Public observer slides for handout – contains noACIC information

Chair's presentation

Dupilumab for treating moderate to severe atopic dermatitis [ID1048]

2nd Appraisal Committee meeting

Committee B

Vice Chair: Sanjeev Patel

Lead team: Diar Fattah, Danielle Preedy and Stephen Smith

ERG: Aberdeen HTA Group

NICE technical team: Sharlene Ting, Ahmed Elsada, Jasdeep Hayre

10th May 2018

Background

Atopic dermatitis (also known as atopic eczema)

- Chronic, inflammatory, immune-mediated skin condition
  - ❖ Skin: red, thickened, dry, scaly plaques, bleeding, oozing, cracking, flaking and **itching**
- UK prevalence: 2.5% adults

Dupilumab (Dupixent, Sanofi Genzyme)

- Fully human monoclonal antibody
  - ❖ Inhibits inflammation
- **Marketing authorisation: "moderate to severe** atopic dermatitis in **adults** who are candidates for systemic therapy"
- Administration by subcutaneous injection
  - ❖ Dose: initial 600 mg then **300 mg once every 2 weeks**
    - ➢ **If no response, stop after 16 weeks**
  - ❖ Can be used with topical medications

Appraisal consultation document: preliminary recommendation

1.1 Dupilumab is **not recommended**, within its marketing authorisation, for treating moderate to severe atopic dermatitis in adults when systemic therapy is suitable

- ✓ **clinically effective** and **innovative**
- ✗ cost-effectiveness estimates: **high** (£29,792 to £77,701 per QALY gained) and **uncertain**
  - **no economic analyses included committee preferences** (more information on later slides)

QALY, quality-adjusted life year

Appraisal consultation document: consultation responses

- Consultee comments from:
  - Sanofi Genzyme (Company)
    - **new evidence, revised model, updated patient access scheme**
  - Allergy UK*
  - British Association of Dermatologists
  - National Eczema Society

- Commentator comments from:
  - Centre of Evidence-based Dermatology, University of Nottingham

- Web comments from:
  - 1 consultant physician
  - 11 patients/carers

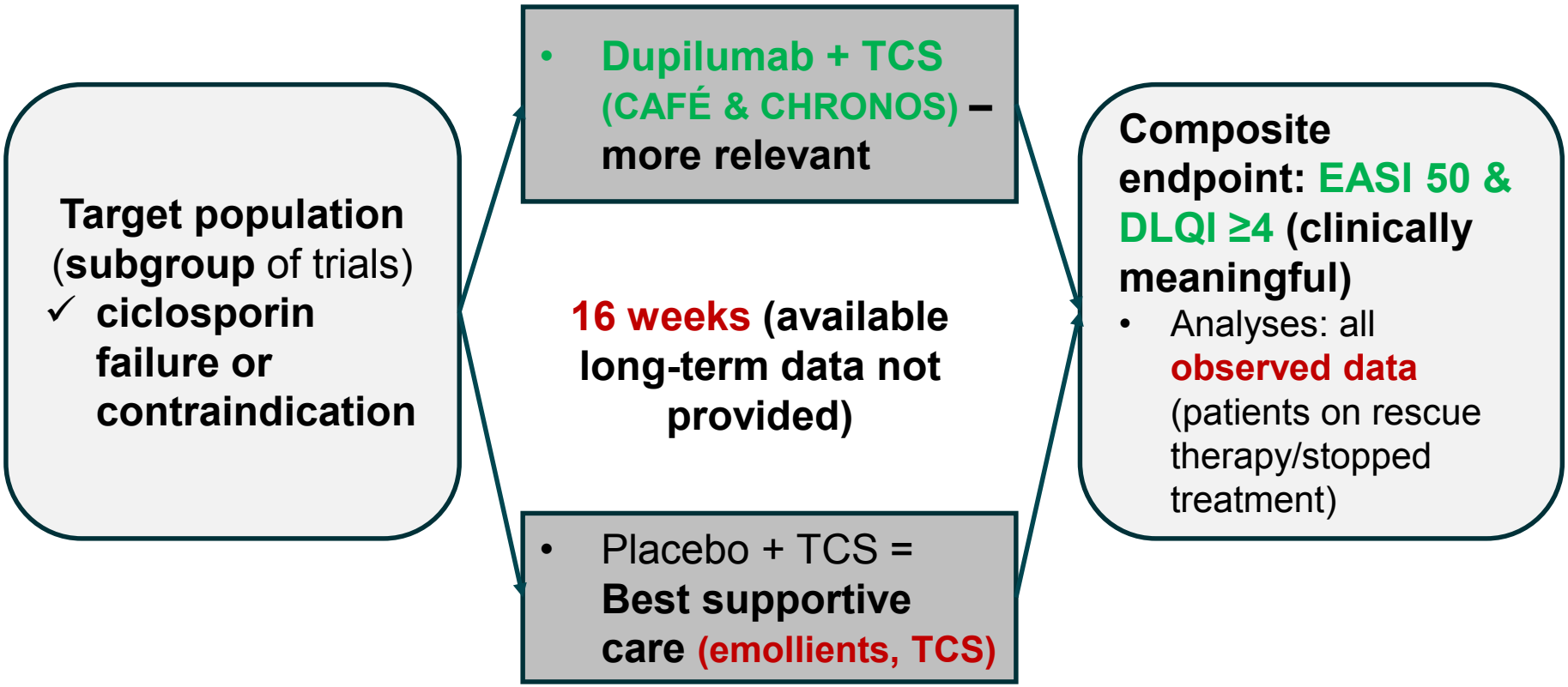
*received in a late patient organisation statement

