Upadacitinib, abrocitinib and tralokinumab for moderate to severe atopic dermatitis

Multiple technology appraisal

For committee – contains AIC information, CIC information redacted

Technology appraisal committee B – 17 March 2022

Chair: Charles Crawley

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Companies: AbbVie, Pfizer and Leo Pharma

NICE

Multiple technology appraisal

Three STA have been merged into one MTA

- Due to the capacity challenges of COVID in summer 2021, three dermatitis STAs were merged into 1 MTA.

STA, Single Technology Appraisal; MTA, Multiple Technology Appraisal; ACM, Appraisal Committee Meeting

Atopic dermatitis

- Atopic dermatitis, also called atopic eczema, a chronic inflammatory skin condition that mainly affects children, though is also common in adults. One in 5 children and 1 in 10 adults in the UK have AD
- Characterised by red blotchy rash, dry, itchy and inflamed skin with scaly plaques, bleeding, oozing, cracking and flaking. Itching is the most disruptive symptom
- Typically an episodic disease where patients experience flares (a worsening of symptoms) and remissions. Increased risk of skin infections, which may become systemic
- Diagnosis of AD is based on the clinician's assessment together with patient history.
- Disease severity is not consistently classified, different tools used in clinical practice (EASI, IGA, SCORAD or BSA)
- An estimated 7% of adults in the UK have moderate to severe atopic dermatitis (from TA534), of which 27% are estimated to be eligible for systemic therapy and 53% would require second-line treatment – therefore approximately 20,000 adults and 2,500 adolescents would require second-line treatment.
- There are no curative treatments for AD – treatment is based on reducing symptom burden

Measuring clinical effectiveness (1/2)
EASI and DLQI are used in clinical practice

Eczema Area and Severity Index (EASI): 0 to 72			
Assesses disease at 4 body regions, and measures 4 clinical signs (erythema, induration / papulation, excoriation and lichenification) on a scale of 1-3, proportionate to surface area			
0 – 7	**7.1 – 21**	**21.1 – 50**	**50.1 – 72**
No eczema	Moderate	Severe	Very severe
Response	• EASI 50, EASI 75, EASI 90 or absolute reduction from baseline • EASI 50 = ≥ 50% reduction in EASI score from baseline		

Dermatology Life Quality Index (DLQI): 0 to 30		
10-item questionnaire covering 6 domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment; 0(no impact) to 3 (worst impact)		
0 – 1	**6 – 10**	**11 – 20**
No effect	Moderate effect	Large effect
Response	≥4 point improvement considered a clinically important difference	

Investigator's Global Assessment (IGA): 0 to 4				
Clinician's impression of patient's eczema based on severity of erythema, papulation / induration, oozing / crusting and lichenification				
0	**1**	**2**	**3**	**4**
Clear	Almost clear	Mild	Moderate	Severe

Measuring clinical effectiveness (2/2)

Different perspectives on clinically important differences:

- In TA534 (dupilumab) and TA681 (baricitinib), the committee concluded that the composite outcome of EASI 50 plus a 4-point DLQI improvement was appropriate for decision-making
- British Association of Dermatologists: EASI 75 or fall in IGA ≥ 2
- Clinical expert: Reducing severity of eczema to mild (EASI <6, IGA 0 or 1)
- Other measures used in atopic dermatitis
    - HOME (Harmonising Outcome Measures for Eczema) initiative patient reported outcomes:
        - Itch / Skin pain numeric rating scale (NRS)
        - Patient Oriented Eczema Measure (POEM)
    - Atopic Dermatitis Sleep Scale (ADSS)

Treatment pathway: 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**

What are the most appropriate comparators for the interventions?
How does the treatment pathway differ in clinical practice?

Treatment pathway: Adolescents

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. methotrexate, azathioprine, mycophenolate mofetil**

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

+ **Dupilumab (TA534)**

Upadacitinib

Abrocitinib

What are the most appropriate comparators for the interventions? Are there other considerations for treatment choice for adolescents?

Patient organisation perspectives

Eczema Outreach Support (EOS), a national support charity offering a range of direct and personalised support services to families of children with eczema in the UK

National Eczema Society (NES), UK charity support people with information and advice about eczema and its management

Living with AD

- AD is a complex condition characterised by chronic dry skin condition
- Constant itchiness is one of the most challenging aspects of eczema; it can result in reduced social interaction and inability to work and study.
- Face a daily struggle to live with AD. (i.e. sleepless nights, constant scratching and unpredictable flares) – 51.70% of young people reported that itching was an issue 'most days'.
- AD can have a devastating effect on not only a person's physical but also mental health - 52.25% of parents/carers reported that when their child's eczema was at its worst, it made their mood low.
- A 2012 British Skin Foundation survey found that 47% of respondents with skin disease had been victims of verbal abuse and a further 1 in 6 people having self-harmed.

Itchiness can be intense, relentless and unbearable

Caring for a child or adult with eczema can be time-consuming and exhausting, both physically and emotionally.

Patient organisation perspectives

Current care

- Current treatments available are limited in number and effectiveness.
    - Patient survey: 42% of adults and 30% of parent respondents don't have confidence in the abilities of healthcare professionals to treat their own or their child's eczema.
- Inconsistencies across clinical practice – lack of access to phototherapy, insufficient guidance on topical steroids and initiating systemic immunosuppressants, long-term use of antihistamines
- Many families would prefer not to use steroid treatments – because of potential to sting, increased burden of administration and fear of steroid withdrawal and side effects
- Concerns over prolonged immunosuppressants use – further highlighted during the pandemic

Potential benefits/concerns related to new treatment

- New treatment options could improve quality of life (psychological wellbeing)
- Additional treatment options for people with AD, increasing the likelihood that they will find a treatment that works effectively for them

The psychological impact of new treatments being available should not be underestimated, especially for families who believe they are at the "end of the road" with current options.

