NICE National Institute for Health and Care Excellence

Slides for public - redacted

Baricitinib for treating moderate to severe atopic dermatitis [ID1622]

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Company: Eli Lilly

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Key issues

- **Population / Comparators:** Are patients who have not yet had systemic immunosuppressants a relevant population for baricitinib? Are systemic immunosuppressants a relevant comparator?
  - Should the baricitinib trial data from all patients or EU-only patients be used, given differences in baseline severity and clinical practice for Japanese patients?
- **Response definition:** EASI 50 + Δ DLQI ≥ 4, or EASI 75?
  - **Utilities:** If EASI 50 + Δ DLQI ≥ 4 is preferred, should the utilities from the baricitinib trials be used, or those from TA534 (dupilumab)?
- **Sequencing:** How should sequences of baricitinib and dupilumab (and vice versa) be considered in decision making?
- **BSC modelling:** Which approach to modelling best supportive care best reflects clinical practice?
- **Baricitinib / dupilumab week 16-52 discontinuation rates:** Should these be based on conditional response rates, or all-cause discontinuation?
- **QoL waning:** Should an assumption be applied that some patients lose QoL gain on baricitinib and/or dupilumab over time (applied in TA534 for dupilumab)?

DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index

Atopic dermatitis

- Atopic dermatitis, also called atopic eczema, a chronic inflammatory skin condition that mainly affects children, though is also common in adults
- Characterised by skin that is red and inflamed (erythema), thickened and leathery (lichenification) and dry (xerosis) with scaly plaques, bleeding, oozing, cracking and flaking
- Itching is the most disruptive symptom
- Increased risk of skin infections, which may become systemic
- Typically an episodic disease where patients experience flares and remissions.
  - People with moderate to severe atopic dermatitis experience ~10 flares per year, each lasting over 15 days
- Disease severity is not consistently classified, different tools used in clinical practice (EASI, IGA, SCORAD or BSA)
- ~56,187 adults in England have moderate to severe atopic dermatitis (company estimate)

BSA = Body surface area; IGA = Investigator's Global Assessment; SCORAD = SCORing Atopic Dermatitis

Measuring clinical effectiveness (1/2)

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			
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)

Itch / Skin pain numeric rating scale (NRS): 0 (“none”) to 10 (“worst imaginable”)		
≥4 to <7	7 to <9	≥9
Moderate	Severe	Very severe

Atopic Dermatitis Sleep Scale (ADSS): 0 to 29 (assesses impact of itch on sleep). 3 items:		
1) difficulty falling asleep	2) frequency of waking	3) difficulty getting back to sleep

Patient Oriented Eczema Measure (POEM): 0 to 28
7 questions scored from 0 (no days) to 4 (every day) on the presence of itch, sleep disturbance, bleeding, weeping/oozing, cracked, flaking and dry/rough skin

Different perspectives on clinically important differences:

- In TA534 (dupilumab), the committee concluded that 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)
- HOME initiative recommends (for trials): EASI to assess signs (for example, skin lesions); POEM and Itch NRS to assess symptoms; DLQI to assess QoL

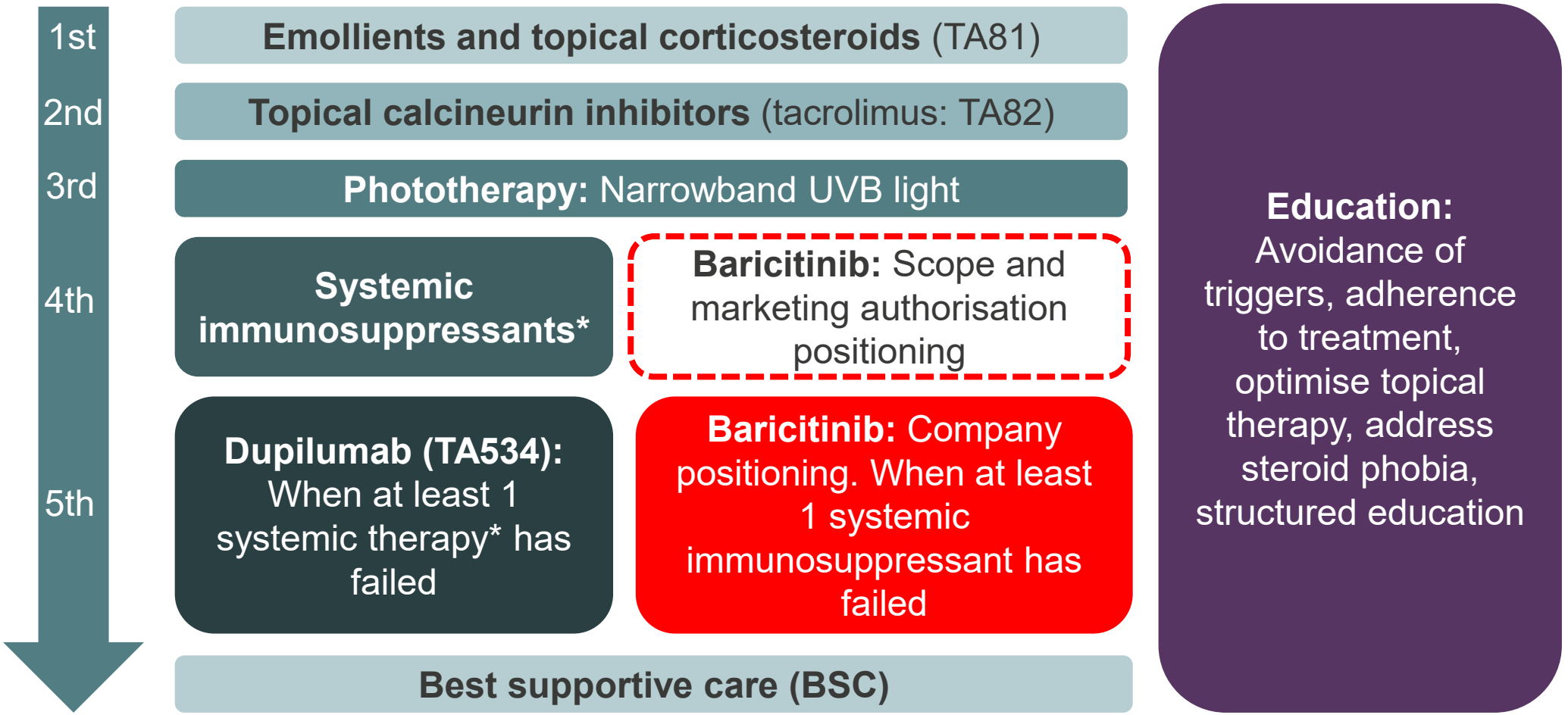
HOME = Harmonising Outcome Measures for Eczema;
POEM = Patient Oriented Eczema Measure

Baricitinib (Olumiant, Eli Lilly)

Marketing authorisation	• Treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy
Company proposed population	• Adults with moderate to severe atopic dermatitis who have failed ≥ 1 systemic immunosuppressant due to intolerance, contraindication or inadequate disease control
Mechanism of action	• Janus-associated kinase (JAK) 1 and 2 inhibitor
Administration	• 4mg once-daily oral. An optional 2mg down-titration dose is appropriate for some patients (those 75 years or older, or with a history of chronic / recurrent infections) • The company considers that baricitinib will be used in combination with topical corticosteroids (TCS) in clinical practice
Price	• £805.56 (list price) for a 28-tablet pack of 2mg / 4mg baricitinib. Average annual cost of £10,508.24 for a treatment course • A simple patient access scheme (PAS) discount is in place for baricitinib. A revised PAS discount will take effect following a positive recommendation in atopic dermatitis

Baricitinib positioning in treatment pathway

Atopic dermatitis treatment pathway



Q. Where is baricitinib likely to be used in clinical practice?

* E.g. ciclosporin, methotrexate, azathioprine, mycophenolate mofetil

Decision problem (1/2)

	NICE scope	Company submission / ERG comments
Population	Adults with moderate to severe atopic dermatitis that had inadequate response or intolerance to existing topical treatments	**Company:** Adults with moderate to severe atopic dermatitis who have failed ≥ 1 systemic immunosuppressant **ERG:** submission population restrictive; baricitinib likely to be used at same point as immunosuppressants. Trial population skewed to severe disease
Subgroups	• Skin colour subgroups • Moderate and severe disease • Ciclosporin-naïve and previously treated	**Company:** Subgroup data not available, or not considered plausible / relevant **ERG:** Evidence suggests different outcomes based on skin type, although likely driven by baseline severity and clinical practice differences • Presenting disease severity subgroups would have been plausible and beneficial
Intervention	Baricitinib with and without topical corticosteroids (TCS)	**Company:** • Baricitinib with (base case) and without TCS • Baricitinib with TCS represents typical AD management; used as company base case **ERG / technical team:** in line with NICE scope. In TA534, committee focused on dupilumab with TCS

TCS = Topical corticosteroids

Decision problem (2/2)

	NICE scope	Company submission / ERG comments
Comparators	• Phototherapy including UVB radiation or PUVA • Systemic immunosuppressive therapies • Alitretinoin (in people with atopic dermatitis affecting the hands) • Dupilumab • Best supportive care (including emollients, topical corticosteroids, phototherapy, psychological support and rescue therapy)	**Company:** • Dupilumab and best supportive care included as comparators • Phototherapy and systemic immunosuppressants omitted as comparators as baricitinib positioned after them • Alitretinoin omitted as a comparator as indicated for hand eczema **ERG:** systemic immunosuppressants are relevant comparators
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	**Company:** • Measures of disease severity and symptom control (IGA, EASI, Itch / Skin pain NRS) • Maintenance of response available from JAIN • Adverse effects of treatment **ERG:** Satisfied with outcomes