Summary of consultees, commentators and web comments

	Consultation comments
Unmet need	• **Few effective options** for severe disease, **variable access**, **targeted treatment** with minimal side effects
Treatments burdensome	• Applying emollients: time consuming and tiring "*My children do not want me … near them when I am sticky*"
Disease impact underestimated	• Severe disease: significant burden on **all aspects** of life
Disease impact not considered	• Education/work/**productivity**, social/personal **relationships** • **Benefit to society, carers and family** not in QALYs
Dupilumab	• Innovative and **life-changing** • Likely used in **severe disease** after all systemic therapies • Should be an option after **failing 1 systemic therapy**, not all
Company's decision problem	• Subgroup with only ciclosporin (only used short term) • No active comparators (other systemic therapies) • BSC: not well represented by placebo groups in trials • No separate results for moderate and severe disease

QALY, quality-adjusted life year

Company's original base case, committee's conclusions and consultation comments



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

Appraisal consultation document key issues (section 3.25), company's revisions and ERG's views

Issue	Committee's conclusions	Company revised? ERG views
1	Best supportive care (BSC): has other treatments	Partially (see slide 16) **ERG: ✓ but in line with trial data?**
2	Preferred analysis: had rescue therapy? → 'non-responder'	✓ **ERG: ✓ (ICER increases by £63)**
3	Do not pool 'responders' and 'non-responders' in BSC	✓ **ERG: ✓ (ICER decreases by £653)**
4	Dupilumab constant yearly stopping rate (3.7%): low	Partially (see slide 15) – do new rates include people on rescue therapy?
5	Utility values **specific** to dupilumab 'non-responders'	Partially – average dupilumab & BSC 'non-responder' values **ERG: ✓ (minor impact)**
6a	BSC loss of utility benefit: occurs rapidly; how fast?	✓ (see slide 11)
6b	Dupilumab loss of utility benefit: data or TCS use	Partially (see slides 12-14) – no data on loss of benefit in 'responders' over time
7	BSC costs overestimated	× – model amended (see issue 3) **ERG: ✓**
8	Injection site reaction and A&E visits costs underestimated	✓ **ERG: ✓ (minor impact)**

A&E, Accident & Emergency; ICER, incremental cost-effectiveness ratio; TCS, topical corticosteroids

Company's new evidence on long-term effectiveness: open-label extension study

- international, **ongoing** (Oct 2013)
- weekly dupilumab (**unlicensed dose**)
  - ✓ topical corticosteroids
  - × no systemic/oral medications (can have as **rescue therapy**)
- [redacted] people from phase 1-3 trials (no adverse effects stopping study) **or** met parent trial criteria
  - ✓ [redacted] **'dupilumab-exposed'**
  - × [redacted] 'dupilumab-naïve'
- Few participants ([redacted]) at longest follow up ([redacted]; data cut: [redacted])

- **ERG:** open-label extension study is uncontrolled, non-randomised; [redacted]