Technologies

	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

Decision problem (1/2)

	Final scope	Company submission/ EAG comments
Population	People with moderate to severe atopic dermatitis	**EAG**: people with moderate to severe atopic dermatitis including subgroups for: ○ **adolescents** aged 12 to 18 years and ○ **adults** aged 18 years and older ▪ People are eligible for systemic treatment on inadequate response to topical treatments and who have **not received prior systemic therapy**. ▪ People who **achieve inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy**
Intervention	Abrocitinib, tralokinumab and upadacitinib with and without topical corticosteroids (TCS)	**Systemic-naïve (first-line) population:** • Upadacitinib • Abrocitinib (added after consultation – see Issue 4) **Systemic-experienced (second-line) population**: • Upadacitinib, Abrocitinib, tralokinumab **Adolescents (first and second-line)** • Upadacitinib, Abrocitinib

Decision problem (2/2)

	Final scope	Assessment group rationale
Comparators	• Phototherapy including with ultraviolet (UVB) radiation or psoralen-ultraviolet A (PUVA) • Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) • Oral corticosteroids • Alitretinoin (in people with atopic dermatitis affecting the hands) • Dupilumab • Baricitinib • Best supportive care (combination of emollients, low to mid potency topical corticosteroids, and rescue therapy including higher potency topical or oral corticosteroids or topical calcineurin inhibitors)	**First-line systemic treatment:** Ciclosporin A (CsA) – azathioprine or methotrexate may also be used but expert clinical opinion limited this to CsA for the purposes of analysis (the only licensed treatment) **Second-line systemic treatment:** • Dupilumab • Baricitinib Both with or without topical corticosteroids (TCS) although clinical advice suggests predominantly with TCS Phototherapy and oral corticosteroids not to be relevant comparators – based on clinical advice
Outcomes	• measures of disease severity • measures of symptom control • disease free period/maintenance of remission • time to relapse/prevention of relapse • adverse effects of treatment • health-related quality of life	**EAG**: • Primary outcome: EASI 50 + ΔDLQI ≥4 • Secondary outcome: EASI 75 • EQ-5D • proportion of people who discontinue treatment • number of days free from TCS during treatment; • proportion of people requiring use of rescue therapy during treatment • serious adverse effects of treatment

Key issues

Key: Large impact  Small/moderate impact  Unknown impact 

No.		ICER impact
1	EMA safety review of JAK inhibitors	
2	Adolescents – Limited data available for NMA results	
3	Adults 1st line – Uncertainty in CsA clinical outcomes	
4	Adults 1st line - Treatment sequencing in clinical practice	
5	All - BSC effect waning not included in the base case	
6	All - Counterintuitive response/discontinuation as a model driver	
7	All - Uncertainty and heterogeneity in NMA results	

Key issue 1: Safety review of JAK inhibitors

- EMA has started a safety review of JAK inhibitors including baricitinib (already recommended) and Abrocitinib, Upadacitinib (in this appraisal). – initial findings expected Sep 2022.
- Preliminary findings suggest an increased risk of major cardiovascular problems (i.e. heart attack, stroke) and developing cancer.
- MHRA introduced new measures for tofacitinib to minimise risk of major adverse cardiovascular events and malignancies including restricting use (unless there are no suitable treatment alternatives) in:
  - patients older than 65 years of age
  - people who are current or past smokers
  - individuals with other cardiovascular (such as diabetes or coronary artery disease)
  - other malignancy risk factors

How would the safety review affect the use of JAK inhibitors in clinical practice?
When would JAK inhibitors be used first-line, or before dupilumab?

Clinical effectiveness overview

NICE National Institute for Health and Care Excellence

Overview of clinical evidence

	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

Treatment regimens – concomitant topical steroids

TA534/TA681: "*The clinical experts explained that [dupilumab/baricitinib] is likely to be offered alongside topical corticosteroids. The committee therefore agreed to focus on the evidence for 'combination therapy'*"

- All 3 technologies provided RCT evidence using as a monotherapy or combination therapy (in addition to topical corticosteroids) – EAG included cost-effectiveness results for monotherapy in the assessment report
- Lead team presentation focuses on combination therapy where evidence is available

Comparative evidence available in NMA by population	Monotherapy		Combination therapy	
	EASI 50 +DLQI ≥4	EASI 75	EASI 50 +DLQI ≥4	EASI 75
Adults - first-line systemic treatment	✗	✗	✗	✓
Adults - Second-line systemic treatment	✓	✓	✓	✓*
Adolescents	✗	✓	✗	✗

*Evidence for baricitinib comparison only available here.

Q: Is it appropriate to focus on clinical evidence from combination trials for the new treatments?

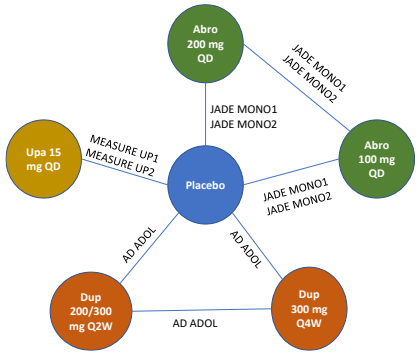
Network meta-analysis overview

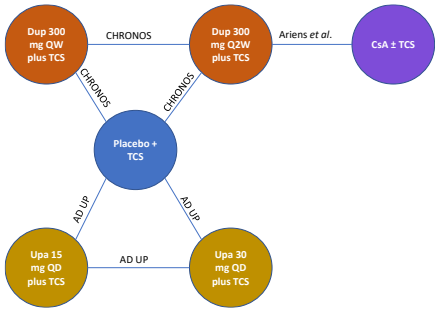
- Primary outcome: EASI 50 + DLQI ≥4
- Secondary outcome: EASI 75

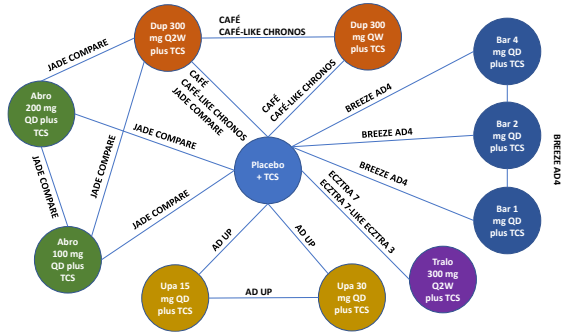
- Primary analysis: random effect model with an informed prior for between trial heterogeneity

EAG comments:

- There is likely to be substantial between-trial heterogeneity that would be ignored using a fixed effect model - using a RE model with an informed prior for the between-trial heterogeneity enables ability to take into account between-trial heterogeneity without the analysis being overwhelmed by an uninformed prior.







