Public observer slides – no ACIC information

Lead team presentation

Dupilumab for treating adults with moderate to severe atopic dermatitis [ID1048]

1st Appraisal Committee meeting

Committee B

Chair: Amanda Adler

Lead team: Diar Fattah, Danielle Preedy and Stephen Smith

ERG: Aberdeen HTA Group

NICE technical team: Sharlene Ting, Ahmed Elsada

6th March 2018

Background

Atopic dermatitis (also called atopic eczema)

- Chronic, remitting-relapsing, pruritic, inflammatory, immune-mediated skin condition
- Skin may be red/inflamed, thickened/leathery and dry with scaly plaques, bleeding, oozing, cracking, flaking and itching (pruritus)

Epidemiology

- Prevalence in UK adults is 2.5%
  - ❖ Different estimates for prevalence of moderate to severe disease within the 2.5% of adults with atopic dermatitis
    - ➢ Company: 7%
    - ➢ ERG: 53-67% depending on assessment tool used
    - ➢ Professional feedback: 15-23%

Definition of severity

Background

- Large number of instruments to assess severity such as EASI, POEM, SCORAD
- No NICE clinical guideline in adults
  - ❖ CG57 (Atopic eczema in under 12s) recommends a holistic approach considering severity and quality of life

Company

- No consensus on most appropriate tool
- No tool captures all key aspects of the disease
- Single measurement may over- or under-estimate severity because of relapsing-remitting nature of condition
- Used IGA and EASI in its trials

- ❖ ***Given the remitting-relapsing nature of atopic dermatitis, how should moderate to severe disease be defined?***
- ❖ ***How can levels of severity be defined using EASI and DLQI?***

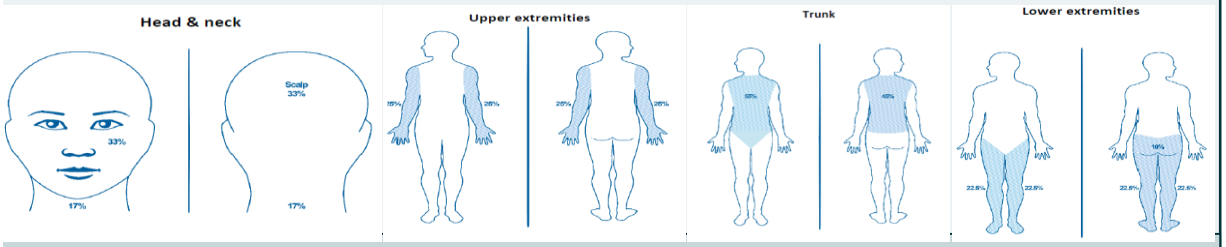
DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigators' Global Assessment; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis

Measuring clinical effectiveness – clinician assessed

Eczema Area and Severity Index (EASI); 0 to 72

- Weighted score (0 to 72) of 4 affected areas
  - ❖ 0 (no eczema); 7.1-21 (moderate); 21.1-50 (severe); 50.1-72 (very severe)
- Response considered as EASI 50, EASI 75 or absolute reduction from baseline
  - ❖ EASI 50: ≥50% reduction in EASI score from baseline
  - ❖ Different perspectives on minimum clinically important difference
    - ➢ European Medicines Agency: co-primary outcomes in dupilumab trials at 16 weeks, EASI 75 and IGA 0/1 & ≥2 point improvement from baseline
    - ➢ British Association of Dermatologists: at 16 weeks, EASI 50 or 6-point improvement from baseline
    - ➢ Research studies: 6.6-point improvement from baseline

Body region	Erythema	Edema/ papulation	Excoriation	Lichenification	Area score	Multiplier	Score
Head/neck	(+	+	+	)	x	x 0.1	
Trunk	(+	+	+	)	x	x 0.3	
Upper extremities	(+	+	+	)	x	x 0.2	
Lower extremities	(+	+	+	)	x	x 0.4	
The final EASI score is the sum of the 4 region scores							____ (0-72)



Investigator's Global Assessment (IGA); 0 to 4

- Clinician's impression of patient's eczema based on severity of erythema, infiltration, papulation and oozing/crusting
- Score: 0 (clear), 1 (almost clear), 3 (moderate) to 4 (severe)

❖ ***What are clinically meaningful changes in EASI and IGA?***

Measuring clinical effectiveness – patient reported

Patient Oriented Eczema Measure (POEM); 0 to 28

- 7 questions scored 0 (no days) to 4 (every day) on the presence of itch, sleep disturbance, bleeding, weeping/oozing, cracked, flaking and dry/rough skin
- 0-2 (clear or almost clear), 8-16 (moderate), 17-24 (severe), 25-28 (very severe)
- Response considered as POEM 25 (≥25% reduction in POEM score from baseline) or absolute reduction from baseline
  - ❖ Different perspectives on minimum clinically important difference
    - ➢ British Association of Dermatologists: POEM 25 at 16 weeks
    - ➢ Research studies: 3.4-point reduction from baseline

Pruritus Numerical Rating Scale (NRS); 0 to 10

- Patients rate intensity of itch from 0 (“no itch”) to 10 (“worst imaginable itch”)
- ≥4 to <7 (moderate); ≥7 to <9 (severe); ≥9 (very severe)

Dermatology Life Quality Index (DLQI); 0 to 30

- 10 questions scored 0 (no impact) to 3 (worst impact): symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment
- 0-1 (no effect); 6-10 (moderate effect); 11-20 (large effect)
- ≥4 point improvement (clinically important difference)

❖ ***What is considered a clinically meaningful change in DLQI?***

Dupilumab
(Dupixent)
Sanofi Genzyme

Marketing authorisation
"moderate to severe atopic dermatitis in adults who are candidates for systemic therapy"

