NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

For public – information REDACTED

Pre-meeting briefing

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

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

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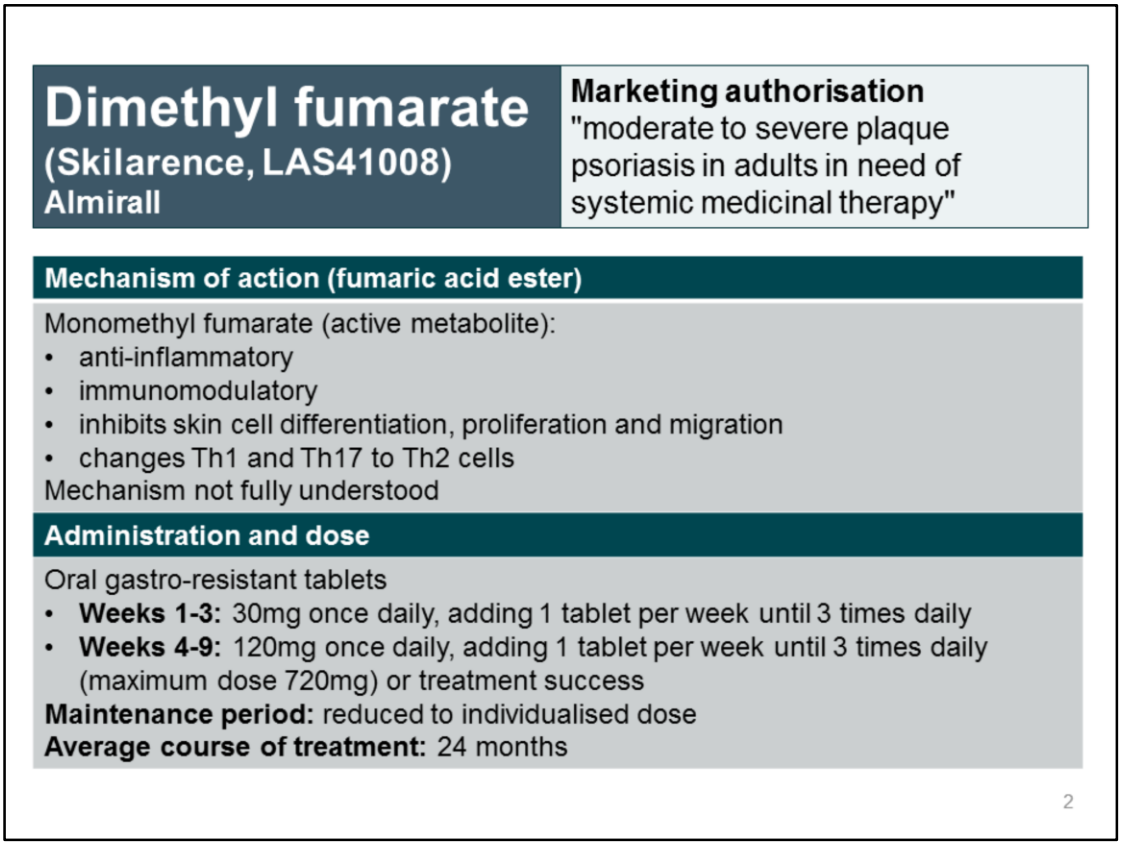

Sources: EMA website [http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002157/WC500226211.pdf Accessed 17/05/2017]. Company submission: Table 2, pages 15-16; section 2.1, page 23; Table 4, pages 26-27.

Key issues for consideration
Clinical effectiveness

- Unclear position of the technology:
  - alternative to non-biologics? No evidence submitted for standard non-biologics
  - alternative to biologics or apremilast?
  - when non-biologics are not appropriate or not effective AND for whom biologics are unsuitable (do not meet criteria) → between 3rd/4th line?
- What are appropriate comparators?
  - company compares against fumaric acid esters (fumaderm), apremilast and biologics, not standard non-biologics – is this appropriate for the position of the technology?
- Generalisability of BRIDGE trial (appropriate population, comparators and design)?
- Definition of severity (BRIDGE included PASI>10, PGA 3-5, BSA >10; mean PASI 16.3±6.0, mean DLQI 11.5±6.7, 58% PGA moderate), previous TA guidance (severe: PASI≥10, DLQI>10)
- Is dimethyl fumarate a clinically-effective treatment?
  - does treatment wane (evidence?)

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Key issues for consideration
Cost effectiveness

- Clinically appropriate positioning of DMF in treatment and comparator sequences?
- Appropriate time horizon (10 years or lifetime)?
- Appropriate dose for etanercept and ustekinumab (low or high)?
- Quality of life:
  - during induction, should QoL be different between treatments because of early response?
  - are increments for a <PASI50 response and a PASI90 response for a treatment with poor response likely to be the same as those for a treatment with good response?
- Does the fumaderm study give a plausible estimate for DMF maintenance dose? (end of induction mean dose lower than in BRIDGE)
- What fortnightly cost should be applied to those trialling treatments?
  - best supportive care as drawn from Fonia?
  - assume immediate response from responders and take a weighted average: (% PASI75 non-responders x BSC cost) + (% PASI75 responders x Fonia cost for non-biologic or biologic)?
- How should the costs of Fonia be viewed given the patient group and current NHS reference costs?
- Should non-serious adverse events leading to discontinuation be costed?
- Innovation

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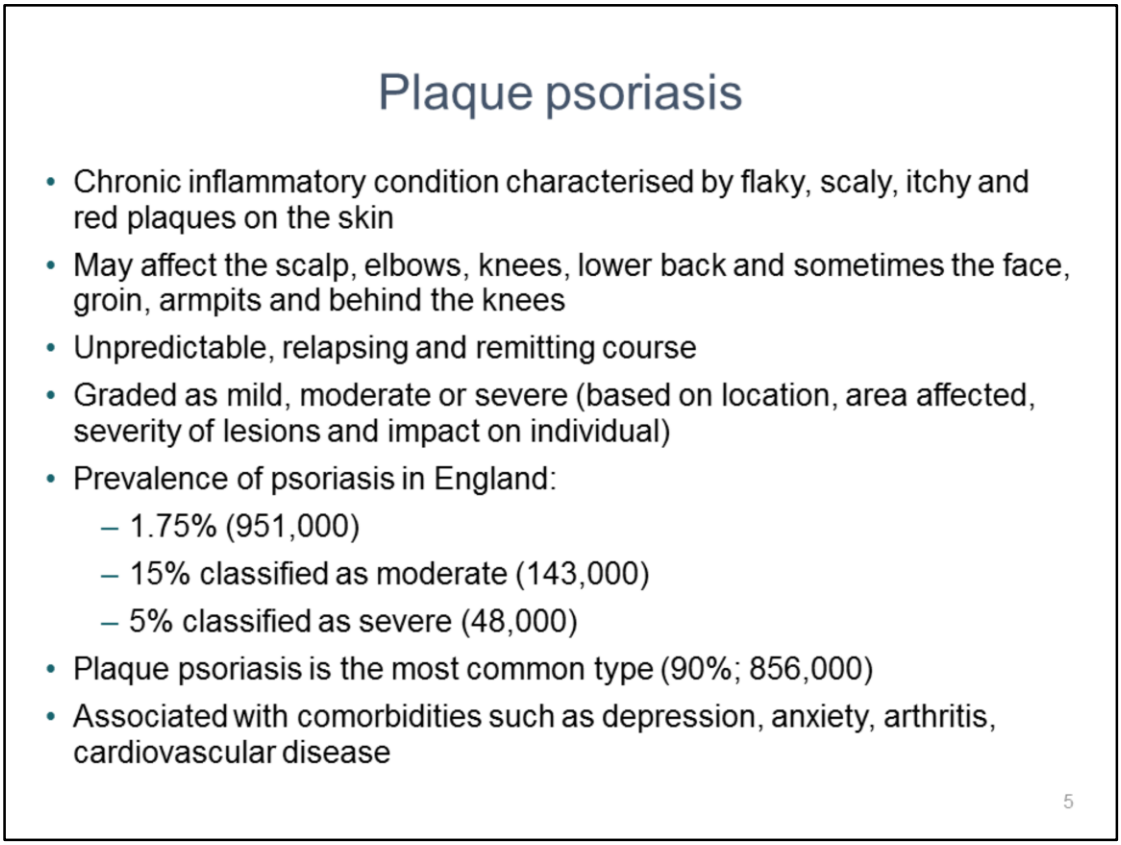
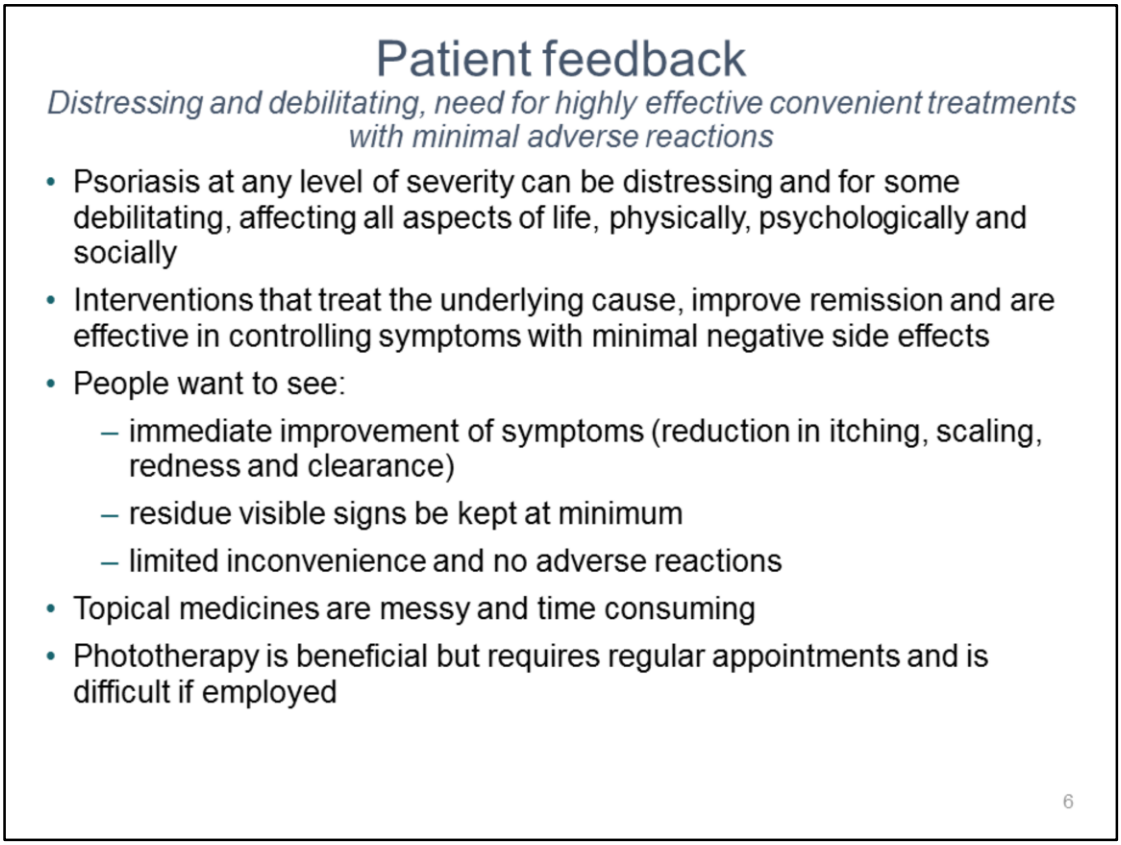
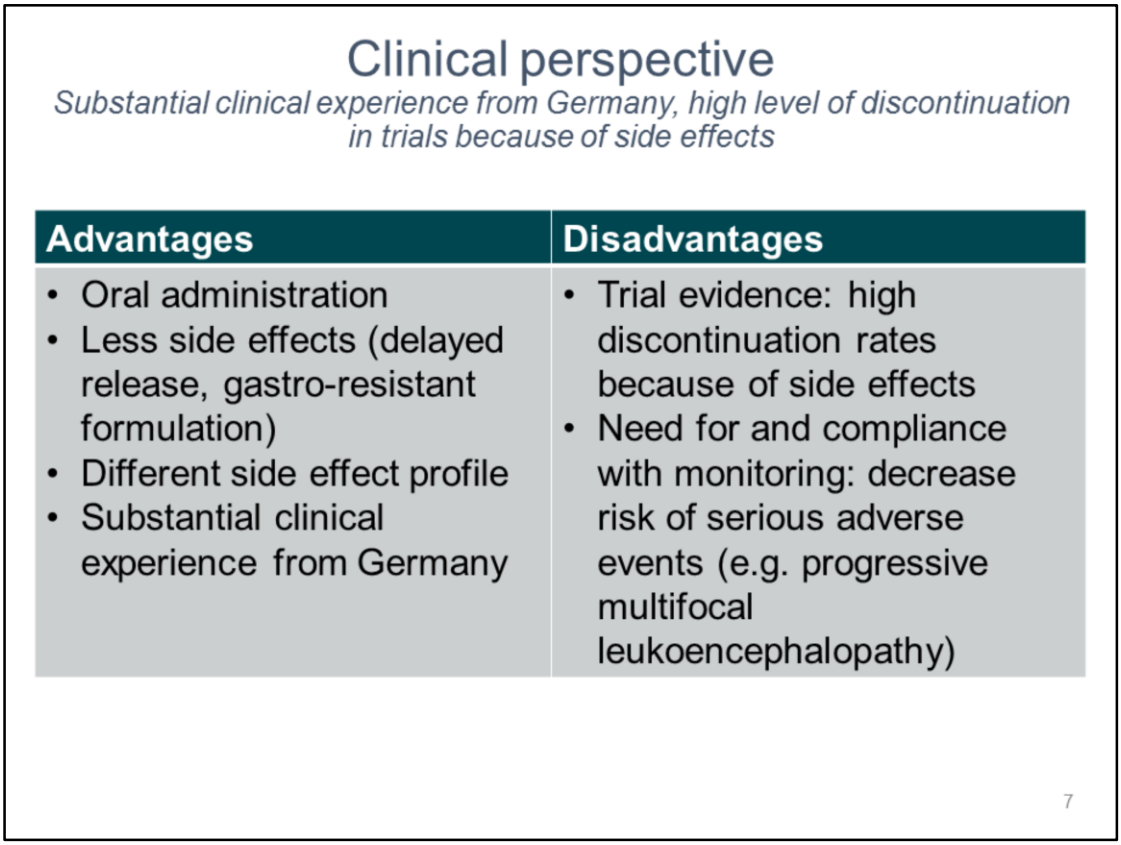


Sources: Final NICE scope: page 1. Company submission: page 8; section 3.2, page 30.



Source: Psoriasis and Psoriatic Arthritis Alliance (PAPAA).



Sources: British Association of Dermatologists. UK Clinical Pharmacy Association.

Decision problem – population

Company submission focuses on a specific subgroup

NICE scope	Company submission
Adults with moderate to severe chronic plaque psoriasis	Adults with moderate to severe chronic plaque psoriasis in whom: - other non-biological systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or not effective - are considered unsuitable for biological therapy
Company rationale	
Represents clinical practice. UK dermatologists suggest profile of a typical patient on fumaric acid esters is: • pre-biological (does not meet criteria for NICE recommended biologics) • relatively stable condition, not acute or severe • in need of longer term maintenance • other systemic treatments are not effective; contraindicated or intolerant to methotrexate and ciclosporin	

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Sources: NICE final scope: page 2. Company submission: Table 1, page 12; pages 36-37. Clarification response: A1, page 1.

Decision problem – comparators

Company submission does not include standard non-biological systemic therapies

NICE scope	Company submission
• Fumaric acid esters (unlicensed use) • Systemic non-biological therapies (inc. acitretin, ciclosporin, methotrexate, phototherapy ± psoralen, apremilast) • Systemic biological therapies (inc. etanercept, adalimumab, secukinumab, ustekinumab, ixekizumab) • Best supportive care	• Fumaric acid esters (e.g. fumaderm) • Apremilast • Systemic biological therapies (inc. etanercept, adalimumab, secukinumab, ustekinumab, ixekizumab*) • Best supportive care (for people in whom biologic therapies are not tolerated or contraindicated)^

Company rationale

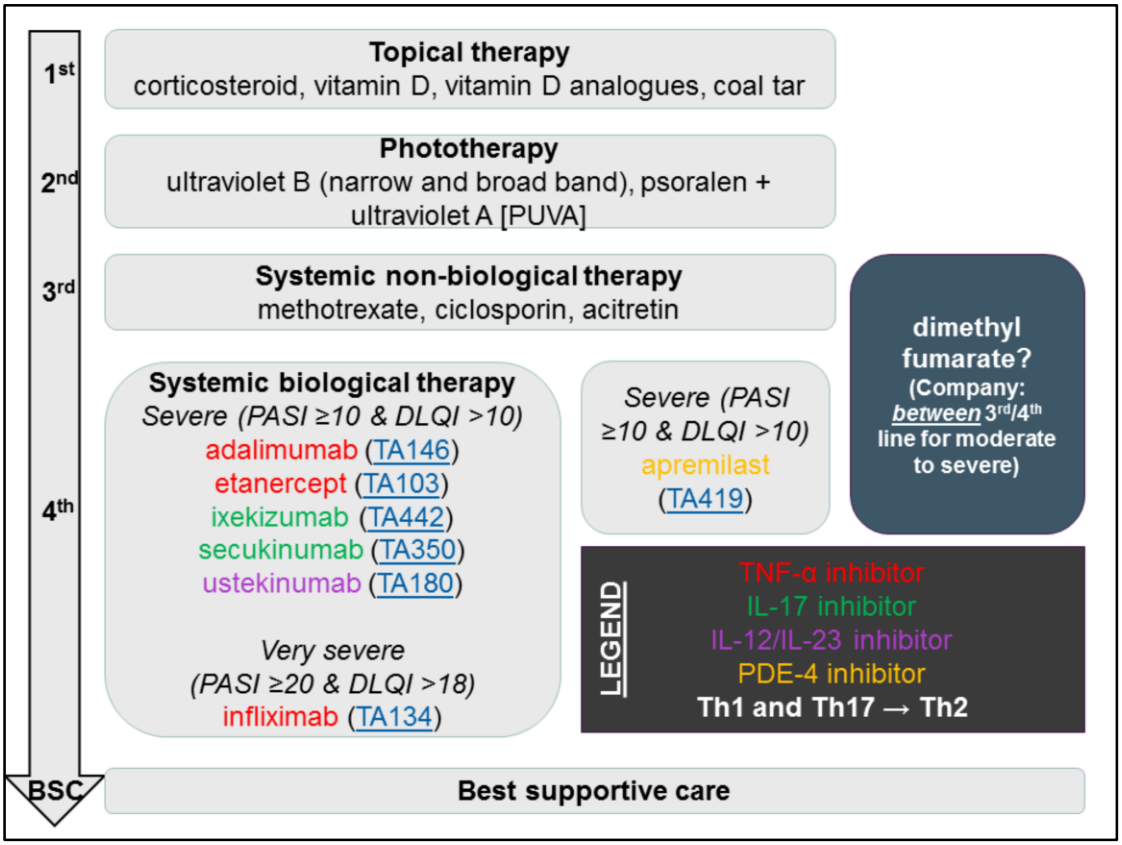
Given position of DMF after standard non-biological systemic therapies are not effective or are not appropriate:

- methotrexate, ciclosporin and acitretin are not relevant comparators
- phototherapy is not a comparator because it is used before systemic therapies

*Company does not list ixekizumab in its decision problem but includes it in its network meta analysis and economic model

^Company omits best supportive care from its systematic review/network meta-analysis

Sources: NICE final scope: page 2. Company submission: Table 1, pages 12-13; Table 24, pages 79-80; Table 26, pages 84-85. Clarification response: A2, page 3.



Sources: NICE Psoriasis guideline (CG153; https://www.nice.org.uk/guidance/cg153). NICE technology appraisals (TA146, TA103, TA442, TA350, TA180, TA134, TA419). Company submission: pages 36-37.