Cost effectiveness overview

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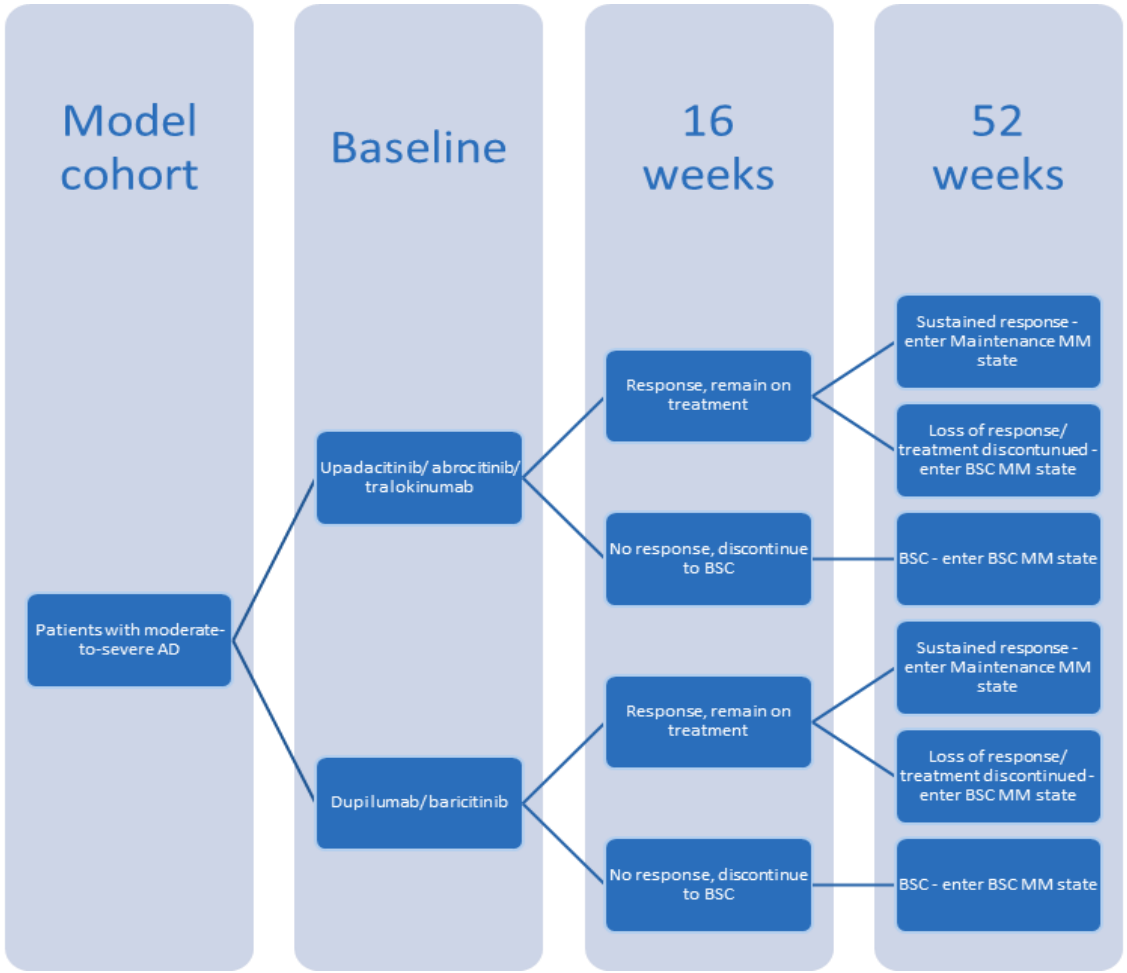
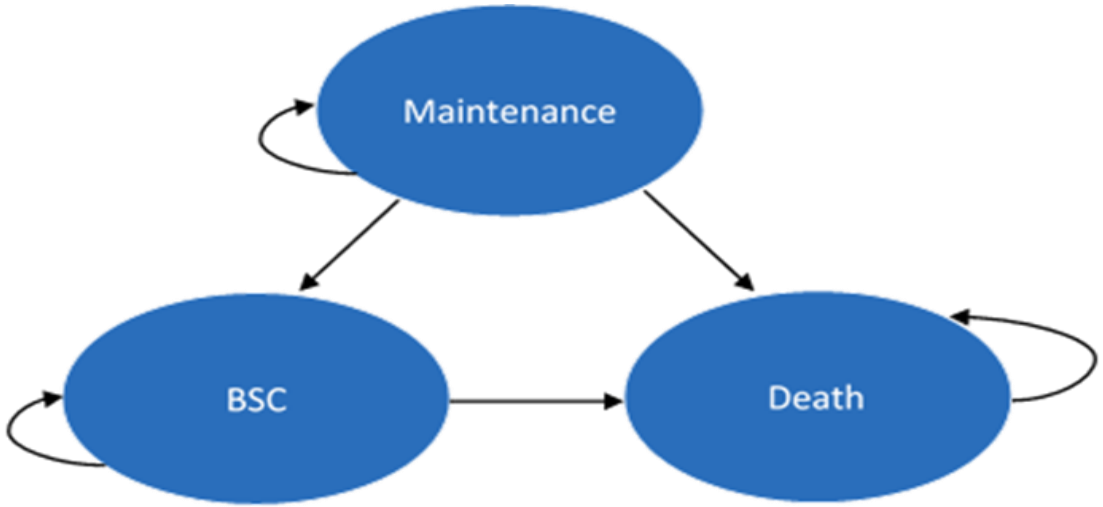
EAG ’s model structure

Short-term decision tree model (week 16 response assessment)



Long-term Markov model included responders who sustain their response between week 16 and 52 and are still on treatment



Key assumptions

Input	Assumptions
Baseline characteristics	Data from the upadacitinib trials were used to inform the baseline characteristics in the EAG economic model including MEASURE 1 and 2, AD-UP based on clinical advice on generalisability of the trial evidence to clinical practice
Treatment waning and discontinuation	All patients that discontinue or lose response transition to the best supportive care state over time. Rates of active treatment waning as agreed in TA534.
Mortality	No assumed effect on mortality – use ONS life tables
Time horizon, discounting, perspective	Lifetime horizon, 3.5% discount rate and NHS and social services perspective
Adverse events	Costs of serious AEs with an incidence of >5% in any treatment arm were included: injection site reaction, allergic conjunctivitis, infectious conjunctivitis, oral herpes, upper respiratory tract infection and acne. No disutilities modelled.
Costs	In line with TA681 – includes drug administration costs, concomitant medication costs, health care resource use costs (monitoring costs) and flare costs
Resource use	Health care resource use in the economic model is based on the ERG estimates for TA534 and the company estimates for TA681
Flare	The receipt of rescue medication was accepted as a proxy for flare. Costs only included in the model

Incorporating NMA results

- Log odds ratios from the NMA were used to estimate Week 16 treatment response probabilities in the model
- These odds were applied to a baseline level of treatment response for patients who would have otherwise been on BSC – EAG considered based on clinical expert opinion that upadacitinib trials (MEASURE UP 1 & 2 and AD UP) trials were most appropriate to use for modelling placebo response