Mechanism of action

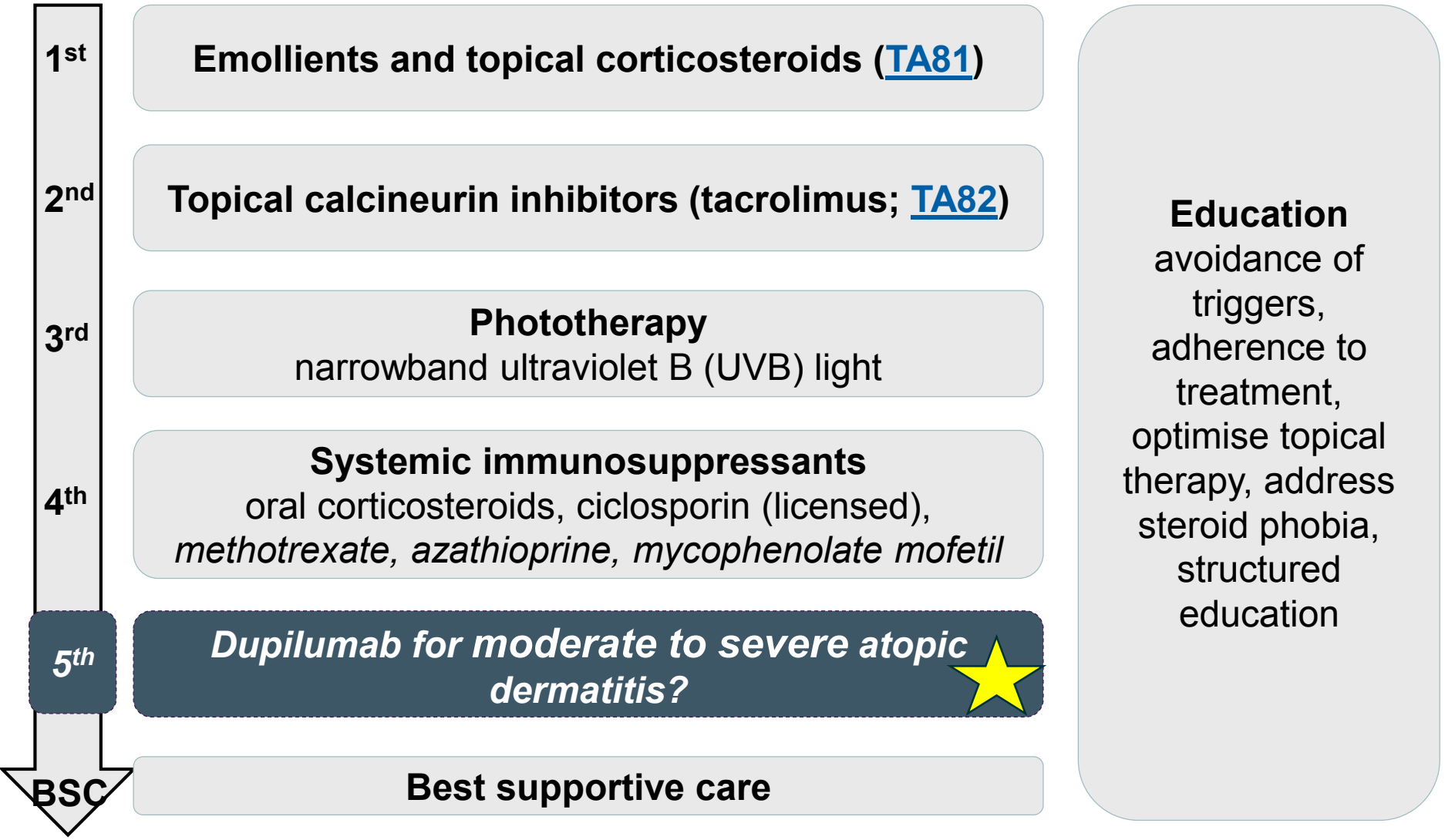
- Fully human monoclonal antibody
- Binds to interleukin-4 and -13 receptors (key mediators)
- Inhibits inflammation

Administration and dose

- Subcutaneous injection (thigh or stomach)
- Initial 600 mg dose, followed by 300 mg once every 2 weeks (no dose adjustments)
  - ❖ If no response after 16 weeks, stop treatment
  - ❖ If partial response after 16 weeks, some patients may improve with continued treatment
- Can be used with or without topical corticosteroids
- Can be used with topical calcineurin inhibitors (e.g. tacrolimus) only for problem areas (such as, the face, neck, intertriginous and genital areas)

❖ ***Would dupilumab be used as monotherapy or in combination with other topical medications?***

Treatment pathway and company's positioning of dupilumab adapted from International Eczema Council guidance



❖ ***Where would dupilumab fit in the treatment pathway?***

Patient and clinical perspective

Life-limiting, debilitating and isolating, need for effective treatment with minimal adverse reactions. Clinicians consider dupilumab a step change in managing atopic dermatitis

Impact of atopic dermatitis

- life-limiting, isolating, debilitating
- affects all aspects of life: physical, psychological, social, financial
- severe disease: painful, intolerable itch affecting sleep, linked to depression and suicide
- negative impact on quality of life

Current options

- not very effective for severe disease
- phototherapy is inconvenient and can be painful
- systemic therapy (immunosuppressants) linked to severe side effects and comorbidities

People would like

- effective treatments with few side effects
- dupilumab after 1 immunosuppressant

Dupilumab

- first targeted biologic
- not an immunosuppressant
- linked to fewer side effects
- effective
- clinicians routinely use validated tools (such as EASI), so using dupliumab would not require additional assessment

EASI, Eczema Area and Severity Index

Decision problem – population and comparator

Company focused on narrower population than NICE scope and marketing authorisation to reflect likely position of dupilumab in NHS practice

NICE scope
Population: adults with moderate to severe atopic dermatitis who are candidates for systemic therapy
Comparators: phototherapy, immunosuppressive therapy, oral steroids, best supportive care, alitretinoin for hands

Company's decision problem: candidates for systemic therapy and for whom topical and systemic immunosuppressants (ciclosporin) are inadequately effective, not tolerated or contraindicated

Comparator in company's base case: best supportive care (emollients, low-to-mid potency topical corticosteroids, and rescue therapy of higher potency topical or oral corticosteroids or topical calcineurin inhibitors)

ERG: decision problem and likely position of dupilumab appropriate, but

- clinicians use other drugs off-label such as azathioprine and methotrexate if ciclosporin cannot be taken
- best supportive care should include phototherapy and systemic therapy

❖ ***What is included in 'best supportive care'?***

Key clinical evidence and company's base case

4 phase III trials

- 2 for monotherapy and 2 for combination therapy
- dupilumab at 2 doses (300 mg every other week [licensed] or every week [unlicensed]) for 16 weeks

'Monotherapy' trials (dupilumab *vs* placebo)
SOLO 1 & SOLO 2

'Combination' therapy trials (dupilumab + topical corticosteroids *vs* placebo + TCS)
CAFÉ & CHRONOS

Primary endpoints of trials at 16 weeks – company did not use in its base case
SOLO 1 & 2 and CHRONOS: EASI 75 and IGA 0/1 & ≥2-point improvement from baseline
CAFÉ: EASI 75

Company's base case

- ✓ **Subgroup**: history of ciclosporin failure or contraindication
- ✓ **2 separate analyses**: 'monotherapy and 'combination'; using 'all observed' data that include patients who had rescue therapy or stopped study treatment
- ✓ **Comparison**: dupilumab (licensed dose) *vs* best supportive care (data from placebo groups)
- ✓ **Endpoint**: EASI 50 & DLQI ≥4 (**different** to trials' primary endpoints)
- ✓ **Other outcomes**: EQ-5D, adverse events

❖ ***Is the company's modelled endpoint appropriate?***

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigators' Global Assessment; TCS, topical corticosteroids

Key phase III trials – design

DESIGN: international (UK sites), randomised, stratified (IGA 3 or 4), double-blind, parallel-group, 16-week treatment

- **SOLO 1 & 2:** stratified (Japan or rest of world); responders (EASI 75 or IGA 0/1) re-randomised to 36-week dupilumab (4 different doses) or placebo [**SOLO-CONTINUE**]; non-responders 12-week follow up
- **CAFÉ:** stratified (ciclosporin naïve or not), 12-week follow up
- **CHRONOS:** stratified (Japan or rest of world), 36 week maintenance; 12 week follow up