NRS = Numeric rating scale; PUVA = Psoralen and ultraviolet A; UVB = Ultraviolet B

Patient and professional group comments

Impact on quality of life

- Itchiness is one of the most challenging aspects of atopic dermatitis, and can be intense and unbearable. Social life and ability to work are impacted, with psychological and emotional impact on carers

Need for treatment choices

- People with moderate to severe atopic dermatitis need more treatment choice:
  - Topical steroids are time-consuming to apply and have long-term side effects (skin thinning). Reducing their use is a key aim for patients
  - Systemic immunosuppressants have significant long-term side effects and substantial monitoring requirements
  - Not all patients respond to dupilumab, some develop conjunctivitis and others are fearful of injections
- Baricitinib has a different mode of action and safety profile to current treatments
  - Valuable treatment option for people with poor symptom control
  - Symptom improvement with baricitinib is quicker than dupilumab

Tech report issue 1: Positioning

Baricitinib restricted to after immunosuppressants

Company

- Baricitinib positioned where there is a high unmet need: failed ≥ 1 systemic immunosuppressant (IS): only option is dupilumab / BSC
- Same population as BREEZE-AD4 (JAIN), and NICE TA534 (dupilumab)
- Dupilumab does not achieve disease control in all patients and has tolerability issues, including injection site reactions and eye disorders

ERG

- Clinical advice: baricitinib acts similarly to other systemic IS. Would be given after topicals as an alternative to systemic IS
- Unmet need for alternative options at this point in the treatment pathway

Clinical experts

- Company's proposed positioning generally appropriate. Consistent with dupilumab
- Baricitinib may also be used as a more targeted alternative to IS. Physicians would welcome this positioning

Tech report issue 2: Comparators

Company omitted immunosuppressants as a comparator

Company

- Baricitinib positioned in patients whose only remaining treatment options are dupilumab or BSC. These are therefore the only relevant comparators
- The population in the company's decision problem is the same as TA534 (dupilumab). In TA534, BSC was accepted as the only comparator
- Baricitinib (like dupilumab) is used long-term. IS are short-term
- Company unable to do a valid ITC with ciclosporin due to a lack of data. An ITC presented in TA534 versus ciclosporin was not considered robust by the ERG

ERG

- Agrees that the company's ITC with ciclosporin should not be used to inform decision making. Acknowledges limited evidence available to compare baricitinib with IS
- Clinical expert – most patients have ≥2 IS before dupilumab. Systemic IS are a relevant comparator in patients for whom ≥ 1 systemic IS has failed

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Q. Are systemic IS a relevant comparator for baricitinib?

Tech report issue 2: Comparators

Second immunosuppressant often used in practice

Clinical experts

- At TE clinical experts were asked what proportion of people would be offered the treatments below in NHS practice, following failure on first-line IS. The company also sought the opinion of a UK consultant dermatologist
- Results indicate that a second systemic IS is often used, with methotrexate used more commonly than ciclosporin

Subsequent treatment	First-line ciclosporin			First-line methotrexate			First-line azathioprine		
	Expert 1	Expert 2	Company	Expert 1	Expert 2	Company	Expert 1	Expert 2	Company
Dupilumab	10%	60%	[redacted]	10%	75%	[redacted]	10%	50%	[redacted]
Azathioprine	20%	5%	[redacted]	20%	5%	[redacted]	0%	0%	[redacted]
Methotrexate	60%	35%	[redacted]	0%	0%	[redacted]	40%	30%	[redacted]
Mycophenolate mofetil	0%	0%	[redacted]	0%	0%	[redacted]	0%	0%	[redacted]
Ciclosporin	0%	0%	[redacted]	60%	20%	[redacted]	40%	15%	[redacted]
BSC	10%	0%	[redacted]	10%	0%	[redacted]	10%	0%	[redacted]
Other	0%	0%	[redacted]	0%	0%	[redacted]	0%	0%	[redacted]

Tech report issue 6: Sequencing

Baricitinib / dupilumab likely to be used sequentially

Company

- Baricitinib not intended to be used in a treatment sequence with dupilumab in UK clinical practice. Baricitinib positioned as a treatment option alongside dupilumab
- No data available on impact of prior baricitinib use on dupilumab efficacy as a follow-on treatment (or vice versa)

ERG

- Clinicians want to use dupilumab and baricitinib sequentially
- Considering baricitinib as a mutually exclusive alternative implies that its recommendation would prohibit dupilumab usage (undesirable)

Clinical experts

- Uncertainty as to likely treatment pathway. Dupilumab appears to have better efficacy than baricitinib – as such, likely to be prioritised. However, baricitinib may be used first in certain situations, e.g. flares, certain co-morbidities, needle phobia
- The efficacy of baricitinib or dupilumab as a follow-on is unlikely to be affected by the prior use of the other drug, as they have different mechanisms of action

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Q. Should baricitinib be appraised as part of a treatment sequence with dupilumab?

Clinical effectiveness

Overview of baricitinib trial programme

Trial:	BREEZE-AD4 (JAIN)	BREEZE-AD7 (JAIY)	BREEZE-AD1 (JAHL)	BREEZE-AD2 (JAHM)
Inadequate response/ intolerance to:	Topical therapy **and** ciclosporin	Topical **or** systemic therapy	Topical **or** systemic therapy	Topical **or** systemic therapy
Interventions	Baricitinib + TCS vs. Placebo + TCS	Baricitinib + TCS vs. Placebo + TCS	Baricitinib vs. Placebo	Baricitinib vs. Placebo

BREEZE-AD3 (JAHN)
52-week extension study

Subgroup with inadequate response/intolerance to topical therapy **and** ciclosporin*

Subgroup with inadequate response/intolerance to topical therapy **and** ciclosporin*

Subgroup with inadequate response/intolerance to topical therapy **and** ciclosporin*

* 'JAIN-like' patients

Pooled

Pooled

Combo therapy: Scenario analysis

Combo therapy: Base case

Monotherapy: Scenario analysis

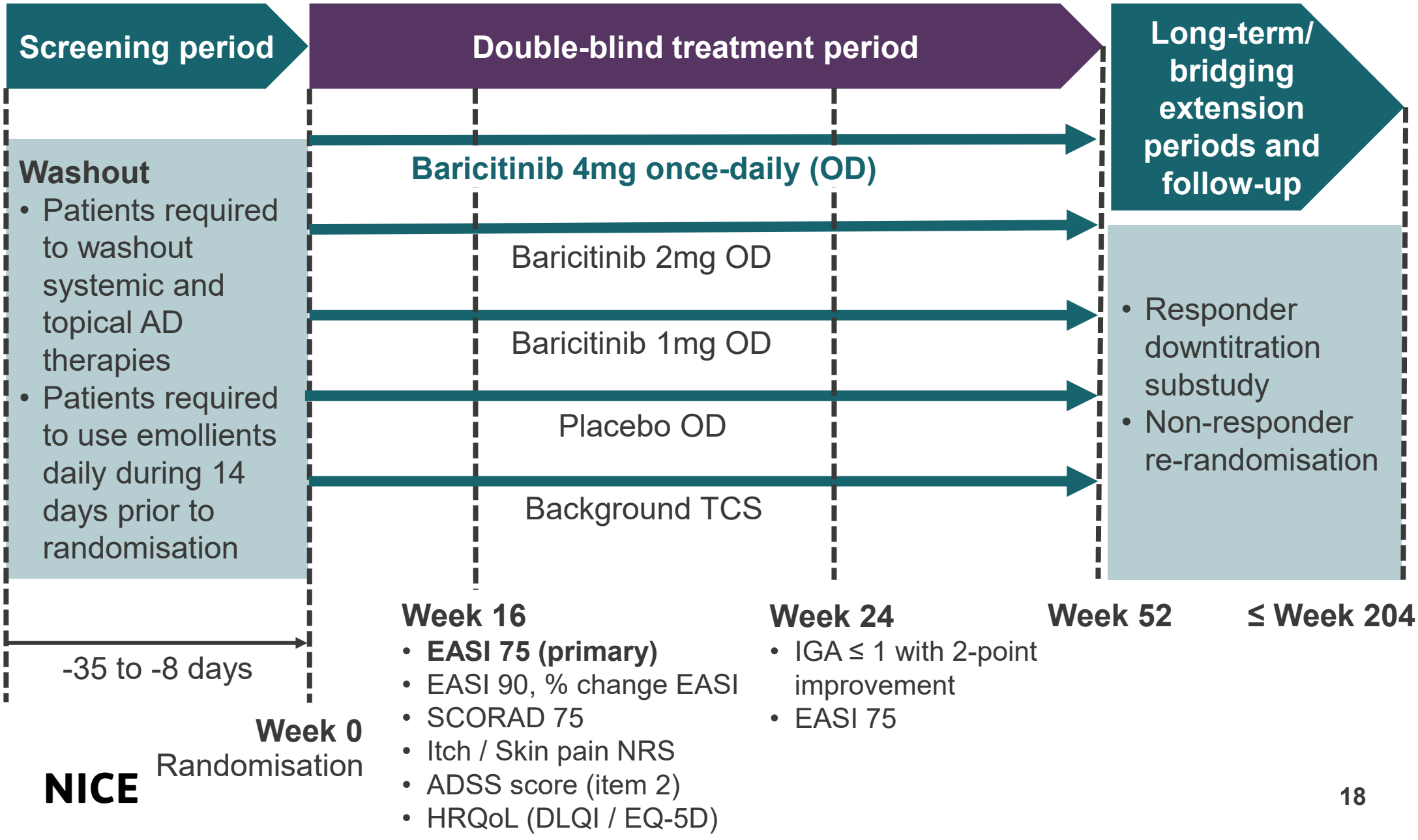
Red box indicates trials informing baricitinib clinical effectiveness in model. Reflects company positioning of baricitinib in combination with TCS