Population	Baseline response	Source
Monotherapy		
Adults - Second-line systemic treatment	[redacted]	Pooled placebo response data from Measure UP 1 [redacted] and Measure UP 2 [redacted]
Adolescents	[redacted]	Pooled placebo response data from Measure UP 1 ([redacted]) and Measure UP 2 [redacted]
Combination therapy		
Adults - first-line systemic treatment	[redacted]	AD UP – [redacted] patients responded to placebo at Week 16
Adults - Second-line systemic treatment	[redacted]	AD UP – [redacted] patients responded to placebo at Week 16

Utility values – response to treatment

- All key trials collected EQ-5D-5L data, which were mapped to the EQ-5D-3L using the van Hout crosswalk algorithm in the company submissions
- EAG used treatment-specific baseline utility values
- Because of limitations associated with missing data, uncertainty due to small numbers and relevance of the populations for utility values, the EAG adopted a drug class approach for utility values in the model.
  - Janus Kinase (JAK) inhibitors (abrocitinib, baricitinib and upadacitinib) – split into high and low dose, derived from upadacitinib EQ-5D trial data
  - Monoclonal antibodies (dupilumab and tralokinumab). – derived from tralokinumab EQ-5D trial data

Health state	JAK inhibitor – low dose	JAK inhibitor – high dose	Monoclonal antibody	Data source
Adult first-line systemic treatment, combination therapy - EASI 75				
Baseline	[redacted]	[redacted]	-	AD UP CSA assumed to be the same as JAK inhibitors.
Responder	[redacted]	[redacted]	-	
Adult second-line systemic treatment, combination therapy - EASI 50 + DLQI ≥4				
Baseline	[redacted]	[redacted]	[redacted]	JAK inhibitors – AD UP Monoclonal antibody – ECZTRA 7 and ECZTRA 7-like subgroup from ECZTRA 3
Responder	[redacted]	[redacted]	[redacted]	

Is it appropriate to use different baseline utilities for the initial 16-week response period?
Is it appropriate to use class specific utility values?

Utility values – BSC state

- Utility for the best supportive care health state was derived from weighting responder and non-responder utilities – derived from upadacitinib placebo utility values for the relevant population as baseline characteristics

BSC	Utility value	Source/ assumptions
Adult first-line systemic treatment, combination therapy - EASI 75		
Responder	[redacted]	AD UP. Combination data used as patients in the BSC likely to get TCS as a subsequent treatment.
Non-responder	[redacted]	
Weighted average	[redacted]	Responders to BSC = [redacted]
Adult second-line systemic treatment, combination therapy - EASI 50 + DLQI ≥4		
Responder	[redacted]	AD UP
Non-responder	[redacted]	
Weighted average	[redacted]	Responders to BSC = [redacted]

What is the most appropriate source of data for utility values for those that do not respond to treatment in the long-term?

Adolescent population

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Key clinical trials: adolescents, monotherapy

EASI50 + DLQI ≥4
EASI75

Abrocitinib (12 weeks)

JADE – MONO1 JADE-MONO2

[redacted]

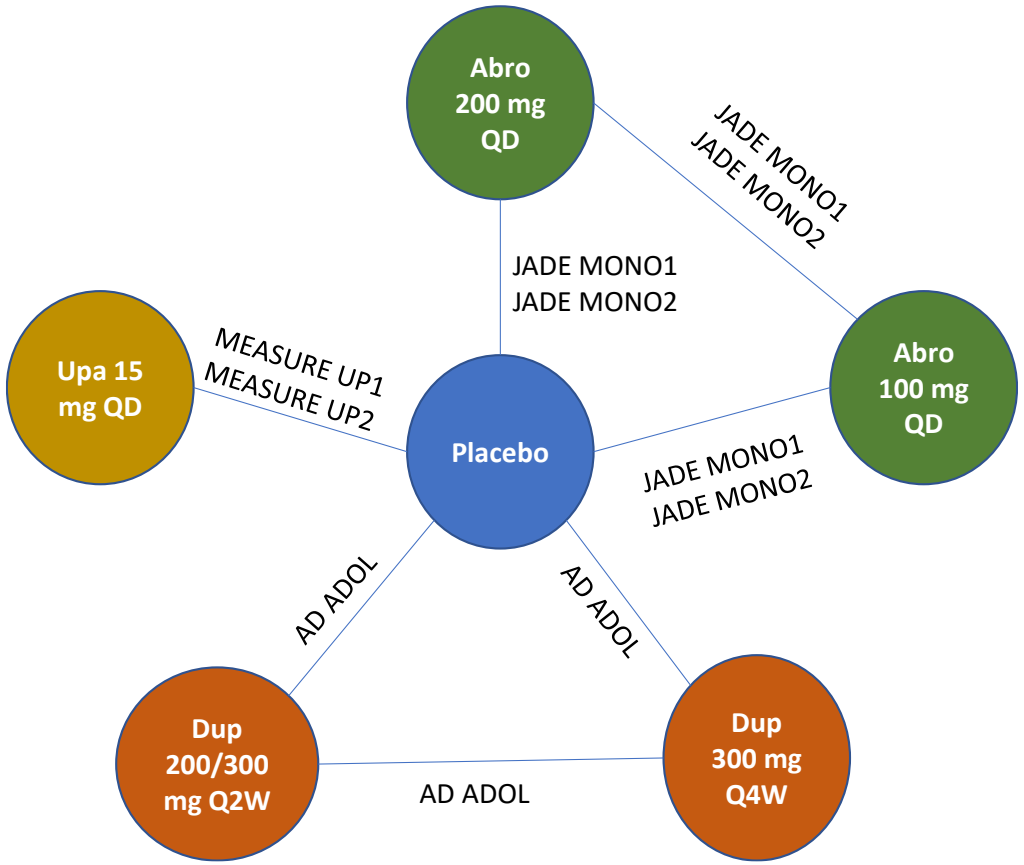
Upadacitinib (16 weeks)

MEASURE UP1 MEASURE UP2

[redacted]

NICE

NMA results: adolescents, monotherapy (EASI 75)



Comparison	Pair-wise analysis OR (95% CI)	NMA OR (95% CrI)
Treatments versus placebo		
Abrocitinib 200 mg	[redacted]	[redacted]
Abrocitinib 100 mg	[redacted]	[redacted]
Dupilumab 200/300 mg	7.89 (3.24 to 19.21)	[redacted]
Upadacitinib 15mg	[redacted]	[redacted]
Treatment versus dupilumab		
Abrocitinib 200 mg	NA	[redacted]
Abrocitinib 100 mg	NA	[redacted]
Upadacitinib 15mg	NA	[redacted]

EASI50 + DLQI ≥4
EASI75

Key clinical trials: adolescents, combination therapy

Abrocitinib (12 weeks)

JADE – TEEN

[redacted]

Upadacitinib (16 weeks)

AD UP

[redacted]

(Adolescent subgroup included in AD UP)

Meta-analysis results: adolescents

Pair wise meta-analysis (combination therapy)

- Treatment effect comparison versus placebo with TCS, OR (95% CI)

	Abrocitinib 200mg +TCS	Abrocitinib 100mg + TCS	Upadacitinib 15mg +TCS
EASI 75	[redacted]	[redacted]	[redacted]

- Both upadacitinib and abrocitinib with TCS are statistically significantly more effective than placebo with TCS.

