Public observer slides – no ACIC information

Lead team presentation

Dimethyl fumarate for treating moderate to severe plaque psoriasis [ID776]

1st Appraisal Committee meeting

Committee B

Lead team: Miriam McCarthy, Nigel Westwood, Stuart Williams

ERG: Warwick Evidence

NICE technical team: Sharlene Ting, Jasdeep Hayre

21st June 2017

Summary of evidence

Clinical effectiveness

<u>BRIDGE randomised controlled trial results at 16 weeks</u>

- dimethyl fumarate *vs* placebo: higher PASI 75 levels
- dimethyl fumarate *vs* fumaderm: comparable levels (37.5% *vs* 40.3%)

<u>Network meta-analysis results at induction</u>

- Dimethyl fumarate *vs* all other treatments (fumaderm, apremilast, biologics): lowest probability of being ranked best for achieving PASI 75

Cost effectiveness

- Modelled in a treatment sequence
- Base case: dimethyl fumarate → adalimumab → ustekinumab→ best supportive care *vs* no dimethyl fumarate in the treatment sequence

<u>Incremental cost-effectiveness ratios (ICERs) for base case</u>

- Company (10 year horizon): dimethyl fumarate sequence is dominant
- ERG (lifetime horizon): £10,193

PASI Psoriasis area and severity index

Key issues for decision making

- Where would dimethyl fumarate fit in the treatment pathway?
- What are the most appropriate comparators?
- Is the BRIDGE trial
  - representative of moderate to severe psoriasis as defined in the NHS?
  - provide evidence to inform the company's chosen population – prior use of a systemic non-biologics?
- Is dimethyl fumarate, regardless of disease severity, clinically effective compared to
  - fumaderm
  - apremilast
  - biologics?
- Can the model inform decisions on the company's target population?
- Do the treatment sequences reflect clinical practice?
- Do people benefit from treatment soon after starting or later?
- Should the model include the costs of non-serious adverse events leading to stopping treatment?

Clinical effectiveness

Dimethyl fumarate
(Skilarence, LAS41008)
Almirall

Marketing authorisation
"moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy"

Mechanism

Monomethyl fumarate (active metabolite): fumaric acid ester

- acts on the immune system by changing cell types (Th1 and Th17 to Th2 cells)
- stops skin cells from multiplying and migrating

Administration and dose

Oral gastro-resistant tablets

- **Weeks 1-3:** 30 mg once daily, adding 1 tablet per week until 3 times daily
- **Weeks 4-9:** 120 mg once daily, adding 1 tablet per week until 3 times daily (maximum dose 720mg) or treatment success

Maintenance period: reduced to individualised dose

Average course of treatment: 24 months

Plaque psoriasis

- Chronic inflammatory skin disease characterised by flaky, scaly, itchy, red plaques
- Affects scalp, elbows, knees, back and sometimes face, groin, armpits and behind knees
- Unpredictable; relapsing and remitting course
- Graded mild, moderate or severe based on location, area affected, severity of lesions and impact on individual
- Prevalence of psoriasis in England:
  - 2% (951,000)
  - Plaque subtype 90% (856,000)
  - 15% classified as moderate (143,000)
  - 5% classified as severe (48,000)
- Associated with depression, obesity, anxiety, arthritis, cardiovascular disease

Patient and professional feedback

- Psoriasis at any level of severity can be distressing and debilitating, affecting all aspects of life, physically, psychologically and socially
- Need interventions that treat the cause, improve remission and control symptoms with minimal negative side effects
- People want immediate improvement of symptoms, with limited inconvenience and no adverse reactions
- Large body of clinical experience from Germany for dimethyl fumarate
- Side effect profile is different; fewer side effects from delayed release, gastro-resistant formulation
- Need compliance with monitoring to decrease risk of serious adverse events; high rates of discontinuation because of side effects in trials

Key outcome measures

Severity of psoriasis

Psoriasis Area and Severity Index (PASI)

- assess erythema, infiltration, desquamation and body surface area involvement on head, trunk, upper and lower limbs
- score: 0 (no psoriasis) to 72 (most severe disease)
- PASI 75 = 75% improvement from baseline

Physician Global Assessment (PGA)

- measure physician's impression of condition
- score: 0 (clear) to 5 (severe)

Body surface area (BSA)

- percentage of body surface area affected
- 75% reduction in body surface area: clinically meaningful

Quality of life

Dermatology Life Quality Index (DLQI)