Rescue therapy

- Before 2 weeks: patients stop study treatment
- After 2 weeks: if patients take topical medications as rescue therapy, they continue study treatment. If patients take systemic drugs as rescue therapy, they stop study treatment and resume it later
- Patients stopping study treatment complete all visits and assessments

ERG: only 1 of 4 trials was stratified at randomisation for previous use of immunosuppressant therapy (ciclosporin)

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigators' Global Assessment

Key phase III trials for target population

POPULATION (all trials): adults with chronic moderate to severe atopic dermatitis (≥3 years; IGA ≥3, BSA ≥10%, **pruritus NRS ≥3**), inadequate treatment in ≥6 months with topical meds

	MONOTHERAPY	COMBINATION (with topical corticosteroids)	
trial population	**SOLO 1 & 2:** topical medications failed SOLO 1: n=671 SOLO 2: n=708	**CAFÉ: EASI ≥20**; cannot take or ciclosporin failed n=325	**CHRONOS: EASI ≥16**; medium or higher potency TCS failed n=740
TARGET population	**SOLO-CAFÉ-like**	**CAFÉ & CHRONOS-CAFÉ-like**	
	SOLO 1 & 2: *post hoc* subgroup of patients who previously used immunosuppressants (commonly ciclosporin) **n=288 (21%)**	**CAFÉ: whole population** including those who were ciclosporin naïve and those whose disease was inadequately treated with ciclosporin **n=325**	**CHRONOS: *post hoc* subgroup** of patients who cannot take ciclosporin or whose disease did not adequately respond to ciclosporin **n=137 (19%)**

❖ ***Would dupilumab be offered with or without corticosteroids in the NHS?***

BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigators' Global Assessment; n, number of patients; NRS, Numerical Rating Scale; TCS, topical corticosteroids

Baseline characteristics of target population

ERG: EASI and pruritus scores are slightly higher while DLQI and EQ-5D scores are slightly lower than respective values in individual trials indicating subgroups have more severe disease

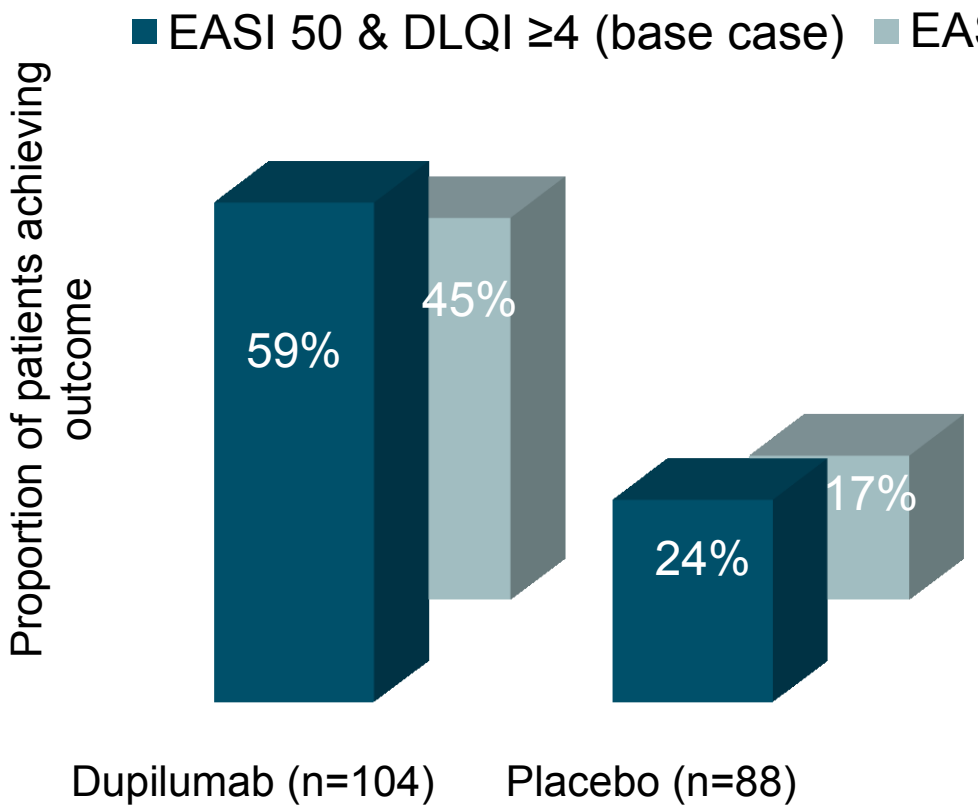
	SOLO-CAFÉ-like		CAFÉ & CHRONOS-CAFÉ-like	
	dupilumab^ (n=104)	placebo (n=88)	dupilumab^ + TCS (n=130)	placebo + TCS (n=169)
Age in years*	38 (14)	39 (13)	38 (13)	38 (13)
Men, %	72	63	59	60
BMI in kg/m²*	25 (5)	26 (5)	25 (4)	26 (5)
Caucasian, %	72	59	93	90
Asian, %	22	34	5	7
Years with AD*	29 (14)	30 (15)	30 (15)	29 (15)
Percent BSA with AD*	59 (22)	60 (24)	57 (19)	59 (22)
EASI [0-72, >20=severe]*	**37 (15)**	**36 (14)**	**34 (11)**	**35 (12)**
IGA [0-4, 4=severe]*	3.7 (0.5)	3.6 (0.5)	3.5 (0.5)	3.5 (0.5)
Weekly average of peak daily pruritus NRS [0-10, >6=severe]*	8 (2)	8 (2)	7 (2)	7 (2)
POEM [0-28, >24=severe]*	22 (5)	22 (6)	20 (6)	20 (6)
DLQI [0-30, >10=very large effect]*	**16 (7)**	**17 (8)**	**15 (8)**	**15 (8)**
EQ-5D utility*	0.58 (0.32)	0.52 (0.38)	0.72 (0.25)	0.63 (0.32)

*Mean (standard deviation); ^licensed dose (300 mg every 2 weeks); AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; IGA, Investigator's Global

❖ ***Are the subgroups representative of moderate to severe atopic dermatitis patients seen in NHS clinical practice?***

Key outcomes for target population at 16 weeks – Monotherapy

Dupilumab significantly reduces disease severity and improves quality of life compared with placebo. Large proportion of patients in placebo group met criteria for treatment response



