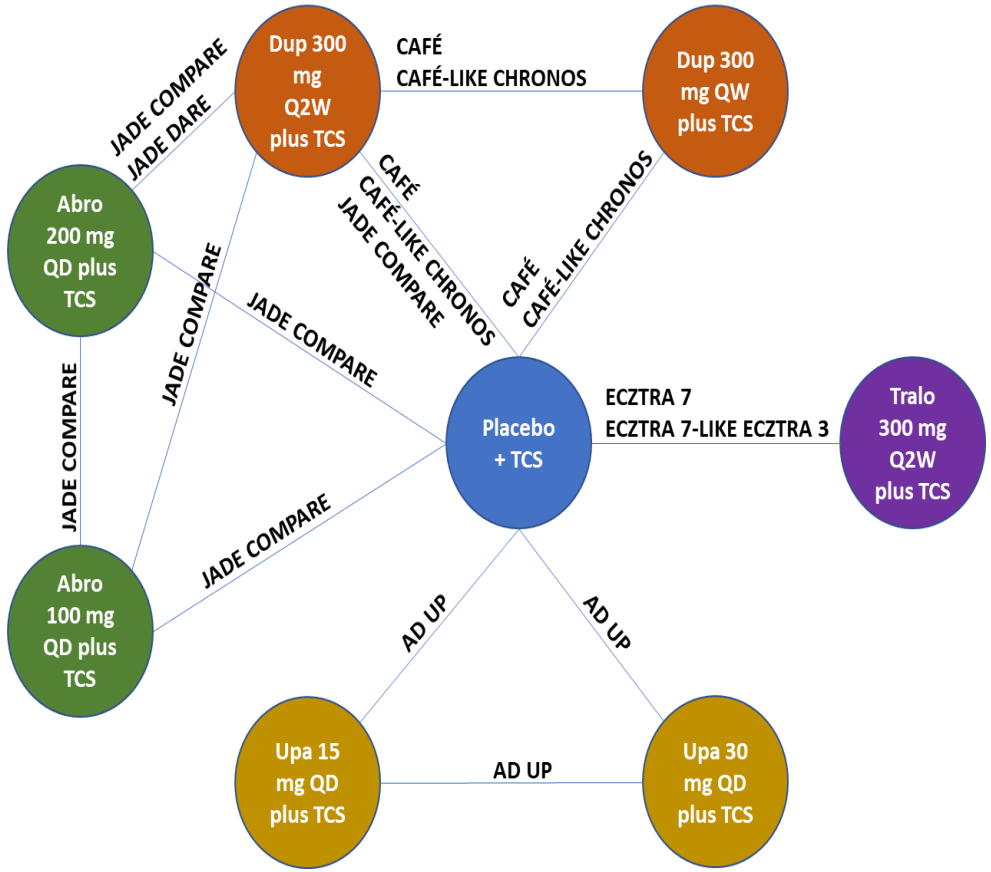
NMA results – EASI 75

adults, first-line treatment, vs placebo and CsA (includes JADE DARE)

Comparison	Pair-wise meta-analysis OR (95% CI)	NMA OR (95% CrI)	
		Fixed effect	Random effects
Treatments versus placebo + TCS			
Abro 200 mg QD + TCS	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]
Dup 300 mg Q2W + TCS	5.82 (3.56 to 9.52)	[redacted]	[redacted]
Dup 300 mg QW + TCS	5.07 (3.62 to 7.11)	[redacted]	[redacted]
CsA + TCS	NA	[redacted]	[redacted]
Upa 30 mg QD + TCS	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	[redacted]	[redacted]	[redacted]
Treatments versus CsA + TCS			
Abro 200 mg QD + TCS	NA	[redacted]	[redacted]
Abro 100 mg QD + TCS	NA	[redacted]	[redacted]
Upa 30 mg QD + TCS	NA	[redacted]	[redacted]
Upa 15 mg QD + TCS	NA	[redacted]	[redacted]