- 10 questions: symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment
- score: 0 (no effect) to 30 (extremely large effect)
- 5 point difference: clinically meaningful

1st

Topical therapy
corticosteroid, vitamin D, vitamin D analogues, coal tar

2nd

Phototherapy
UVB, psoralen + ultraviolet A [PUVA]

3rd

Systemic non-biological therapy
methotrexate, ciclosporin, acitretin

dimethyl fumarate?

dimethyl fumarate?
company position

4th

Systemic biological therapy
Severe (PASI ≥10 & DLQI >10)
adalimumab (TA146)
etanercept (TA103)
ixekizumab (TA442)
secukinumab (TA350)
ustekinumab (TA180)
Very severe
(PASI ≥20 & DLQI >18)
infliximab (TA134)

Severe (PASI ≥10 & DLQI >10)
apremilast
(TA419)

dimethyl fumarate?

LEGEND
TNF-α inhibitor
IL-17 inhibitor
IL-12/IL-23 inhibitor
PDE-4 inhibitor
Th1 and Th17 → Th2

BSC

Best supportive care

DLQIDermatology Life Quality Index, PASIPsoriasis area and severity index

Decision problem

Company focuses on specific subgroup, omits non-biologics as comparators and psoriasis symptoms on face, scalp, nails, joints

NICE scope – Population	Company submission
Adults with moderate to severe chronic plaque psoriasis	*Specific subgroup*: "for whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and … unsuitable for biologic therapy"
NICE scope – Comparators	**Company submission**
• Fumaric acid esters (unlicensed use) • Systemic non-biologics (inc. acitretin, ciclosporin, methotrexate, phototherapy ± psoralen, apremilast) • Systemic biologics (inc. etanercept, adalimumab, secukinumab, ustekinumab, ixekizumab) • Best supportive care	Omitted systemic non-biologics (except apremilast)
NICE scope – Outcomes	**Company submission**
	Omitted psoriasis symptoms on the face, scalp, nails and joints

Current practice / comparators

1st Topical therapy

2nd Phototherapy

3rd Systemic non-biologics

4th Systemic biologics or apremilast

BSC Best supportive care

Marketing authorisation

"in need of systemic medicinal therapy"

Company proposed position?

No clinical or cost-effectiveness evidence submitted

Evidence BRIDGE ([redacted] systemic naïve)

Alternative to non-biologics?

- **When non-biologics are not appropriate/not effective AND**
- **Unsuitable for biologics?**

Same as apremilast?

Patients who:
- Do not meet NICE criteria for biologics
- Stable disease; not acute or severe
- Need long-term maintenance
- Non-biologics not effective or not suitable

Position and comparators – ERG comments

Population

- Contradictory positioning in company submission:
  - alternative to non-biologics & before biologics (3rd line)
  - only when other standard biologics are unsuitable or contraindicated (between 3rd and 4th line)
  - used similar to apremilast (4th line)
- Majority of evidence not in people ready for biologics:
  - [redacted] in BRIDGE trial were **systemic treatment naïve**

Comparators

- Company omitted systemic non-biologics:
  - unknown efficacy of dimethyl fumarate *vs* non-biologics
  - can use dimethyl fumarate after topical therapies (feedback from ERG clinical advisor)

- ***Where would dimethyl fumarate fit in the treatment pathway?***
- ***What are the most appropriate comparators?***

BRIDGE

Company-funded, phase 3, multicentre, 2:2:1 randomised, double-blind, placebo-controlled

[redacted] locations in 4 countries
0 in UK

Population: 704 adults with moderate to severe chronic plaque psoriasis ≥ 12 months

Key inclusion: PASI>10, PGA 3-5, BSA>10, prior systemic therapy or systemic naïve

- Dimethyl fumarate
- Fumaderm (fumaric acid)
- Placebo

Co-primary outcomes at week 16
- PASI 75
- PGA "clear" (0) or "almost clear" (1)

Key secondary outcomes
- PASI 50 and PASI 90
- DLQI
- Adverse events

Follow-up at 3, 8, and 16 weeks

Duration of study

4 week screening	16 week treatment (induction)	12 month follow up

BSA Body surface area, DLQI Dermatology Life Quality Index, PASI Psoriasis area and severity index, PGA Physician Global Assessment

Baseline characteristics

65% men, mean age 44 years, 99% Caucasian, 80% systemic naïve
Severity: 58% PGA moderate, mean PASI 16.3, mean DLQI 11.5