Best supportive care

Clarification response: B1, page 35:

Best supportive care was assumed to be similar to the pre-biological patients in Fonia et al. (2010) which included systemic treatments, inpatient admission days, A&E visits, outpatient visits, day ward admissions and phototherapy sessions.

Place of DMF (LAS41008) in the existing treatment pathway

Company submission: Table 1, page 12:

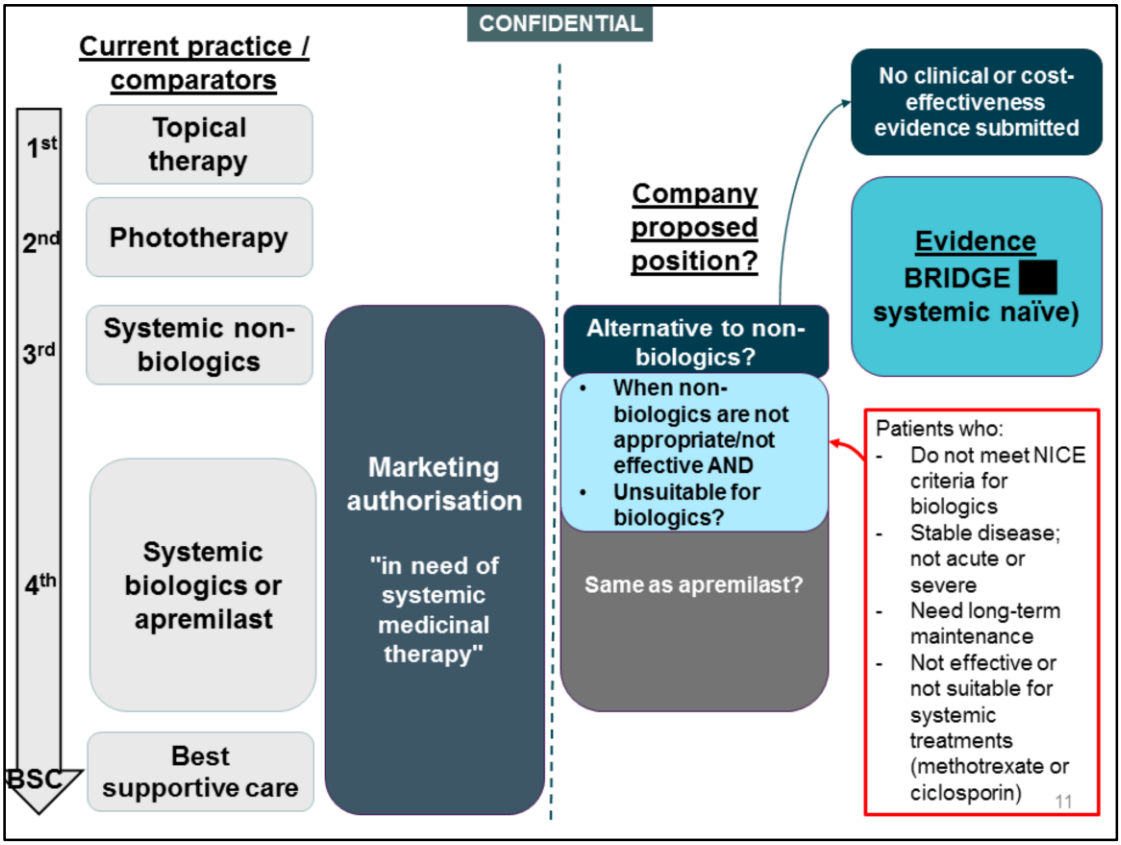
The anticipated patient population is more specific than both the licensed indication and that specified in the scope.

In clinical practice it is anticipated that DMF will offer patients and clinicians an additional systemic, non-biologic treatment option. It will be used in patients for whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference.

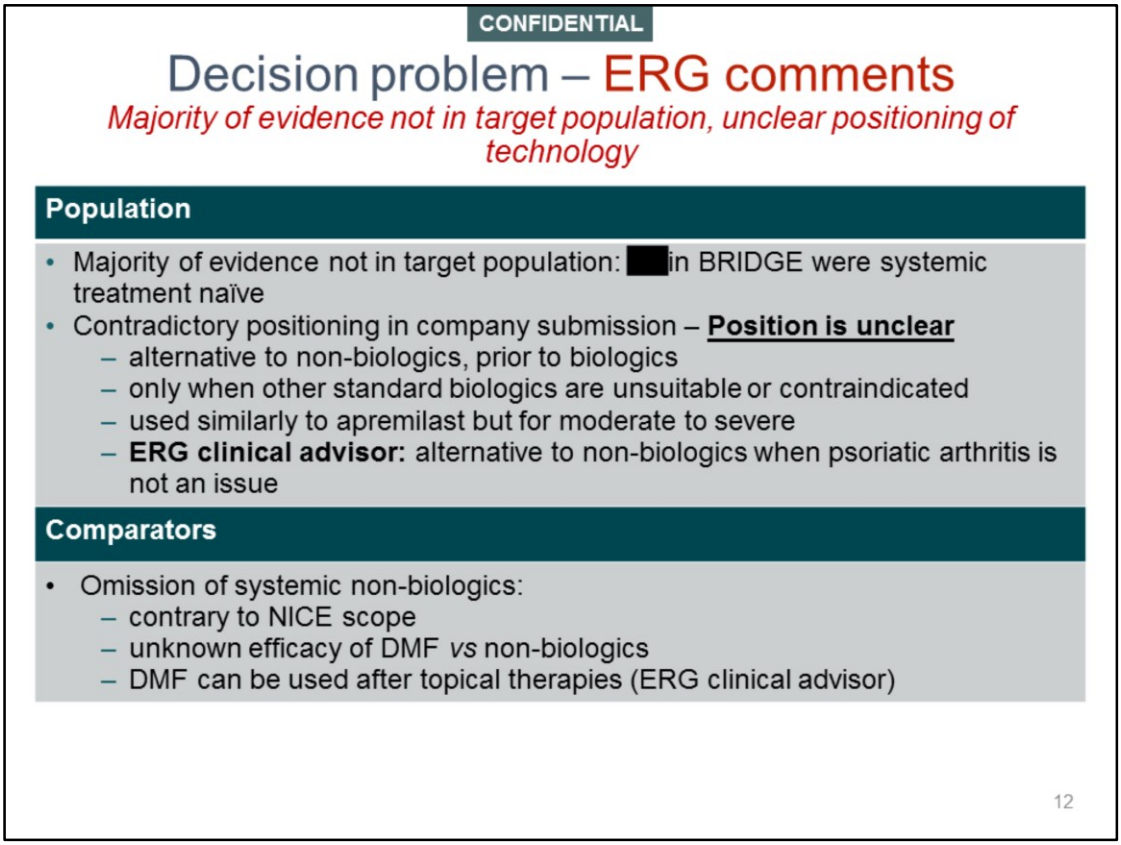
In the current treatment pathway DMF (LAS41008) will occupy a similar position to

apremilast but with DMF (LAS41008) being suitable for patients with moderate to severe psoriasis.

Company submission: pages 36-37:
DMF will offer an additional treatment option for patients in whom other oral systemic therapies (methotrexate, ciclosporin and acitretin) are clinically inappropriate through lack of efficacy, contraindications, tolerability and/or toxicity issues, or patient preference. It will be used as an alternative to current systemic non-biological treatments and in common with other oral systemic therapies use is anticipated prior to biologics.



Sources: Company submission: pages 36-37. Clarification response A1, page 1.



Source: ERG report: section 1.1, page 11; section 1.3, page 15; section 1.6.2, page 23; section 2.2, pages 32-33; section 3.3, page 39; section 3.5, page 40; section 4.1.2, page 44.

Decision problem – outcomes

Company submission does not include psoriasis symptoms on the face, nail, scalp and joints

NICE scope	Company submission
• Severity of psoriasis (inc. psoriasis area and severity index [PASI]) • Psoriasis symptoms on the face, scalp, nails and joints • Response rate • Remission rate • Relapse rate • Mortality • Adverse effects of treatment • Health-related quality of life (inc. dermatology life quality index [DLQI])	• Severity of psoriasis (inc. psoriasis area and severity index [PASI]) • Response rate • Remission rate • Relapse rate • Mortality • Adverse effects of treatment • Health-related quality of life (inc. dermatology life quality index [DLQI])
Company rationale	
Data on the complications of psoriasis (including nail, scalp and joint outcomes) is not available for DMF*	

*Company excluded scalp and nail psoriasis from their systematic review and network meta-analysis (CS, page 79 and 85)

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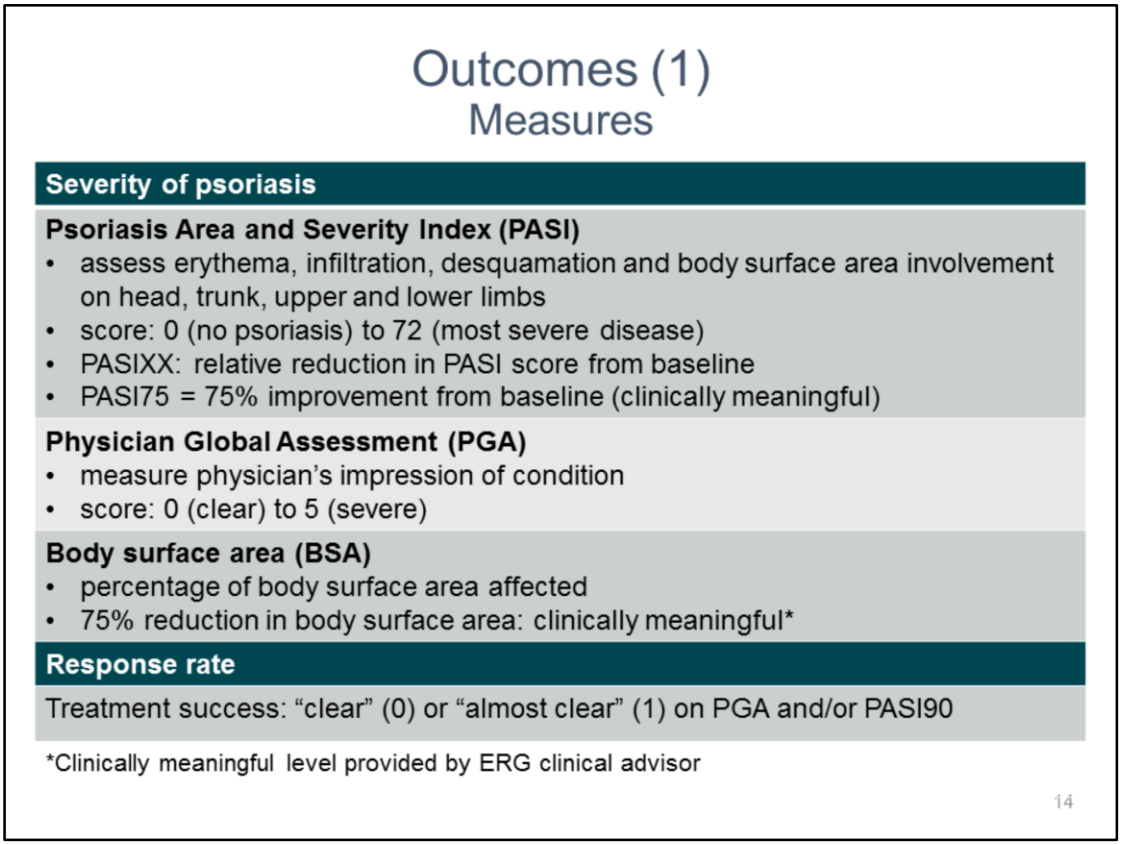
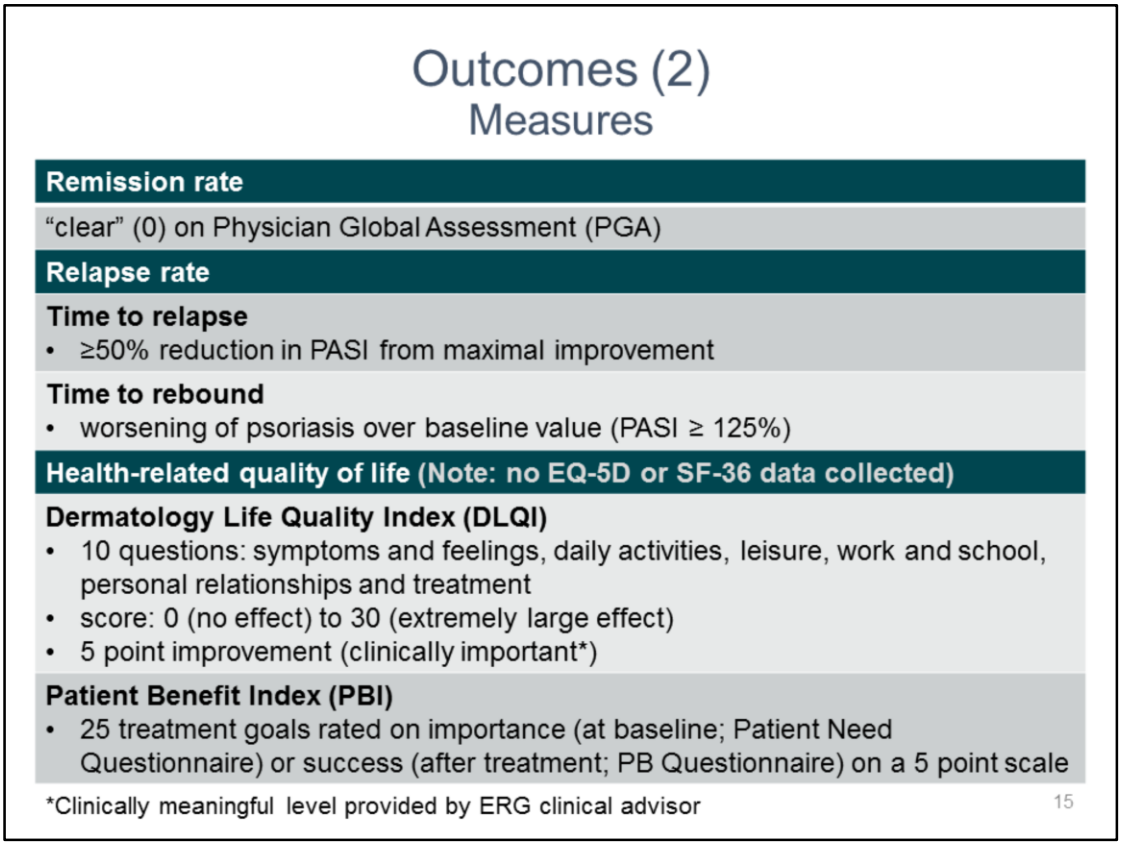
Sources: NICE final scope: page 3. Company submission: Table 1, page 13.



Sources: Company submission: Table 7, pages 44-45. Company Appendix: Appendix 3, pages 5-9. ERG report: section 4.1.6, page 64. http://ard.bmj.com/content/64/suppl_2/ii65 [Accessed 17/05/2017].



Sources: Company submission: Table 7, pages 44-45. Company Appendix: Appendix 3, pages 5-9. ERG report: section 4.1.6, page 64. http://ard.bmj.com/content/64/suppl_2/ii65 [Accessed 17/05/2017].

Decision problem – subgroups

Company submission compares systemic naïve and prior systemic or PUVA use in post hoc analysis

NICE scope	Company submission
• previous use of systemic non-biological therapy • previous use of biological therapy • severity of psoriasis (moderate, severe)	• previous use of systemic therapy or PUVA* • severity of psoriasis (moderate, severe based on PASI and PGA) • age (≤35, 35-≤55, ≥55 years) • sex (male, female) • race (Caucasian)
Company rationale	
Post hoc analysis of systemic naïve and prior systemic use: queries during regulatory process	

*Company only states systemic therapy in its decision problem but additionally included previous PUVA therapy in its post hoc subgroup analysis

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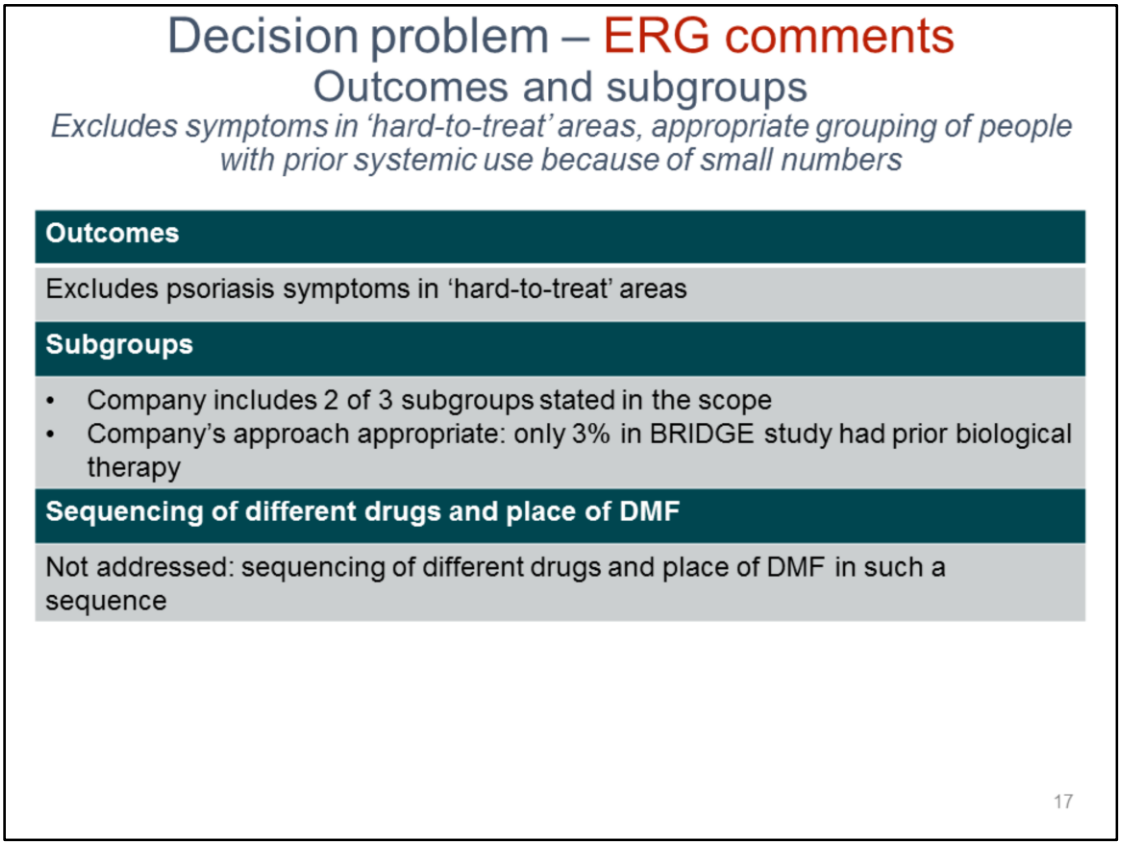
Sources: NICE final scope: page 4. Company submission: Table 1, page 14; section 4.8, pages 68-75. Clarification response: A2, page 3.



Source: ERG report: section 1.1, page 11; section 1.3, page 15; section 1.6.2, page 23; section 3.4, page 40; section 3.5, page 40; section 4.1.2, page 44.