*[redacted] had treatment blinded in parent study

Disease severity in CAFÉ/CHRONOS subgroup and open-label extension study

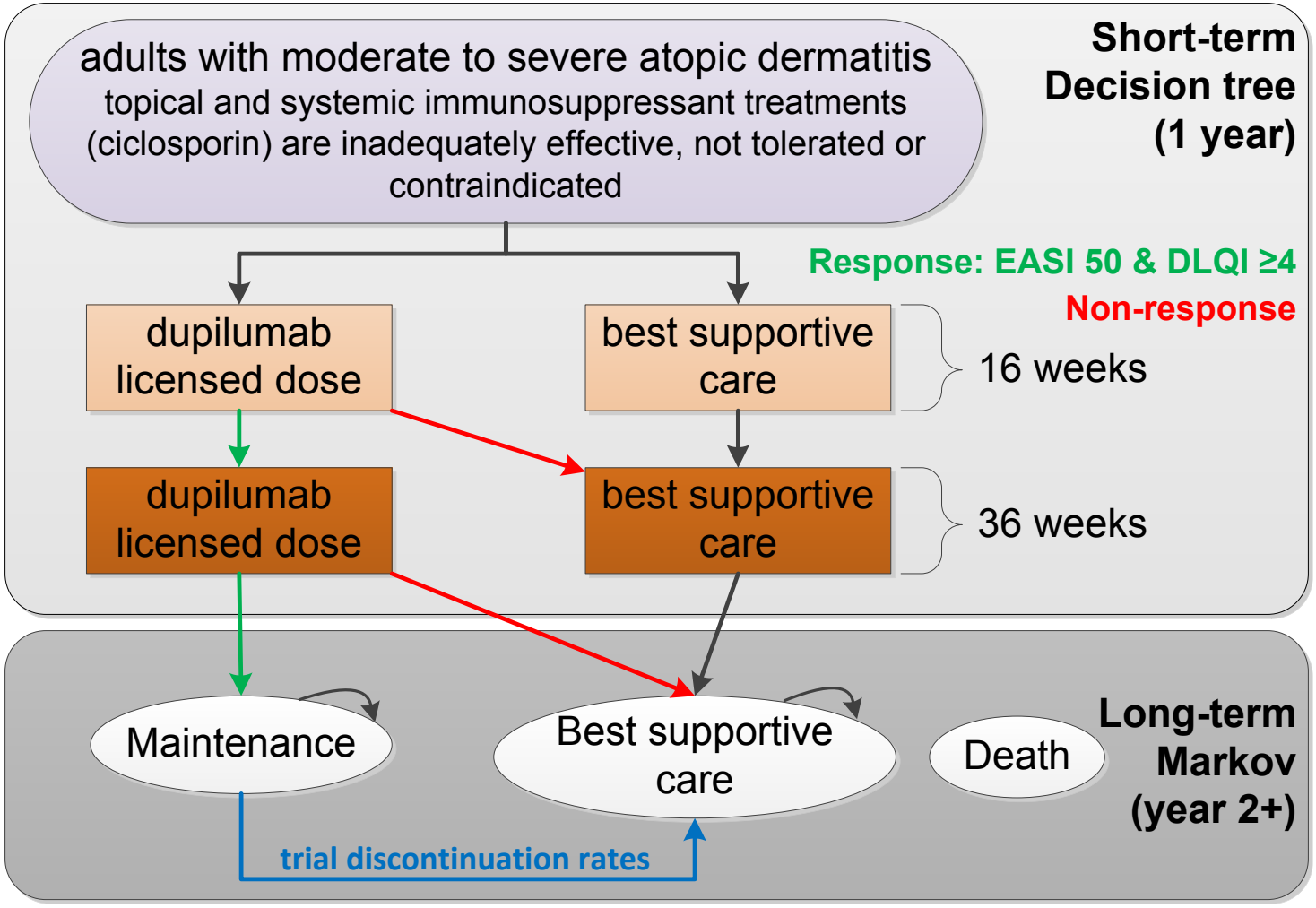
Measure	'Moderate'	'Severe'	Baseline mean (SD)		
			CAFÉ & CHRONOS subgroup, n=299	Open-label extension study	
				'dupilumab-exposed' subgroup, [redacted]	All [redacted]
EASI	7.1 – 21	21.1 – 50	35 (12)	[redacted]	[redacted]
DLQI	6 – 10	11 – 20	15 (8)	[redacted]	[redacted]
POEM	8 – 16	17 – 24	20 (6)	[redacted]	[redacted]