Demographics

- 65% men
- Mean age: 44.4 ± 14.5 (18 to 87) years
- 99% Caucasian

Severity of psoriasis

- Mean PASI: 16.3 ± 6.0
- Mean BSA : 21.7% ± 12.1
- PGA moderate (score=3): 57.9%
- PGA moderate to severe (score=4): 33.8%
- PGA severe (score=5): 4.3%
- Mean DLQI: 11.5 ± 6.7

History of systemic medication

- Standard non-biologics (methotrexate, ciclosporin, acitretin): 19%
- Biologics (adalimumab, etanercept, brodalumab, secukinumab, ustekinumab): 3%
- Fumaderm or apremilast: 3.7%

BSA Body surface area, DLQI Dermatology Life Quality Index, PASI Psoriasis area and severity index, PGA Physician Global Assessment

Results – PASI, PGA and DLQI at 16 or 52 weeks

Dimethyl fumarate better than placebo and comparable to fumaderm

Outcome	Dimethyl fumarate (n = 267)	Fumaderm (n = 273)	Placebo (n = 131)	Dimethyl fumarate vs placebo	Dimethyl fumarate vs fumaderm
PASI 75	37.5%	40.3%	15.3%	22.2% (10.7 to 33.7)*	-2.8% (-14 to 8.4)*
PGA 0 or 1	33.0%	37.4%	13.0%	20.0% (8 to 30)*	4.0% (-15 to 7)*
PGA 0 (clear)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse rate at 52 weeks^	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean DLQI (SD)[b]	[redacted] 5.4 (6.1)	[redacted] 6.1 (7.2)	[redacted] 8.5 (6.9)	-3.2 (-4.7 to -1.8)	-0.7 (-1.8 to 0.5)

*risk difference (99.24% confidence intervals), [a]ERG calculated risk difference and 95% confidence intervals, [b]Observed numbers provided in company clarification response (least square means and 95% confidence intervals), [DLQI]Dermatology Life Quality Index, [PASI]Psoriasis area and severity index, [PGA]Physician Global Assessment, ^Relapse rate (≥50% reduction in PASI from maximal improvement)

Definition of severity and subgroup analysis results

ERG: severity is unlikely to be an effect modifier

Previous NICE Technology Appraisals guidance definitions:
Severe: PASI≥10 and DLQI>10 **Very severe:** PASI≥20 and DLQI>18

Subgroup	Dimethyl fumarate vs placebo*	
	PASI 75	PGA 0 or 1
PASI moderate (score 10 to 20) ([redacted])	[redacted]	[redacted]
PASI severe (score >20) ([redacted])	[redacted]	[redacted]
PGA moderate (score=3) ([redacted])	[redacted]	[redacted]
PGA severe (score 4 or 5) ([redacted])	[redacted]	[redacted]

*risk difference (95% confidence intervals), DLQIDermatology Life Quality Index, PASIPsoriasis area and severity index, PGAPhysician Global Assessment

- ***How is moderate/severe psoriasis defined in clinical practice?***
- ***Is the BRIDGE population representative of moderate to severe psoriasis as defined in the NHS?***

Target population (prior systemic use): baseline characteristics [redacted]

	Systemic naïve (n = 538)			Pre-treated with systemic (n = 133)		
	Dimethyl fumarate ([redacted])	Fumaderm ([redacted])	Placebo ([redacted])	Dimethyl fumarate ([redacted])	Fumaderm ([redacted])	Placebo ([redacted])
% Men	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% PASI: moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% PGA: moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSA*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Mean (standard deviation), [BSA]Body surface area, [DLQI]Dermatology Life Quality Index, [PASI]Psoriasis area and severity index, [PGA]Physician Global Assessment