Model dashboard - adolescents

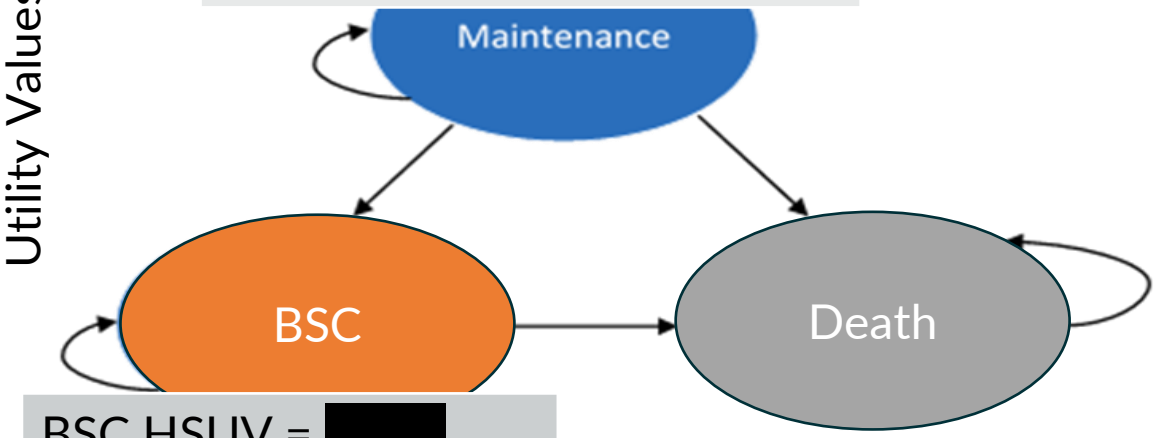
Response

	Response at week 16 (from NMA)	Response at week 52	Long-term annual discontinuation
Abrocitinib - 100 mg	[redacted]	[redacted]	[redacted]
Abrocitinib - 200 mg	[redacted]	[redacted]	[redacted]
Dupilumab	58.5%	55.5%	5.1%
Upadacitinib - 15 mg	[redacted]	[redacted]	[redacted]

Utility Values

JAK-inhibitor HSUV = [redacted]

IL-13 inhibitor HSUV = [redacted]



BSC HSUV = [redacted]

Markov trace (1 year +)

[redacted]

Key issue 2: limited data availability for adolescents

Population	Monotherapy		Combination therapy	
	EASI 50 +DLQI ≥4	EASI 75	EASI 50 +DLQI ≥4	EASI 75
Adolescents	✗	✓	✗	✗

- Data on primary outcome (EASI 50 +DLQI) and combination therapy were not available.
- EAG considered that the adolescent population monotherapy analyses may potentially underestimate the relative effectiveness of the treatments.
- NMA is based on small sample size across multiple trials
- Discontinuation rate is also based on very low numbers of patients at week 52 - Pooled data from Measure UP 1 (n/N = 6/32) and Measure UP 2 (n/N = 2/22).

Are cost effectiveness results generalisable to adolescents treated in NHS clinical practice?

Adult population: first-line treatment

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EASI50 + DLQI ≥4
EASI75

Key clinical trial results
adults, first line treatment, combination therapy

Upadacitinib (16-week)

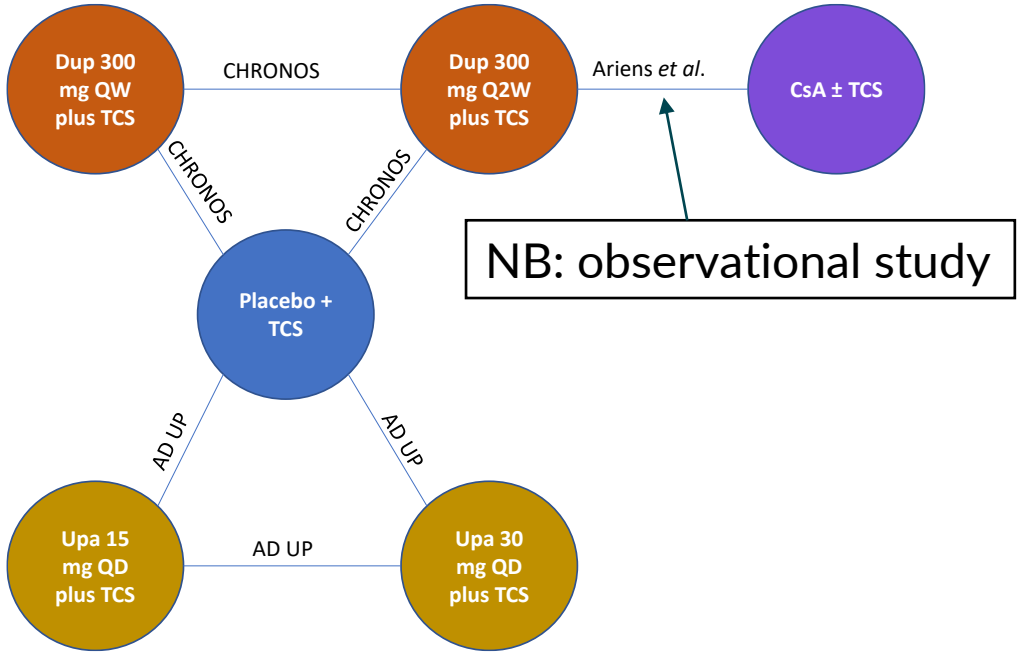
Abrocitinib (12 and 16-week)