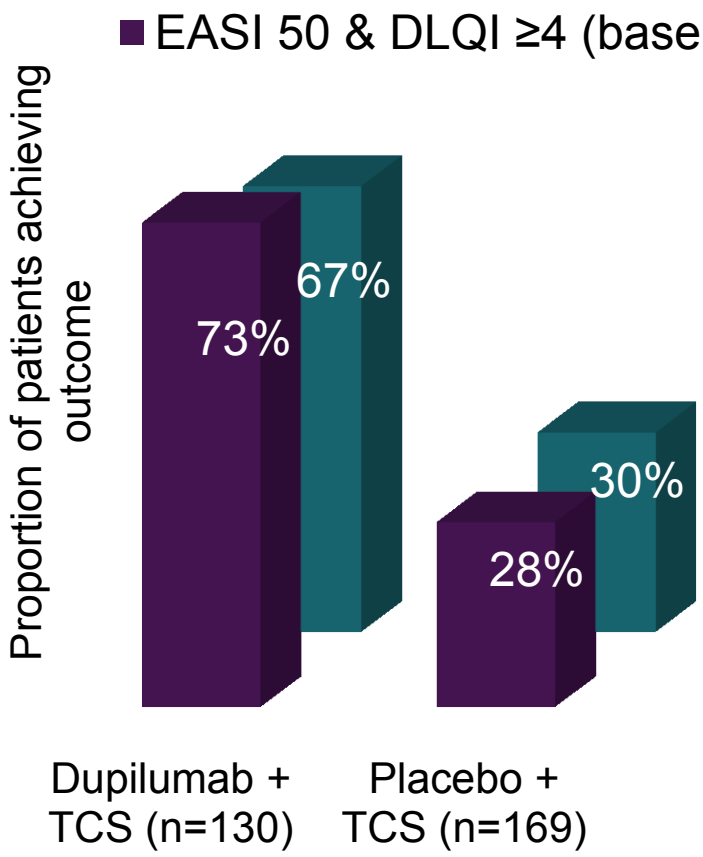
esponse	dupilumab^ *vs* placebo: difference (95% CI)
DLQI ≥4	35% (20.7 to 48.8)
	28% (14.7 to 41.6)

❖ ***Is dupilumab clinically effective compared with placebo?***

CI, confidence intervals; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; number of patients

Key outcomes for target population at 16 weeks – Combination

Dupilumab + corticosteroids significantly reduces disease severity and improves quality of life compared with placebo + corticosteroids. Large proportion of patients in placebo group met criteria for treatment response



roportion chieving response efined as:	dupilumab^ + TCS *vs* placebo + TCS: difference (95% CI)
ASI 50 & DLQI ≥4	45% (34.4 to 56.1)
ASI 75	37% (25.4 to 48.1)

❖ ***Is dupilumab in combination with topical corticosteroids clinically effective compared to placebo in combination with topical corticosteroids?***

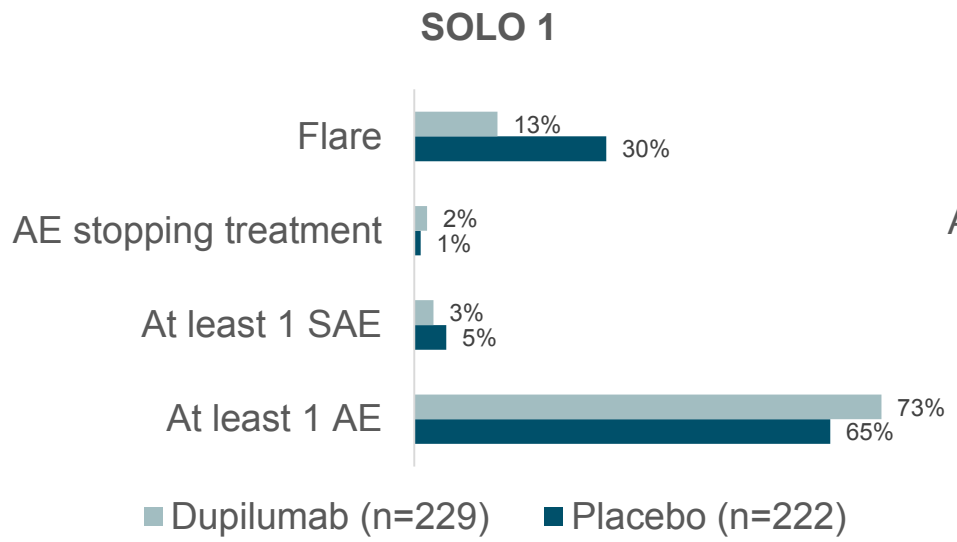
CI, confidence intervals; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; n, number of patients; TCS, topical corticosteroids

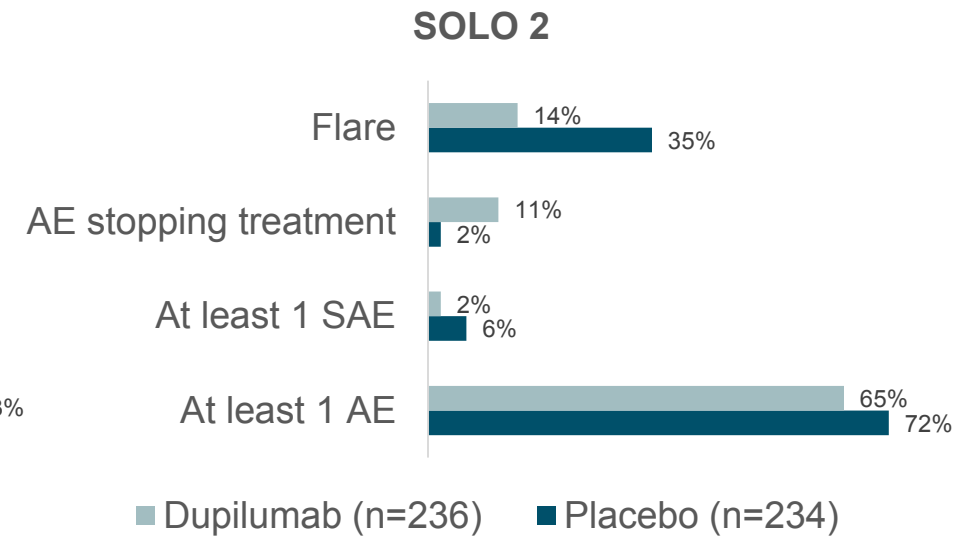
ERG critique of clinical evidence

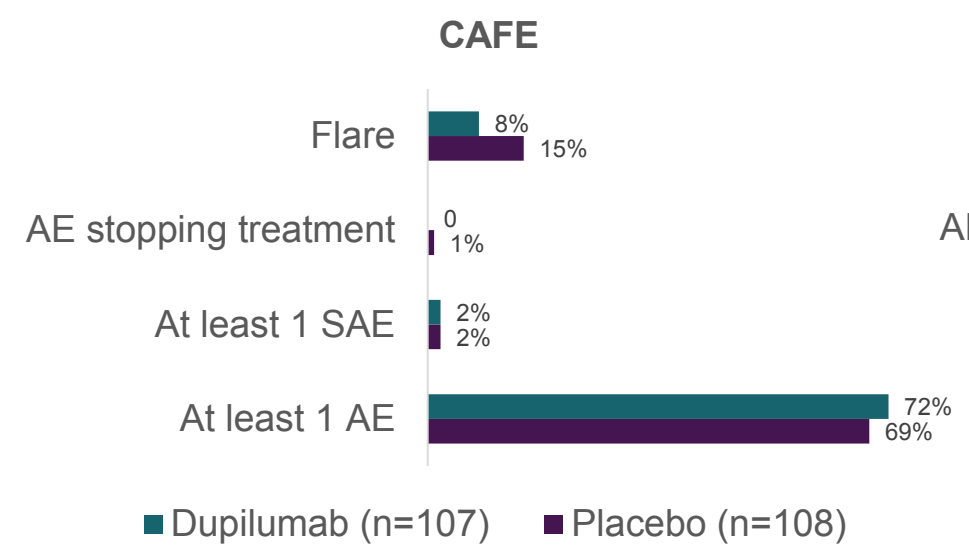
- Selection of clinical trials comparing dupilumab with placebo is appropriate
  - most relevant comparator is best supportive care
- Analyses using 'all observed' data that includes patients who had rescue therapy are appropriate
  - reflects clinical practice
- Some of the patients in the target population came from *post hoc* subgroups
  - trials were not stratified at randomisation for previous use of immunosuppressant therapy
- Target population had more severe disease compared with whole population in individual trials