Target population (prior systemic use): post hoc analysis results

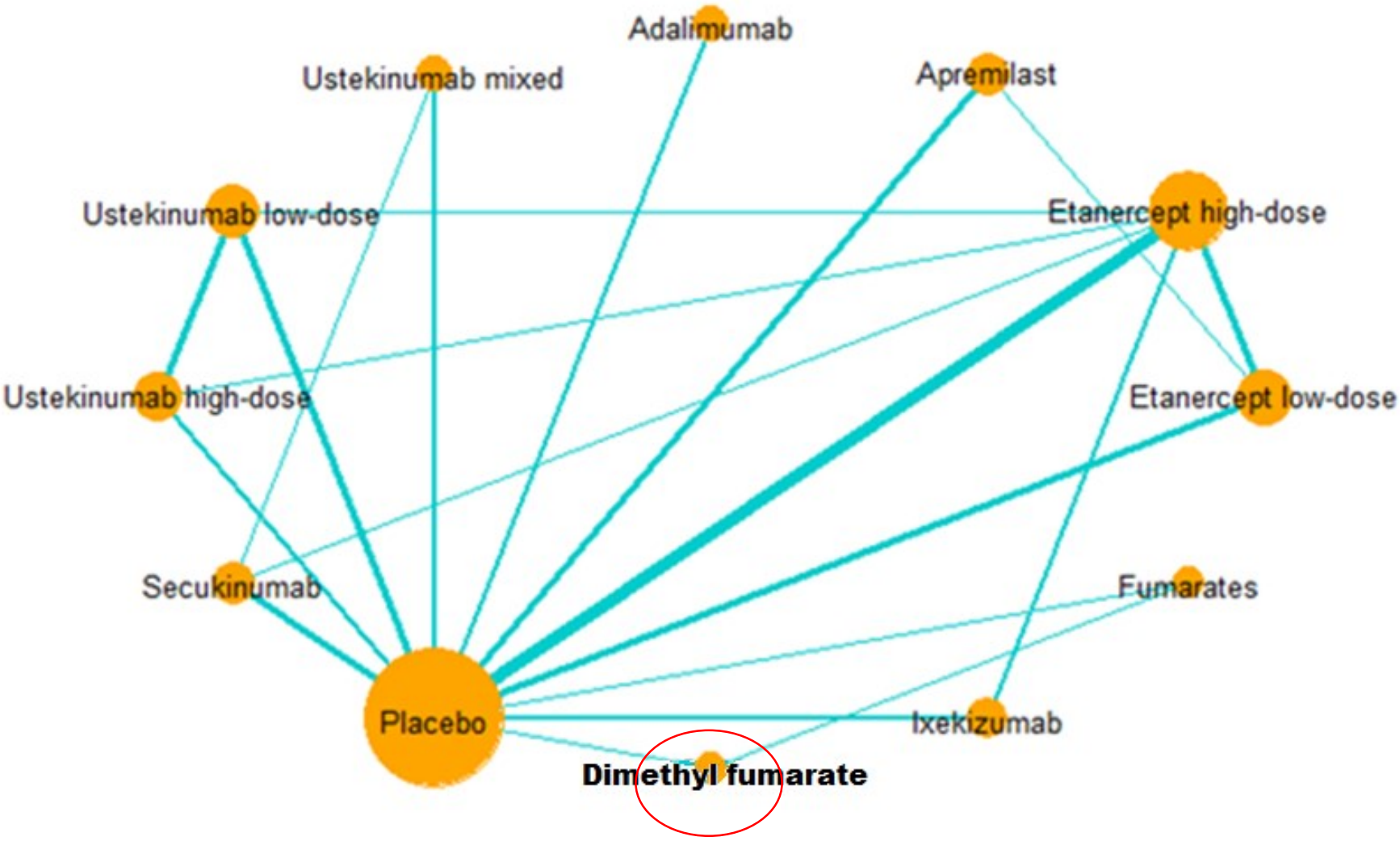
Arms [redacted]

	Systemic naïve (n = 538)			Pre-treated with systemic (n = 133)		
	Dimethyl fumarate ([redacted])	Fumaderm ([redacted])	Placebo ([redacted])	Dimethyl fumarate ([redacted])	Fumaderm ([redacted])	Placebo ([redacted])
PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate vs placebo*	[redacted]			[redacted]		
Dimethyl fumarate vs fumaderm*	[redacted]			[redacted]		
PGA 0 or 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate vs placebo*	[redacted]			[redacted]		
Dimethyl fumarate vs fumaderm*	[redacted]			[redacted]		

*risk difference (95% confidence intervals), [PASI]Psoriasis area and severity index, [PGA]Physician Global Assessment

- ***Are the BRIDGE results for all patients generalisable to the company's target population (prior systemic use)?***

Network meta-analysis: Bayesian approach
Common comparator is placebo



Base case (all patients): PASI response (PASI 50/75/90) at induction [redacted]

PASI Psoriasis area and severity index

Base case: Absolute probabilities (PASI 50/75/90 at induction)

Dimethyl fumarate better than placebo. Probability of response lowest compared to other active treatments