JADE – COMPARE

JADE – DARE

NMA results – EASI 75 only

adults, first-line treatment



Analysis	Pairwise meta-analysis OR (95% CI)	NMA OR (95% CrI)
Treatments versus placebo		
Upa 30 mg QD + TCS	[redacted]	[redacted]
Upa 15 mg QD + TCS	[redacted]	[redacted]
Dupilumab 300 mg Q2W + TCS	5.82 (3.56 to 9.52)	[redacted]
Dupilumab 300 mg QW + TCS	5.07 (3.62 to 7.11)	[redacted]
CsA + TCS	NA	[redacted]
Treatments versus CsA		
Upa 30 mg QD + TCS	NA	[redacted]
Upa 15 mg QD + TCS	NA	[redacted]

Model dashboard – adults first-line

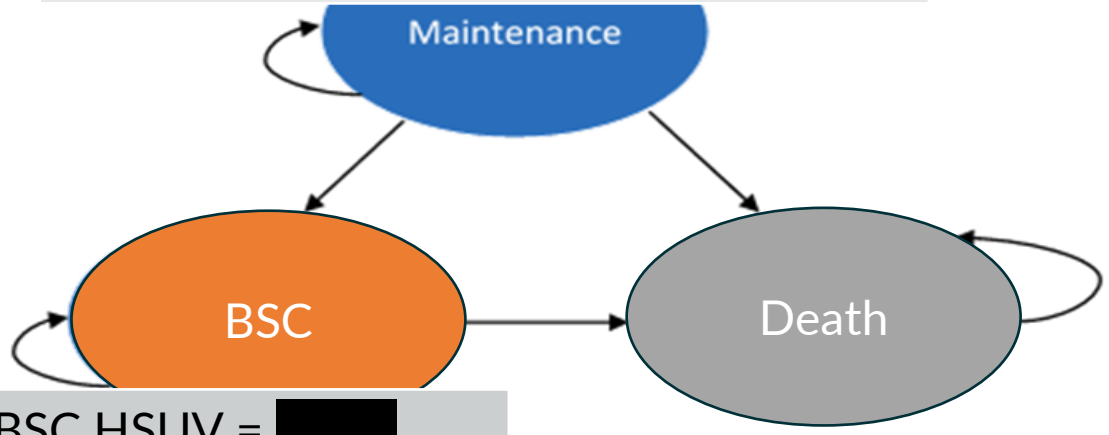
Response

	Response at week 16 (from NMA)	Response at week 52	Long-term annual discontinuation
Ciclosporin A	[redacted]	[redacted]	[redacted]
Upadacitinib 15mg	[redacted]	[redacted]	[redacted]
Upadacitinib 30mg	[redacted]	[redacted]	[redacted]

Utility Values

Low-dose JAK-inhibitor HSUV = [redacted]

High-dose JAK-inhibitor HSUV = [redacted]



BSC HSUV = [redacted]

Markov trace (1 year +)

[redacted]

Key issue 3: Comparison with ciclosporin A

EAG comments

- For first-line systemic treatments, there is limited data for creating a comparison. The only licensed treatment is ciclosporin A (CsA) – although some clinicians now favour methotrexate in the first line setting
- Results for the comparison of upadacitinib and CsA for the first-line treatment are derived from observational data (Ariens et al.)
- Ariens *et al*. provides the results of a regression analysis of patient level data for patients treated with dupilumab in the placebo controlled RCT CHRONOS and patients treated with CsA in daily practice at the Department of Dermatology and Allergology, University Medical Center (UMC) Utrecht, the Netherlands.
- No baseline risk adjustment sensitivity analysis was conducted.

Is the comparison with ciclosporin A appropriate?

Key issue 4: Treatment sequencing in clinical practice

- Company proposed upadacitinib as first-line treatment in the care pathway.

- Pfizer originally positioned abrocitinib as a second-line systemic treatment, in comparison to baricitinib and dupilumab. After consultation, consider that efficacy profiles for abrocitinib are comparable to upadacitinib which is also positioned for first-line systemic treatment – therefore expect QALY gain to be comparable.

- In the assessment, populations were defined by treatment sequence as:
  adult first-line systemic treatment population: adults who are eligible for systemic treatment (ciclosporin [CsA]) on inadequate response to topical treatments.
  adult second-line systemic treatment population: adults who achieve inadequate response to, cannot tolerate, or are contraindicated to CsA.

- EAG noted that a lack of clinical data on the effectiveness of sequences of AD treatments, especially changing drug class

How would sequencing of treatments be considered in clinical practice?

Adult population: second-line treatment

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EASI50 + DLQI ≥4
EASI75

Key trial results
adults, second-line treatment, combination therapy

Upadacitinib (16-week)
AD UP

[redacted]

Abrocitinib (12 and 16-week)
JADE - COMPARE

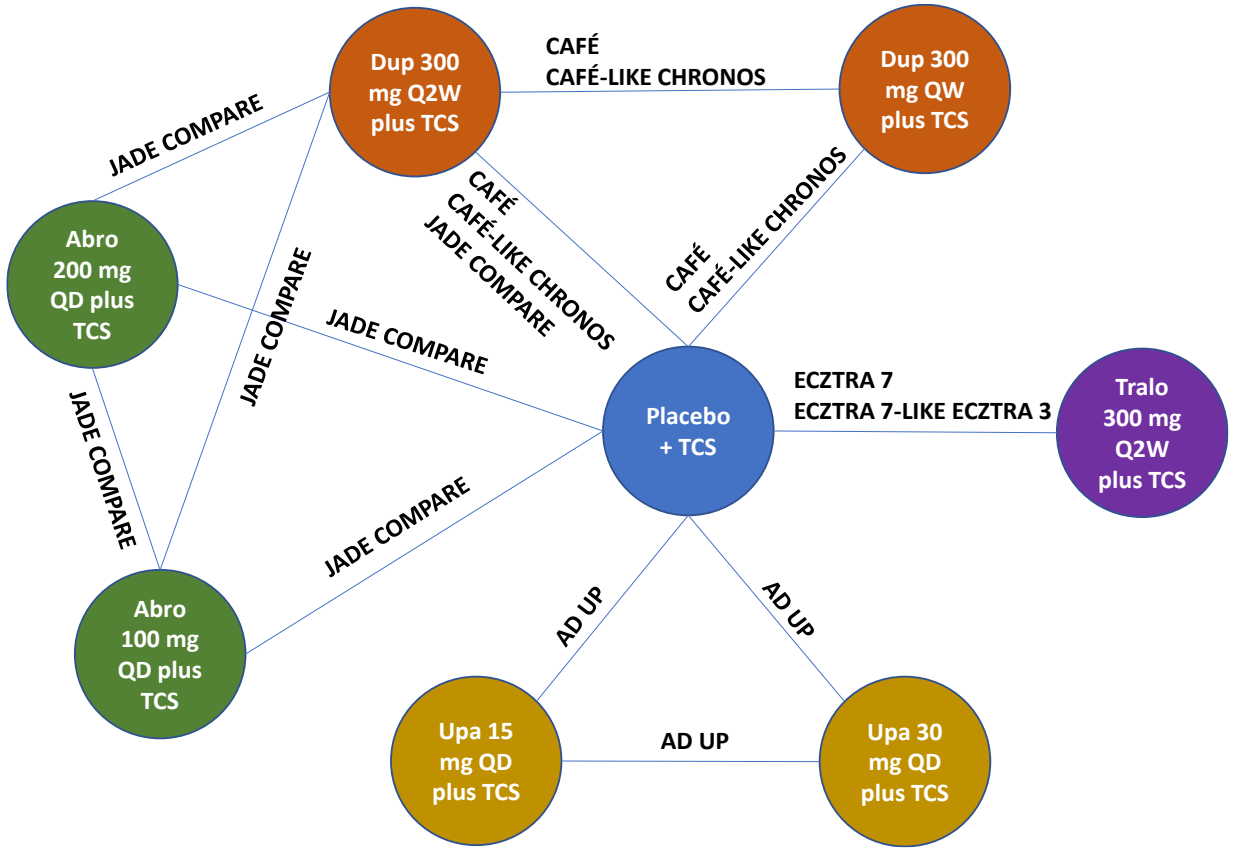
[redacted]