Clinical evidence

1 Phase 3 randomised controlled trial

BRIDGE (dimethyl fumarate, fumaderm, placebo)

Network meta-analysis

dimethyl fumarate, fumaderm, apremilast, biologics (*adalimumab, etanercept, ixekizumab, secukinumab, ustekinumab*), placebo

No evidence on non-biologics (methotrexate, ciclosporin, acitretin)

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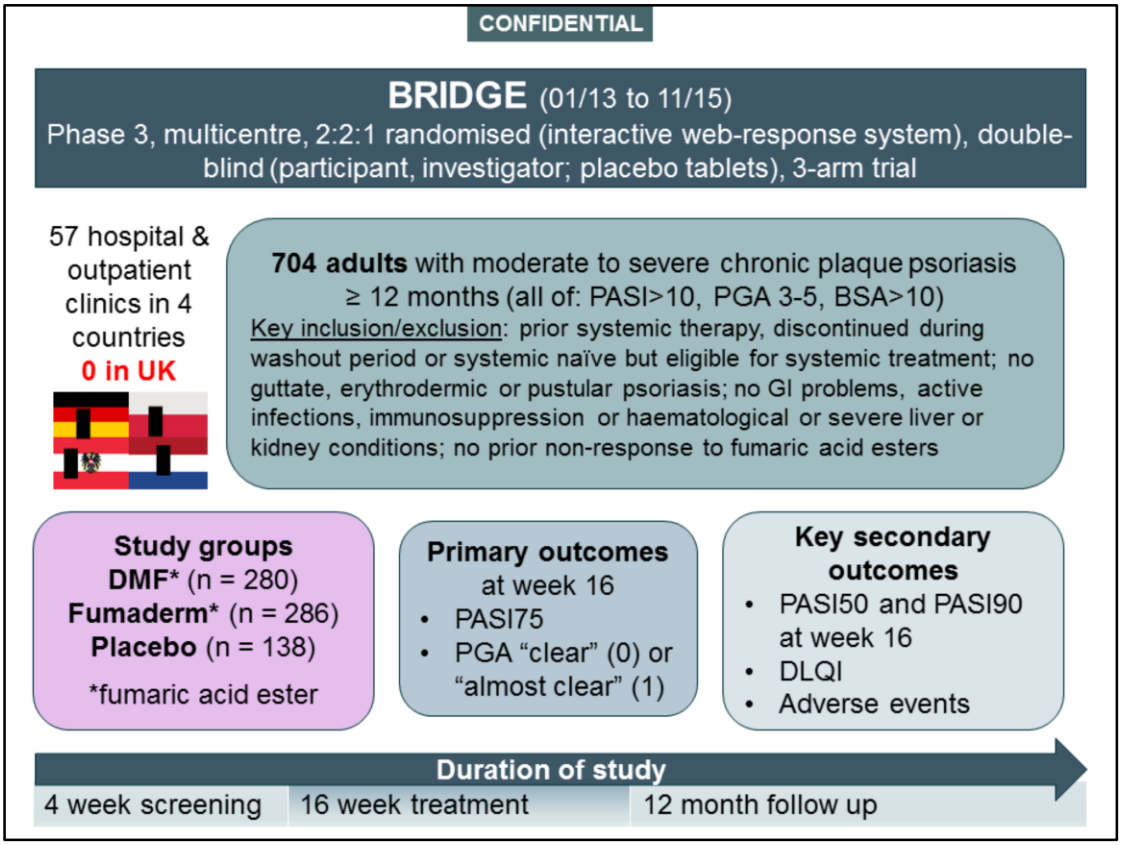

Sources: Company submission: section 1.3, page 16; Figure 5, page 41; Table 7, pages 42-45. Ref 48 Company CSR: page 4. https://clinicaltrials.gov/ct2/show/NCT01726933 (Accessed 26/05/2017).

Company clinical evidence for DMF: BRIDGE study (sponsored by Almirall S.A.).

BRIDGE RCT

Participant flow and analysis sets

Discontinuation rates are high but similar for DMF and fumaderm

	DMF	Fumaderm	Placebo	Total
Randomised	280	286	138	704
Treated (SAS)	279	283	137	699
Discontinuation during treatment	103 (37%) [64 AE, 12 NE, 3 NC]	107 (38%) [70 AE, 9 NE, 7 NC]	39 (28%) [6 AE, 20 NE, 1 NC]	249
Completed induction	176 (63%)	176 (62%)	98 (72%)	450
Discontinuation after treatment*	26 (15%)	23 (13%)	32 (33%)	81
Followed up	150	153	66	369
Completed RCT	42 (15%)	51 (18%)	17 (12%)	110

AE adverse events, DMF dimethyl fumarate, NC non-compliance, NE lack of efficacy, *no data on reasons in CS

Safety analysis set (SAS): randomised + ≥ 1 treatment dose
Full analysis set (FAS): SAS + ≥ 1 PASI & PGA after baseline (267 DMF, 273 Fumaderm, 131 Placebo)

Sources: Company submission: Table 9, page 48; section 4.5 including Figure 6 and Table 10, pages 52-54. Clarification response: A3, pages 3-4; A7, pages 5-6. ERG report: section 4.1.3, pages 46-47.

Key reasons for treatment discontinuation are listed in the table. Reasons such as consent withdrawn, lost to follow-up, other have not been included.

The ERG does not agree that the FAS constitutes an intention-to-treat population and considers the SAS more appropriate, being a modified intention-to-treat analysis (ERG report: section 4.1.7, page 66). The ERG agrees that the SAS and FAS results are comparable for the primary outcomes.

BRIDGE RCT – quality assessment

Good quality; large sample – balanced at baseline, generalisable to UK
Primary analysis not ITT, limited long-term follow up, high drop out rates (imbalanced between groups)

Company and ERG agree:

- Randomisation and treatment allocation: appropriately conducted
- Treatment arms: similar in prognostic factors at screening
- Study participants and outcomes: reflect and relevant to UK

Company assessment	ERG assessment
Blinding of treatment allocation	
Yes	Yes, unclear if blinding maintained (AEs)
Unexpected imbalances in drop outs between groups	
No. Drop out rates comparable in both treatment arms	Yes. Drop out rates very high, reasons imbalanced between treatment and placebo arms*
Intention-to-treat analysis conducted	
Yes. Close as possible to the intention-to-treat population	No. Full analysis set does not include 33 randomised individuals

*Discontinuation due to adverse events: 23% DMF, 25% fumaderm and 4% placebo

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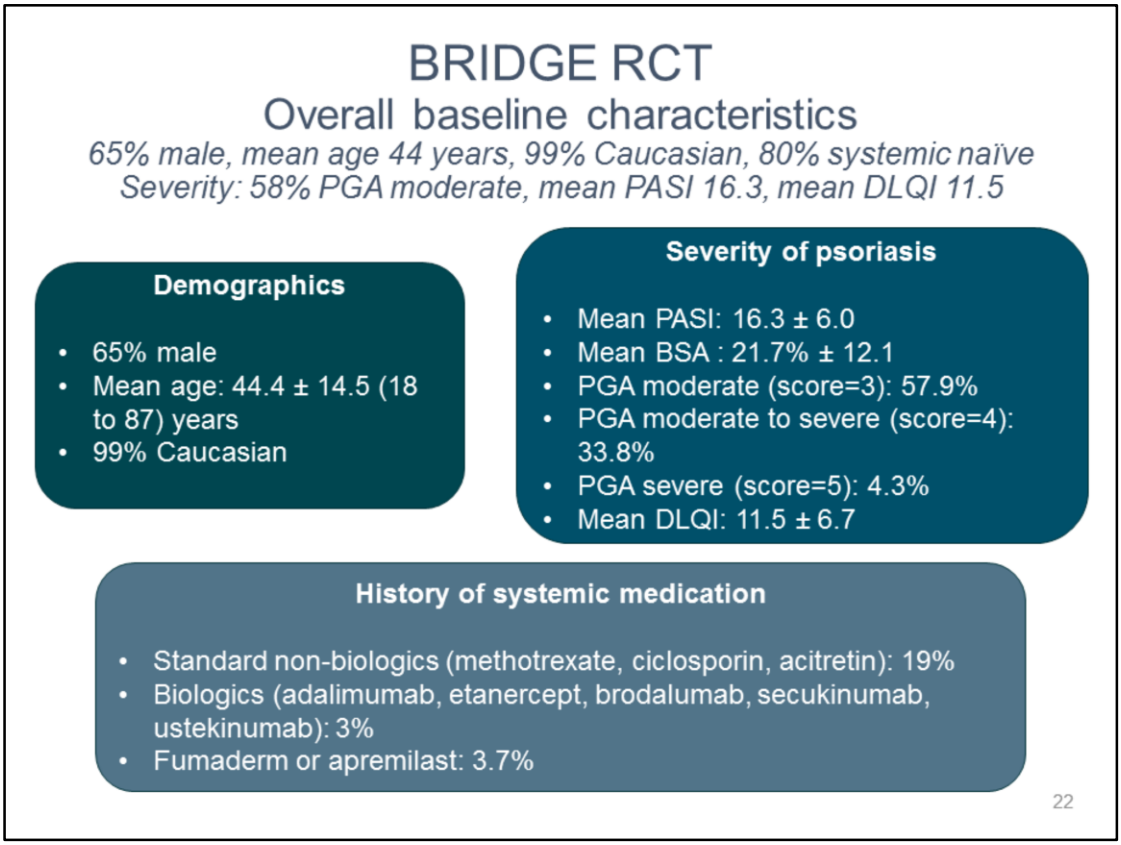
Sources: Company submission: Table 12, pages 56-57. Clarification response: A3, page 4. ERG report: Table 5, page 56.

*Source: Figure 6 of CS (page 53) which differs from data provided in Table 47 (CS, page 129) [24%, 24.4% and 5.8% for DMF, fumaderm and placebo respectively]



Source: Company submission: Table 11, page 55; Table 22, page 74.

CONFIDENTIAL

BRIDGE RCT

Results – full analysis set

[redacted]: *DMF significantly better than placebo and comparable to fumaderm*
SAS and FAS results are broadly similar (data for SAS not shown)

Outcome	DMF (n = 267)	Fumaderm (n = 273)	Placebo (n = 131)	DMF vs placebo	DMF vs fumaderm
PASI75	37.5%	40.3%	15.3%	22.2 (10.7 to 33.7)*	-2.8 (-14 to 8.4)*
PGA 0 or 1	33%	37.4%	13%	20 (8 to 30)*	4 (-15 to 7)*
PGA 0 (clear)	6.4%	7.7%	0.8%	5.6 [redacted]	-1.3 [redacted]
Relapse rate at 12 months	10.1%	12.5%	27.5%	[redacted]	[redacted]
Days to relapse, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Days to rebound, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*risk difference (99.24% confidence intervals), [a]ERG calculated risk difference and 95% confidence intervals, [SE]standard error

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Sources: Company submission: section 4.7, pages 57-58, pages 62-64. ERG report: Table 7, page 71.

BRIDGE RCT

Results: Secondary outcomes (FAS) – DLQI

DMF significantly better than placebo up to 2 months and comparable to fumaderm

Outcome	DMF (n = 267)	Fumaderm (n = 273)	Placebo (n = 131)	DMF vs Placebo*	DMF vs Fumaderm*
Mean DLQI (SD) at week 16[a]	n = 253 5.4 (6.1)	n = 259 6.1 (7.2)	n = 118 8.5 (6.9)	-3.2 (-4.7 to -1.8)	-0.7 (-1.8 to 0.5)
Mean DLQI (SD) at 2 months	4.8 (5.6)	5.4 (6.1)	7.8 (6)	-3 (-4.9 to 1.2)	-0.7 (-2.1 to 0.7)
Mean DLQI (SD) at 6 months	5.8 (6.7)	6.6 (5.8)	7.6 (6.3)	-2.5 (-5.5 to 0.5)	-1 (-3.1 to 1.2)
Mean DLQI (SD) at 12 months	7.8 (6.6)	8 (5.7)	7 (6)	0.6 (-2.4 to 3.6)	-0.1 (-2.3 to 2.1)

[a]Observed numbers provided in company clarification response
*Least square means, 2-sided 95% confidence intervals

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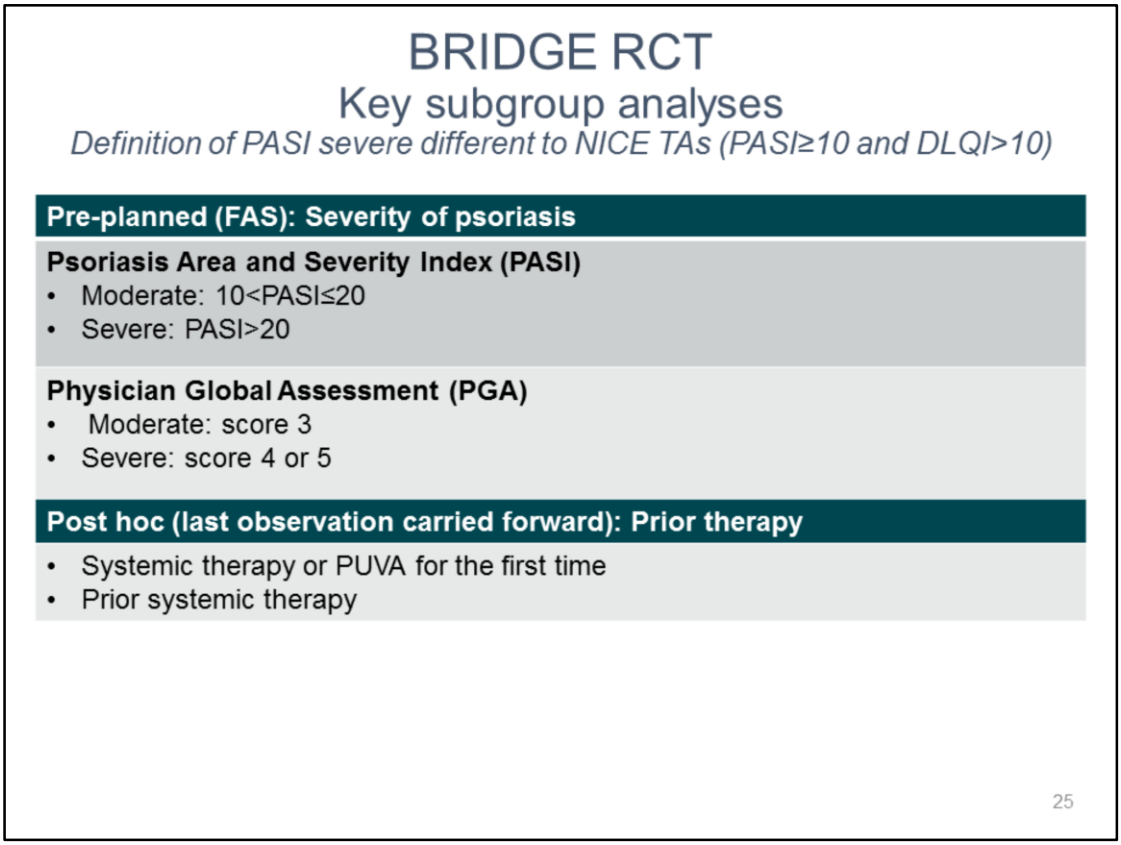
Sources: Company submission: Table 17, page 66. Clarification response: A6, page 5.



Source: Company submission: pages 68-75.

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BRIDGE RCT

Definition of severity

Difference in definition of psoriasis severity from previous NICE technology appraisal guidances

NICE TA guidances	BRIDGE RCT		
	Inclusion criteria (moderate to severe)	Baseline values	Subgroup analysis
Moderate: NA	PASI>10	mean PASI 16.3±6.0	**PASI** moderate (score 10 to 20) [redacted]
Severe: PASI≥10 and DLQI>10	PGA 3-5	mean DLQI 11.5±6.7	**PASI** severe (score >20) [redacted]
Very severe: PASI≥20 and DLQI>18	BSA>10		NA
			PGA moderate (score=3) [redacted]
			PGA severe (score 4 or 5) [redacted]

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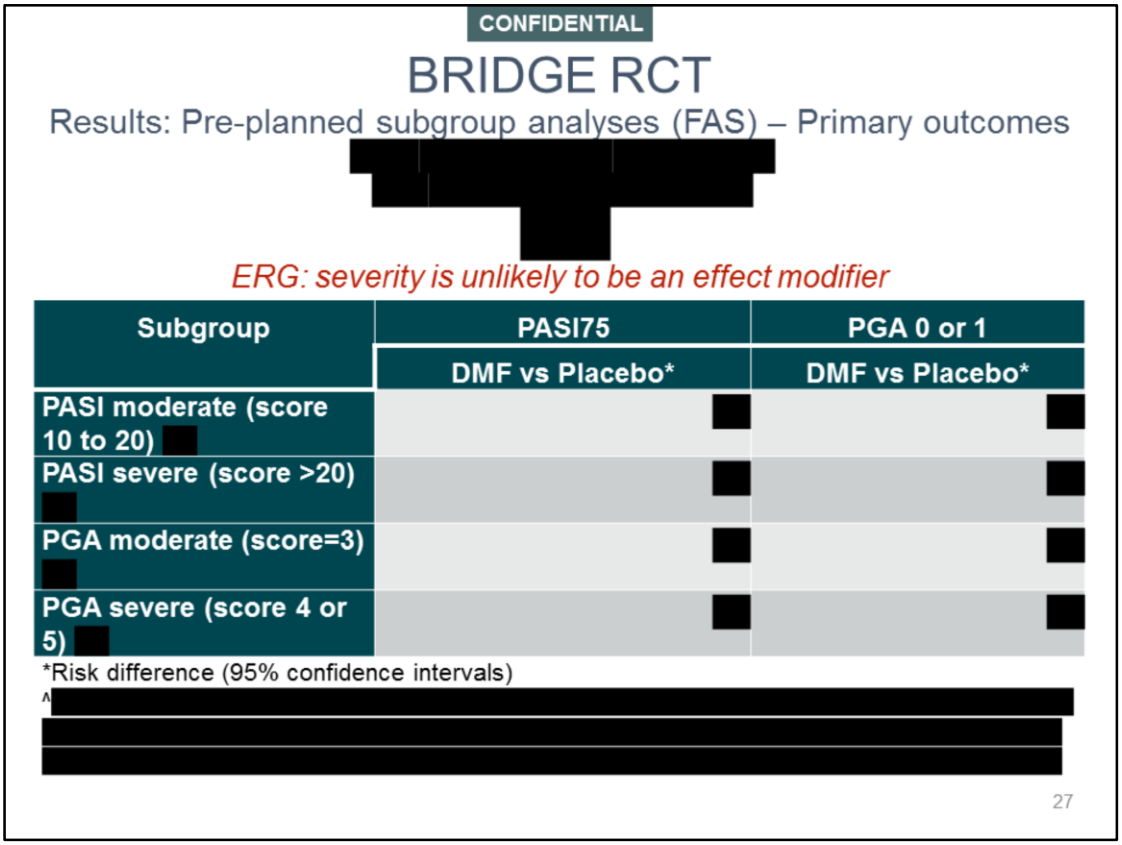
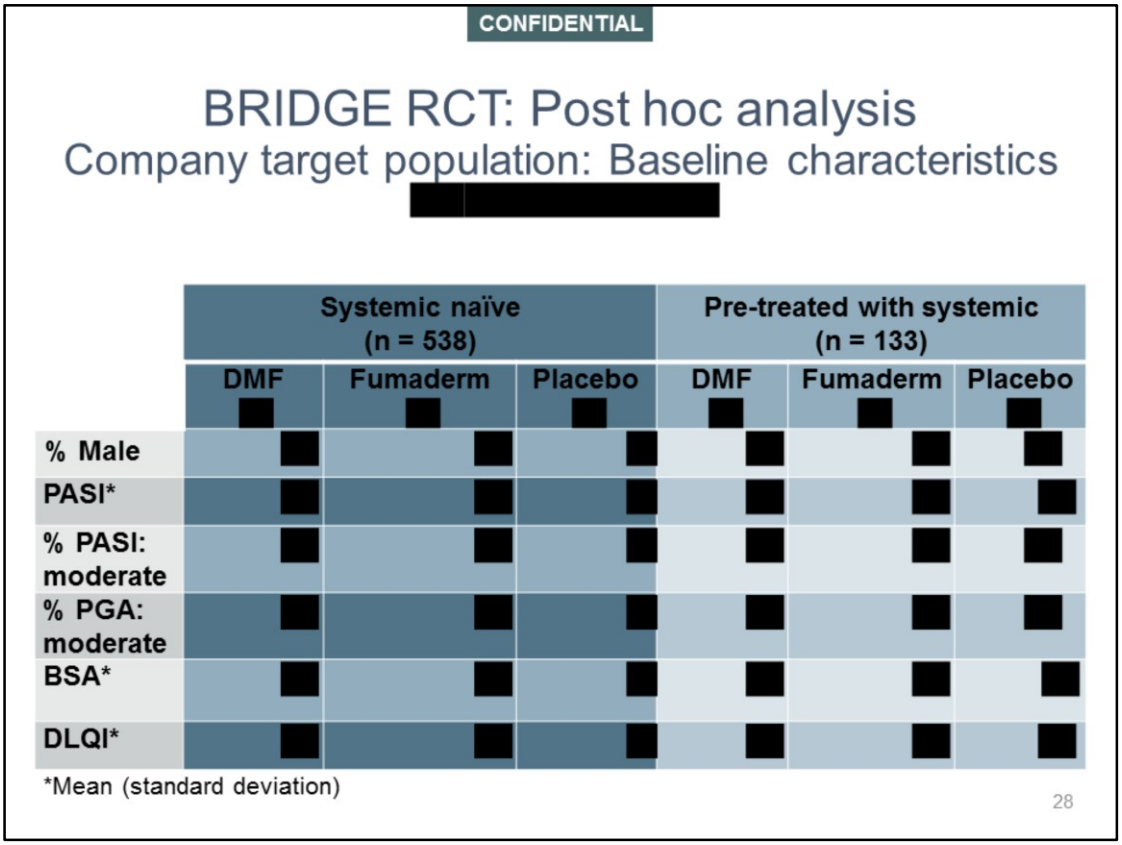
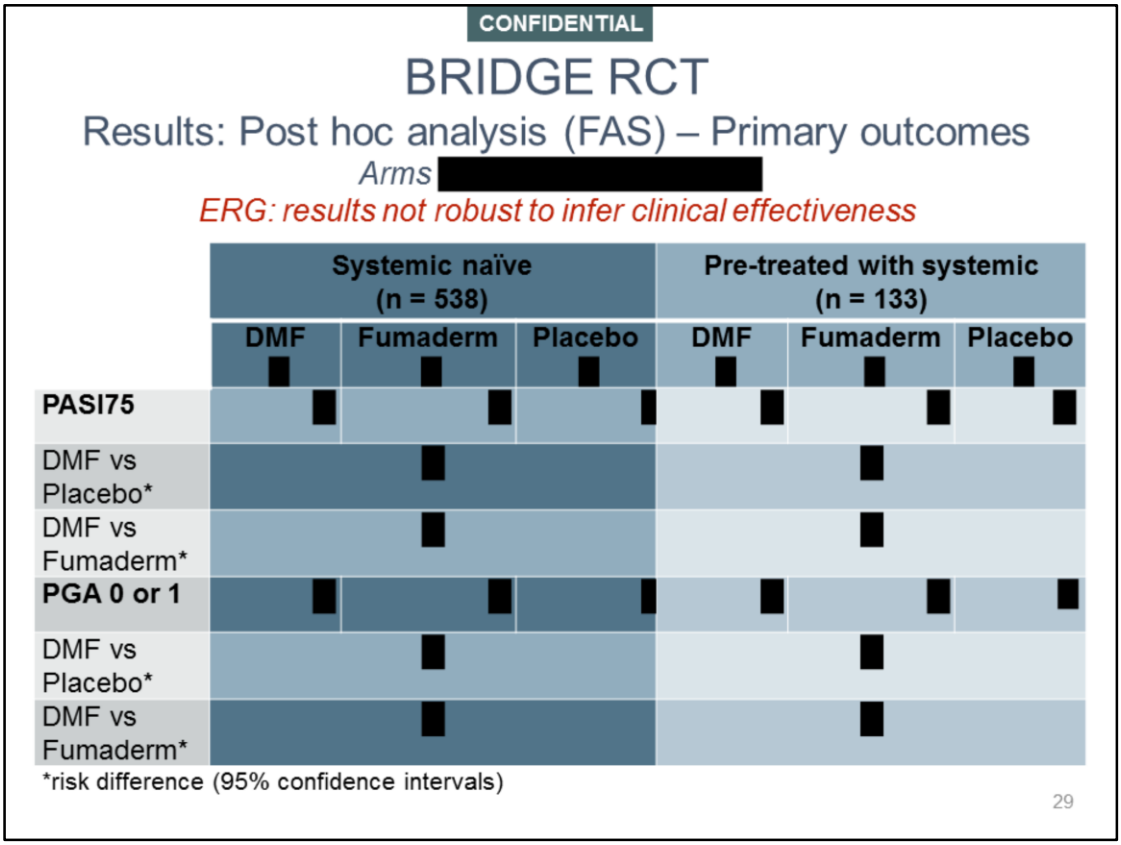