Intervention	Primary: PASI 75*	PASI 50*	PASI 90*
Placebo	0.05 (0.05, 0.06)	0.16 (0.14, 0.17)	0.01 (0.01, 0.01)
Dimethyl fumarate	**0.18 (0.12, 0.25)**	**0.38 (0.29, 0.48)**	**0.05 (0.03, 0.09)**
Fumaderm	0.23 (0.16, 0.31)	0.45 (0.36, 0.55)	0.08 (0.05, 0.12)
Apremilast	0.27 (0.23, 0.32)	0.50 (0.45, 0.56)	0.10 (0.08, 0.12)
Adalimumab	0.64 (0.58, 0.70)	0.83 (0.79, 0.87)	0.36 (0.31, 0.43)
Etanercept low-dose 25mg	0.38 (0.34, 0.42)	0.62 (0.57, 0.66)	0.16 (0.13, 0.18)
Etanercept high-dose 50mg	0.54 (0.51, 0.57)	0.76 (0.74, 0.78)	0.28 (0.25, 0.30)
Ixekizumab	0.91 (0.89, 0.93)	0.98 (0.97, 0.98)	0.74 (0.71, 0.78)
Secukinumab	0.83 (0.80, 0.86)	0.94 (0.93, 0.96)	0.61 (0.56, 0.65)
Ustekinumab low-dose 45mg	0.73 (0.69, 0.76)	0.89 (0.87, 0.91)	0.46 (0.42, 0.50)
Ustekinumab high-dose 90mg	0.77 (0.74, 0.80)	0.91 (0.89, 0.93)	0.52 (0.47, 0.56)
Ustekinumab mixed 45/90mg	0.67 (0.62, 0.71)	0.85 (0.82, 0.88)	0.39 (0.34, 0.45)

*Median (95% credible intervals), [PASI]Psoriasis area and severity index

❖ ***Is dimethyl fumarate clinically effective compared to fumaderm, apremilast and biologics?***

Safety

Higher stopping rates with dimethyl fumarate than placebo, but comparable to fumaderm

Short-term safety (BRIDGE)	Dimethyl fumarate (n = 279)	Fumaderm (n = 283)	Placebo (n = 137)
Treatment emergent adverse event leading to stopping of treatment*	24%	24%	6%
Treatment-related adverse event	74%	74%	40%
Serious treatment emergent adverse event	3%	3%	4%
Treatment-related serious treatment emergent adverse event	0%	1%	0%

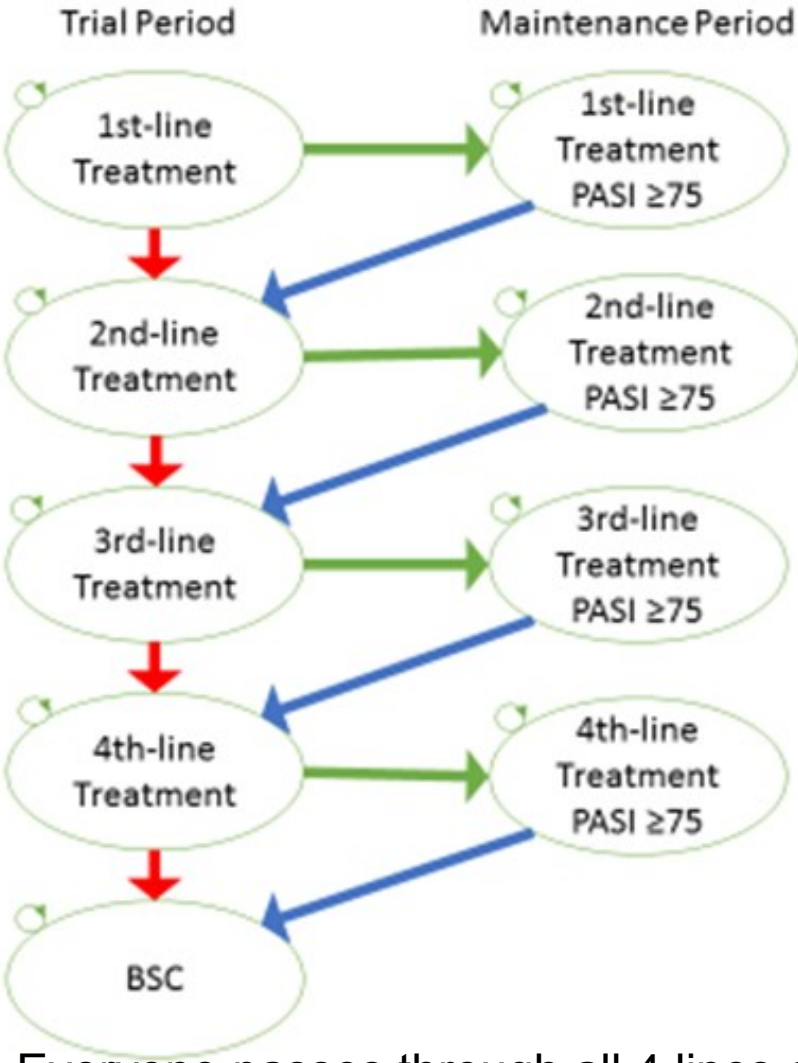
*most common events were [redacted]