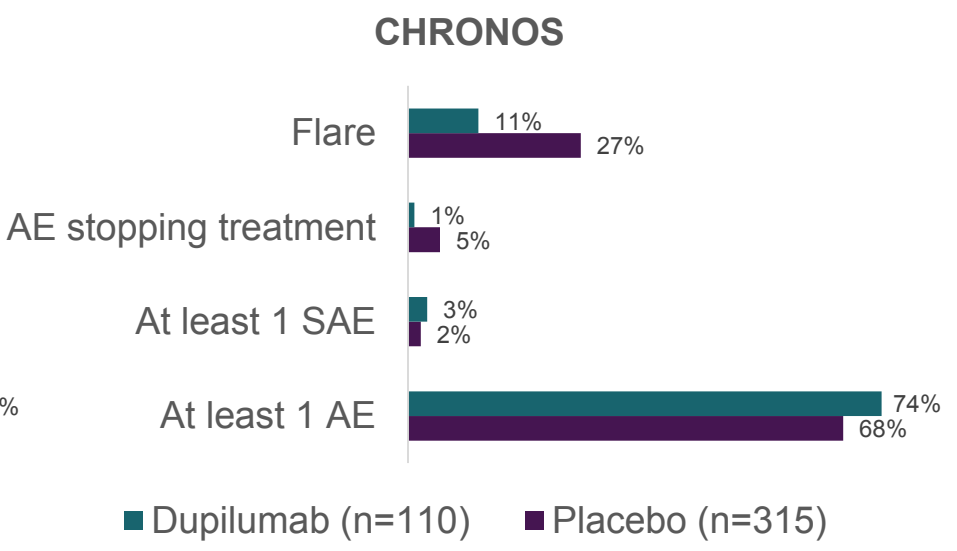
Adverse events at 16 weeks – trial population

Adverse events leading to stopping treatment generally low
Flares higher in placebo than dupilumab groups





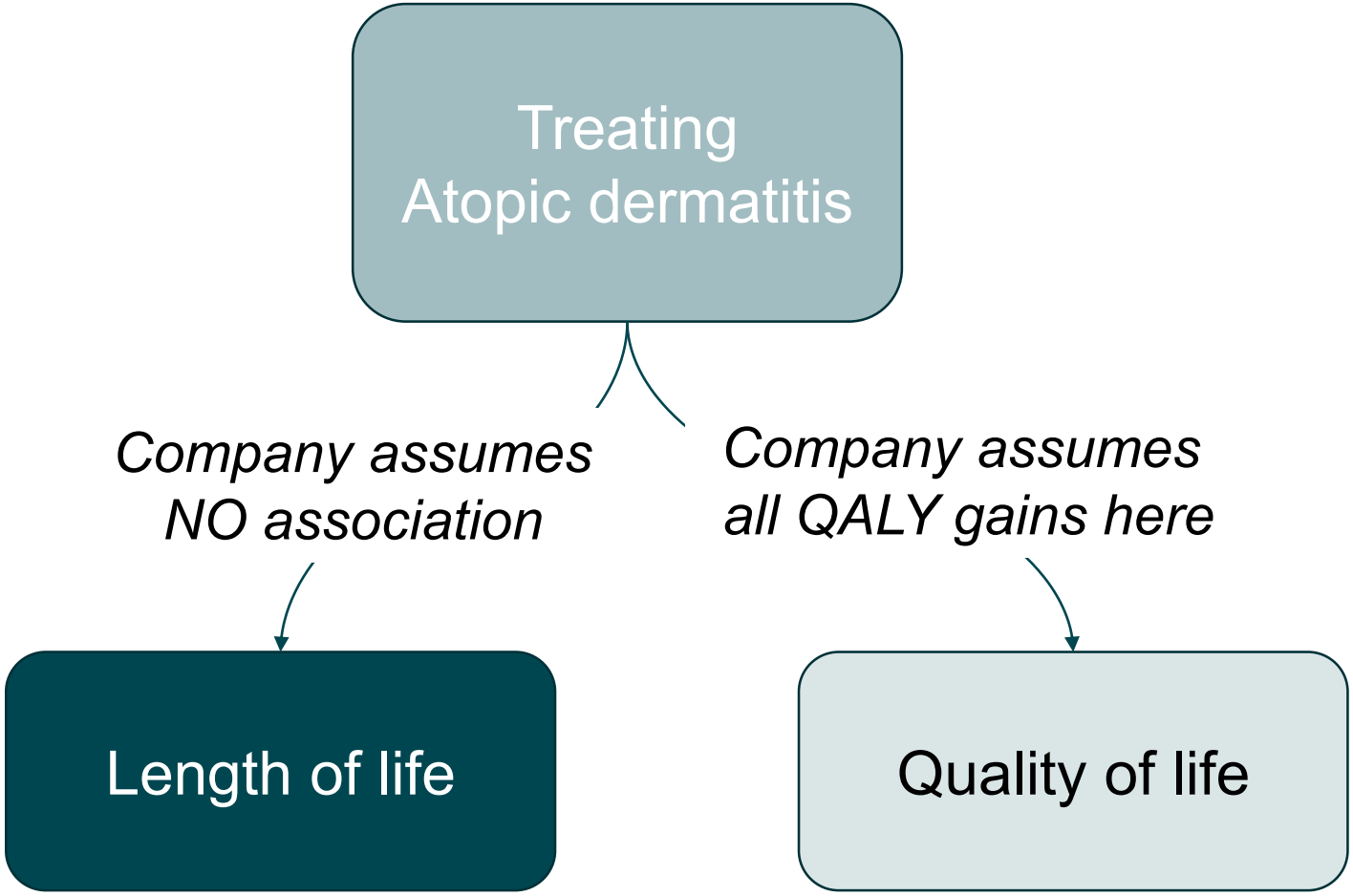




(S)AE, (serious) adverse event

Cost effectiveness

Where do the QALY gains come from?