Sources: ERG report: Table 9, page 73. Company submission: Figures 13 and 14, page 71.



Sources: Company submission: Table 21, page 73. Clarification response: A9, page 9.

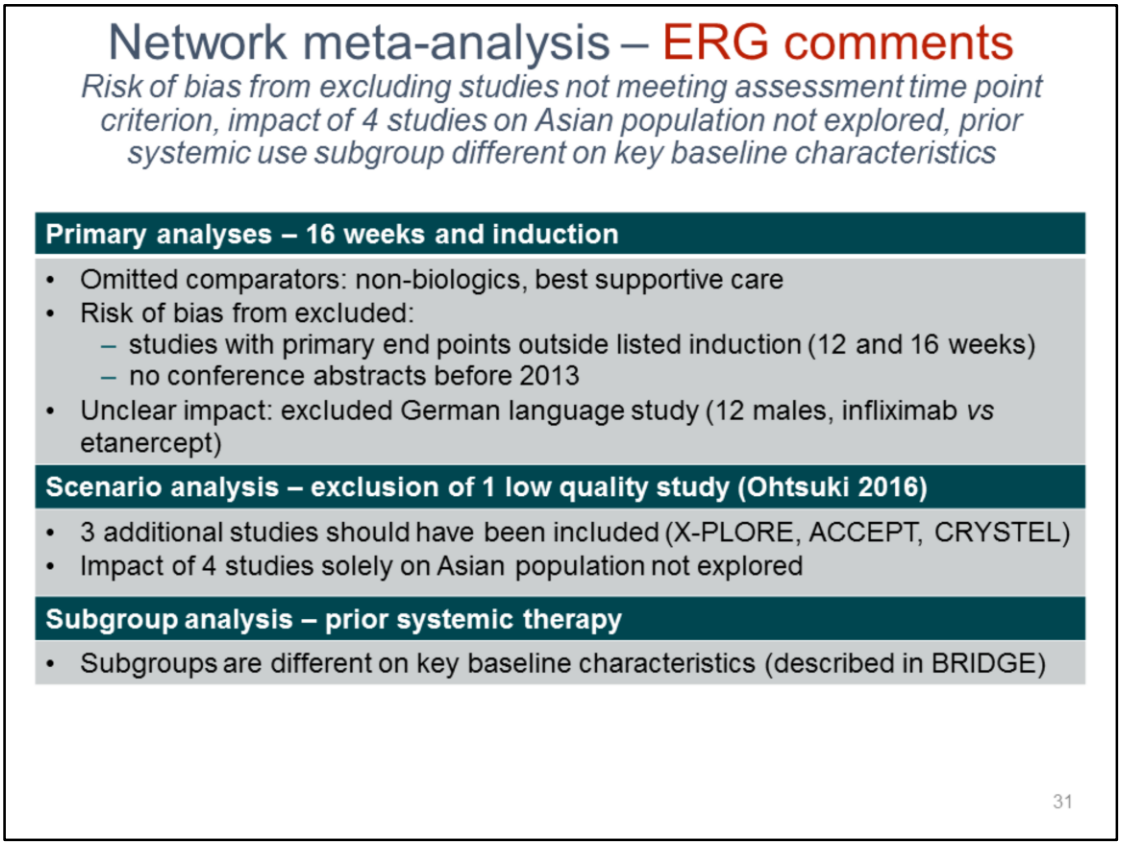


Source: Company submission: Tables 22 and 23, page 74-75.

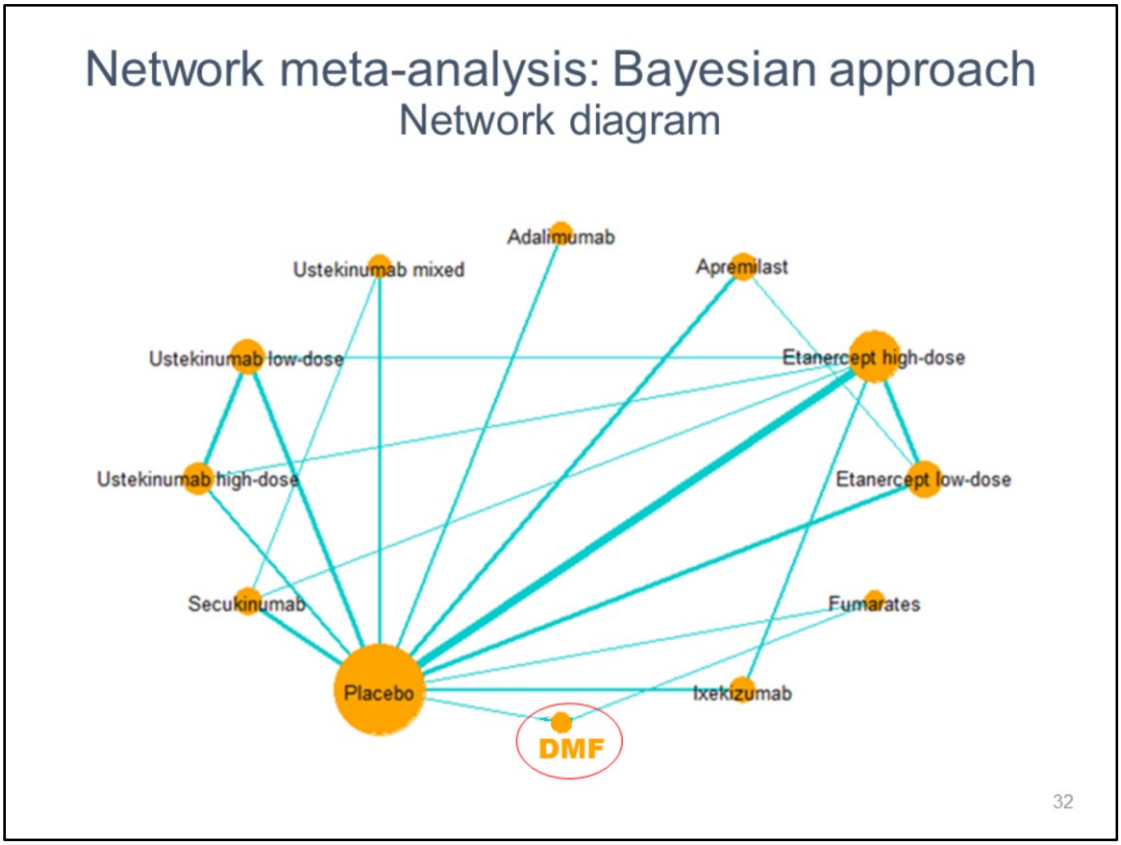
Network meta-analysis
Included studies – base case

Treatment	Studies
DMF	BRIDGE
Fumaderm	BRIDGE
Apremilast	ESTEEM 1, ESTEEM 2, Papp 2012, LIBERATE, Ohtsuki 2016
Adalimumab	Asahina 2010, CHAMPION, X-PLORE
Etanercept low-dose 25mg	Gottlieb 2003, LIBERATE, Leonardi 2003, Papp 2005, PRISTINE, Van de Kerkhof 2008, PRESTA, CRYSTEL
Etanercept high-dose 50mg	ACCEPT, Bachelez 2015, Bagel 2012, FIXTURE, Gottlieb 2011, Leonardi 2003, Papp 2005, PRESTA, PRISTINE, Strober 2011, UNCOVER -2, UNCOVER -3, Tyring 2006, CRYSTEL
Ixekizumab	UNCOVER -1, UNCOVER-2, UNCOVER -3
Secukinumab	CLEAR, ERASURE, FEATURE, FIXTURE, JUNCTURE
Ustekinumab low-dose 45mg	ACCEPT, LOTUS, PEARL, PHOENIX 1, PHOENIX 2, The Japanese Ustekinumab Study Group
Ustekinumab high-dose 90mg	ACCEPT, PHOENIX 1, PHOENIX 2, The Japanese Ustekinumab Study Group
Ustekinumab mixed-dose	AMAGINE-2, AMAGINE-3, CLEAR

Source: Company submission: Table 25, page 83.



Source: Company submission: Table 25, page 83. ERG report: section 1.6.2, page 23; section 4.1, pages 42-45; section 4.1.3, pages 48-49; section 4.3, pages 77-78, 84-85.



Source: Company submission: Figure 23, page 106.

Network meta-analysis – ERG comments

Assumptions

Studies are adequately similar to be pooled

Assumption	Company assessment	ERG assessment
Homogeneity	• Not considered	• Assumption satisfied: unclear • Statistical, clinical or methodological heterogeneity not explored; no pairwise comparisons
Similarity	• Similarity of studies on age, sex, ethnicity, duration of psoriasis, psoriatic arthritis, baseline PASI • No major imbalances	• Assumption: satisfied
Inconsistency	• Assumption: satisfied • Deviance information criterion values checked in consistency and inconsistency models	• Assumption: satisfied

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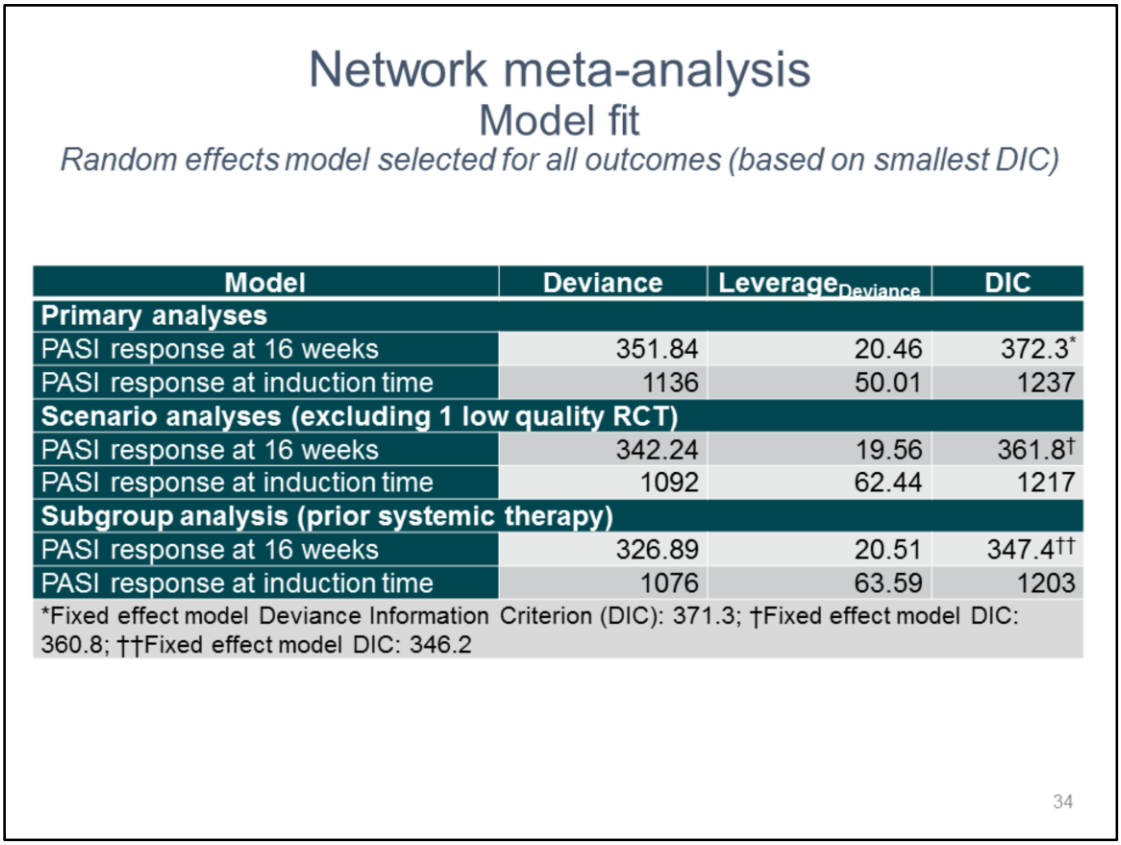
Sources: ERG report: section 1.6.2, page 23; section 4.1, pages 42-45; section 4.1.3, pages 48-49; -104, section 4.3, pages 77-78, 84-85. Company submission: Tables 46, pages 99-104, 127.



Network meta-analysis

Model fit

Random effects model selected for all outcomes (based on smallest DIC)

Model	Deviance	$Leverage_{Deviance}$	DIC
Primary analyses			
PASI response at 16 weeks	351.84	20.46	372.3*
PASI response at induction time	1136	50.01	1237
Scenario analyses (excluding 1 low quality RCT)			
PASI response at 16 weeks	342.24	19.56	361.8†
PASI response at induction time	1092	62.44	1217
Subgroup analysis (prior systemic therapy)			
PASI response at 16 weeks	326.89	20.51	347.4††
PASI response at induction time	1076	63.59	1203

*Fixed effect model Deviance Information Criterion (DIC): 371.3; †Fixed effect model DIC: 360.8; ††Fixed effect model DIC: 346.2

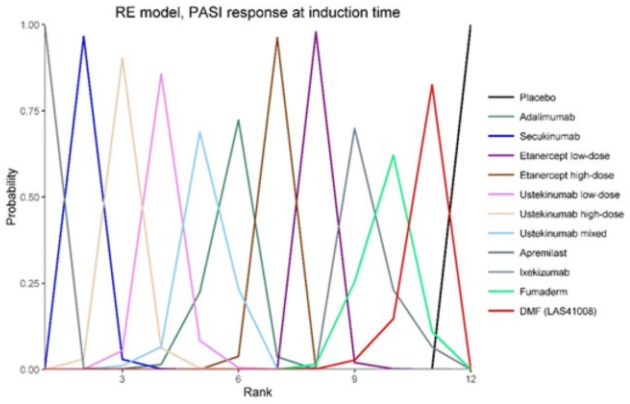
34

Source: Company submission: Table 45, page 126.

Network meta-analysis

Base case: Random effects multinomial (probit-link) PASI response (PASI 50/75/90) at induction

DMF (red line) has the lowest probability of treatment response vs other active treatments



35

Source: Clarification response: Figure 4, page 30.