Treatment stopping rates reported in 2 long term retrospective studies:

- 17% (171 of 984 people after 44.1 months)
- 24% (42 of 176 people, after 28 months)

Cost effectiveness

Company model – Structure



Everyone passes through all 4 lines of treatment, even if it is best supportive care (2 week cycle)

- Markov state transition model
- 2 week cycle length
- 2 treatment sequences
- Treatment-specific trial periods (induction: 10, 12 and 16 weeks)
- Responders treatment stopping rate (discontinuation): constant annual 20%

Death at any time (independent of treatment or response status)

- NHS/PSS
- 3.5% discount rate

Adverse events not considered

No underlying disease progression assumed

Company model and base case – ERG comments

Baseline characteristics	Attributes affect all-cause mortality: • lower proportion of men (50% in model vs 66% in BRIDGE) • higher baseline age (50 in model vs 44 years in BRIDGE) Average weight 77.8kg*
Time horizon	10 year time horizon insufficient for treatment sequences to play out → over-estimates health benefits → ≥25 years **Key driver of ICER**
Rate of stopping treatments	Should be treatment specific because of different routes of administration and side effect profiles
Non-serious adverse events	In BRIDGE, dimethyl fumarate has higher non-serious adverse event rates than placebo leading to stopping treatment → increased GP visits and/or prescriptions

*FUTURE retrospective study

- ***Do the baseline characteristics of the modelled population reflect the NHS population in terms of sex, age and weight?***
- ***Which time horizon is appropriate?***
- ***Is a 20% constant rate over time of stopping treatment appropriate for all treatments?***
- ***Should non-serious adverse events leading to stopping treatment be modelled given the cost implications such as increased GP visits?***

Company model – Health states

Trial period or induction	• Treatment-specific response at 10, 12 or 16 weeks (based on NICE guidance)

Maintenance period	• Responders after induction (≥PASI 75) continue on treatment
	• Cohort split into people with:
	  • PASI 75 to 90
	  • PASI >90

Best supportive care	• PASI response of placebo arm in network meta-analysis
	• Cohort split into people with:
	  • PASI <50
	  • PASI 50 to 74
	  • PASI 75 to 90
	  • PASI >90

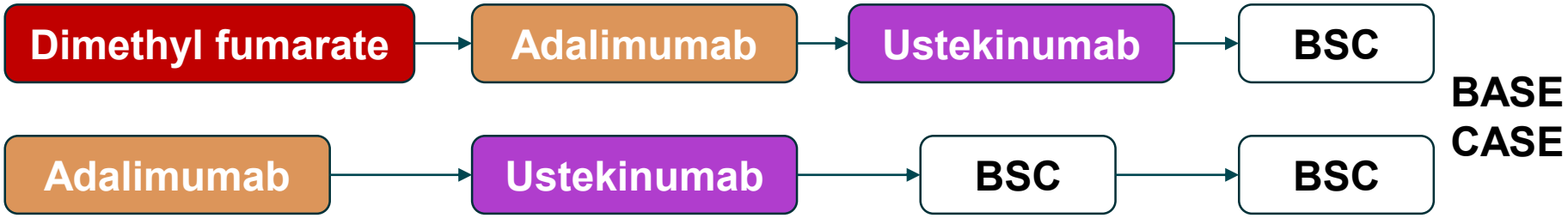
PASI Psoriasis area and severity index

Company model – Transition probabilities

Induction trial to maintenance	• PASI 75 response (based on network meta-analysis; constant over time) • Proportion of patients achieving a PASI 75 response at end of induction • Fumaderm assumed to be the same as dimethyl fumarate in base case
Maintenance to next treatment or best supportive care	• All cause, constant annual treatment stopping rate of 20% (based on TA368/BADBIR) • Move to best supportive care: inadequate response to last active treatment
Any state to death	• Age-specific mortality rates (time dependent) • Background age specific annual mortality rates from UK life tables