Key clinical trials

BREEZE-AD4 (JAIN) Double-blind, randomised, placebo-controlled trial	BREEZE-AD7 (JAIY) Double-blind, randomised, placebo-controlled trial
Interventions (52-week treatment period) • Baricitinib (4mg)*: n=92 • Placebo: n=93	**Interventions** (16-week treatment period) • Baricitinib (4mg)*: n=[redacted] • Placebo: n=[redacted]
Key inclusion criteria • Age ≥ 18 years • Moderate to severe AD: EASI ≥ 16, IGA ≥ 3, BSA ≥ 10% • Inadequate response to topical medication • Contraindication / intolerance / inadequate response to ciclosporin	**Key inclusion criteria** • Age ≥ 18 years • Moderate to severe AD: EASI ≥ 16, IGA ≥ 3, BSA ≥ 10% • Inadequate response to topical medication
Primary outcome: EASI 75 at week 16	**Primary outcome:** IGA ≤ 1 at week 16
Locations: 14 countries across Europe, Asia and South America. N=[redacted] UK patients	**Locations:** 10 countries across Europe, Asia, South America and Australia. No UK patients

* Other baricitinib doses (2mg, 1mg) not relevant, as SmPC dose is 4mg

BREEZE-AD4 (JAIN) study design



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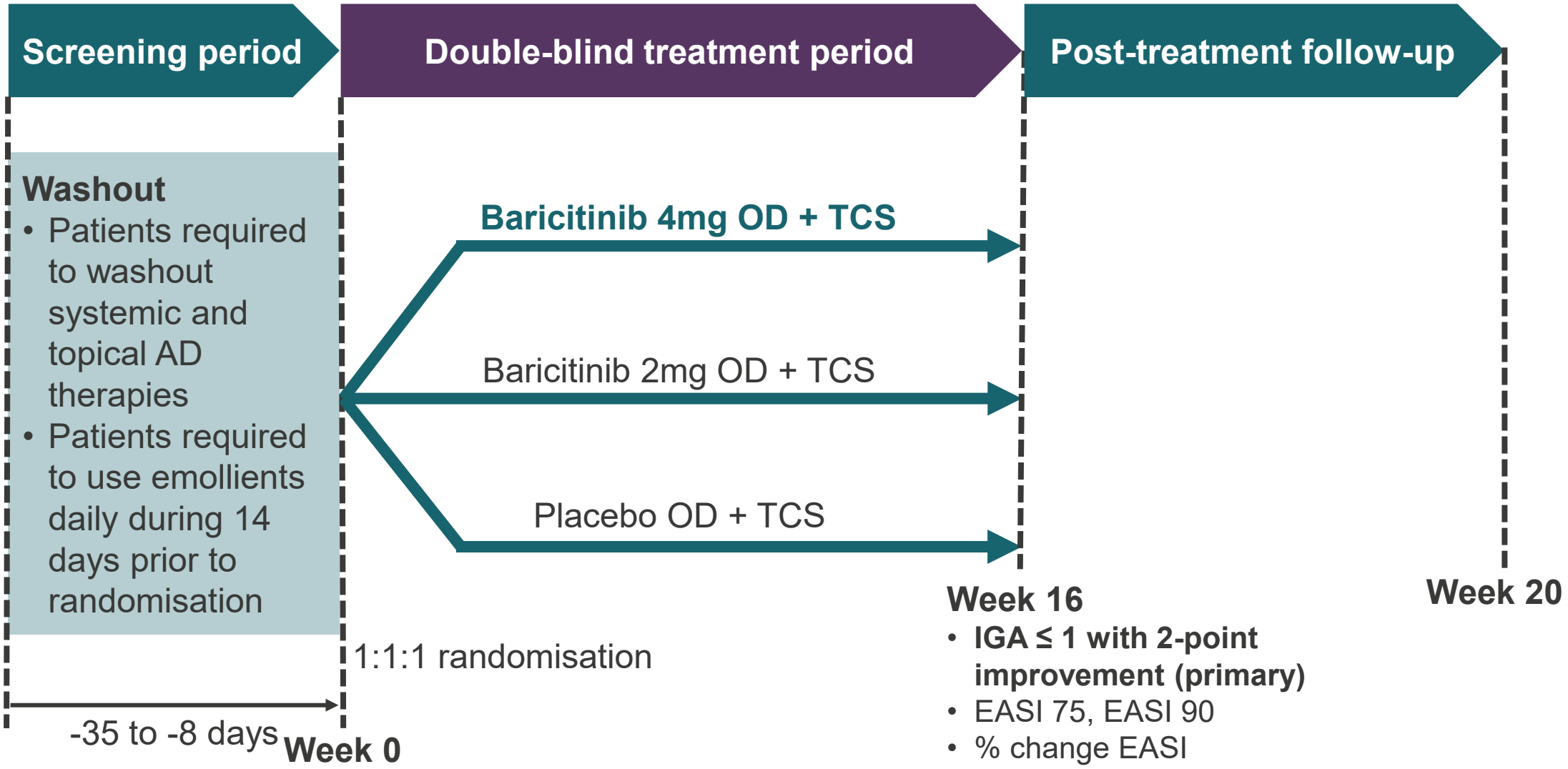
BREEZE-AD7 (JAIY) study design



'JAIN-like' (ciclosporin-failed) subgroup from JAIY used in the economic model

OD = Once daily

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Baseline characteristics

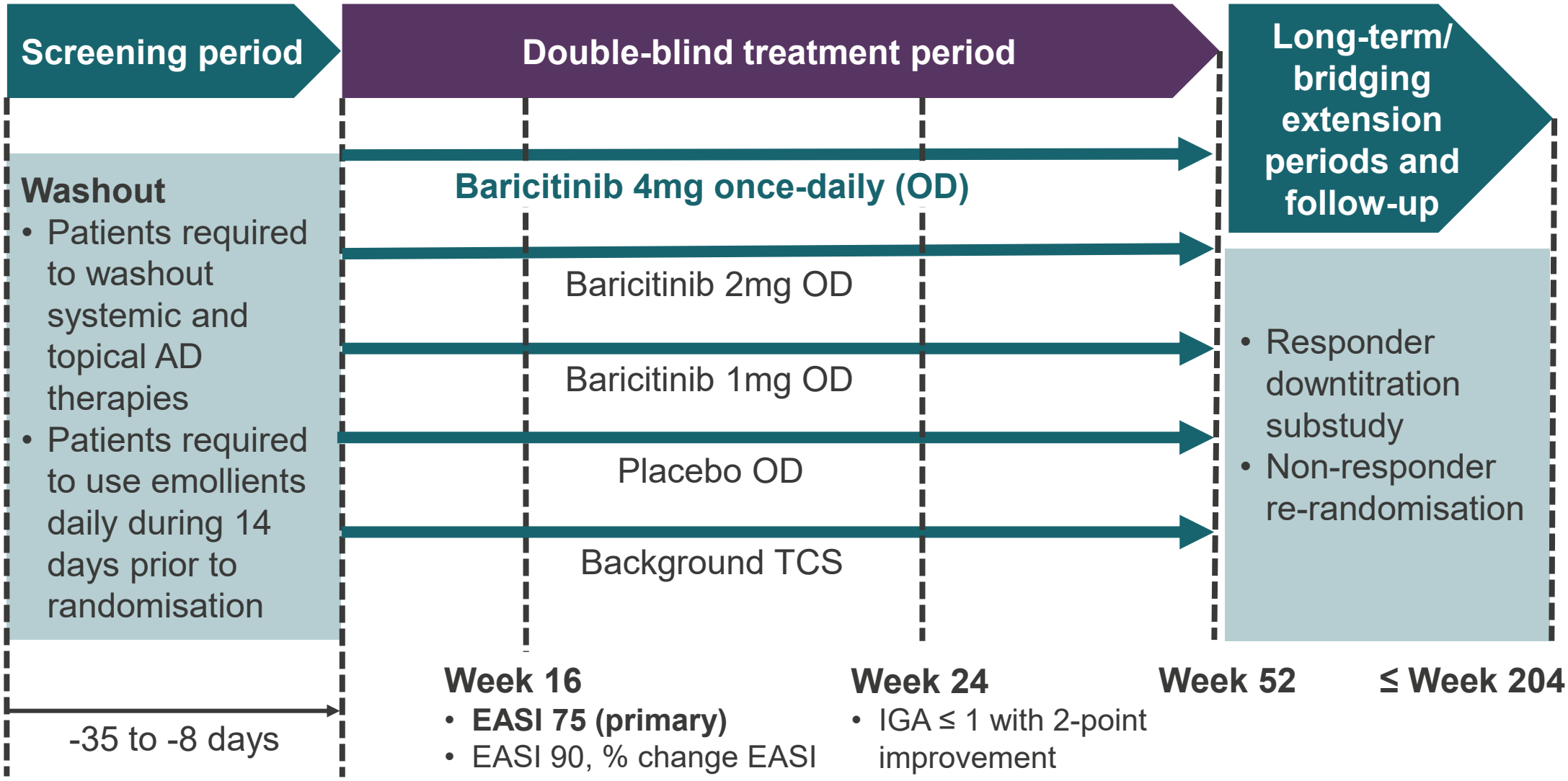
Informs base case economic analysis

Characteristic	BREEZE-AD4 (JAIN)		BREEZE-AD7 (JAIY)		JAIN+JAIY JAIN-like	
	PBO (n=93)	BARI 4mg (n=92)	PBO (n=[redacted])	BARI 4mg (n=[redacted])	PBO (n=[redacted])	BARI 4mg (n=[redacted])
Age (years), mean (SD)	39 (14)	39 (13)	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	47	38	[redacted]	[redacted]	[redacted]	[redacted]
Caucasian, %	80	77	[redacted]	[redacted]	[redacted]	[redacted]
Asian, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other, %	[redacted]	[redacted]	[redacted]	*	*	*
BMI (kg/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A
IGA of 4 at screening, %	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A
EASI, mean (SD)	31 (11.6)	33 (13.7)	[redacted]	[redacted]	[redacted]	[redacted]
POEM, mean (SD)	21 (5.7)	21 (6.0)	[redacted]	[redacted]	[redacted]	[redacted]
DLQI, mean (SD)	14.5 (6.9)	14.0 (8.1)	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L VAS score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A