Network meta-analysis

Base case: Random effects multinomial (probit-link) PASI response (PASI 50/75/90) at induction

DMF better than placebo but probability of response lowest vs other active treatments

Intervention	Median rank (95% CrI)	SUCRA
Ixekizumab	1 (1, 1)	100.0%
Secukinumab	2 (2, 3)	90.7%
Ustekinumab high-dose	3 (2, 4)	81.5%
Ustekinumab low-dose	4 (3, 5)	72.4%
Ustekinumab mixed	5 (4, 6)	62.3%
Adalimumab	6 (5, 7)	56.6%
Etanercept high-dose	7 (6, 7)	45.8%
Etanercept low-dose	8 (8, 8)	36.2%
Apremilast	9 (9, 11)	24.0%
Fumaderm	10 (9, 11)	19.8%
DMF	11 (9, 11)	11.0%
Placebo	12 (12, 12)	0.0%

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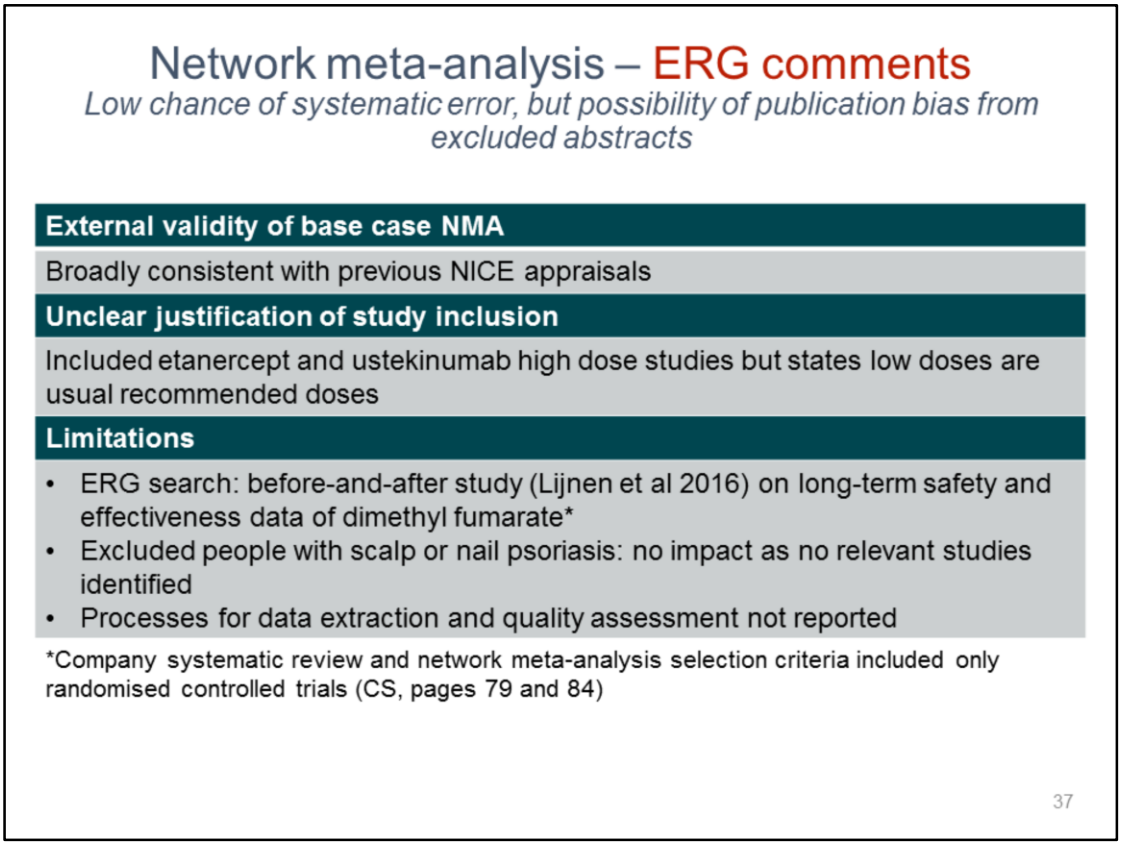
Source: Clarification response: Table 20, page 31.



Source: ERG report: section 1.6.2, page 23; section 4.1, pages 42-45; section 4.1.3, pages 48-49; section 4.3, pages 77-78, 84-85.

CONFIDENTIAL

Short-term safety (BRIDGE)

Comparable levels of adverse events in treatment arms, which were higher than placebo

Short-term safety	DMF (n = 279)	Fumaderm (n = 283)	Placebo (n = 137)
Treatment emergent AE leading to discontinuation*	24%	24%	6%
Treatment-related AE	74%	74%	40%
Serious treatment emergent AE	3%	3%	4%
Treatment-related serious TEAE	[redacted]	[redacted]	[redacted]

*most common events were gastrointestinal-related disorders

38

Sources: Company submission: Table 47, pages 128-129, 136. ERG report: Table 13, page 76; section 4.4, page 86.

CONFIDENTIAL

TEAE leading to discontinuation (BRIDGE – SAS)

	DMF n = 279	Fumaderm n = 283	Placebo n = 137
Any event	67 (24.0)	69 (24.4)	8 (5.8)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]

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Source: ERG report: Table 12, pages 75-76.

CONFIDENTIAL

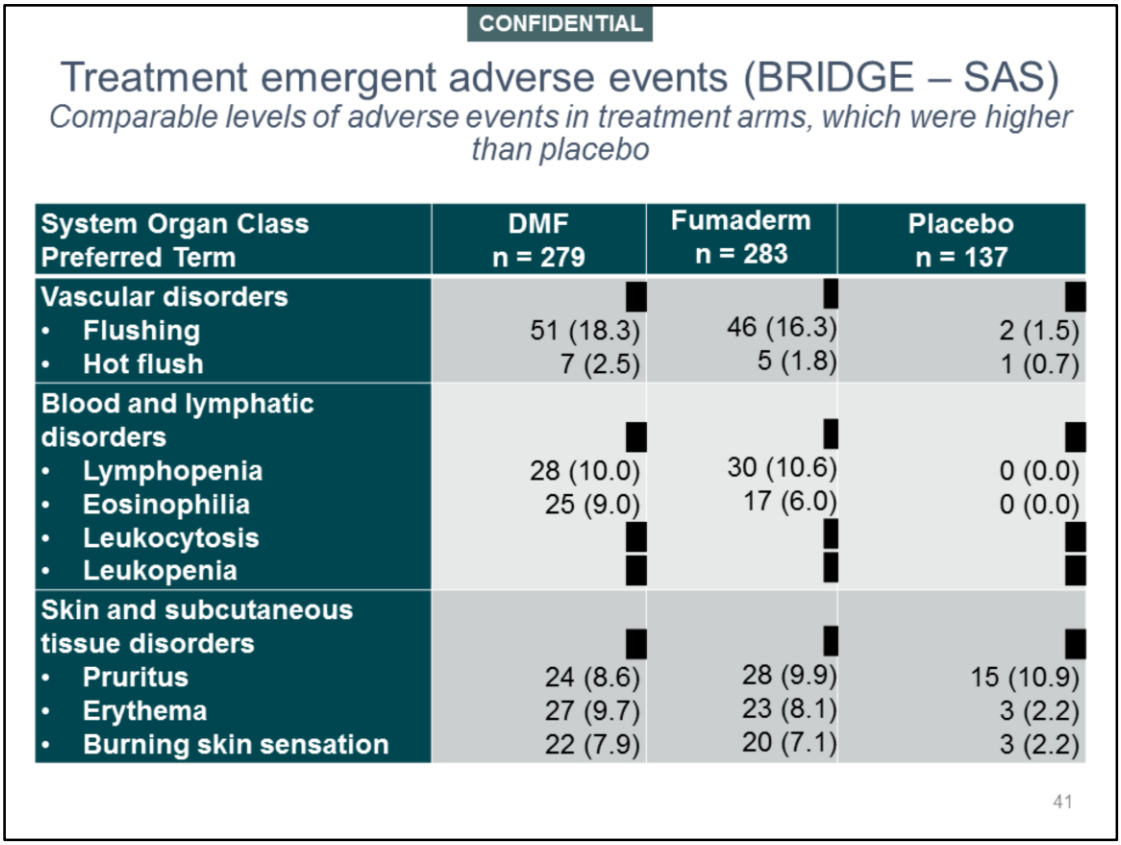
Treatment emergent adverse events (BRIDGE – SAS)

Comparable levels of adverse events in treatment arms, which were higher than placebo

System Organ Class Preferred Term	DMF n = 279	Fumaderm n = 283	Placebo n = 137
Gastrointestinal disorders	175 (62.7)	179 (63.3)	41 (29.9)
• Diarrhoea	108 (38.7)	113 (39.9)	22 (16.8)
• Abdominal pain upper	56 (20.1)	64 (22.6)	11 (8.0)
• Abdominal pain	55 (19.7)	45 (15.9)	7 (5.1)
• Nausea	30 (10.8)	24 (8.5)	5 (3.6)
• Flatulence	15 (5.4)	16 (5.7)	7 (5.1)
• Vomiting	13 (4.7)	19 (6.7)	2 (1.5)
• Abdominal discomfort	[redacted]	[redacted]	[redacted]
• Abdominal distension	[redacted]	[redacted]	[redacted]
• Dyspepsia	[redacted]	[redacted]	[redacted]
• Constipation	[redacted]	[redacted]	[redacted]
• Gastrointestinal disorder	[redacted]	[redacted]	[redacted]

40

Source: ERG report: Table 14, pages 76-77.



CONFIDENTIAL

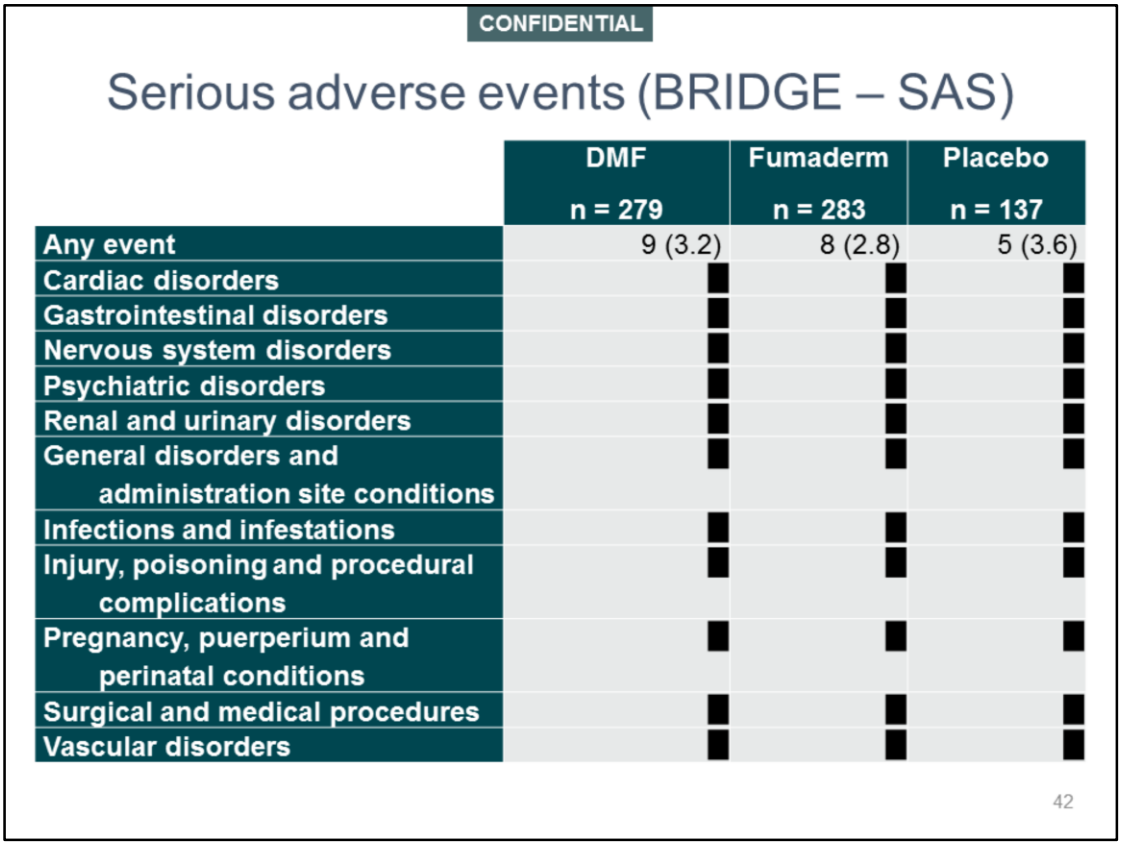
Treatment emergent adverse events (BRIDGE – SAS)

Comparable levels of adverse events in treatment arms, which were higher than placebo

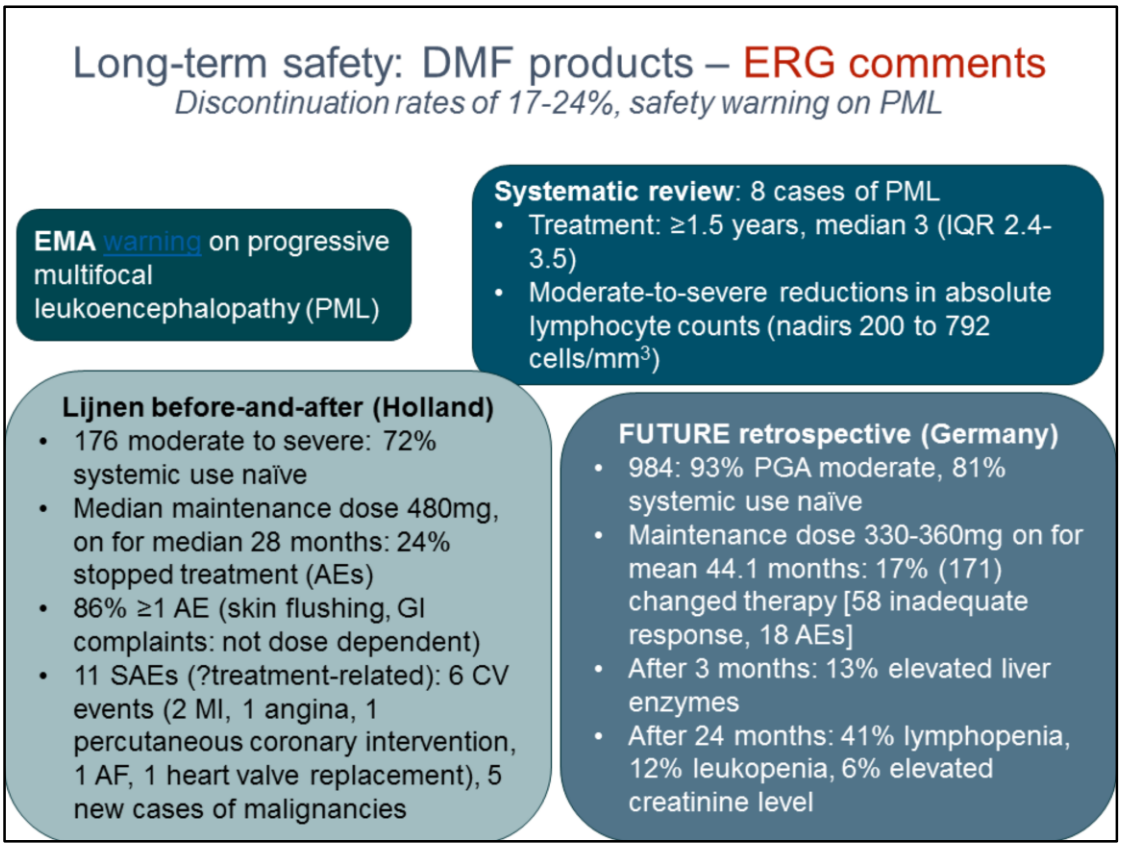
System Organ Class Preferred Term	DMF n = 279	Fumaderm n = 283	Placebo n = 137
Vascular disorders	[redacted]	[redacted]	[redacted]
• **Flushing**	51 (18.3)	46 (16.3)	2 (1.5)
• **Hot flush**	7 (2.5)	5 (1.8)	1 (0.7)
Blood and lymphatic disorders	[redacted]	[redacted]	[redacted]
• **Lymphopenia**	28 (10.0)	30 (10.6)	0 (0.0)
• **Eosinophilia**	25 (9.0)	17 (6.0)	0 (0.0)
• **Leukocytosis**	[redacted]	[redacted]	[redacted]
• **Leukopenia**	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
• **Pruritus**	24 (8.6)	28 (9.9)	15 (10.9)
• **Erythema**	27 (9.7)	23 (8.1)	3 (2.2)
• **Burning skin sensation**	22 (7.9)	20 (7.1)	3 (2.2)

41

Source: ERG report: Table 14, pages 76-77.



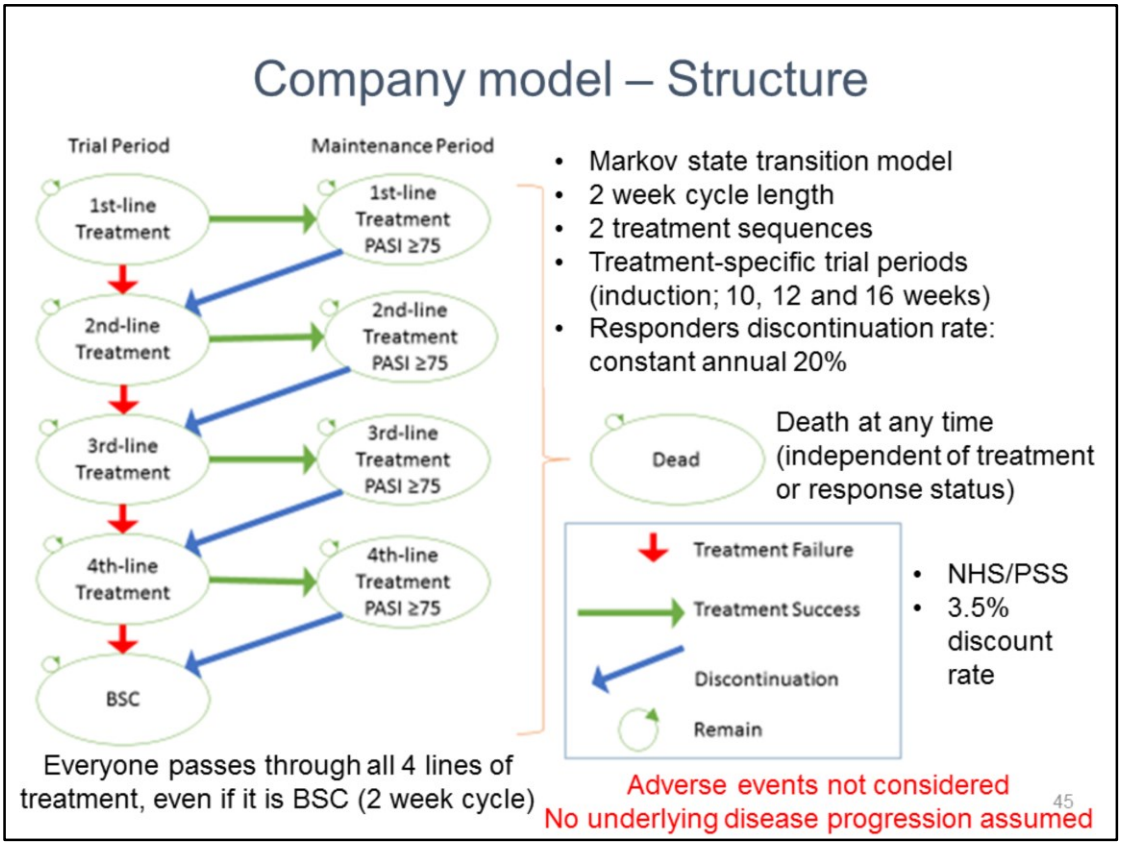
Source: ERG report: Table 13, page 76.



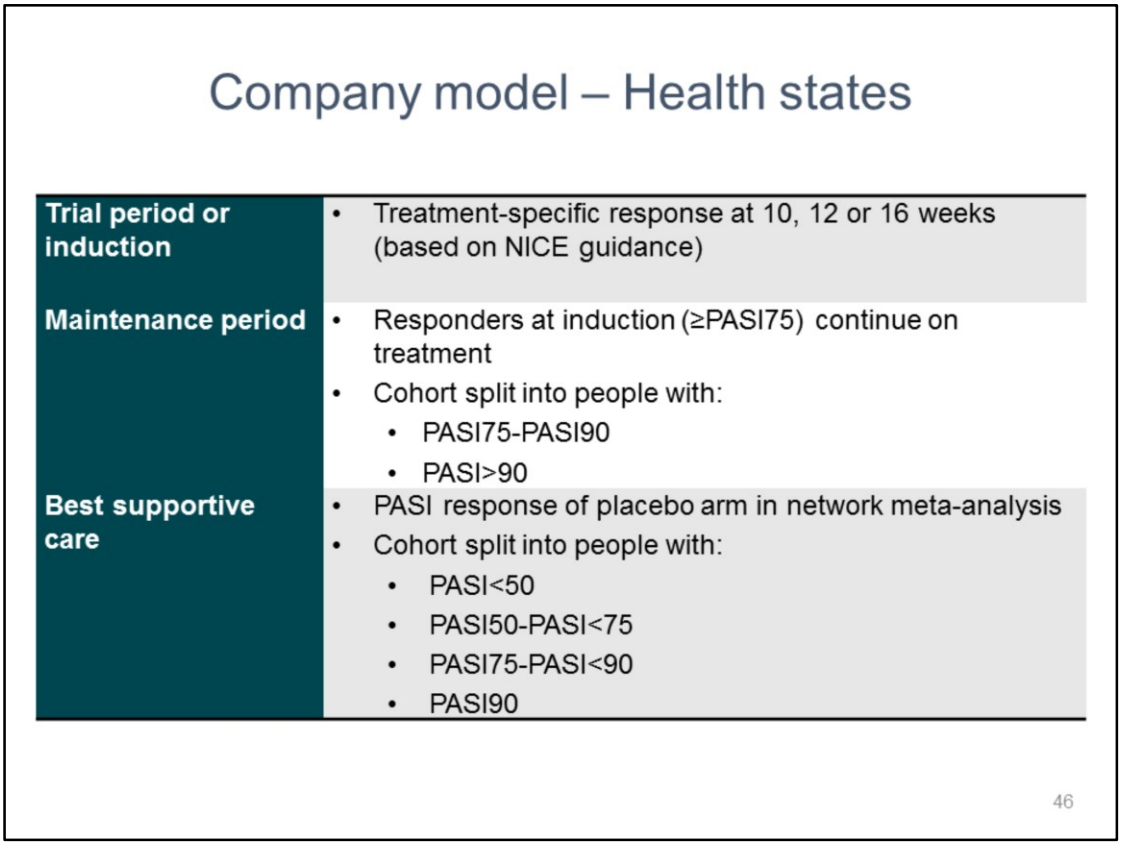
Sources: Company submission: page 136. ERG report: section 2.3, pages 34 and 36; section 4.4, pages 85-86.