- **ERG:** open-label extension study patients have less severe disease than CAFÉ/CHRONOS subgroup

❖ ***Can data from the open-label extension study be used to support company's assumptions on the long-term effectiveness of dupilumab in the revised base case?***

DLQI, Dermatology Life Quality Index (0-30); EASI, Eczema Area and Severity Index (signs; 0-27); n, number of patients; POEM, Patient-oriented Eczema Measure (symptoms; 0-28); SD, standard deviation

Company model – original base case



- Lifetime horizon, annual cycle
- QALY gains from improved QoL, not extension of life

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; QALY, quality-adjusted life year; QoL, quality of life

Loss of utility benefit with best supportive care

Committee: Company stated BSC effect likely due to trial supervision improving adherence (stop after study ends). Benefit lost applied only to BSC. Committee agreed benefit of BSC likely lost fairly rapidly but how rapidly was uncertain

- **Company:**

Loss of benefit at:	Year 2	Year 3	Year 4	Year 5+
Original base case (feedback from 5 dupilumab investigators)	63%	91%	100%	**100%**
Revised base case (less rapid loss of benefit)	25%	50%	75%	**100%**
Sensitivity analysis: extrapolation / curve fitting of '**time to 1st rescue/stopping study**' (CHRONOS, BSC, 52 weeks)	82%	90%	94%	**96%**

ERG: sensitivity analysis rescue therapy → part of BSC → not good proxy

❖ ***How should long-term loss of utility benefit in best supportive care be modelled?***

BSC, best supportive care

Loss of utility benefit with dupilumab (1)

Committee: Should use long-term study data. Benefit lost in BSC because of trial supervision should apply to dupilumab (common trial protocol) → relative decline to BSC using TCS use in CAFÉ as proxy (51% in dupilumab *vs* 17% in BSC)

Company's original submission	Company's revisions / conclusions
• Loss of utility benefit in Years 2, 3, 4 and 5+: 2%, 5%, 7% and 8% • Based on feedback from 5 dupilumab trial investigators	• Open label extension study [redacted], [redacted] 'dupilumab-exposed': ❖ [redacted] ❖ TCS use decreased by [redacted] from baseline • EAMS **(1st patient: May 2017)** clinicians' feedback on 177 patients: maintenance of treatment effect and significant reduction in TCS use • **Revised base case: unchanged → plausible**

BSC, best supportive care; EAMS, Early Access to Medicines Scheme; TCS, topical corticosteroids

Open-label extension study results up to 100 weeks
'Dupilumab-exposed': had dupilumab before entering study

- **Company:** Open-label extension study data show [redacted]

	Baseline	Week 48	Week 76	Week 100
Number of 'dupilumab-exposed' patients reaching EASI 50 & DLQI ≥4	[redacted]	[redacted]	[redacted]	[redacted]
Number of 'dupilumab-exposed' patients providing data at time point Note: ongoing study, patients enter at different times → not drop outs	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of EASI 50 & DLQI ≥4 'responders'	[redacted]	[redacted]	[redacted]	[redacted]

- **ERG:** agrees with company → data can inform possible loss of benefit

❖ ***Do the open-label extension study data provide evidence for lack of loss of benefit with dupilumab?***

*number reaching treatment response / total number at that time point; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; QALY, quality-adjusted life year;

Loss of utility benefit with dupilumab (2)

- **Company:**
  - Disagrees with committee that without trial effect and TCS use, some of dupilumab benefit will be rapidly lost because:
    - both study groups had same mandated clinical contact **but** BSC had:
      - more TCS use (CAFÉ: 17% reduction in BSC *vs* 51% in dupilumab)
      - more rescue therapy (CHRONOS: 108 days in BSC *vs* 19 days in dupilumab)

      → unable to separate impact of these additional treatments
    - applying relative loss of benefit based on TCS reduction in CAFÉ → numbers too low at year 5 and do not match open-label extension study data or clinical insight

- **ERG:** agrees with company → use of relative decline based on TCS use requires strong assumptions → difficult to justify based on observed data