Q. Are these populations representative of who would have baricitinib?

BMI = Body mass index; PBO = Placebo; POEM = Patient Oriented Eczema Measure; SD = Standard deviation; VAS = Visual analogue scale

BREEZE-AD4 (JAIN) study design



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JAIN key results: EASI 75 and IGA ≤ 1

Significant improvements at week 16 for EASI 75

Primary endpoint: EASI 75 (week 16)*

	PBO (n=93)	BARI 4mg (n=92)
Week 16 response**	[redacted]	[redacted]
P-value vs PBO	[redacted]	[redacted]
Week 24 response	[redacted]	[redacted]
P-value vs PBO	[redacted]	[redacted]

Secondary endpoint: IGA ≤ 1

	PBO (n=93)	BARI 4mg (n=92)
Week 16 response	[redacted]	[redacted]
P-value vs PBO	[redacted]	[redacted]
Week 24 response	[redacted]	[redacted]
P-value vs PBO	[redacted]	[redacted]

* Graphs: primary censoring (missing/non-responder discontinuation, TCS/systemic rescue tx)

** Tables: secondary censoring (missing/non-responder discontinuation, systemic rescue tx)

JAIN key results: Itch and Skin pain NRS

Secondary endpoint: Δ Itch numeric rating scale (NRS) ≥ 4

	PBO (n=85)	BARI 4mg (n=78)
Week 16 response	8.2%	38.2%
P-value vs PBO		
Week 24 response		
P-value vs PBO		

Secondary endpoint: Skin pain NRS

	PBO (n=93)	BARI 4mg (n=92)
Week 16 CFB	-1.56	-3.02
P-value vs PBO		
Week 24 CFB		
P-value vs PBO		

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Only patients with a ≥ 4 Itch NRS at baseline; CFB = Change from baseline
Primary censoring (missing/non-responder discontinuation, TCS/systemic rescue tx)

JAIN results: Health-related quality of life

DLQI: Mean change from baseline

≥ 4-point DLQI improvement

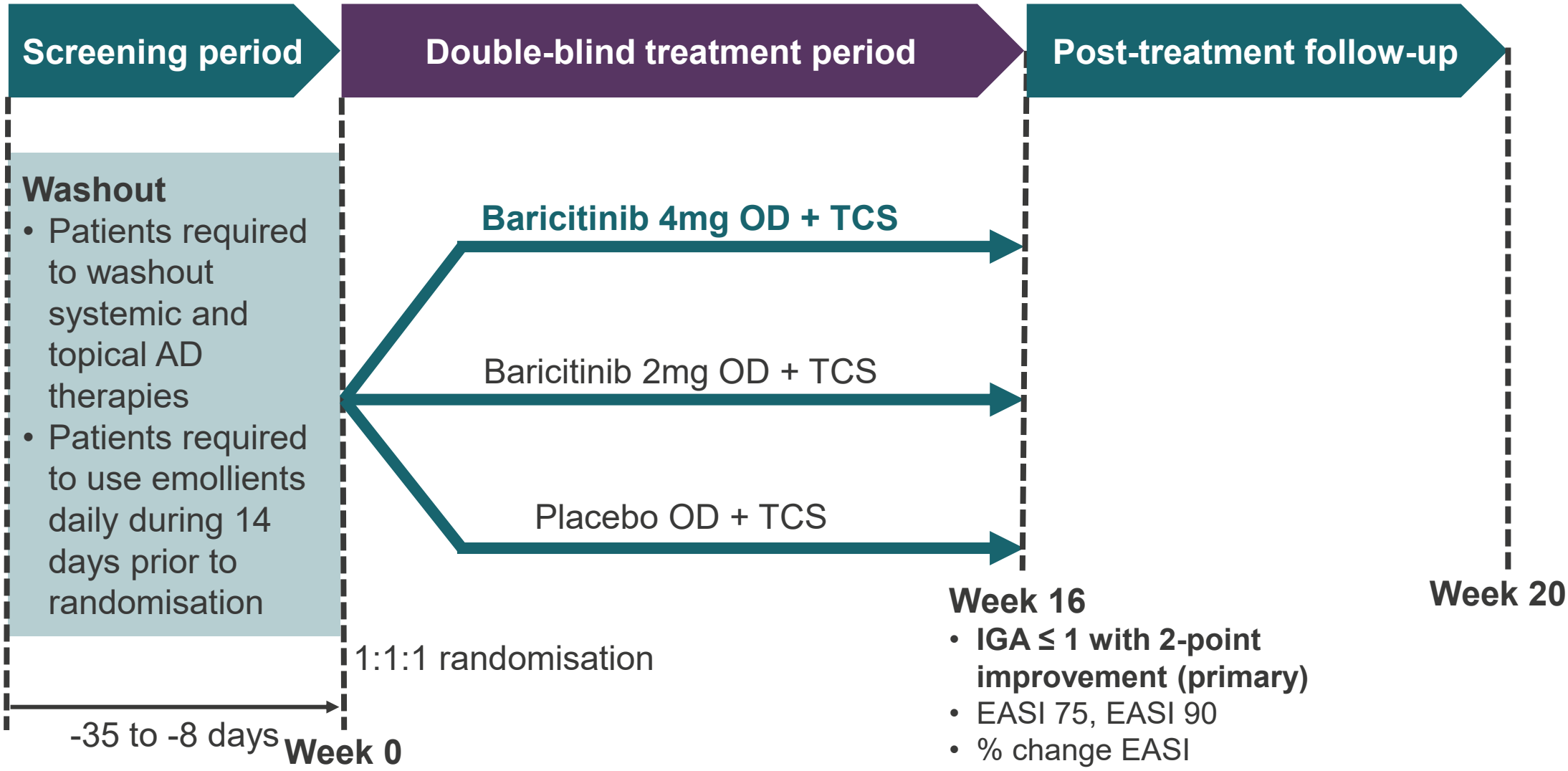
EQ-5D-5L results at week 16

EQ-5D-5L	VAS score		Health Index Score	
	PBO (n=93)	BARI 4mg (n=92)	PBO (n=93)	BARI 4mg (n=92)
Mean change from baseline, LSM	[redacted]	[redacted]	[redacted]	[redacted]
P-value vs. placebo	[redacted]	[redacted]	[redacted]	[redacted]

LSM = Least squares mean; VAS = Visual analogue scale

Primary censoring (missing/non-responder discontinuation, TCS/systemic rescue tx)

BREEZE-AD7 (JAIY) study design



'JAIN-like' (ciclosporin-failed) subgroup from JAIY used in the economic model

OD = Once daily

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JAIY key results: IGA ≤ 1 and EASI 75

Intent-to-treat population (not all failed ciclosporin)

Primary endpoint: IGA ≤ 1 at week 16*

Week

	PBO (n=[redacted])	BARI 4mg (n=[redacted])
Week 16 response**	[redacted]	[redacted]
P-value vs PBO	[redacted]	[redacted]

Secondary endpoint: EASI 75

Week

	PBO (n=[redacted])	BARI 4mg (n=[redacted])
Week 16 response	[redacted]	[redacted]
P-value vs PBO	[redacted]	[redacted]

% of patients

* Graphs: primary censoring (missing/non-responder discontinuation, TCS/systemic rescue tx)

** Tables: secondary censoring (missing/non-responder discontinuation, systemic rescue tx)

JAIY key results: Itch and Skin pain NRS

Intent-to-treat population (not all failed ciclosporin)

Secondary endpoint: Δ Itch numeric rating scale (NRS) ≥ 4

	PBO (n=[redacted])	BARI 4mg (n=[redacted])
Week 16 response	[redacted]	[redacted]
P-value vs PBO	[redacted]	[redacted]

Secondary endpoint: Skin pain NRS

	PBO (n=[redacted])	BARI 4mg (n=[redacted])
Week 16 CFB	[redacted]	[redacted]
P-value vs PBO	[redacted]	[redacted]

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Primary censoring (missing/non-responder discontinuation, TCS/systemic rescue tx)

Tech report issue 11: Japanese patients

Region is a treatment effect modifier

Trial	Regions	Relative risk vs. placebo (EASI 75)	P-value
BREEZE-AD4 (JAIN)	Europe (n=[redacted])	[redacted]	[redacted]
	Japan (n=[redacted])	[redacted]	
	ROW (n=[redacted])	[redacted]	
BREEZE-AD7 (JAIY)	Europe (n=[redacted])	[redacted]	[redacted]
	Japan (n=[redacted])	[redacted]	
	ROW (n=[redacted])	[redacted]	
Pooled JAIN + JAIN-like JAIY	Europe (n=[redacted])	[redacted]	[redacted]
	Japan (n=[redacted])	[redacted]	
	ROW (n=[redacted])	[redacted]	