NMA results – EASI 50 + DLQI>4, combination

adults second-line treatment – vs placebo and dupilumab



Comparison	Pair-wise meta-analysis OR (95% CI)	NMA OR (95% CrI)	
		Fixed effect	Random effects
Treatments versus placebo + TCS			
Abro 200 mg QD + TCS	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]
Dup 300 mg Q2W + TCS	7.05 (4.22 to 11.77)	[redacted]	[redacted]
Dup 300 mg QW + TCS	6.60 (4.09 to 10.66)	[redacted]	[redacted]
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]
Upa 30 mg QD + TCS	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	[redacted]	[redacted]	[redacted]
Treatments versus Dup 300 mg every 2 weeks + TCS			
Abro 200 mg QD + TCS	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]
Tralokinumab + TCS	NA	[redacted]	[redacted]
Upa 30 mg QD + TCS	NA	[redacted]	[redacted]
Upa 15 mg QD + TCS	NA	[redacted]	[redacted]

Pooled cost-effectiveness estimate for high & low doses

***ACD committee conclusions**:*

- *'the decision to start treatment would be based on the overall effectiveness of the drug and not on efficacy evidence of individual doses…preferred to pool the results of the high and low doses, using a proportional weighting of each treatments' expected dose distribution in clinical practice'*

EAG update:

- The EAG consulted its clinical experts who advised that dosing decisions depend on the treating clinician, and these decisions vary hugely. Clinical experts were unable to provide the expected dose distribution in clinical practice. For a pooled cost-effectiveness estimate for each of the treatment options that have high and low dose, the EAG has assumed a 50:50 low-/high- dose distribution, in the absence of robust data.

Consultation comments:

- **AbbVie**: No comment
- **Pfizer**: we explored a scenario with a pooled cost-effectiveness estimate for abrocitinib 200 mg and 100 mg doses. Our revised estimate of the proportion of patients who are likely to receive each dose [redacted] for the 200 mg dose and [redacted] for the 100 mg dose [redacted]

What is the most appropriate dose distribution in clinical practice?

Pooled cost-effectiveness estimate for high & low doses

Summary of product characteristics wording	
Abrocitinib	• The recommended dose is either 100 mg or 200 mg once daily. • 200 mg is the recommended starting dose for most patients, particularly those with severe disease • 100 mg once daily is the recommended starting dose for patients aged ≥ 65 years, adolescents (12 to 17 years old), and for those who have risk factors for developing an adverse reaction to abrocitinib or those who are less likely to tolerate the adverse reactions. The dose may be decreased or increased based on tolerability and efficacy.
Upadacitinib	• The recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation. • 30 mg once daily may be appropriate for patients with high disease burden; patients with an inadequate response to 15 mg once daily. • 15 mg once daily is the recommended for patients ≥ 65 years of age; should be considered for maintenance. • 15 mg once daily is recommended for adolescents weighing at least 30 kg.

Tralokinumab dosing schedule – 4 weekly dosing

Summary of product characteristics	
Tralokinumab	• The recommended dose is an initial dose of 600 mg (four 150 mg injections) followed by 300 mg (two 150 mg injections) administered every 2 weeks. • At prescriber's discretion, **every fourth week dosing may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment**. The probability of maintaining clear or almost clear skin may be lower with every fourth week dosing. • Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve further with continued treatment every other week beyond 16 weeks.

EAG original scenario analysis:

- Data on the number of patients entering maintenance phase by dose in ECZTRA 3 (ECZTRA 7-like subgroup) were extracted - [redacted] switched to 4 weekly dosing – this is presented as a scenario

Consultation comments:

- **LEO Pharma:** LEO Pharma would like to make the EAG and committee aware of the treatment option of Q4W dosing for tralokinumab. This will be an option in clinical practice based on feedback LEO Pharma has received from leading clinicians in the UK. In addition, Q4W dosing was one of the scenarios run by the EAG in the initial appraisal and we recommend this is revisited for the base case as this will become common practice

What is the proportion of patients who have Q4W dosing in clinical practice? Would this dosing schedule be maintained over the full time horizon?

Alternative utility value source scenarios

***ACD committee conclusions**:*

- *using different baseline utility values introduced unnecessary complexity, making it difficult to interpret the results…it would like to see an analysis that uses standard utility values for health states, regardless of treatment*

EAG update:

- The EAG extracted overall health-state utilities values (HSUVs) based on data from AD UP. The HSUVs were implemented in the EAG model for all treatments, irrespective of drug class and for BSC.