Tralokinumab (16-week)
ECZTRA 3 ECZTRA 7

[redacted]

NMA results – EASI 50 + DLQI>4, combination

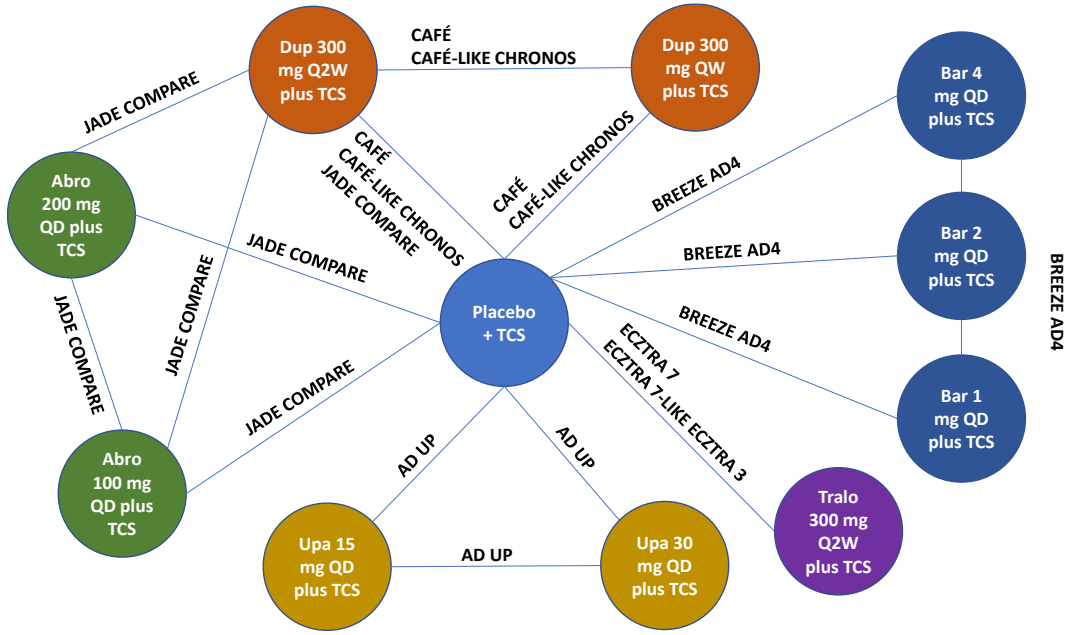
adults second-line treatment



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

NMA results – EASI 75, combination

adults second-line treatment – allows comparison with baricitinib



Comparison	Pair-wise meta-analysis OR (95% CI)	NMA OR (95% CrI)
Treatments versus placebo		
Abro 200 mg QD + TCS	[redacted]	[redacted]
Abro 100 mg QD + TCS	[redacted]	[redacted]
Bar 4 mg + TCS	2.22 (1.11 to 4.44)	[redacted]
Tralokinumab + TCS	[redacted]	[redacted]
Upa 30 mg QD + TCS	[redacted]	[redacted]
Upa 15 mg QD + TCS	[redacted]	[redacted]
Treatments versus Bar 4 mg plus TCS		
Abro 200 mg QD + TCS	NA	[redacted]
Abro 100 mg QD + TCS	NA	[redacted]
Tralokinumab + TCS	NA	[redacted]
Upa 30 mg QD + TCS	NA	[redacted]
Upa 15 mg QD + TCS	NA	[redacted]

Model dashboard – adults second-line

Response

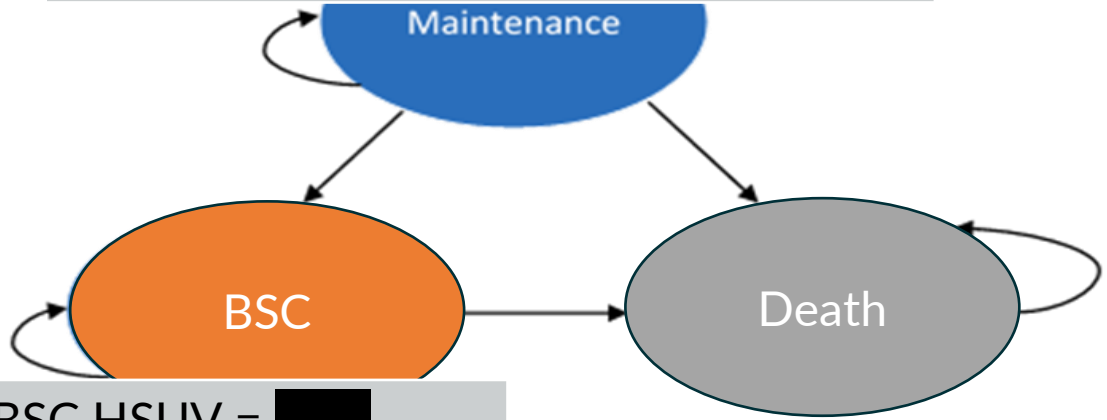
	Response at week 16 (from NMA)	Response at week 52	Long-term annual discontinuation
Dupilumab	[redacted]	[redacted]	[redacted]
Upadacitinib 15mg	[redacted]	[redacted]	[redacted]
Upadacitinib 30mg	[redacted]	[redacted]	[redacted]
Abrocitinib 100mg	[redacted]	[redacted]	[redacted]
Abrocitinib 200mg	[redacted]	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]	[redacted]