- **ERG:** differences in efficacy in Japanese patients likely to be driven by differences in baseline disease severity and clinical practice rather than ethnicity
- Company did a scenario analysis in its original submission using the EU population of JAIN vs CAFÉ (dupilumab) based on EASI 75 response. Incremental ICERs were less favourable for baricitinib in the EU population scenario

Tech report issue 11: Japanese patients

Technical engagement responses

Company

- Patients in the baricitinib trials are representative of UK clinical practice.
- Trials not designed to assess efficacy specifically in Japanese patients. Japanese subpopulation was small (~[redacted]% of pooled JAIN/JAIY JAIN-like pooled population)
- Baseline severity and rates of rescue therapy higher in Japanese patients (clinical practices differences) and do not suggest a specific effect of Japanese ethnicity on baricitinib effectiveness
- A scenario analysis in the EU population has minimal ICER impact

ERG

- EU scenario analysis may be more clinically relevant. **However**, company did not update the assumptions other than response rates, and the sample size is smaller
- Used the data from all patients, due to lack of data for EU-only scenario

Clinical experts

- Eczema and immunology may be different in Asian patients, which could make them harder to treat. Clinical practice (e.g. access to new drugs) also differs

Q. Should the data from Japanese patients in the baricitinib trials be included?

Adverse events

Nasopharyngitis most common baricitinib AE

- Company's safety analysis used 2 datasets: 1) JAIN trial (n=93 PBO and n=92 4mg BARI); 2) Integrated safety analysis dataset* (n=[redacted] PBO and n=[redacted] 4mg BARI)

Treatment-emergent adverse events (TEAEs) affecting >3% of patients, n (%)

	JAIN		Integrated analysis	
	Placebo	4mg BARI	Placebo	4mg BARI
Patients with ≥1 TEAE	50 (53.8)	69 (75.0)	[redacted]	[redacted]
Nasopharyngitis	12 (12.9)	24 (26.1)	[redacted]	[redacted]
Headache	6 (6.5)	7 (7.6)	[redacted]	[redacted]
Influenza	2 (2.2)	6 (6.5)	-	-
Abdominal pain, upper	2 (2.2)	5 (5.4)	-	-
Diarrhoea	3 (3.2)	5 (5.4)	-	-
Oral herpes	3 (3.2)	5 (5.4)	-	-
Oedema, peripheral	0 (0.0)	4 (4.3)	-	-
Abdominal pain	3 (3.2)	3 (3.3)	-	-
Back pain	3 (3.2)	3 (3.3)	-	-
Asthma	[redacted]	[redacted]	-	-
Dry eye	[redacted]	[redacted]	-	-
Fatigue	[redacted]	[redacted]	-	-
Blood creatinine phosphokinase increased	-	-	[redacted]	[redacted]
Upper respiratory tract infection	-	-	[redacted]	[redacted]

* Comprising data from BREEZE-AD1, -AD2 and -AD7 (JAIY) trials

Indirect treatment comparison vs dupilumab

Necessary as no H2H data versus dupilumab

- No H2H studies available comparing baricitinib with dupilumab. Company conducted ITC using the Bucher method, using the pooled populations for its base case

Baricitinib trials	Dupilumab trials	Indirect comparison (week 16)	
		EASI 75*	EASI 50 + Δ DLQI ≥ 4
JAIN	LIBERTY AD CAFÉ	Odds ratio [redacted] ([redacted]), p=[redacted] **in favour of dupilumab**	Odds ratio [redacted] ([redacted]), p=[redacted] **in favour of dupilumab** (secondary censoring)
JAIY ('JAIN-like' subgroup)	LIBERTY AD CHRONOS (CAFÉ-like subgroup)		

ERG: heterogeneity between baricitinib and dupilumab trials in 1) baseline severity (higher in dupilumab trials), 2) proportion of Asian patients (higher in baricitinib trials, shown to be effect modifier)

- Trial design differences (washout period, censoring) likely to favour dupilumab
- Agrees that some trial heterogeneity is an expected ITC limitation. Although this heterogeneity does not significantly reduce the validity of the ITC, it should be considered when interpreting the results

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* Updated after technical engagement; ITC = Indirect treatment comparison

Tech report issue 12: ITC heterogeneity

Differences in trial populations/designs evident

Trial population baseline characteristics		JAIN + JAIY JAIN-like		CAFÉ + CHRONOS CAFÉ-like	
		Placebo	4mg BARI	Placebo	300mg DUPI
Race	White	[redacted]	[redacted]	89.9	93.1
	Asian	[redacted]	[redacted]	1.8	0.8
	Other	[redacted]	[redacted]	7.1	5.4
Baseline scores, mean (SD)	EASI	[redacted]	[redacted]	34.8 (12)	33.6 (10.5)
	SCORAD	[redacted]	[redacted]	68.7 (12.8)	69.3 (12.9)
	IGA	[redacted]	[redacted]	3.5 (0.5)	3.5 (0.5)
	DLQI	[redacted]	[redacted]	14.8 (7.7)	14.6 (7.5)
	BSA affected	[redacted]	[redacted]	58.9 (21.7)	57.3 (18.5)
	POEM	[redacted]	[redacted]	19.9 (6)	19.8 (6.1)
	HADS	[redacted]	[redacted]	13.2 (8.1)	12.8 (7.9)

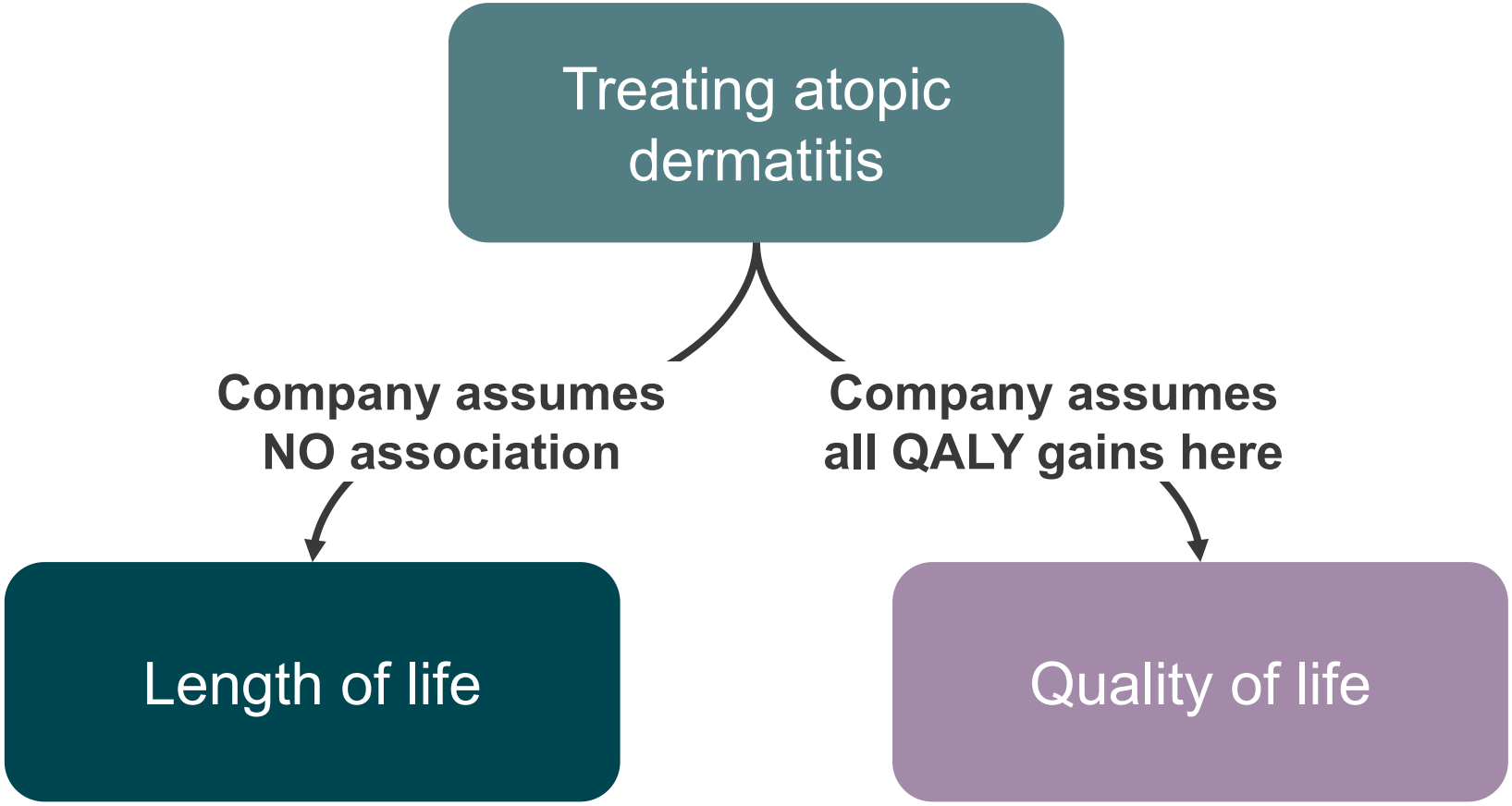
- Other differences between trials may favour dupilumab:
  - **TCS washout:** Patients in baricitinib trials had a 2-week washout for topical treatments prior to randomisation. In the dupilumab trials, patients could apply medium / low-potency TCS during 2 weeks prior to randomisation
  - **Censoring:** baricitinib patients censored as non-responders after having rescue medication. In the dupilumab trials, all observed data was used

NICE

Q. Are the baricitinib and dupilumab trial populations and designs sufficiently comparable for a robust ITC?

Cost effectiveness

Where do the QALY gains come from?