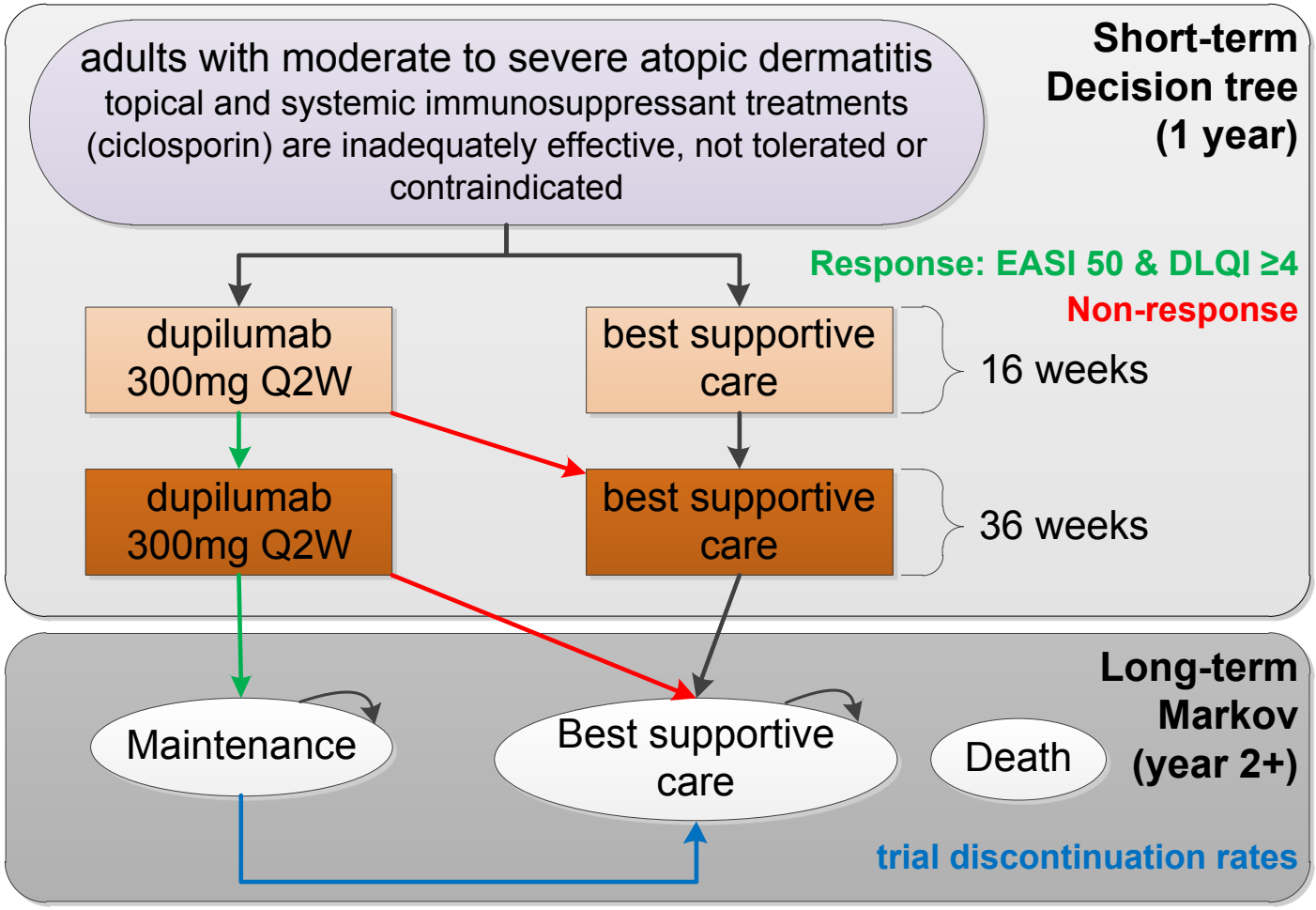


Increase in QALYs comes only from improvement in quality of life, rather than increasing length of life

QALY, quality-adjusted life year

Company model – base case

ERG: model largely meets requirements of NICE reference case. No long-term longitudinal data → uncertainty about extrapolation assumptions



- Hybrid model (decision tree and Markov state transition): lifetime horizon, annual cycle
- Best supportive care data from trial placebo groups
- 2 analyses: dupilumab mono and combination therapy
- Company assumes response starts at 8 weeks rather than at end of 16-week treatment period

- Monotherapy baseline characteristics: 38 years, 60% men, EASI 34, weekly pruritus NRS 6.8
- Combination baseline characteristics: 38 years, 65% men, EASI 36, weekly pruritus NRS 7.6

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, numerical rating scale; Q2W, every 2 weeks

Extrapolating effectiveness from 16 weeks up to 52 weeks (1 year)

- All trials except CHRONOS provided data up to 16 weeks
- CHRONOS provided data up to 52 weeks
  - ❖ Company used overall population in CHRONOS to derive probability of response at week 52 conditional on having responded at week 16
  - ❖ Probability of response at week 52 of **0.94** for dupilumab and **0.77** for BSC applied to 'target population'

	Proportion of patients achieving response (EASI 50 & DLQI ≥4)			
	Monotherapy		Combination	
Time point	dupilumab^	BSC	dupilumab^	BSC
Week 16	59%	24%	73%	28%
Week 52	55%	18%	69%	21%

^licensed dose (300 mg every 2 weeks); BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index

❖ ***Are the probabilities of response for dupilumab (94%) and best supportive care (77%) at 52 weeks plausible?***

Extrapolating dupilumab effectiveness beyond 1 year trial period

Dupilumab response at 52 weeks continued in Markov 'Maintenance' health state

- Annual stopping rates of dupilumab
  - **Monotherapy**: annual stopping probability **0.063**
    - Patients who stopped SOLO-CONTINUE study at 52 weeks (SOLO 1 & 2 patients achieving treatment response (EASI 75 or IGA 0/1 at 16 weeks) re-randomised to 36-week dupilumab treatment at 4 doses or placebo)
  - **Combination**: annual stopping probability **0.037**
    - Patients achieving treatment response (EASI 50 & DLQI ≥4) at 16 weeks who stopped CHRONOS study at 52 weeks

- ***How should stopping rates for dupilumab after 1 year be modelled?***
- ***Are yearly stopping rates of 6.3% for responders of dupilumab monotherapy and 3.7% for responders of combination therapy clinically reasonable?***

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigators' Global Assessment

‘Stopping rule’

Treatment stops for non-responders

- Clinical trials 16 week induction treatment co-primary efficacy outcomes: EASI 75 and IGA 0/1 (+ ≥2 point improvement from baseline)
- Company base case and economic model treatment response: EASI 50 and DLQI ≥4
- Dupilumab summary of product characteristics: patients with partial response at 16 weeks may improve with continued treatment
- Professional feedback: patients starting at high absolute EASI score, disease involving extensive body surface area, and patients for whom atopic dermatitis mainly affects the head and face may take longer to achieve EASI 50; 24 weeks is a more realistic time frame to evaluate treatment response

❖ ***What stopping rule should be applied bearing in mind NICE must appraise drugs within their marketing authorisation?***

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigators’ Global Assessment

Health-related quality of life

- EQ-5D-3L data from **trial population** valued at UK tariffs → utility values for subgroups
  - Company: quality of life depends on EASI and pruritus scores, used to calculate utility weights specific to target subgroups

Target subgroup	Parameter	dupilumab^	BSC*
Monotherapy	All patients at week 16	0.830	0.718
Baseline utility: 0.55	Week 16 EASI 50 +DLQI ≥4 responder	0.855	-
Combination	All patients at week 16	0.898	0.811
Baseline utility: 0.66	Week 16 EASI 50 +DLQI ≥4 responder	0.904	-

^licensed dose (300 mg every 2 weeks); ***Aggregate utility applied for all patients as they do not move health states according to response**; BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index