Health state	Utility value (standard error)	Source
First-line population (combination therapy) - EASI 75		
Baseline	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 responder	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 non-responder	[redacted]	Data supplied AbbVie - AD UP trial
Second-line population (combination therapy) - EASI 50 + DLQI ≥4		
Baseline	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 responder	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 non-responder	[redacted]	Data supplied AbbVie - AD UP trial
Second-line population (combination therapy) - EASI 75		
Baseline	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 responder	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 non-responder	[redacted]	Data supplied AbbVie - AD UP trial

Abbreviations: EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index.

Alternative utility value source scenarios

Consultation comments:

- **Abbvie:** agrees with the Committee's preference for a common HSUV baseline value (Section 3.20), where it is assumed that randomisation to placebo or active treatment do not impact on baseline HSUV. AbbVie believe that applying the upadacitinib clinical trial data from AD UP and dupilumab clinical trial data from TA534 for HSUV are reasonable options, since this reflects the available evidence for responders. However, due consideration for the results of Heads UP is appropriate as additional benefit is likely to be conferred on patients with response per EASI 90 or EASI 100 criteria.
- **Leo Pharma:** no comment
- **Pfizer**:
    - we agree with the committee that there is no clinical rationale for the EAG's use of different baseline utility values across therapies. We agree with the suggestion from the EAG that the utility associated with being a responder may differ by treatment which was also recognised by the NICE committee in the ACD. It is logical to expect that responders (defined as EASI 50 + DLQI ≥4) on a treatment providing higher thresholds of response (e.g., EASI90) would have a higher utility score.
    - Pfizer proposed an alternative approach: apply a common baseline utility and utility value associated with being a EASI 50 + DLQI ≥4 responder to all treatments, with additional utility benefits applied based on the proportion of patients achieving EASI75 and EASI90 within the trials. This analysis demonstrated that higher levels of EASI response are associated with greater improvements in utility.

What is the most appropriate source for utility values?
Should additional HSUVs based on higher response be considered?

Best supportive care waning – Markov trace

***ACD committee conclusions**:*

- *The committee noted that changes to the best supportive care waning… [favoured] treatments that most quickly result in patients entering the low cost, high utility best supportive care health state. . concluded it wanted further analysis of consistency with previous appraisals that could explain [this uncertainty].*

EAG base case – no treatment waning

TA534 treatment waning scenario

EAG update:

- EAG applied BSC waning and used the BSC waning proportions (a weighted average utility value for the health state comprised of the average utility for BSC and baseline utility from CHRONOS).. For example, in Year 2, 57% of BSC patients returned to baseline utility and 43% retained the benefits of BSC (weighted average utility of responder and non-responder to BSC). By Year 5, 97% of BSC patients have returned to baseline utility.
- Also provide a scenario using utility values from TA534

Best supportive care waning

Consultation comments:

- **Abbvie:** AbbVie has explored the issue by varying the BSC HSUV.
- **Leo Pharma**: agree with the recommendation of the committee to explore a long-term utility waning effect in patients treated with BSC. This was an assumption in the tralokinumab STA model and also in previous appraisals such as TA534.
- **Pfizer**: Clinical opinion provided to the company indicated that the response to BSC seen in clinical trials would be expected to drop off quickly, with one clinician stating that utility for BSC would be more comparable to that of non-responders.

Other comments from commentators

British Association for dermatologists (BAD)

- Real-world effectiveness data, such as that from the A-STAR registry, are likely to be more representative of the patient populations treated within NHS clinics than cohorts enrolled in trials.

- 'Best supportive care' (BSC) is defined in this model as a single health care state. Costs of BSC are calculated by the weighted average of responders and non-responders at 16 weeks (as guided by the NMA of clinical effectiveness). This is likely to be an underestimate of true costs of BSC. We do not feel it is appropriate to have a single BSC state or that this state should be assumed to be stable for the duration of modelling (5 years).

Eczema Outreach Support (EOS)

- Current recommendations denies adolescents access to a treatment that may provide significant relief from the chronic condition, and may lead to avoidable suffering for young people struggling to manage the physical and mental impact of the condition

Key issues

No.	Key issues at ACM2
1.	The indirect comparisons of first line treatments with ciclosporin are highly uncertain
2.	Expected dosing distribution (upadacitinib and abrocitinib) and schedules (tralokinumab)
3.	Use of alternative utility value scenarios
4.	Effect of best supportive care waning assumptions on cost-effectiveness results

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

NICE National Institute for Health and Care Excellence

Thank you.