Cost effectiveness

44



Sources: Company submission: Figure 30, page 163. ERG report: section 5.2.2, page 110.



Sources: Company submission: Table 53, page 164 and pages 169-170. ERG report: section 5.2.2, page 110.

Company model – Transition probabilities

Induction trial to maintenance	• PASI75 response (based on network meta-analysis; constant over time) • Proportion of patients achieving a PASI75 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 discontinuation 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

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Sources: Company submission: Table 53, page 164 and pages 169-170. ERG report: section 5.2.2, page 110.

Company model and base case – ERG comments

Strengths: York model, base case: standard sources – QoL, resource use
Limitations: comparator sequences with apremilast not fully explored

	Company model and base case	ERG comments and amendments
Population	Moderate to severe plaque psoriasis, cannot take systemic non-biologics: 50% male, baseline age 50 years, average weight 77.8kg*. Representative of BRIDGE	BRIDGE: 66% male, average age 44 years. Attributes affect all-cause mortality in model
Comparators	As per scope, plus infliximab. Main comparators: best supportive care or apremilast because of positioning	Comparator sequences with apremilast not fully explored. **Full set of analyses comparing DMF with BSC and apremilast**
Time horizon	10 years. Appropriate to capture all costs and effects as per prior NICE analyses	Sufficient for single treatments. Inadequate for sequences, over-estimates health benefits → ≥25 years. **Lifetime horizon**

BSC best supportive care, DMF dimethyl fumarate, *FUTURE retrospective study

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Sources: Company submission: pages 192-193. ERG report: pages 170-172.

Company base case model – ERG comments

40 year horizon: on treatment

At 10 years, 67% on BSC in DMF sequence vs 73% in no-DMF sequence

	Proportion of people on treatment in treatment sequence DMF→Ada→Ust→BSC				Proportion of people on treatment in comparator sequence Ada→Ust→BSC		
	DMF	Ada	Ust	BSC	Ada	Ust	BSC
Baseline	100%	0%	0%	0%	100%	0%	0%
10 years	2%	9%	18%	**67%**	7%	16%	**73%**
20 years	0%	1%	4%	82%	1%	3%	83%
30 years	0%	0%	1%	66%	0%	0%	66%
40 years	0%	0%	0%	27%	0%	0%	27%

ADA adalimumab, BSC best supportive care, DMF dimethyl fumarate, UST ustekinumab

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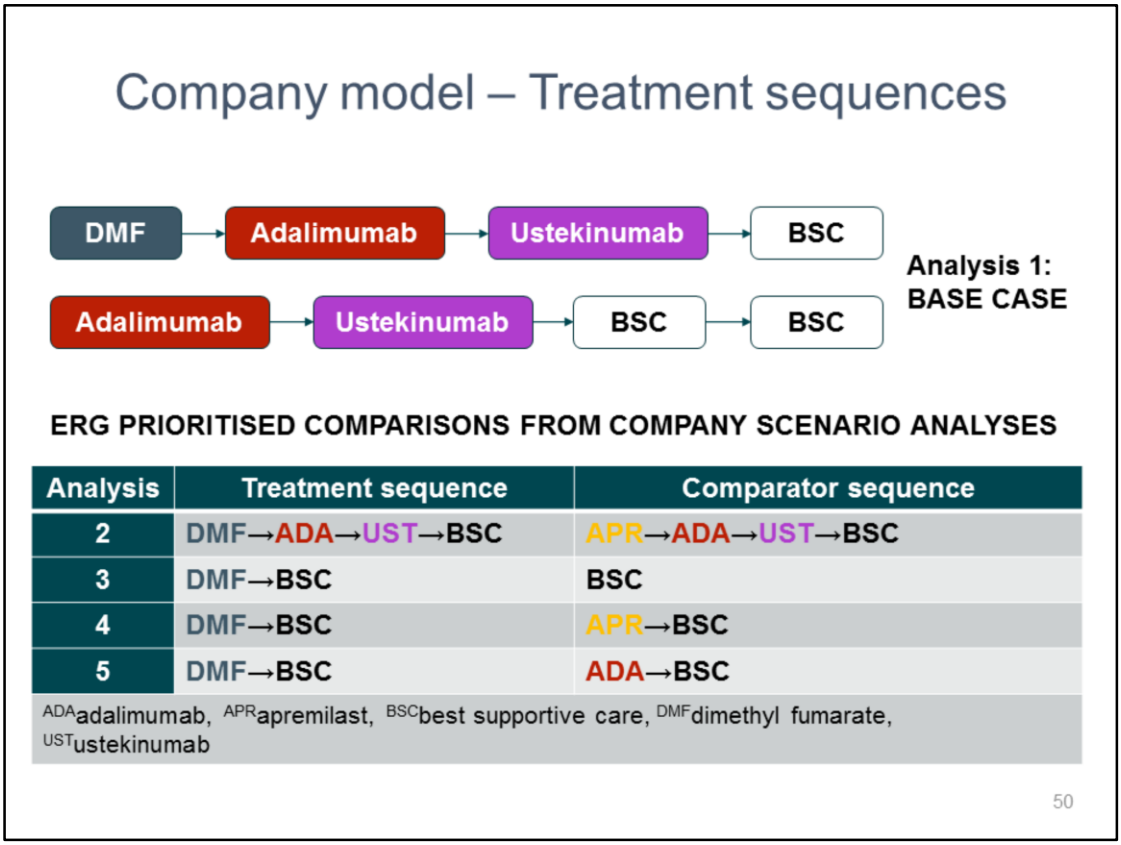
Source: ERG report: Table 42, page 126.



Sources: Company submission: Table 76, pages 192-193. ERG report: pages 156-165.

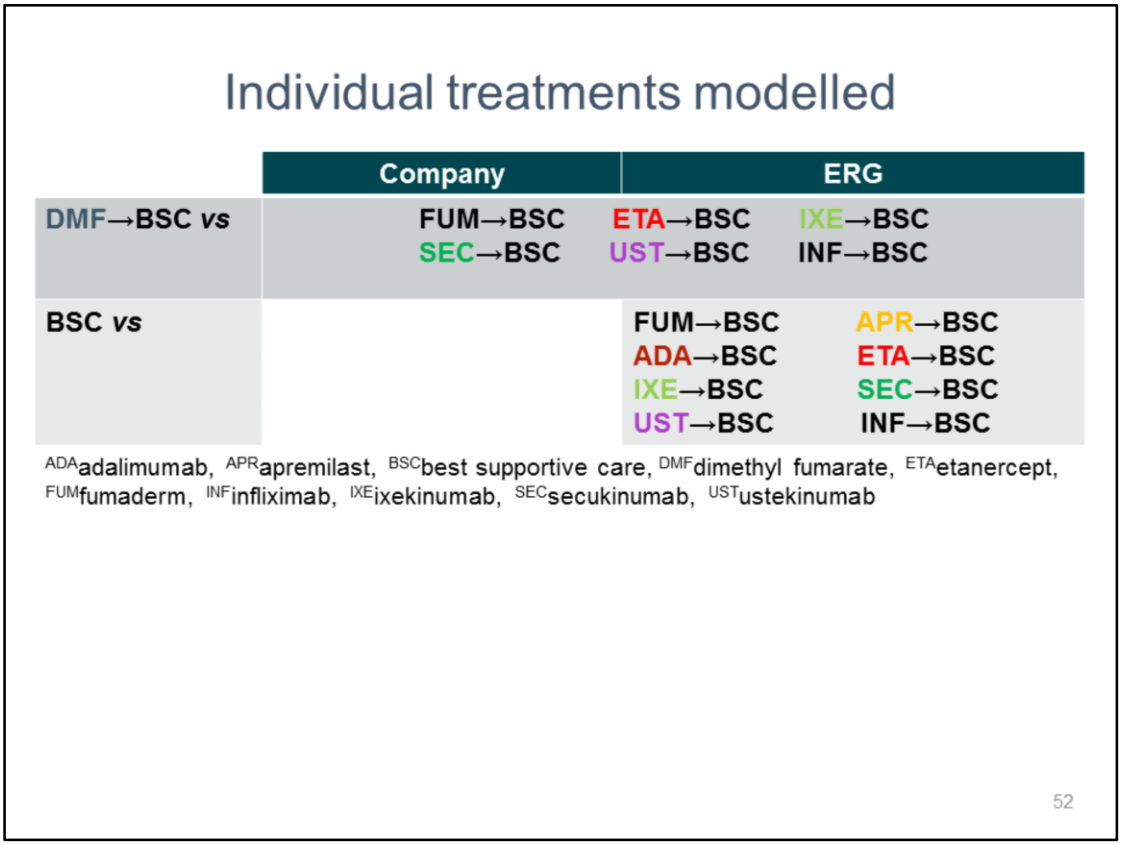
Other treatment sequences modelled

	Company	ERG
DMF before biologics	DMF→ETA→ADA→UST *vs* ETA→ADA→UST→BSC	DMF→ETA→UST→BSC *vs* ETA→UST→BSC
	DMF→ADA→SEC→BSC *vs* ADA→SEC→BSC	
DMF *vs* apremilast before biologics	DMF→ADA→SEC→BSC *vs* APR→ADA→SEC→BSC	
DMF before biologics *vs* DMF after biologics	DMF→ADA→UST→BSC *vs* ADA→UST→DMF→BSC	
		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

51

Sources: Company submission: Figure 30, page 163. ERG report: section 5.2.2, page 110.



Sources: Company submission: pages 192-193. ERG report: pages 170-172.

Company model and base case – ERG comments

Discontinuation rates

Treatment-specific discontinuation rates should be used

Company model and base case	ERG comments and amendments
• All patients: discontinue at a constant rate of 20% annually • No long-term evidence available for DMF discontinuation	• Treatments have different administration routes and side effect profiles • Study (Arnold) used in company's sensitivity analysis on treatment-specific discontinuation rates is preferred

	Arnold treatment survival rates				Company sensitivity analysis
	1 year	2 year	3 year	5 year	Annual discontinuation
Fumaric acid esters	46%	41%	35%	25%	14%
Methotrexate	43%	27%	20%	10%	NR
Ciclosporin	16%	0%	0%	0%	NR
Acitretin	37%	23%	23%	16%	NR
Adalimumab	70%	53%	49%	49%	9%
Etanercept	60%	48%	38%	29%	16%
Ustekinumab	90%	83%	83%	75%	4%
Infliximab	53%	37%	37%	11%	33%

Sources: Company submission: Table 65, page 181. ERG report: section 5.3.2, Table 47, pages 134-135.

Company model and base case – ERG comments

Clinical effectiveness estimates

Fumaderm, low dose etanercept and low dose ustekinumab values preferred

Parameter	Company model and base case	ERG comments and amendments
Treatment response	Treatment effects are constant for any line of therapy. Treatment sequences contain treatments with different modes of action	-
Fumaderm	Assumed to be the same as DMF	NMA estimates favour fumaderm over DMF. **Fumaderm values used**
Etanercept and ustekinumab	NMA estimates for high doses used	Low dose NMA estimates are more appropriate. **Low dose NMA estimates used**
Infliximab	Average of reported values in secukinumab (TA350) and apremilast (TA419)	-

DMF dimethyl fumarate, NMA network meta-analysis

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Sources: Company submission: Table 65, page 181. ERG report: section 5.3.2, pages 134-135.

Company model base case and ERG exploratory analyses

Inputs: Health utilities – values

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

Baseline HRQoL: 0.07 (Revicki et al. 2008, to ensure consistency with previous NICE TAs)

PASI response	Mean HRQoL increment (standard error)*	
	All patients^	Severe: 4th quartile DLQI
PASI<50	0.05 (0.01)	0.12 (0.03)
PASI50-75	0.17 (0.04)	0.29 (0.06)
PASI75-90	0.19 (0.04)	0.38 (0.08)
PASI90+	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

HRQoL improvements from mapped DLQI values collected from BRIDGE, used in sensitivity analysis

PASI response	DMF	Fumaderm	Placebo
<PASI50	0.03	0.02	0.01
PASI50 to PASI75	0.11	0.10	0.08
PASI75 to PASI90	0.14	0.14	0.09
PASI90	0.19	0.16	0.18

Source: ERG report: Table 28, page 96.

Company model – ERG comments
Health-related quality of life

QoL increments	**Company**	For 1st line treatment induction: no QoL increment compared to baseline; for same treatments from ≥ 2nd line in sequence: QoL increment applied
	ERG	Increases total QALYs in sequences with more treatments. **Equalise trial period QoL values between treatments at baseline value**
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: reduce baseline QoL for severe to 0.5**
Age-related QoL	**ERG**	Extended time horizon → increasing comorbidities → age weighted QoL. No survival treatment effects → no impact if only the base QoL is weighted. To impact results: QoL increments associated with PASI responses must be weighted

QoL quality of life

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Sources: Company submission: Table 65, page 181. ERG report: section 5.3.2, pages 134-135.

Company model
Inputs: Resources and costs – summary

- Company included the following costs:
  - Treatment acquisition costs (recommended daily dose and list price on BNF)
  - Treatment administration costs
  - Monitoring costs
  - Outpatient visits
  - A&E visits
  - Day ward admissions
  - Phototherapy
  - Best supportive care
  - Non-responder cost (£225 per cycle, range from £45.04 to £348.22 per cycle)
- Excluded from model: adverse event management costs

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Company model and base case – ERG comments

Dosing, drug acquisition costs and wastage

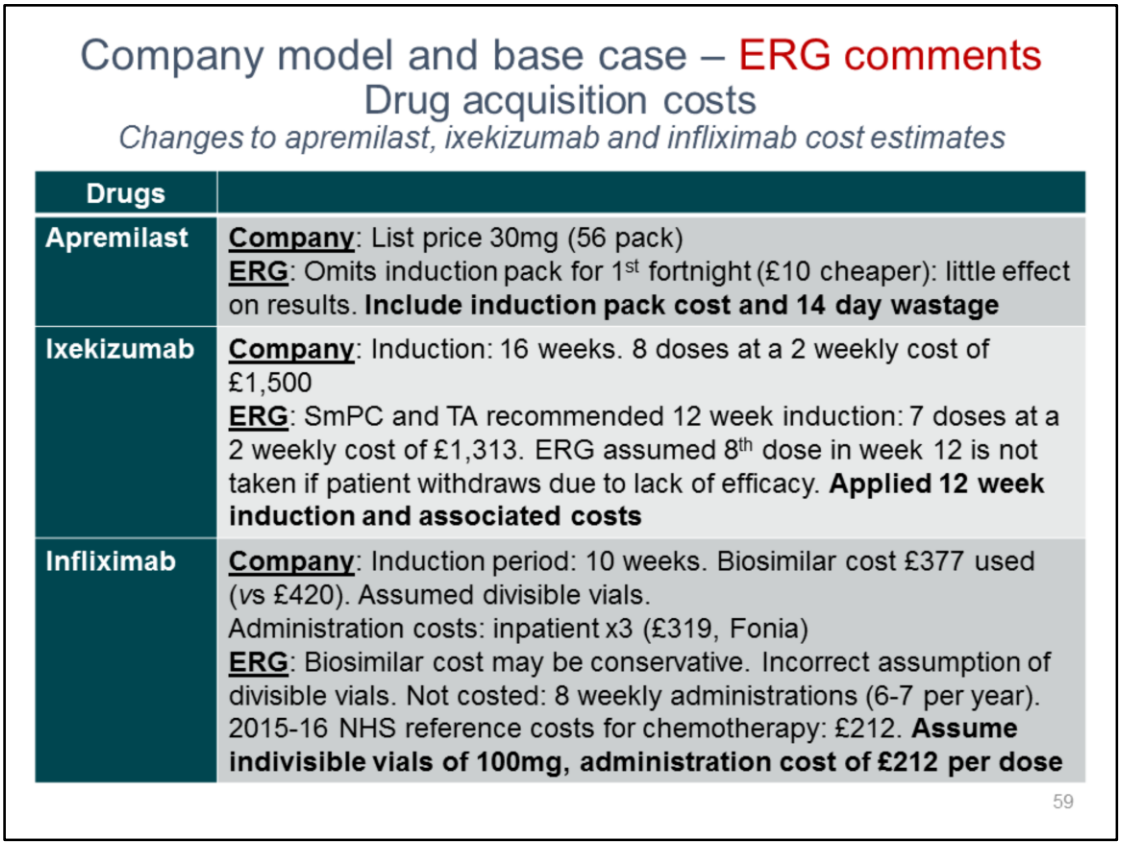
Source estimates for DMF and fumaderm induction and maintenance doses applied in scenario analyses

Drugs	
Dimethyl fumarate	**Company**: Patients follow the recommended dosing & guidelines. 30mg and 120mg tablets: same cost £2.12 per tablet; Induction average daily dose of 624mg; cost £117 fortnightly; Maintenance average daily dose of 360mg; cost £89 fortnightly **ERG**: Applies DMF induction dose to fumaderm (higher than in literature*) Assumes maintenance dose from literature on fumaderm good responders to DMF (less than BRIDGE) **Scenario analyses:** • **Fumaderm induction dose: 70% DMF** • **DMF maintenance dose: 70% BRIDGE trial weeks 10-16 average dose** • **DMF and fumaderm maintenance dose: 480mg^**
Fumaderm	Cost per tablet £2.52 (German cost per tablet of €2.43 at January 2017 exchange rate £2.07 plus undocumented import charge of 22%)
Wastage not included. **Applied 14 days wastage to DMF and fumaderm**	

DMFdimethyl fumarate, *FUTURE retrospective study on fumaderm, ^Lijnen study on high dose DMF in moderate to severe psoriasis, 28% prior systemic treatment

58

Sources: Company submission: Table 65, page 181. ERG report: section 5.3.2, pages 134-135.



Sources: Company submission: Table 65, page 181. ERG report: section 5.3.2, pages 134-135.

Company model and base case – ERG comments

Best supportive care costs

Slight increase from £185 to £189

Company model and base case	ERG comments and amendments
Same for pre- and post-biologics as psoriasis is not a disease that progresses • Costs from Fonia for pre-biologics: ➢ £1249.40 per annum of pre-biologic systemic treatments ➢ £1.14 of other supportive drugs ➢ £2956.70 of inpatient visits, outpatient visits, A&E visits, day ward admissions and phototherapy Total annual cost £4207 adjusted for inflation to 2014/15 prices £4798, £185 per fortnight	Total annual cost higher than £4,629 adjusted for inflation cost in clarification response Applying the 2015 dermatology outpatient cost rather than adjusting for inflation that in Fonia increases this slightly to £4,701 per annum, £189 per fortnight

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Sources: Company submission: Table 65, page 181. ERG report: section 5.3.2, pages 134-135.

Company model and base case – ERG comments

Non-responder costs

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 disadvantage 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 STA [TA419]

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Sources: Company submission: pages 178, 180-181. ERG report: pages 120-121.