BADBIR British Association of Dermatologists Biologic Interventions Register, PASI Psoriasis area and severity index

Treatment sequences overview – ERG comments



ERG: inserting a treatment into a sequence results in gains in patient quality-adjusted life-year, regardless of how poorly it performs clinically because it delays best supportive care

Company and ERG explored different positions of dimethyl fumarate in a range of comparisons:

- Dimethyl fumarate before biologics *vs* no dimethyl fumarate before biologics (including base case)
- Dimethyl fumarate before biologics *vs* apremilast before biologics
- Dimethyl fumarate before biologics *vs* dimethyl fumarate after biologics

BSC best supportive care

Base case and other treatment sequences modelled

	Comparisons
Dimethyl fumarate before biologics *vs* no dimethyl fumarate before biologics	**BASE CASE (Company and ERG): DMF→ADA→UST→BSC *vs* ADA→UST→BSC**
	Company: **DMF→ETA→ADA→UST *vs* ETA→ADA→UST→BSC** **DMF→ADA→SEC→BSC *vs* ADA→SEC→BSC**
	ERG: DMF→ETA→UST→BSC *vs* ETA→UST→BSC
Dimethyl fumarate *vs* apremilast before biologics	**Company and ERG: DMF→ADA→UST→BSC *vs* APR→ADA→UST→BSC**
	Company: DMF→ADA→SEC→BSC *vs* APR→ADA→SEC→BSC
Dimethyl fumarate before biologics *vs* dimethyl fumarate after biologics	**Company and ERG: DMF→ADA→UST→BSC *vs* ADA→UST→DMF→BSC**
	ERG: **DMF→APR→ADA→UST *vs* APR→ADA→UST→DMF** **DMF→ETA→UST→BSC *vs* ETA→UST→DMF→BSC**

ADAadalimumab, APRapremilast, BSCbest supportive care, DMFdimethyl fumarate, ETAetanercept, SECsecukinumab, USTustekinumab

- ***Do the treatment sequences reflect clinical practice?***
- ***Which comparisons are relevant to the decision problem?***

Company model and ERG exploratory analyses Inputs: Health utilities – values

ERG used QoL increments for all patients and those with 4th quartile DLQI (severe) derived from NICE TA103 (etanercept)

Baseline HRQoL for all patients: 0.70 (Revicki et al. 2008, to ensure consistency with previous NICE Technology Appraisals)

PASI response	Mean HRQoL increment (standard error)*	
	All patients^	Severe: 4th quartile DLQI**
PASI<50	0.05 (0.01)	0.12 (0.03)
PASI 50-75	0.17 (0.04)	0.29 (0.06)
PASI 75-90	0.19 (0.04)	0.38 (0.08)
PASI 90+	0.21 (0.05)	0.41 (0.09)

*Values taken from Woolacott et al. 2006. Grouping of all patients and severe as taken directly from Woolacott et al. 2006

^Company only used "All patients" QoL increment in its base case

**Baseline HRQoL adjusted to 0.50 to overcome quality of life ceiling effects

HRhealth related, DLQIDermatology Life Quality Index, PASIPsoriasis area and severity index, QoLquality of life

Company model – ERG comments
Health-related quality of life

QoL increments	**Company**	For 1st line treatment induction: QoL does not improve compared to baseline; for same treatments from 2nd line in sequence: QoL improvement applied
	ERG	QoL improves more in sequences with more treatments. **All treatments during the trial period are given the same baseline QoL values**
QoL ceiling effects	**Company**	Base case QoL 0.70 with a ceiling of 1.00
	ERG	Company results: little effect between all-patient and severe QoL increments. Ceiling effects: maximum gain of 0.30. **ERG Scenario analysis: arbitrarily reduce baseline QoL for severe to 0.5**
Age-related QoL	**ERG**	Extended time horizon → more comorbidities → age-weighted QoL. Model does not assume that treatment extends life → no impact if only the base QoL is weighted. To impact results: QoL increments associated with PASI responses must be weighted

PASIPsoriasis area and severity index, QoLquality of life

❖ ***What is the most appropriate way of modelling increases in QoL?***

Company model and base case – ERG comments
Costs in people who do not respond to treatment
Halved non-responder costs from £225 to £121 ***Key model input***