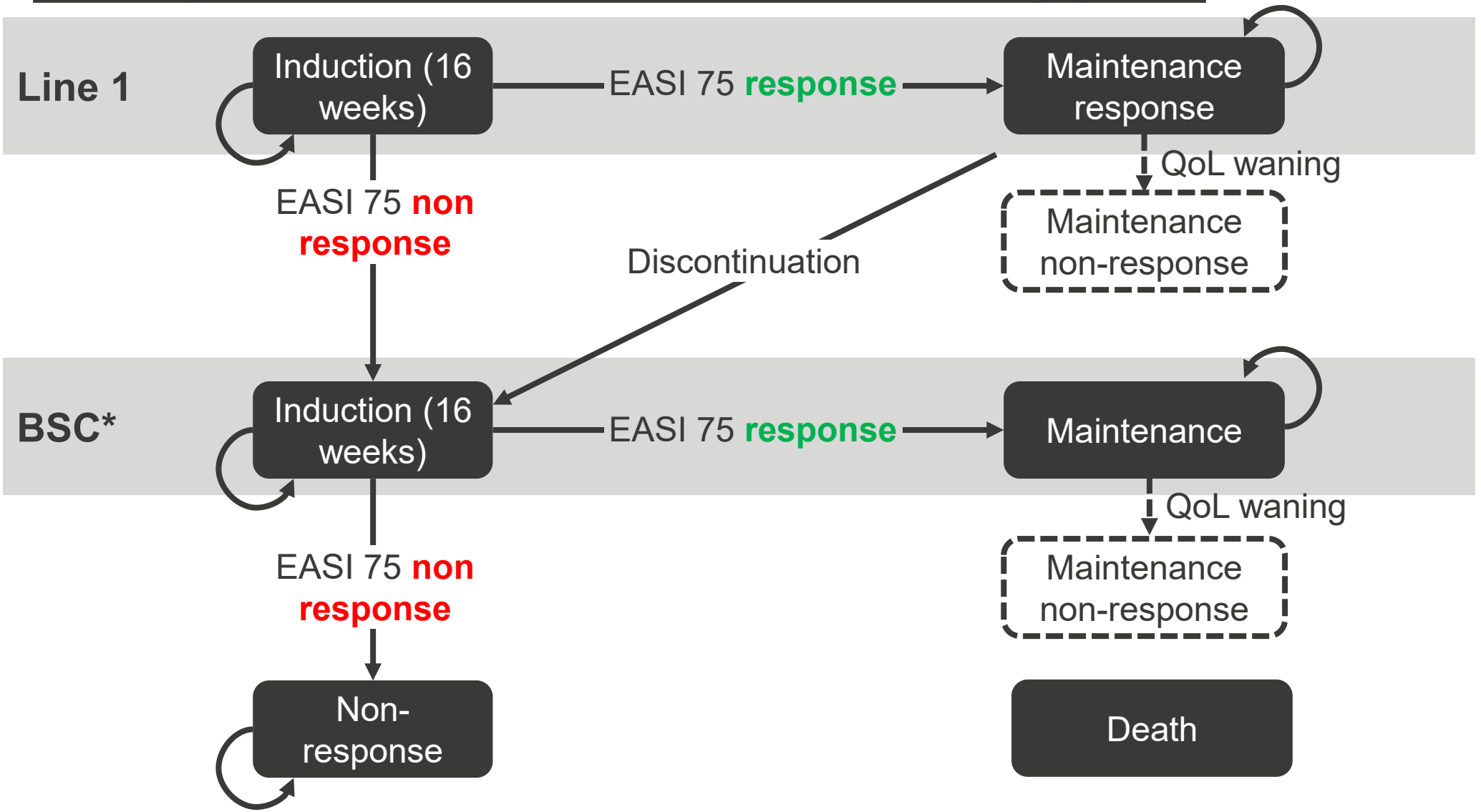


Increase in QALYs comes only from improvement in quality of life in the maintenance response health state, rather than increasing length of life

QALY = Quality-adjusted life year

Overview of model structure

Company base-case model structure after technical engagement



NICE

* For sequencing scenarios another line is included prior to BSC. Baseline induction utility: 0.6182; Non-response utility: 0.7627; Response utility: 0.8492

Comparison of baricitinib model vs TA534

Company positioning same as dupilumab

	Dupilumab (TA534)	Baricitinib company base case*
Structure	1-year decision tree, followed by 3-state Markov model: 1) Maintenance; 2) BSC; 3) Death	4-state Markov model: 1) Induction (16 weeks), 2) Maintenance; 3) Non-response; 4) Death. Each line of therapy has induction and maintenance states
Response outcome	EASI 50 + Δ DLQI ≥ 4	EASI 75
Cycle length	1 year, with half-cycle correction	4 weeks, no half-cycle correction
Time horizon	Lifetime	Lifetime (62 years)
Utilities	Baseline: 0.66; Dupilumab induction: 0.891; Dupilumab responders: 0.898; BSC all patients: 0.797	Baseline: 0.6182; Non-response: 0.7627; Response: 0.8492
Response rates at week 16	**Dupilumab:** 73.1%; **BSC:** 27.8%	**Baricitinib:** 42.28%; **Dupilumab:** 57.16%; **BSC:** 22.22%
Discontinuation and QoL waning	**Dupilumab:** 6.1% discontinue weeks 16-52; 3.7% annually year 2+. QoL waning applied **BSC:** 57%-97% return to baseline utility over 5 years**	**Baricitinib:** [redacted] discontinue weeks 16-52; [redacted] annually year 2+ **Dupilumab:** 17.9% discontinue weeks 16-52; 5.1% annually year 2+. TA534 QoL waning for baricitinib and dupilumab **BSC:** TA534 QoL waning applied

* After technical engagement; ** Committee-preferred sensitivity analyses

Tech report issue 5: Assessment timepoint

Uncertainty whether 12 or 16 weeks

Company

- Model assumes response is assessed at 16 weeks, same as dupilumab
- Original draft SmPC stated 'consideration should be given to discontinuing treatment in patients who have shown no response after 12 weeks of treatment' but this has been updated if there is…
- '…no evidence of therapeutic benefit after 8 weeks'

ERG

- BREEZE-AD4 (JAIN) results show a response before week 12 across many outcomes, including EASI 75 and DLQI
- ERG satisfied that 16-week timepoint is reasonable. It aligns with dupilumab and was the primary endpoint timepoint in the baricitinib trials. However, new SmPC wording does not prevent an earlier assessment
- No scenario modelled; however 12-week assessment likely to favour baricitinib

Clinical experts

- Better to be consistent between drugs. 16 weeks aligns better with dupilumab, 12 weeks with other systemics

Q. Does an assessment at 16 weeks reflect clinical practice?

Tech report issue 4: Response definition

EASI 75 correlates with QoL, but inconsistent with TA534

Company – EASI 75 used to define response in its revised base case

- Composite outcome responders in original submission did not have QoL gain based on baricitinib trial data. Company changed to EASI 75 response after engagement
- EASI 75 was primary / key secondary endpoint in the baricitinib trials. Correlates better with QoL improvement based on the trial data
- Move towards EASI 75 to assess treatment response (more relevant for determining response)

Clinical experts / stakeholders

- **Experts:** EASI 50 represents significant improvement / EASI 75 being aspirational. Patients achieving EASI 50 + ΔDLQI ≥ 4 likely to have improved QoL
  - DLQI best QoL measure, recommended by HOME (although doesn't include itch)

ERG

- EASI 75 inconsistent with TA534 (may not be acceptable in clinical practice)
- ERG prefers to retain EASI 50 + ΔDLQI ≥ 4, but presents scenario with EASI 75

NICE

Q. Which definition of response should be used?

HOME = Harmonising Outcomes in Eczema Initiative

Tech report issue 10: Utilities (1/2)

ERG prefers TA534 utilities when composite endpoint is used

Company

- Company used 2 utilities in original submission, from the JAIN / JAIY trials: 0.7800 for responders, 0.5979 for non-responders (for EASI 50 + Δ DLQI ≥ 4 endpoint)
- Company updated these after technical engagement for EASI 75, incorporating baseline, response and non-response utilities to allow for QoL waning

ERG

- Original utilities flawed as company applied utility change for responders, but ignored higher utility change for non-responders
- Using one health state for all responding patients fails to capture magnitude of response
- ERG favours TA534 utilities when EASI 50 + Δ DLQI ≥ 4 is used
- Generally satisfied with the company's updated EASI 75 utilities. However, as ERG favours EASI 50 + Δ DLQI ≥ 4, these cannot be used in its base case
- Acknowledge Sanofi's criticisms of using TA534 utilities (next slide). However, on balance ERG does not consider it unreasonable to use these values

Tech report issue 10: Utilities (2/2)

Sanofi – using TA534 utilities may not be appropriate

Sanofi (dupilumab)

- Using TA534 utilities does not take into account adverse event differences between dupilumab and baricitinib

Overview of proposed utility values

Patient group in model	EASI 50 + Δ DLQI ≥ 4			EASI 75
	Company (from baricitinib trials)	**ERG** (from TA534)		**Company and ERG** (from baricitinib trials)
		Baricitinib / dupilumab	Best supportive care	
Baseline	0.5979	0.66	0.66	0.6182
Non-response		0.797	0.797	0.7627
Response	0.7800	0.898	0.797	0.8492