Company model and base case – ERG comments
Inpatient costs
Scenario analyses £336 to £477 on inpatient costs

Company model and base case	ERG comments and amendments
Fonia: implied £336 unit cost adjusted for inflation to 2015-16 prices	Fonia estimates reasonable as comparators are recommended for severe population. Suggestions: cost per day are higher for shorter than longer stays. Cost per day falling as the number of complications and comorbidities increases and the length of stay increases. **Scenario analyses: £477 unit cost to inpatient days, differentiated* unit cost of £408 for pre-biologic period and £477 for post biologic period (underestimates if plaque psoriasis admissions tend to be elective rather than non-elective)**

*Fonia only provides estimates that permit the mean number of inpatient days per year to be inferred; average length of stay may be the same pre-biologic and post biologic, with the rate of admission being the main determinant of the mean number of inpatient days

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Sources: Company submission: Table 65, page 181. ERG report: section 5.3.2, pages 134-135.

Company model and base case – ERG comments

Outpatient and monitoring costs

Monitoring costs added to base case and reduction of visits in scenario analysis

	Company model and base case	ERG comments and amendments
Outpatient costs	£101 cost per outpatient visit from 2014-15 NHS reference costs	Unable to source quoted costs. 2015-16 consultant led follow up cost £99. These differences have minimal impact upon results. **ERG applied the 2015-16 cost**
Monitoring costs		Model assumes full blood counts are required every month but does not cost any visit. **Base case: added routine outpatient monitoring schedule at £36 cost of a 9.22 minute GP appointment (PSSRU 2016 Unit Costs of Health and Social Care). Scenario analysis: reduce frequency of tests to draft SmPC**

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Sources: Company submission: Table 65, page 181. ERG report: section 5.3.2, pages 134-135.

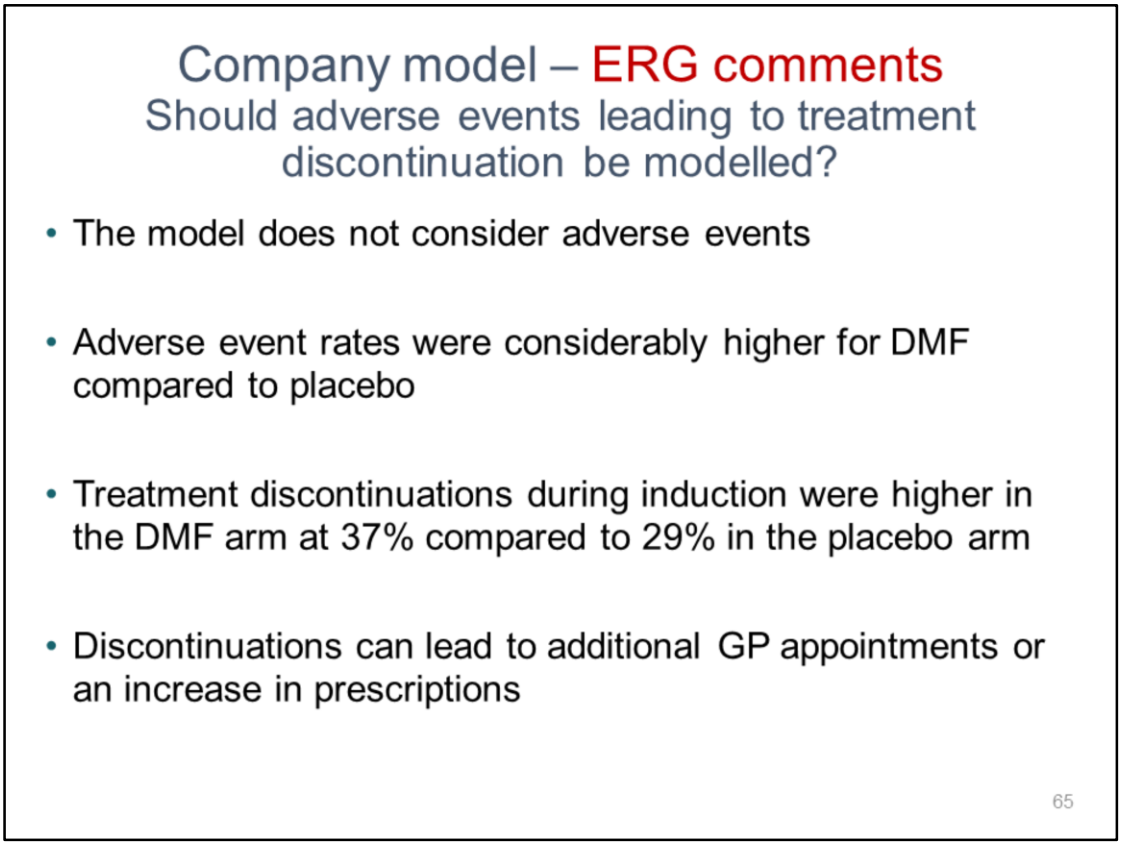
Company model and base case – ERG comments

Titration and subcutaneous injection costs

Sensitivity analysis increasing down titration monitoring

	Company model and base case	ERG comments and amendments
Titration costs	Up-titration monthly monitoring for DMF and fumaderm *vs* every 2 months for apremilast and biologics	Model assumes down titration of mean 5 daily tablets to 3, suggesting at least 2 visits. Company assumes responders on DMF or fumaderm require 1 outpatient visit every 2 months *vs* 1 outpatient visit every 3 months for apremilast and biologics. **Down titration monitoring visits may be underestimated. Sensitivity analysis adding 2 outpatient visits for responders of DMF and fumaderm**
Subcutaneous injection costs	No allowance in model	ERG agrees. Biologics are typically self injected (one off training costs of 3 hours nurse time). Exception: severe patients move straight from oral to infliximab with no further treatments

Sources: Company submission: Table 65, page 181. ERG report: section 5.3.2, pages 134-135.



Sources: Company submission: Table 65, page 181. ERG report: section 5.3.2, pages 134-135.

ERG exploratory analysis

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	Company	ERG changes
Time horizon	10 years	Lifetime
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
Non-responder cost	£225/fortnight	£121/fortnight (outpatient costs separate)
Outpatient monitoring		Additional £36 for GP appointments for blood tests

Source: ERG report: pages 153-154.

Company and ERG base case results – list prices

	Probabilistic ICERs (£/QALY)			
	All patients QoL increment*		Severe QoL increment*	
	Company	ERG	Company	ERG
1	Dominated	£10,193	NA	£5,550
2	Confidential PAS – see part 2 slides			
3	NA	£25,567	NA	£13,700
4	Confidential PAS – see part 2 slides			
5	NA	£68,225 SW	NA	£35,634 SW

Analysis 1 (base case): DMF→ADA→UST→BSC *vs* ADA→UST→BSC
Analysis 2: DMF→ADA→UST→BSC *vs* APR→ADA→UST→BSC
Analysis 3: DMF→BSC *vs* BSC
Analysis 4: DMF→BSC *vs* APR→BSC
Analysis 5: DMF→BSC *vs* ADA→BSC

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

ADAadalimumab, APRapremilast, BSCbest supportive care, DMFdimethyl fumarate, USTustekinumab (apremilast has a patient access scheme, PAS)
*Refers to all patient QoL estimates and severe patient QoL estimates taken from TA103 (etanercept), not severity of psoriasis

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Sources: Company submission: Table 76, pages 192-193. ERG report: pages 156-165.

Other treatment sequences: Company and ERG deterministic base case results for all patients – list prices

Treatment comparisons	ICERs	
	Company	ERG
DMF before biologics		
DMF→ETA→ADA→UST *vs* ETA→ADA→UST→BSC	Dominated	NA
DMF→ADA→SEC→BSC *vs* ADA→SEC→BSC	Confidential PAS – part 2	
DMF→ETA→UST→BSC *vs* ETA→UST→BSC	NA	£15,964
DMF *vs* apremilast before biologics		
DMF→ADA→UST→BSC *vs* APR→ADA→UST→BSC	Confidential PAS – part 2	
DMF→ADA→SEC→BSC *vs* APR→ADA→SEC→BSC	Confidential PAS – part 2	
DMF before biologics *vs* DMF after biologics		
DMF→ADA→UST→BSC *vs* ADA→UST→DMF→BSC	£86,324	£88,456 SW
DMF→APR→ADA→UST *vs* APR→ADA→UST→DMF	Confidential PAS – part 2	
DMF→ETA→UST→BSC *vs* ETA→UST→DMF→BSC	NA	£90,581 SW

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

ADAadalimumab, APRapremilast, BSCbest supportive care, DMFdimethyl fumarate, ETAetanercept, SECsecukinumab, USTustekinumab (apremilast and secukinumab have patient access schemes, PAS)

Sources: Company submission: Table 76, pages 192-193. ERG report: pages 156-165.

Individual treatments: Company and ERG deterministic base case results for all patients – list prices

Treatments	Compared with DMF→BSC		Compared with BSC	
	Company	ERG	Company	ERG
Dimethyl fumarate→BSC			£35,256	£25,567
*Fumaderm→BSC	£31,887	£34,207 SW	NA	£27,849
Apremilast→BSC	Confidential PAS – see part 2 slides			
Adalimumab→BSC	£68,054	£65,934 SW	NA	£56,850
^Etanercept→BSC	£57,079	£70,444 SW	NA	£52,806
Ixekizumab→BSC	Confidential PAS – see part 2 slides			
Secukinumab→BSC	Confidential PAS – see part 2 slides			
^Ustekinumab→BSC	£65,748	£65,822 SW	NA	£58,006
**Infliximab→BSC	£65,951	£77,272 SW	NA	£68,719

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

*Clinical effectiveness estimates for fumaderm are from network meta-analysis
^CS uses high dose, ERG uses low dose
**ERG includes infliximab administration cost
BSC best supportive care, DMF dimethyl fumarate, Na not available
(apremilast, ixekizumab and secukinumab have patient access schemes, PAS)

Sources: Company submission: Table 76, pages 192-193. ERG report: Tables 67 and 68, pages 170 and 172.

ERG scenario analyses (1)

- 10 year time horizon
- Company NMA results:
  - systemic or PUVA experienced
  - excluding low quality studies
- Quality of life (QoL):
  - QoL gains for PASI75 responders from start of the trial period rather than the start of the maintenance period
  - Arbitrarily reduce baseline QoL to 0.6
  - QoL increments of Woolacott for severe patients (reduce baseline QoL to 0.5 to avoid ceiling effects)
  - QoL estimates from DLQI coefficients of secukinumab STA [TA180] reestimation of Woolacott and Currie to BRIDGE DMF DLQI changes
- Discontinuation rates of Arnold

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Source: ERG report: section 5.3.4, pages 154-155.

ERG scenario analyses (2)

- Drug doses:
  - fumaderm trial dose 70% of BRIDGE and DMF maintenance dose of 70% of BRIDGE trial average dose during weeks 10-16 (Reich)
  - DMF and fumaderm maintenance dose of 480mg (Linjen)
  - reduce the etanercept drug costs by 26% to reflect previous assessments' modelling of intermittent etanercept
- Monitoring costs:
  - apply 2 additional outpatient visits among good responders to DMF and fumaderm for down titration
  - reduce the frequency of full blood counts, renal monitoring and liver function tests for DMF and fumaderm to that of the draft DMF SmPC
- Apply £225 cost per fortnight per non-responder trialling a treatment (company base case)
- Apply 2015-16 NHS reference costs per inpatient day of £477, and differentiate unit cost as £408 for the pre-biologic period and £477 for post biologic period.

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Source: ERG report: section 5.3.4, pages 154-155.

ERG scenario analyses – base case deterministic results – list prices

Estimates are sensitive to time horizon, early QoL gain in induction, severe QoL increments, DLQI function of Currie, Arnold discontinuation rates, DMF dosing, non-responder costs during trial periods, inpatient day costs

Base case (DMF-Ada-Ust-BSC *vs* Ada-Ust-BSC)	All patients QoL increment*	Severe QoL increment*
	£12,299	**£6,911**
10 year horizon	Dominant	Dominant
NMA systemic experienced	£12,654	£7,090
NMA exc low quality studies	£11,216	£6,296
PASI75 QoL trial	£10,017	£5,512
Baseline QoL 0.6	£12,299	£6,911
Severe QoL	£6,911	..
QoL DLQI TA180	£13,723	..
QoL DLQI Currie	£8,725	..
Discontinuation rates Arnold	Dominant	Dominant
70% DMF dosing	£20,692	£11,628
DMF 480mg	£25,380	£14,262
Intermittent etanercept	..	..
DMF +2 OP	£13,127	£7,377
DMF monitoring frequency SmPC	**£8,396**	**£4,718**
£225 non-responder	£28,403	£15,961
£477 inpatient day	£14,851	£8,345
£408/£477 inpatient day	£13,108	£7,366

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

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Source: ERG report: section 5.3.4, pages 154-155.

Summary of cost effectiveness results

- DMF dominates in base case:
  DMF→adalimumab→ustekinumab→BSC *vs* ADA→UST→BSC
- Results are sensitive to time horizon, discontinuation rates, DMF costs, DMF monitoring and non-responder costs
- Scenario analyses of different treatment sequences with apremilast result in cost effectiveness estimates in the SW quadrant ranging from £98k to £125k per QALY
- Head-to-head comparisons with single treatments yield cost effectiveness estimates in the SW quadrant ranging from £60k to £130k per QALY
- The main effect in the base case is that DMF delays the adoption of biologics which have very poor cost effectiveness
- ERG's exploratory analysis yield cost effectiveness estimate of £12,299 per QALY over lifetime horizon

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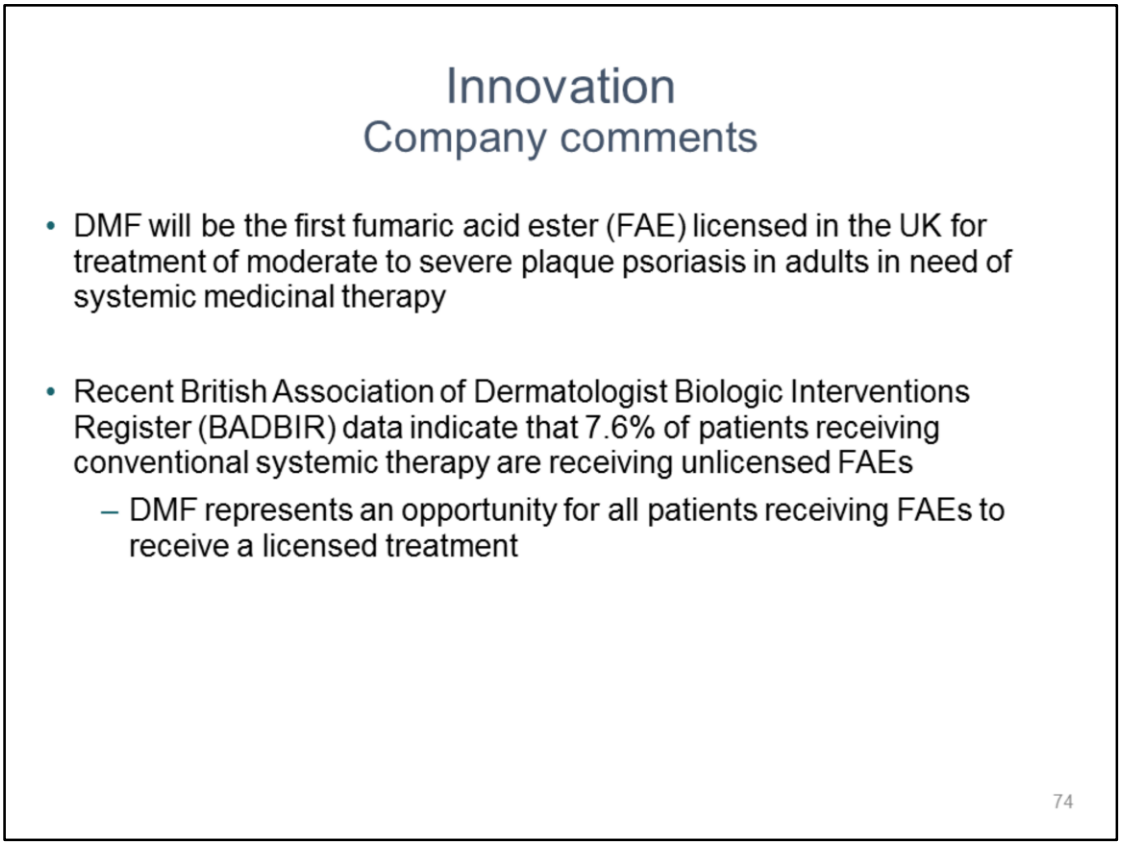
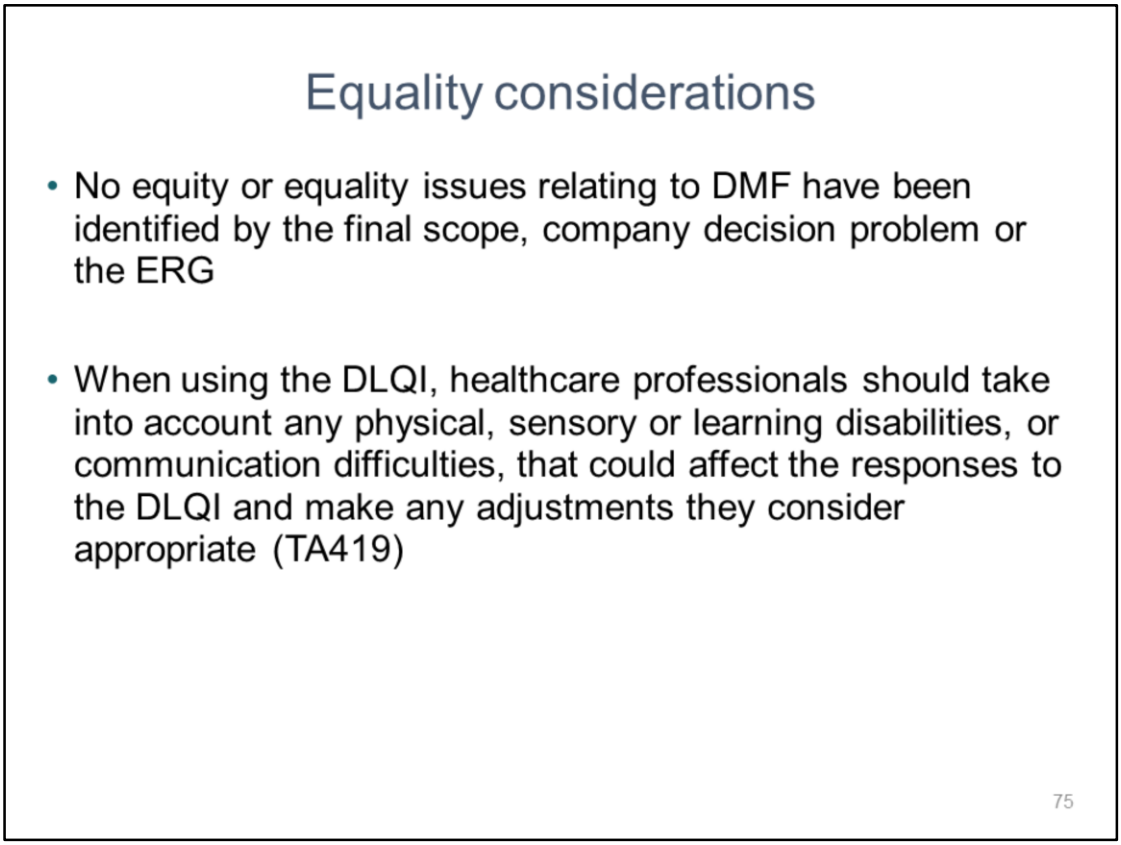


Source: Company submission: section 2.5, page 28.



Sources: ERG report: section 3.5, page 40. TA419.