Utility Values

Low-dose JAK-inhibitor HSUV = [redacted]

High-dose JAK-inhibitor HSUV = [redacted]

Monoclonal antibody HSUV = [redacted]



BSC HSUV = [redacted]

Markov trace (1 year +)

[redacted]

Model dashboard – adults second-line (EASI 75) - baricitinib

Response

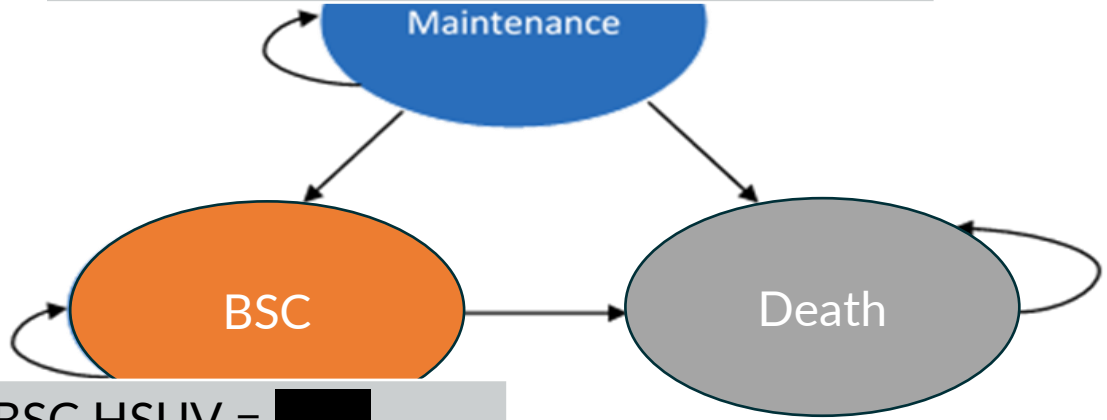
	Response at week 16 (from NMA)	Response at week 52	Long-term annual discontinuation
Baricitinib	[redacted]	[redacted]	[redacted]
Upadacitinib 15mg	[redacted]	[redacted]	[redacted]
Upadacitinib 30mg	[redacted]	[redacted]	[redacted]
Abrocitinib 100mg	[redacted]	[redacted]	[redacted]
Abrocitinib 200mg	[redacted]	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]	[redacted]

Utility Values

Low-dose JAK-inhibitor HSUV = [redacted]

High-dose JAK-inhibitor HSUV = [redacted]

Monoclonal antibody HSUV = [redacted]



BSC HSUV = [redacted]

Markov trace (1 year +)

[redacted]

Key issue 5: BSC effect waning

TA681: *No committee preferred assumption – between company and ERG scenarios*

- *Company scenarios moved some patients permanently into a 'non-response' state, assuming that some patients lose response to best supportive care and return to baseline over time due to decreased treatment adherence after the trial completed.*
- *Data suggested fluctuation between good and bad disease control – ERG considered the approach was flawed because it separated utilities from costs within the model*

EAG

- Did not assume any waning of BSC utility – just weighted utility of responders and non-responders at Week 16
- BSC response probabilities used to weight costs and utilities included in sensitivity analysis

Company

- In all of company models, treatment waning for BSC was applied through loss of utility gain associated with response (return to baseline utility).
- All BSC patients lose response by year 5.

Should BSC effect waning be included the models?

Key issue 6: Response and discontinuation as model drivers

- BSC was not modelled as a treatment option – but is modelled as a health state in the longer term Markov model composed of responders and non-responders in proportions informed by week 16 response data.
- Any modelled non-responders/modelled to discontinue treatment enter into the BSC health state – if this health state was modelled for the full time horizon, this would be cost-effective against dupilumab
- Creates a key model driver to minimise time in response state – staying in response health state (maintenance) reduces cost-effectiveness

Total QALY gain is relatively high compared to other treatments

Does this represent a counterintuitive model driver?
What scenarios are appropriate for dealing with counterintuitive model drivers?

Key issue 7: Uncertainty and heterogeneity

EAG comments - uncertainty:

- Bias and uncertainty from **use of post-hoc subgroups** – very wide confidence intervals due to small sample size and breaks randomisation of RCT
- However, all populations informing the comparison in the second line setting are **clinically homogenous** in terms of people having inadequate response to, not being able to tolerate, or being contraindicated to CsA.
- Methodological heterogeneity contributes to uncertainty:
  - variation across studies in the use of a washout period for TCS before randomisation
  - type and potency of concomitant TCS used
  - type and potency of rescue medication used
- Variation in placebo response – sensitivity analysis **adjusting for differences in placebo response was not possible** for the key comparisons assessing the interventions in combination with TCS. For the comparisons where it was possible the model may be "overfitting" the data and it is likely to be less generalisable to the population of interest than the unadjusted analysis using observed data – therefore unadjusted analyses were used in the economic model

Innovation

- **Pfizer:** Abrocitinib is an oral**, Janus kinase 1 (JAK1)-selective inhibitor** that inhibits several key cytokine signalling pathways known to have an important role in the pathophysiologic characteristics of atopic dermatitis (AD). Unlike baricitinib targets JAK1 and JAK2, abrocitinib selectively blocks JAK1 and is less potent against other JAK isoforms.
- **Abbvie**: Upadacitinib is an oral **selective and reversible JAK inhibitor**. It inhibits the kinase component of JAKs, thereby preventing phosphorylation and slowing intracellular signalling, thus minimising inflammation and itch.
- **Leo Pharma:** Tralokinumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody which specifically binds with **high affinity to circulating IL-13**, a key primary cytokine that causes the signs and symptoms of moderate-to-severe AD.

Equality considerations

- **Skin colour** –
  - Tools for **assessing the severity** of atopic dermatitis and the response to treatment may not be sensitive enough in people with some skin colours.
  - British Association of Dermatologists: **Treatment efficacy may also differ** in people with different skin colours - different ethnic groups have different cytokine pathways in atopic dermatitis, so dupilumab may be more effective in some groups. Th2 cytokines interleukin (IL)-4 and IL-13 predominant in most populations but some Asian populations IL-17 are most predominant.

Cost-effectiveness results

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

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Thank you.