NICE

Q. Which utility values are most appropriate when EASI 50 + Δ DLQI ≥ 4 is used to define response?

Tech report issue 7b: BSC modelling

Uncertainty as to most appropriate approach

Company

- Originally applied an annual discontinuation of 57% from year 2+ for BSC (TA534)
- At TE, company asked to explore scenario with TA534 QoL waning assumptions. Company removed discontinuation and used TA534 waning in updated base case
- Only appropriate to remove BSC discontinuation with waning assumptions applied, due to lower BSC efficacy outside of trial

ERG

- Original model structure did not reflect waxing / waning nature of AD
- CHRONOS trial (dupilumab) placebo data shows that % of BSC patients achieving EASI 50 / 75 to week 52 remained somewhat constant. ERG base case has no BSC discontinuation; costs / utilities weighted average of responders and non-responders
- Suggesting that trial placebo data is unrepresentative of clinical practice while suggesting that intervention arm data is representative is a highly selective approach
- Waning assumptions are methodologically flawed, separating costs from utilities

Experts: BSC patients rarely maintain QoL gain outside of the trial: treatment fatigue

Tech report issue 7b: BSC modelling

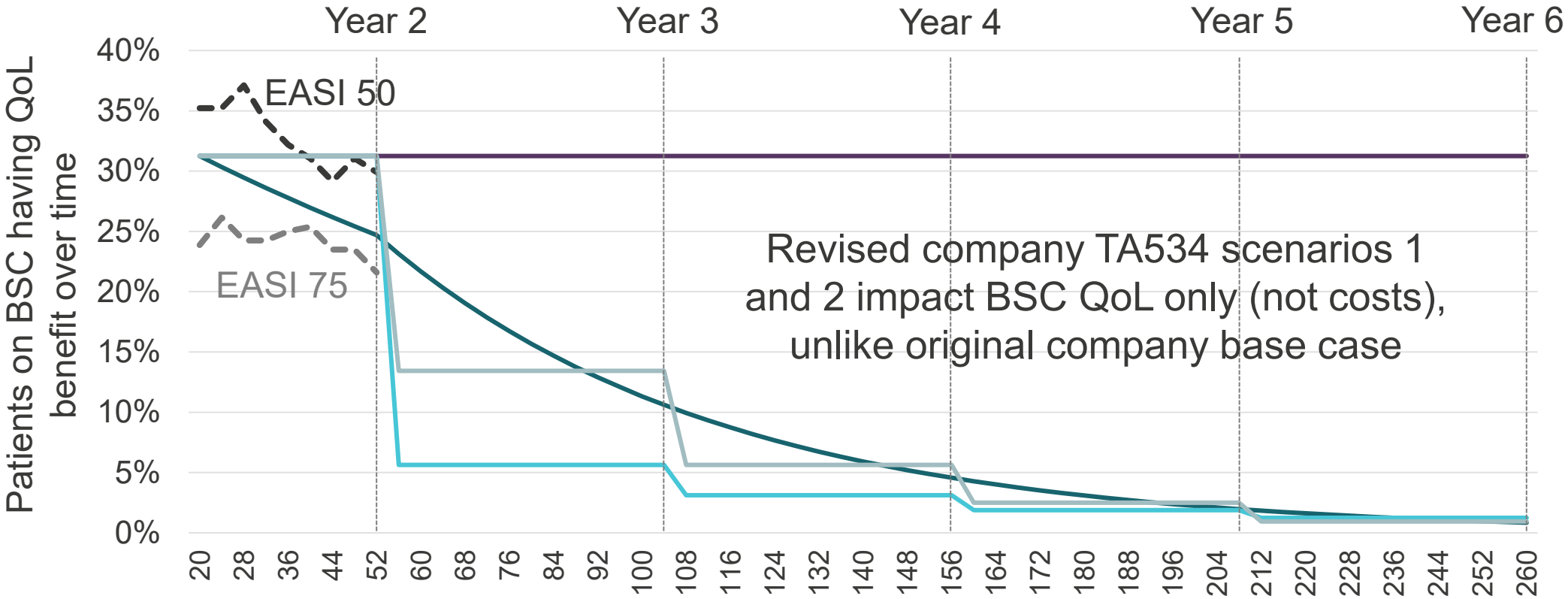
Committee conclusions from TA534

Technical team

- In TA534, company stated that the sustained BSC efficacy was due to trial supervision improving adherence (stop after study ends)
- Committee agreed that the placebo response was high, and that the benefit of BSC is likely lost fairly rapidly, but how rapidly was uncertain
- Committee considered that linking clinical benefit and costs for BSC likely over-estimated its long-term costs, as over time everyone having BSC would be a non-responder and incur higher resource use and costs

Tech report issue 7b: BSC modelling

Overview of modelling approaches



CHRONOS Source: Blauvelt et al. (2017)

EASI 50 response: placebo arm CHRONOS

EASI 75 response: placebo arm CHRONOS

Original company base case

ERG base case

Revised company TA534 SA 1

Revised company TA534 SA 2

SA = Sensitivity analysis

Tech report issues 7b and 9: TA534 waning

Most plausible analyses in TA534	% of patients losing QoL benefit			
	Year 2	Year 3	Year 4	Year 5+
Dupilumab: From trial investigator feedback, supported by 100-week open-label extension study	2%	5%	7%	8%
BSC Sensitivity Analysis 1: From Weibull curve fitted to CHRONOS KM data for time to first rescue treatment / study withdrawal (BSC arm)	82%	90%	94%	96%
BSC Sensitivity Analysis 2: From annual rate of CHRONOS time to first rescue therapy / study withdrawal (BSC arm)	57%	82%	92%	97%

Company: After TE company applied TA534 dupilumab waning for both baricitinib and dupilumab

ERG: Similar criticisms of the QoL waning approach as for patients having BSC

Clinical experts: QoL waning assumptions applied for dupilumab in TA534 not seen in clinical practice. There may be less QoL waning for baricitinib vs. dupilumab as it is not a monoclonal antibody (for which secondary failure may be anticipated)

KM = Kaplan-Meier

Tech report issues 7b / 9: TA534 waning (2/2)

Total QALY loss of ~[redacted] years for BSC

Intervention	Total QALYs			QALY loss from ERG base case	
	No waning (ERG base case after TE)	**TA534 SA1**	**TA534 SA2**	**TA534 SA1**	**TA534 SA2**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib → BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab → BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Q. Which approach to BSC modelling best reflects clinical practice? Should a QoL waning effect for baricitinib and/or dupilumab be applied?

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SA = Sensitivity analysis

Tech report issue 8: Discontinuation rates (1/2)

ERG prefers all-cause discontinuation for week 16-52

Company

- Originally used TA534 dupilumab rates (6.1% week 16-52; 3.7% annually year 2+) for baricitinib
- **After technical engagement:** updated discontinuation rates based on 52-week JAIN data
- Considers conditional probability of response more appropriate up to week 52 than all-cause discontinuation rates, in line with TA534

Clinical experts and ERG

- Inappropriate to assume equivalent discontinuation rates with dupilumab
- All-cause discontinuation rates more appropriate for week 16-52 than conditional response. Loss of efficacy is not only discontinuation factor. However, conditional response rates for week 16-52 discontinuation were accepted in TA534
- **ERG:** Using single discontinuation rate for week 16-52 and week 52+ makes the evaluation of treatment sequences more straightforward

Tech report issue 8: Discontinuation rates (2/2)

Summary of discontinuation rates

	Discontinuation weeks 16-52			Discontinuation week 52+		
	Base case* (EASI 50 + ΔDLQI ≥ 4)	After engagement		Base case* (EASI 50 + ΔDLQI ≥ 4)	After engagement	
		EASI 75	EASI 50 + ΔDLQI ≥ 4		EASI 75	EASI 50 + ΔDLQI ≥ 4
Baricitinib (C)	6.1%	[redacted]	[redacted]	3.7%	[redacted]	[redacted]
Baricitinib (E)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab (C)	6.1%	17.9%	6.1%	3.7%	5.1%	3.7%
Dupilumab (E)	2.6%	3.6%	2.6%	3.7%	5.1%	3.7%

* Before technical engagement
C = Company; E = ERG

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Q. Which discontinuation rates are most appropriate? Should all-cause discontinuation or conditional response data be used for weeks 16-52?