How the utilities are applied in the model

Treatment	From 0 to 8 weeks	From 8 to 16 weeks	From 16 to 52 weeks	Markov (Year 2+)
dupilumab	baseline utility	utility from all patients at 16 weeks	Responder: utility for responders at 16 weeks **Non-responder: utility from all BSC patients at 16 weeks**	
BSC	baseline utility	utility from **all patients** at 16 weeks*		

***High number of patients in placebo groups showed treatment response at 16 weeks**

Sustained quality of life beyond 1 year trial period

ERG: company assumes utility gains in dupilumab responders are stable over time, but that short-term gains in BSC responders decrease rapidly over time. This creates a large difference in utility values and influences results

- Company assumed that quality of life is not sustained for a proportion of patients, based on feedback from 5 dupilumab trial principal investigators

	Probability of sustained quality of life (%)	
	dupilumab^	best supportive care
Year 2	98	37
Year 3	95	9
Year 4	93	0
Years 5+	92	0

^licensed dose (300 mg every 2 weeks)
BSC: weighted average of utility for all BSC patients during trial period and baseline utility

- Many patients on placebo responded to treatment, but company uses utility values for 'all patients' (responders and non-responders) from 8 weeks onwards
  - Company: adherence to topical regimens likely to vary after trial ends, so response unlikely to continue. Dupilumab responders are likely to use less steroids and emollients (less burdensome)

❖ ***How should health-related quality of life be modelled for dupilumab (monotherapy and combination) and for best supportive care? Based on trial or otherwise?***

Resource use – data sources

DATA SOURCES (A)

- **MAIN** source of resource use for responders and non-responders (clinician and nurse visits): secondary care notes review of 3 years
  - data from 30 patients at year 3 with atopic dermatitis uncontrolled on current systemic therapy and can take dupilumab from 5 NHS hospitals
  - ERG: company only used data from year 3, whereas additional data were available from years 1 and 2
- **SUPPLEMENTED** by Integrated Records review (day case, A&E, hospitalisations)
  - 37 patients with atopic dermatitis on prescription medication from 1 region in England

- Resource use **adjusted for responders only:**
  - 51 dermatologists provided resource use data on 850 patients whose atopic dermatitis was well controlled (proxy for dupilumab responders) or not (proxy for dupilumab non-responders)
  - used to derive multipliers that were applied to resource use data obtained from A

A&E, Accident and Emergency

Adverse events rates

- **Disutility from adverse events not included in model, only costs included**
  - Company: frequency of EQ-5D data collection captured disutility → avoid double counting
  - ERG: 2-weekly data collection may have missed full impact of short-lived adverse events
- Company estimated adverse event rates from individual trials
- Injection site reaction: company assumed to be one-time event
- All other adverse events: company assumed per cycle rates

	Proportion of patients experiencing adverse event			
	Monotherapy		Combination	
	dupilumab^	BSC	dupilumab^	BSC
Injection site reaction	0.881	0	0.091	0
Allergic conjunctivitis	0.114	0.03	0.401	0.188
Infectious conjunctivitis	0.163	0.022	0.255	0.033
Oral herpes	0.135	0.059	0.055	0.11

^licensed dose (300 mg every 2 weeks); BSC, best supportive care

ERG: company had little justification for assuming injection site reaction events are one-time event; more appropriate for company to apply injection site reaction rate on a cycle-by-cycle basis in the dupilumab *Maintenance* health state

Resource use (1): consultations

ERG used estimates from data for all 3 years from secondary care case notes review, while company used data only from year 3

Resource use per patient per year	Dupilumab				Best supportive care: Years 1, 2+	
	Year 1		Years 2+		Company	ERG
	Company	ERG	Company	ERG		
Dermatologist outpatient consultation^						
Responder	4	4.3	2	4.3	**2**	4.3
Non-responder	7	6	7	6	**7**	6
Dermatology related GP consultation^						
Responder	2	6.2	2	6.2	**2**	6.2
Non-responder	12.8	12.8	12.8	12.8	12.8	12.8
Dermatology Nurse visit^						
Responder*	1	1	0.44	0.35	**0.44**	0.35
Non-responder	1	1	0.57	0.46	**0.57**	0.46

*Multiplier (0.77) used to reduce number of visits for responders

^Units: per patient per year

- ***Are the resource use estimates credible?***
- ***Which estimates are preferred?***

GP, general practitioner

Resource use (2): hospital visits and tests

ERG: patients unlikely to be hospitalised

Resource use per patient per year	Dupilumab				Best supportive care: Years 1, 2+	
	Year 1		Years 2+		Company	ERG
	Company	ERG	Company	ERG		
Accident and emergency visit^						
Responder[a]	0.06	0.02	0.06	0.02	0.06	0.02
Non-responder	0.25	0.08	0.25	0.08	0.25	0.08
Hospitalisation^						
Responder[b]	0.03	0.02	0.03	0.02	0.03	0.02
Non-responder	0.23	0.13	0.23	0.13	0.23	0.13
Tests and investigations^						
Responder	0	0	0	0	4	4
Non-responder	4	4	4	4	4	4
Day case^						
Responder	0	0	0	0	0	0
Non-responder	0.17	0.2	0.17	0.2	0.17	0.2

[a]Multiplier (0.25) and [b]Multiplier (0.13) used to reduce number of visits for responders

^Units: per patient per year

- ***Are the resource use estimates credible?***
- ***Which estimates are preferred?***

Company's costs

Parameter	Costs	
Background treatments (per week)	**Responder (assuming 50% reduction)**	**Non-responder**
• Bathing products	£1.36	£2.48
• Emollients	£2.38	£5.73
• Topical corticosteroid (mometasone)	£1.76	£3.47
• Topical calcineurin inhibitors (tacrolimus)	£0	£1.38
Treatment of flares (based on rescue therapy in CHRONOS over 52 weeks)	Dupilumab: £10.41 per year	Best supportive care: £14.03 per year
Full blood count		£3.10
Consultant appointments (average of different types of attendance and multidisciplinary team)		[redacted]
Hospitalisations		£1,795
Accident and Emergency		£137.82
Adverse events		
• Injection site reactions		£104
• Allergic conjunctivitis		£36
• Infectious conjunctivitis		£45.41
• Oral herpes		£36

❖ ***Are the cost estimates credible?***

Company base case results

Monotherapy

	Total			Incremental			
	Costs (£)	Life years gained	QALYs	Costs (£)	Life years gained	QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,749

Combination

	Total			Incremental			
	Costs (£)	Life years gained	QALYs	Costs (£)	Life years gained	QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,419

Dupilumab at licensed dose (300 mg every 2 weeks); BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life year
Model: multiplicative adjustment for age

Company's sensitivity analyses on sustained quality of life in responders

	Probability of sustained quality of life (%)							
	Dupilumab^				BSC			
	Y2	Y3	Y4	Y5+	Y2	Y3	Y4	Y5+
Company base case	98	95	93	92	37	9	0	0
Company's sensitivity analyses								
SA3: BSC – QoL sustained after Y2	98	95	93	92	**37**	**37**	**37**	**37**
SA4: Dupilumab – no decline	**100**	**100**	**100**	**100**	37	9	0	0
SA5: BSC – linear decline	98	95	93	92	**75**	**50**	**25**	**0**
SA6: BSC – linear decline	98	95	93	92	**50**	**25**	**0**	**0**
SA7: Dupilumab – no decline; BSC – 50% decline	**100**	**100**	**100**	**100**	**50**	**50**	**50**	**50**