Company model and base case	ERG comments and amendments
• Based on apremilast (TA419) ERG estimate of £5,850 annual or £225 fortnightly • TA419 ERG estimates range from £45 to £348	• TA419 estimate based on 28 day cycle. Corrected cost for 14 day cycle: £112 per fortnight or £2,925 per annum • Additional changes based on company clarification response: £3,001 per annum or £128 per fortnight • ERG corrected: phototherapy rate from 2.72 to 2.76, inflation rate from 9.8% to 15.6% (June 2008 Fonia) • Adjusted for inflation, non-responder costs are higher for longer treatment sequences. **Applied non-responder costs during trial periods to £121***

*model separately accounts for outpatient visits among non-responders trialling new drugs; broadly in line with the £225 per 28 days estimated by the ERG of the apremilast technology appraisal guidance [TA419]

ERG exploratory analysis

	Company base case	ERG changes
Time horizon	10 years	Lifetime **Key driver of ICER**
Apremilast induction pack cost	Normal pack used	Reduced costs by £10
Ixekizumab trial period	12 weeks (coding error)	12 weeks
Etanercept and ustekinumab dose	High dose	Low dose
Infliximab vials	Vials are divisible	Indivisible vials + admin costs
Trial period QoL at baseline	Different for each treatment	Same for each treatment
Drug wastage	None	14 days of waste
Best supportive care costs	£185/fortnight	£189/fortnight: updating Fonia unit costs
Costs in people not responding to treatment	£225/fortnight	£121/fortnight (outpatient costs separate) **Key model input**
Outpatient monitoring	Not included	Additional £36 for GP appointments for blood tests

❖ ***Which base case inputs are preferred?***

ERG sensitivity analyses
Dimethyl fumarate dosing and monitoring

Dimethyl fumarate and fumaderm dosing	**Company**	• Applies dimethyl fumarate induction dose to fumaderm (624mg from BRIDGE trial *vs* 517mg in literature*) • Assumes dimethyl fumarate maintenance dose (360mg) is the same as fumaderm good responders*
	ERG	**Sensitivity analysis: fumaderm induction dose assumed to be 70% than in BRIDGE trial and dimethyl fumarate maintenance dose assumed to be 70% of the average dose from weeks 10 to 16 from the BRIDGE trial**
Dimethyl fumarate monitoring	**Company**	Model assumes blood tests are required every month but does not cost any visit
	ERG	**Sensitivity analysis: reduce frequency of tests to draft SmPC (every 3 months)** ***At factual inaccuracy check, company confirmed that monitoring for dimethyl fumarate takes place every 3 months***

*FUTURE retrospective study on fumaderm, SmPC summary of product characteristics

❖ ***What is the most common maintenance dose for dimethyl fumarate in clinical practice?***

Company and ERG base case results – list prices

	Probabilistic ICERs (£/QALY)			
	All patients QoL increment*		Severe QoL increment*	
	Company	ERG	Company	ERG
Base case: DMF→ADA→UST→BSC *vs* ADA→UST→BSC	Dominant	£10,193 NE	NA	£5,550 NE

ERG sensitivity analyses on base case: DETERMINISTIC results				
	Deterministic ICERs (QALY)			
	All patients QoL increment*		Severe QoL increment*	
	Company	ERG	Company	ERG
Dimethyl fumarate 70% dosing	NA	£20,692 NE	NA	£11,628 NE
Dimethyl fumarate SmPC monitoring frequency	NA	£8,396 NE	NA	£4,718 NE

Note: Company results based on 10 year horizon, ERG results on lifetime horizon

ADAadalimumab, APRapremilast, BSCbest supportive care, DMFdimethyl fumarate, ICERincremental cost-effectiveness ratio, NAnot available, NEnorth east, QALYquality-adjusted life year, QoLquality of life, SmPCSummary of product characteristics, USTustekinumab

*Refers to all patient QoL estimates and severe patient QoL estimates taken from NICE technology appraisal guidance on etanercept (TA103), not severity of psoriasis

Other treatment sequences: Company and ERG results

Results presented in Part 2 only because they include confidential comparator discounts

Innovation and equality

- Dimethyl fumarate:
  - first fumaric acid ester licensed in the UK for treatment of moderate to severe plaque psoriasis in adults
  - 7.6% of patients receiving conventional systemic therapy are receiving unlicensed fumaric acid esters

- When using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate (TA442 – ixekizumab)

- When using the Dermatology Life Quality Index (DLQI), healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI … (TA442 – ixekizumab)

PASIPsoriasis area and severity index

❖ ***Is dimethyl fumarate innovative?***
❖ ***Are there any equality issues to consider?***

END OF PART 1