Summary of key differences between company and ERG base cases

Assumption	Company	ERG
Response definition	EASI 75	EASI 50 + ΔDLQI ≥ 4
Sequences	Not relevant	Relevant
BSC modelling	• No discontinuation on BSC (costs: weighted average of responders/non-responders) • TA534 BSC QoL waning assumptions applied	• No discontinuation on BSC • No QoL waning assumptions applied (Costs and utilities: weighted average of responders/non-responders)
Baricitinib / dupilumab discontinuation from week 16-52	Based on week 52 response in JAIN conditional on week 16 response	Based on JAIN all-cause discontinuation up to week 52 in responders at week 16
Baricitinib / dupilumab QoL waning assumptions	TA534 dupilumab QoL waning assumptions applied for both baricitinib and dupilumab	No QoL waning assumptions applied

Cost-effectiveness results

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

Additional areas of uncertainty

Issue	Why issue is important	ICER impact
Skin pain numeric rating scale (NRS) and atopic dermatitis sleep scale (ADSS) not included in ITC as outcomes	Clinical advice to ERG is that these outcomes are very important to patients	Unknown
[redacted] in baricitinib clinical trials	Potentially inappropriate to assume that efficacy results in baricitinib trials are transferable to black patients. AD pathology could be more severe in black patients. A potential equalities issue	Unknown
Baricitinib adverse event rates in model [redacted] versus placebo	Some adverse event rates for baricitinib in model [redacted], which lacks face validity. Other adverse events (e.g. headaches) not included in model	Minimal: Adverse events costs represent <0.5% of total costs in baricitinib arm
2mg baricitinib dose in patients aged >75 not modelled	2mg baricitinib dose is less effective than 4mg, but costs the same. As a result, ICERs will be underestimated in these patients	Unknown. Likely to be small, as the proportional of patients aged >75 is small

Innovation and equality issues

Company makes case for innovation

Innovation

- **Company:** Baricitinib has a novel, targeted mode of action, selectively and reversibly inhibiting JAK1 and JAK2
- Oral treatment not associated with adverse events experienced by patients having dupilumab. Potential to simplify the treatment paradigm
- **Stakeholders:** Baricitinib is innovative, but not a 'step change' like dupilumab

Equality issues

- Baricitinib efficacy may differ in people with different skin colours, particularly Black, Asian and Minority Ethnic (BAME) patients. Effects on different skin types considered an equality issue by the British Association of Dermatologists
- Tools for assessing the severity of atopic dermatitis and the response to treatment may not be sensitive enough in people with some skin colours
- Different ethnic groups have different cytokine pathways in atopic dermatitis, which may impact treatment efficacy. Th2 cytokines interleukin (IL)-4 and IL-13 predominate in most populations, but in some Asian populations IL-17 predominates

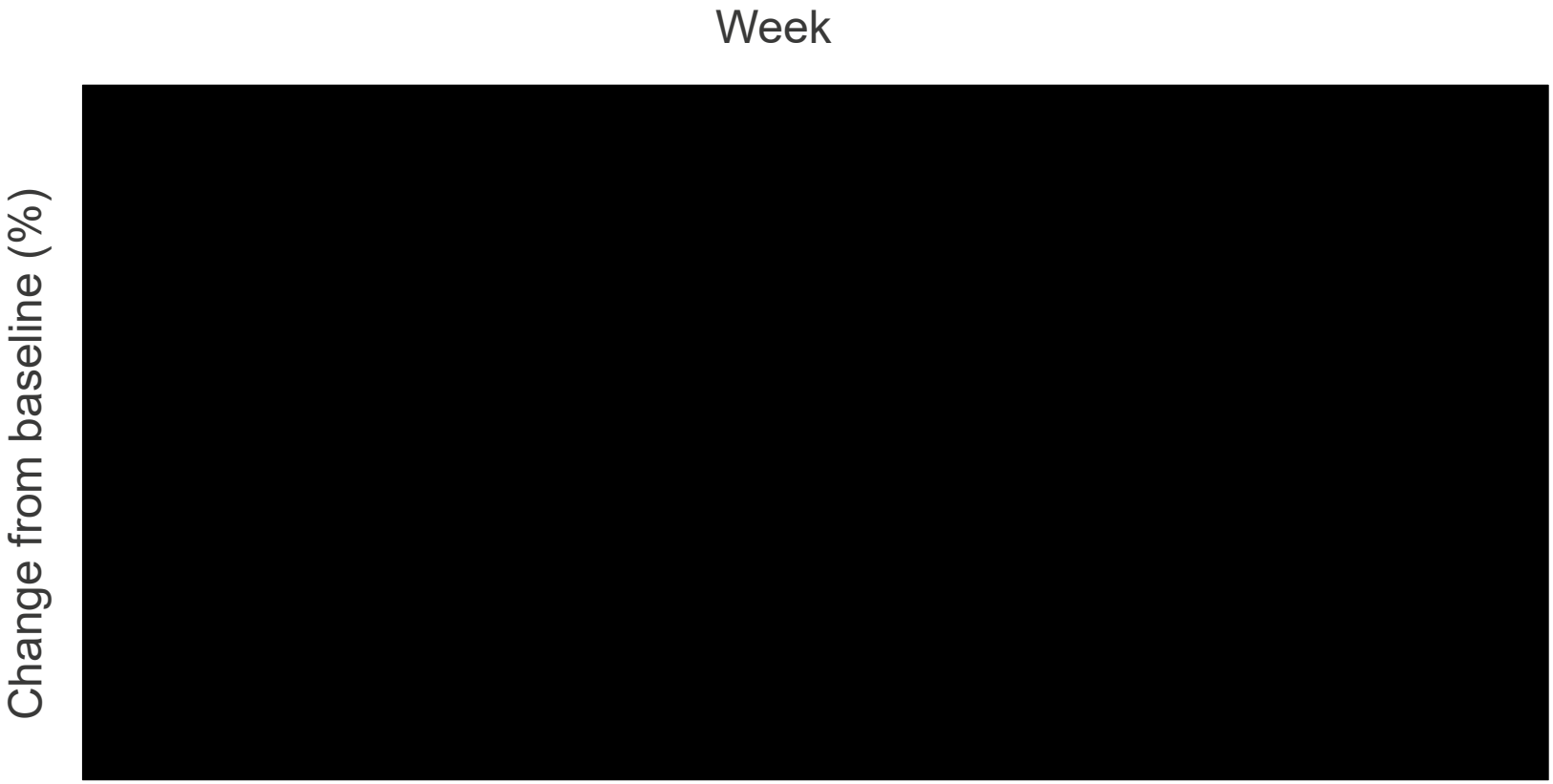
Back-up

Dupilumab for treating moderate to severe AD *(TA534, August 2018)*

Recommendations:

- Dupilumab is recommended as an option for treating moderate to severe AD in adults, only if the disease has not responded to at least 1 other systemic therapy (such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil), or these are contraindicated or not tolerated
- Stop dupilumab at 16 weeks if the AD 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

JAIN key results: EASI change from baseline



	PBO (n=54)	BARI 4mg (n=65)
% change from baseline, LSM (95% CI vs placebo)	[redacted]	[redacted]
P-value vs placebo	[redacted]	[redacted]

CI = Confidence interval; LSM = Least squares mean

Primary censoring (missing/non-responder discontinuation, TCS/systemic rescue tx)

Summary of key differences between company and ERG base cases

Assumption	Company	ERG
Response definition	EASI 75	EASI 50 + ΔDLQI ≥ 4
Sequences	Not relevant	Relevant
BSC modelling	• No discontinuation on BSC (costs: weighted average of responders/non-responders) • TA534 BSC QoL waning assumptions applied	• No discontinuation on BSC • No QoL waning assumptions applied (Costs and utilities: weighted average of responders/non-responders)
Baricitinib / dupilumab discontinuation from week 16-52	Based on week 52 response in JAIN conditional on week 16 response	Based on JAIN all-cause discontinuation up to week 52 in responders at week 16
Baricitinib / dupilumab QoL waning assumptions	TA534 dupilumab QoL waning assumptions applied for both baricitinib and dupilumab	No QoL waning assumptions applied

Tech report issues resolved after tech engagement

	Summary	Stakeholder responses	Technical team
3	Baricitinib trial patients had mean baseline EASIs of [redacted], skewed towards severe disease	• **Experts:** trials are generally representative of who would have baricitinib • **ERG:** maintains that less severe moderate patients were excluded	• Population largely aligns with that accepted in TA534, and is appropriate based on expert feedback
7a	Some elements of BSC costs applied to >100% of patients	• **Company:** agreed to remove BSC costs to avoid duplication	• Company's revised approach is appropriate
13	The assumption of equivalence for baricitinib in flare control is not supported by clinical data	• **Experts:** assumption is unreasonable • **Company:** updated the model to assume equivalence with BSC	• Equivalence with BSC is reasonable based on JAIN data on receipt of rescue medication
14	Company based assumptions around bathing products on TA534. There has been a recent decrease in bathing product use	• **Experts:** bathing products no longer widely used. Tx reduction in non-responders appropriate • **Company:** updated the model to remove these costs	• Removal of bathing product costs reflects clinical practice • Tx reduction in non-responders appropriate

Other issues resolved after technical engagement

- **Censoring rule:** Company, ERG and clinical experts agree that secondary censoring rule better reflects clinical practice. Under the secondary censoring rule, trial data are censored as missing / non-responder only after systemic rescue therapy (not topical)
  - Company used secondary censoring data in updated analyses
- **Dupilumab dosing:** Company corrected the number of dupilumab injections during induction from 10 to 9
- **Monitoring costs:** ERG considered that regular blood tests may be required for baricitinib to monitor increased blood creatinine kinase and lipids, and neutropenia. Company agreed with ERG scenario of 4 blood tests per year, the same as BSC
- **Using relative effectiveness from ITC to model absolute response:** Company agreed to use relative effects vs placebo (rather than an additive method) to calculate response for baricitinib and dupilumab. This limits bias, and better aligns with recommendations in NICE DSU Technical Support Document 5

Decision-making: south-west quadrant ICERs

- **Baricitinib accrues fewer costs than dupilumab, but also fewer QALYs (south-west ICERs)**
- South-west quadrant ICERs are presented as costs saved per QALY lost
- The higher the ICER, the more cost is saved per QALY lost, so high ICERs are better here and the commonly assumed decision rule of accepting ICERs below a given threshold is reversed
  - this is reflected in decision making in previous appraisals with south-west quadrant ICERs (e.g. TA433, TA561)
- Positive recommendations are made when the costs saved are sufficient to cover the QALY loss
- Usually, south-west quadrant ICERs have led to positive recommendations when ICERs are substantially above £30,000 per QALY lost
- As with other decision-making, more certainty is needed the closer to the margins of cost-effectiveness the ICERs are