❖ ***Which quality of life assumptions are preferred?***

^licensed dose (300 mg every 2 weeks); BSC, best supportive care; QoL, quality of life; Y, year

Company's key one-way deterministic sensitivity analyses – monotherapy

		Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
1	**Base case (sustained QoL from years 2 to 5+: 98%, 95%, 93% and 92% [dupilumab] and 37%, 9%, 0% and 0% [BSC])**	[redacted]	[redacted]	[redacted]	**£25,749**
Assumption: sustained quality of life benefit post trial period					
3	Sustained QoL response does not decline after year 2 (37%)	[redacted]	[redacted]	[redacted]	£30,992
4	No decline in dupilumab patients	[redacted]	[redacted]	[redacted]	£25,148
5	Linear decline in utility for BSC patients to year 5 (75%, 50%, 25%, 0%)	[redacted]	[redacted]	[redacted]	£27,308
6	Linear decline in utility for BSC patients to year 5 (50%, 25%, 0%, 0%)	[redacted]	[redacted]	[redacted]	£26,184
7	No decline in dupilumab patients, 50% decline in BSC patients	[redacted]	[redacted]	[redacted]	£33,127
Measure of response					
11	Efficacy evaluation at 16 weeks: EASI 75	[redacted]	[redacted]	[redacted]	£26,611
12	Efficacy evaluation at 16 weeks: EASI 50	[redacted]	[redacted]	[redacted]	£26,117
14	Primary analysis method for response	[redacted]	[redacted]	[redacted]	£27,196

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; incr., incremental; LYG, life years gained; QALY; quality-adjusted life year; QoL, quality of life
Model: multiplicative adjustment for age

Company's key one-way deterministic sensitivity analyses – combination therapy

		Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
1	**Base case (sustained QoL from years 2 to 5+: 98%, 95%, 93% and 92% [dupilumab] and 37%, 9%, 0% and 0% [BSC])**	[redacted]	[redacted]	[redacted]	**£30,419**
Assumption: sustained quality of life benefit post trial period					
3	Sustained QoL response does not decline after year 2 (37%)	[redacted]	[redacted]	[redacted]	£38,267
4	No decline in dupilumab patients	[redacted]	[redacted]	[redacted]	£29,792
5	Linear decline in utility for BSC patients to year 5 (75%, 50%, 25%, 0%)	[redacted]	[redacted]	[redacted]	£32,154
6	Linear decline in utility for BSC patients to year 5 (50%, 25%, 0%, 0%)	[redacted]	[redacted]	[redacted]	£30,901
7	No decline in dupilumab patients, 50% decline in BSC patients	[redacted]	[redacted]	[redacted]	£41,838
Measure of response					
11	Efficacy evaluation at 16 weeks: EASI 75	[redacted]	[redacted]	[redacted]	£32,350
12	Efficacy evaluation at 16 weeks: EASI 50	[redacted]	[redacted]	[redacted]	£31,843
14	Primary analysis method for response	[redacted]	[redacted]	[redacted]	£30,492

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; incr., incremental; LYG, life years gained; QALY; quality-adjusted life year; QoL, quality of life
Model: multiplicative adjustment for age

ERG's exploratory analyses

Key areas of concern

- Company's assumptions about sustained quality of life (key model driver)
  - ERG applied different assumptions
- Method company used to derive resource use based on only 1 year of data from the 30 patients
  - ERG used data from additional 2 years
- Feasibility of defining non-response (EASI 50 & DLQI ≥4) and stopping treatment ('stopping rule')

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

ERG's exploratory analyses on sustained quality of life in responders

	Probability of sustained quality of life (%)							
	Dupilumab				BSC			
	Y2	Y3	Y4	Y5+	Y2	Y3	Y4	Y5+
Company base case	98	95	93	92	37	9	0	0
ERG's exploratory analyses								
SA6: 25% of responders in BSC will sustain QoL beyond 52 weeks	98	95	93	92	**25**	**25**	**25**	**25**
SA7: 50% of responders in BSC will sustain QoL beyond 52 weeks	98	95	93	92	**50**	**50**	**50**	**50**
SA8: 75% of responders in BSC will sustain QoL beyond 52 weeks	98	95	93	92	**75**	**75**	**75**	**75**
SA9: No waning. QoL does not decline in either arm after trial ends	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

❖ ***Which quality of life assumptions are preferred?***

BSC, best supportive care; QoL, quality of life; Y, year

ERG results – monotherapy

	Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
0	**Company's Base Case**	[redacted]	[redacted]	[redacted]	**25,749**
Combines sustained quality of life benefit post trial period and resource use using all available patient data					
6	25% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	32,118
7	50% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	37,378
8	75% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	44,579
9	No waning. QoL does not decline in either arm after trial ends	[redacted]	[redacted]	[redacted]	54,438
10	Removing stopping rule for dupilumab	[redacted]	[redacted]	[redacted]	29,468

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY; quality-adjusted life year; QoL, quality of life
Model: multiplicative adjustment for age

ERG results – combination therapy

	Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
0	**Company's Base Case**	[redacted]	[redacted]	[redacted]	**30,419**
Combines sustained quality of life benefit post trial period and resource use using all available patient data					
6	25% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	39,293
7	50% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	47,274
8	75% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	59,069
9	No waning. QoL does not decline in either arm after trial ends	[redacted]	[redacted]	[redacted]	77,701
10	Removing stopping rule for dupilumab	[redacted]	[redacted]	[redacted]	33,279

❖ ***Which analyses are preferred?***

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY; quality-adjusted life year; QoL, quality of life
Model: multiplicative adjustment for age

Innovation

- Designations:
  - “breakthrough therapy” by US Food and Drug Administration
  - MHRA Promising Innovative Medicine
  - Early Access to Medicine Scheme for severe atopic dermatitis
- Interleukin (IL)-4/IL-13-targeted mechanism of action tackles underlying inflammation associated with T-helper type 2 (Th2) pathway
- Area of high disease burden and unmet need
- No current effective treatments for patients whose disease does not respond to current systemic therapy, or are intolerant, contraindicated or cannot take systemic immunosuppressant therapies
- No targeted biologic therapies
- Benefit to society, carers and family not included in quality-adjusted life year

❖ ***Is dupilumab innovative?***

MHRA, Medicines and Healthcare products Regulatory Agency

Equality issues

- Assessing atopic dermatitis in patients with darker skin tones is complicated
  - more scattered papular lesions, lichen planus-like lesions, prurigo nodularis, lichenification, post-inflammatory changes and extensor involvement in patients with darker skin tones
  - outcome measures may have poor reliability and validity in patients with darker skin tones, because of erythema perception. Eligibility and response criteria based solely on EASI or other such measures of severity may not be sensitive to people with darker skin tones
- 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 predominate in most populations but some Asian populations IL-17 predominate

❖ ***Are there any equality issues to consider?***

EASI, Eczema Area and Severity Index

End of Part 1