❖ ***How should long-term loss of utility benefit with dupilumab be modelled?***

BSC, best supportive care; n, number of patients; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; TCS, topical corticosteroids

Dupilumab stopping rates

Committee: Stopping rate for any reason appears low; should also include **patients having rescue therapy**; long-term data preferred

Company's original submission	Company's revisions / conclusions
• 3.7%: **'responders'** at week 16 who stopped for any reason at week 52 (CHRONOS) • Applied to Markov component from Year 2	• Open-label extension study stopping rates: ❖ 'responders' at weeks 12 and 24 ❖ 'responders' and 'non-responders' at week 52 • **Rates: 2.1%, 2.6%, 3.7%, 5.1% and 6.4%** ❖ ICERs: £27,623 to £30,126 • **Revised base case: unchanged → plausible**

- **ERG:** stopping rates (whole open-label extension study population; **dupilumab-naïve and exposed patients**) appear reasonable and consistent with available data
- **Note: unclear whether rates include patients on rescue therapy**

❖ ***Which stopping rate is most clinically plausible?***

ICER; incremental-cost effectiveness ratio

Company's base case: original and revised

	Original base case	Revised base case
BSC components	Emollients and TCS	**Added** annual phototherapy (6%) and psychological support (7%)
Analysis	All observed	Rescue/stop treatment = 'non-responders'
BSC utility	All patients: 0.811	• 'responders': 0.848 • 'non-responders': 0.773
Dupilumab stopping rate	**3.7%**	**No change**
Dupilumab 'non-responders' utility values	16 weeks and beyond: 0.811	• 16 weeks: 0.821 • 52 weeks and beyond: 0.773
Dupilumab loss of utility benefit (Year 2 to 5+)	**2%, 5%, 7%, 8%**	**No change**
BSC loss of utility benefit (Year 2 to 5+)	**63%, 91%, 100%, 100%**	**25%, 50%, 75%, 100%**
Resource use (case note review)	30 patients	59 patients
Injection site reaction costs	one-off	annual at rate of 9.1%
A&E costs	£137.82	£159.78
Other	Updated costs* and Patient Access Scheme	
ICER	[redacted]	**£28,495**

*latest Healthcare Resource Group and Personal Social Services Research Unit costs; A&E, Accident & Emergency; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; TCS, topical corticosteroids

Sensitivity analyses on loss of utility benefit assumptions for revised base case

	Proportion losing benefit (%)								ICER
	Dupilumab				BSC				
	Y2	Y3	Y4	Y5+	Y2	Y3	Y4	Y5+	
Company revised base case	**2**	**5**	**7**	**8**	**25**	**50**	**75**	**100**	**£28,495**
BSC: Weibull curve fit to CHRONOS 'time to rescue therapy/stopping study'	2	5	7	8	**82**	**90**	**94**	**96**	£27,410
BSC: annual rate for CHRONOS rescue therapy/study stopping	2	5	7	8	**57**	**82**	**92**	**97**	£27,756
Dupilumab: relative decline in TCS use in CAFÉ, 38.4%	**10**	**19**	**29**	**38**	25	50	75	100	£35,303
BSC: Weibull curve fit Dupilumab: relative decline in TCS use	**31**	**35**	**36**	**37**	**82**	**90**	**94**	**96**	£29,169

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; TCS, topical corticosteroids; Y, year

Affect on families and carers

- **Company:**
  - Impact of disease on families / carers' health-related quality of life
  - **No research** on disutility of atopic dermatitis on families / carers
  - Atopic dermatitis → substantial impact → scenario analyses on carers dis-utilities similar to other chronic conditions

Disutility impact on families and carers	ICER
Company revised base case Disutility impact on families and carers: none	£28,495
Carer utility benefit while patient on treatment: 0.01	£27,251
Carer utility benefit while patient on treatment: 0.1	£19,562

❖ ***Should carer utility benefit be included?***

ICER, incremental cost-effectiveness ratio

Key issues

- New evidence: open-label extension study
  - Generalisable to NHS practice?
  - Evidence of long-term loss of benefit in dupilumab 'responders'?
- Disease severity
  - Evidence for moderate and severe disease?
- Assumptions in model
  - Most clinically plausible dupilumab stopping rate?
  - How should long-term loss of benefit in dupilumab and best supportive care be modelled?
- Should utility benefits to carers be included?