Authors

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Additional slides

Non-essential reading

Useful information from submission, clarification response and ERG report

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BRIDGE RCT
Dosing regimens

DMF 30mg or Fumaderm 30mg			
	Week 1	Week 2	Week 3
AM	0	2 (1A, 1P)	2 (1A, 1P)
Noon	0	0	2 (1A, 1P)
PM	2 (1Active, 1Placebo)	2 (1A, 1P)	2 (1A, 1P)
Total daily dose	30	60	90

DMF 120mg or Fumaderm 120mg						
	Week 4*	Week 5	Week 6	Week 7	Week 8	Weeks 9-16
AM	0	1	1	1	2	2
Noon	0	0	1	1	1	2
PM	1	1	1	2	2	2
Total daily dose	120	240	360	480	600	720

*After week 4, reduction to the last tolerated dose allowed in case of intolerability

Source: Company submission: Table 7, pages 43-44; Table 8, page 46.

BRIDGE RCT

Baseline characteristics – demographics

	Safety analysis set			Full analysis set		
	DMF (n = 279)	Fumaderm (n = 283)	Placebo (n = 137)	DMF (n = 267)	Fumaderm (n = 273)	Placebo (n = 131)
Male, n (%)	174 (62)	185 (65)	93 (68)	167 (63)	177 (65)	88 (67)
Age (years)						
Mean±SD	44±15.2	45±13.8	44±14.3	44±15.2	45±13.6	44±14.4
Range	18-80	18-87	18-78	18-80	18-87	18-78
Ethicity, n (%)						
White	275 (99)	280 (99)	137 (100)	263 (99)	271 (99)	131 (100)
Black/African American	1 (0.4)	0	0	1 (0.4)	0	0
Asian	1 (0.4)	3 (1)	0	1 (0.4)	2 (0.7)	0
Other	2 (1)	0	0	2 (0.8)	0	0

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Sources: Company submission: Table 11, page 55. Clarification response: A9, page 9.

Network meta-analysis

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

DMF better than placebo but probability of response lowest vs other active treatments

Intervention	Primary: PASI75*	PASI50*	PASI90*
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)

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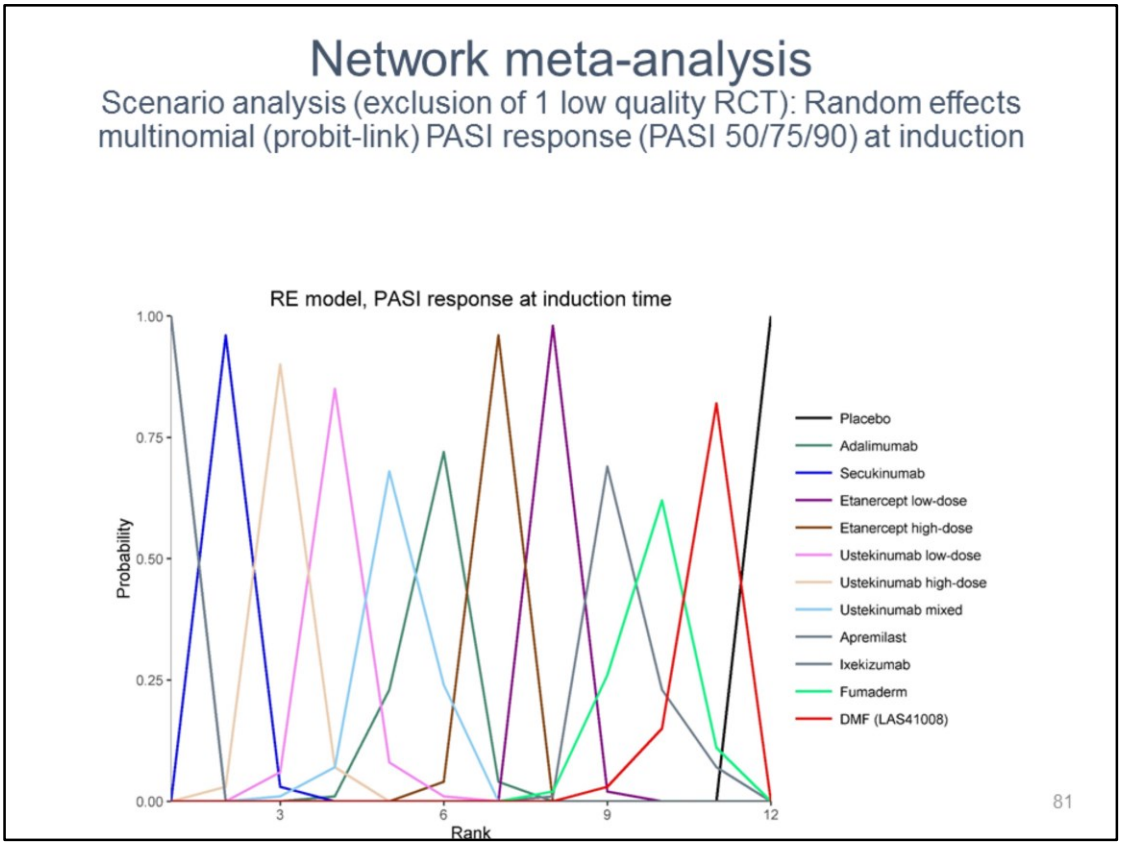
Source: Company submission: Table 38, page 120-121.

Health economic model input

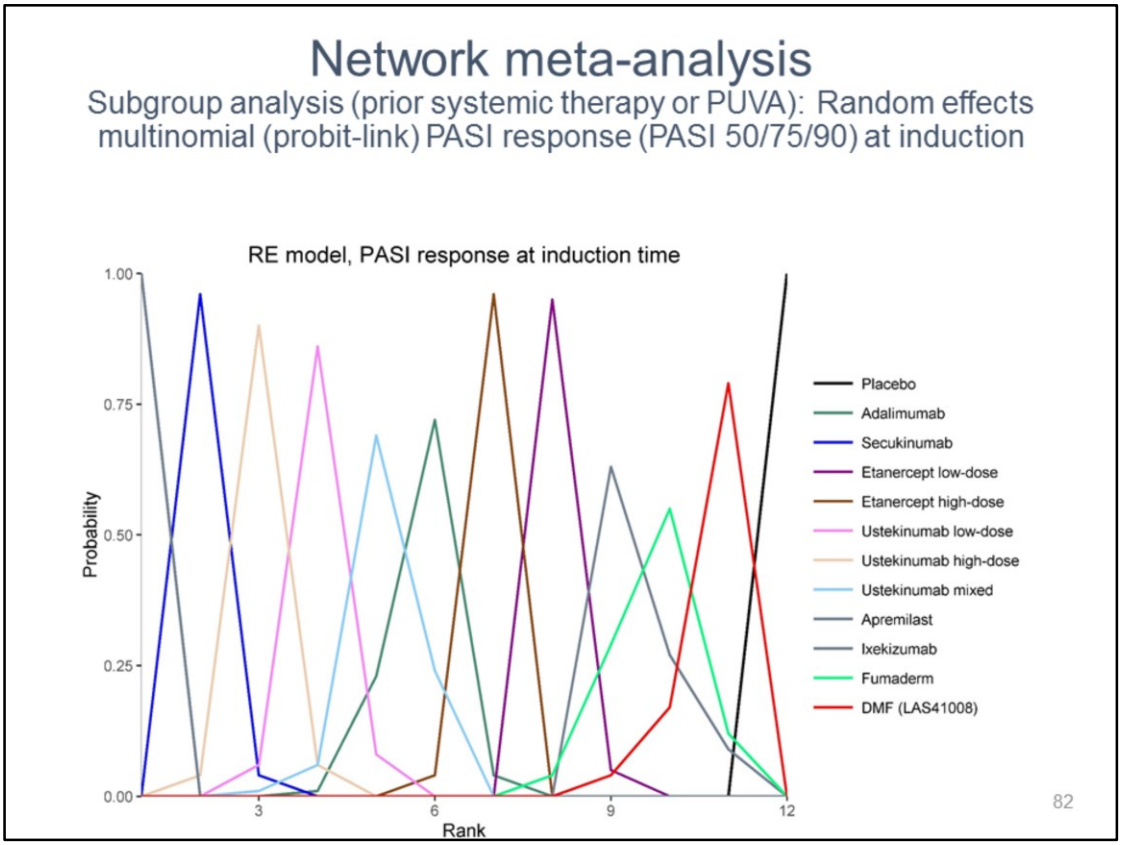
Induction time

Company submission (page 105):

Induction time is the time point at which the primary endpoint was measured in the pivotal studies for each medicine mentioned: 12 weeks for secukinumab, etanercept, ustekinumab, and ixekizumab and 16 weeks for adalimumab, apremilast, fumaderm and DMF.



Source: Clarification response: Figure 6, page 32.



Source: Clarification response: Figure 8, page 34.

Company model – ERG comments

Probability sampling methods

Revised the PSA sampling to equalise various cost elements between treatments rather than sample them independently for each treatment
Revised the PSA to not sample elements that can be argued to be by assumption

Company model ERG comments and amendments
20% annual discontinuation rate – arbitrary distribution for each treatment **sampled value applied equally across treatments**
Administration and resource use – arbitrary distributions, sampled independently for each treatment which overstates uncertainty **assumptions and not sample**
Resource use – sampled separately for each treatment **values applied equally across treatments**
Non-responder costs – samples using arbitrary distribution separately for each treatment **sampled value applied across treatments**
Unit costs applied to resource use are not sampled Uncertainty will be understated in probabilistic modelling. ERG did not address this.

Sources: Company submission: Table 65, page 181. ERG report: section 5.3.2, pages 134-135.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Company evidence submission

15 March 2017

File name	Version	Contains confidential information	Date
ID776_Dimethyl fumarate_Manufacturer submission_15 Mar 17_ACIC updated 14 May 2017	V1.0	Yes	15 March 2017

Contents

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Abbreviations

AE	Adverse event
BID	Twice daily
BSA	Body surface area
BSC	Best supportive care
CG	Clinical guideline
CI	Confidence interval
CrI	Credible interval
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
DMF	Dimethyl fumarate
EMA	European Medicines Agency
FAE	Fumaric acid esters
FAS	Full analysis set
LOCF	Last observation carried forward
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PASI	Psoriasis Area and Severity Index
PBI	Patient Benefit Index
PGA	Physician's Global Assessment
PNQ	Patient Need Questionnaire
PPS	Per protocol set
QD	Once daily
SAS	Safety analysis set
RCT	Randomised controlled trial
SD	Standard deviation
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics

TEAE	Treatment-emergent adverse event
TID	Three times daily
TNF	Tumour necrosis factor

1 Executive summary

Psoriasis

Psoriasis is an inflammatory skin condition which follows a relapsing and remitting course. It is a chronic, painful, disfiguring and disabling disease for which there is no cure.[1] It is thought to be caused by a combination of genetic and environmental risk factors.[2]

Plaque psoriasis is the most common form, accounting for around 90% of cases.[3] It is characterised by well-deliniated red, scaly plaques that vary in extent from a few localised patches to generalised involvement.[3] Lesions cause itching, stinging and pain.[1]

Psoriasis is generally graded as mild, moderate or severe, an assessment which takes into account the extent of the area affected and severity of the lesions. Depending on the severity and location of skin lesions, individuals may experience significant physical discomfort and disability. Itching and pain can interfere with basic functions, such as self-care and sleep.[4] There are also problems related to the treatments used (mess, odour, inconvenience and time), and the effect of living with a highly visible, disfiguring skin disease (difficulties with relationships, difficulties with securing employment and poor self-esteem).[5]

Death directly due to psoriasis is rare but the associated morbidity is significant.[3] In a significant proportion of patients, joints may be affected (psoriatic arthritis).[3] Severe psoriasis may also be associated with increased levels of cardiovascular disease[3,6,7] and an increased risk of major adverse cardiac events.[8] People with psoriasis, particularly severe disease, may also be at increased risk of lymphoma and non-melanoma skin cancer.[3]

Psoriasis is associated with a physical, emotional and social burden.[1,5] Psoriasis can also have a profound impact on mental health. About a third of people with psoriasis experience major psychological distress,[5] and patients with psoriasis have an increased risk of depression, anxiety, and suicidality.[9] It has been estimated that in the UK in excess of 10,400 diagnoses of depression, 7,100 diagnoses of anxiety, and 350 diagnoses of suicidality may be attributable to psoriasis annually.[9]

Disruptions caused by psoriasis treatment, the comorbidities, associated stigma and lack of confidence can have a cumulative impact throughout a person's lifetime and influence major life-changing decisions, alter the course of patients' lives e.g. attainment of life goals, chosen career, desired educational level, and impact social and personal relationships.[10] Psoriasis may reduce an individual's ability to work and negatively impact income levels.[11]

Psoriasis also has a significant impact on the NHS. Psoriasis represents between 1.7 and 5% of the 13 million GP consultations for skin disease each year (i.e. 221,000 - 650,000 consultations per annum).[12] In 2014/15 there were 12,441 hospital admissions for psoriasis (any type) equating to 13,034 finished consultant episodes and 13,358 bed days.[13]

Treatment

There is no cure for psoriasis and the approach to therapy is largely governed by the extent and severity of disease.[3] The aim of treatment is to minimize the extent and severity of the disease to the point at which it no longer substantially disrupts the patient's quality of life.[14]

In clinical practice the treatment pathway as set out in the NICE guideline is applied.[15] Topical therapies are recommended as first-line therapy for milder forms of psoriasis, with phototherapy being recommended as second-line therapy, or for more extensive disease. Conventional non-biologic systemic therapies (methotrexate, ciclosporin and acitretin) are recommended in patients with psoriasis that cannot be controlled with topical treatments alone. Biologic therapies, and more recently apremilast,[16] are recommended for severe disease in patients who have failed to respond to standard systemic therapies and PUVA; or where the person is intolerant to, or has a contraindication to, these treatments. Patients sequence through available therapies depending on clinical need and personal preference. Choice of treatment is based on severity of psoriasis, extent of body surface affected and response to prior treatment.[5] In addition, treatment should be tailored to the individual with consideration of age, co-morbidities and current treatments, personal circumstances (e.g. family planning, alcohol use) and preferences, and risks and benefits of available treatment options.[5]

Unmet need

Currently available systemic treatments are not effective or suitable in all patients. Individual treatment responses vary and the choice of treatment needs to reflect individual patient considerations (e.g. planning to have a family, interactions with treatments for co-morbid conditions or alcohol) and the potential for adverse effects that require treatment discontinuation or limit long-term use.[17,18,19] Additional treatment options are needed to help meet the varying needs of patients requiring systemic medicinal therapy.

Dimethyl fumarate (DMF, LAS41008)

DMF (LAS41008) will be the first fumaric acid ester (FAE) licensed in the UK for treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy. In clinical practice, DMF (LAS41008) will offer patients and clinicians an additional systemic, non-biologic treatment option. FAEs have been used in Germany since 1959[20] where a licensed product Fumaderm®, has been available since 1994.[20] In the UK FAEs are subject to unlicensed use where they have been imported and used since 1999.[21] The British Association of Dermatologists Biologic Interventions Register (BADBIR) data indicate that 7.6% of patients receiving conventional systemic therapy are currently receiving unlicensed FAEs.[22]

In clinical practice, DMF (LAS41008) will be used in a specific subgroup of patients: those for whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference. This submission will focus on this position and subgroup of patients.

In the pivotal Phase 3 randomised controlled trial (BRIDGE) DMF (LAS41008) significantly improved key efficacy outcomes (percentage of patients achieving ≥ 75% in Psoriasis Area and Severity Index (PASI) and percentage of patients achieving a score of 'clear' or 'almost clear' in Physician's Global Assessment (PGA) at week 16) compared to placebo and was demonstrated to be non-inferior to Fumaderm.[23] (See Section 1.3 of the executive summary for a summary of clinical effectiveness)

The adverse events observed with DMF (LAS41008) were consistent with those reported for Fumaderm. Most treatment-related adverse events were classified as mild in severity.

DMF (LAS41008) represents a further treatment option alongside current standard options for the treatment of moderate to severe psoriasis, and no significant change to current practice is anticipated. Administration of oral DMF (LAS41008) will utilise existing NHS infrastructure and resources with no additional requirements above those required for currently available treatments. It is anticipated that any dose reductions or discontinuation of treatment will be managed remotely.

1.1 Statement of decision problem

Details of the decision problem to be addressed are provided in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate to severe chronic plaque psoriasis	The final indication for dimethyl fumarate (DMF) has yet to be approved. It is anticipated that DMF will be used in adults with moderate to severe chronic plaque psoriasis who require systemic medicinal therapy.	The anticipated patient population is more specific than both the licensed indication and that specified in the scope. In clinical practice it is anticipated that DMF will offer patients and clinicians an additional systemic, non-biologic treatment option. It will be used in patients for whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference. In the current treatment pathway DMF (LAS41008) will occupy a similar position to apremilast but with DMF (LAS41008) being suitable for patients with moderate to severe psoriasis.
Intervention	Dimethyl fumarate (LAS41008)	As per scope	
Comparator (s)	• Fumaric acid esters (does not currently have a marketing authorisation in the UK for this indication) • Systemic non-biological therapies (including acitretin, ciclosporin, methotrexate, phototherapy with or without psoralen, apremilast) • Systemic biological therapies	In line with the above positioning of DMF the only appropriate comparators are: • Fumaric acid esters • Apremilast • Systemic biological therapies (including etanercept, adalimumab, secukinumab	In clinical practice DMF (LAS41008) is likely to be positioned where other oral systemic therapies (acitretin, methotrexate, and ciclosporin) are clinically inappropriate for patients through lack of efficacy, contraindications, tolerability and/or toxicity issues, or patient preference. Acitretin, methotrexate, and ciclosporin are therefore not relevant comparators. Phototherapy is

	(including etanercept, adalimumab, secukinumab and ustekinumab, ixekizumab [subject to NICE guidance]) • Best supportive care	and ustekinumab) • Best supportive care (for people in whom biologic therapies are not tolerated or contraindicated).	also not a relevant comparator as its use is usually before systemic therapies which are recommended when phototherapy has been ineffective, cannot be used or has resulted in rapid relapse
Outcomes	The outcome measures to be considered include: • Severity of psoriasis (including psoriasis areas severity index) • Psoriasis symptoms on the face, scalp, nails and joints • Response rate • Remission rate • Relapse rate • Mortality • Adverse effects of treatment • Health-related quality of life (including dermatology quality of life index).	The outcome measures to be considered include: • Severity of psoriasis (PASI50, PASI75 and PASI90) • Response rate • Remission rate • Relapse rate • Mortality • Adverse effects of treatment • Health-related quality of life	Data on the complications of psoriasis (including nail, scalp and joint outcomes) is not available for DMF (LAS41008)
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per the scope. The cost effectiveness of treatments will be expressed in terms of incremental cost per quality-adjusted life year. The time horizon in the base case will be 10 years to enable the model to capture the full costs and benefits of treatment with DMF. Sensitivity analyses will include a 10-year and lifetime time horizon. Costs will be considered from an	

	The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. For the comparators, the availability and cost of biosimilars should be taken into account.	NHS and Personal Social Services Perspective	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • previous use of systemic non-biological therapy • previous use of biological therapy • severity of psoriasis (moderate, severe) Where the evidence allows, sequencing of different drugs and the place of dimethyl fumarate in such a sequence will be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Evidence on the following subgroups will be provided: • Previous use of systemic non-biological therapy • Severity of psoriasis (moderate/severe) • Age	
Special considerations including issues related to equity or equality		None	

1.2 Description of the technology being appraised

Details of the technology being appraised are summarised in Table 2.

Dimethyl fumarate (LAS41008) will be the first licensed fumaric acid ester (FAE) in the UK for treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.

FAEs have been used in Germany since 1959[20] where a licensed product Fumaderm® has been available since 1994.[20] In the UK FAEs are subject to unlicensed use where they have been imported and used since 1999.[21]

Recent British Association of Dermatologist Biologic Interventions Register (BADBIR) data indicate that 7.6% of patients receiving conventional systemic therapy are receiving unlicensed FAEs.[22]

Table 2: Technology being appraised

UK approved name and brand name	Approved name: dimethyl fumarate (DMF) Brand name: Skilarence®▼
Marketing authorisation/CE mark status	Marketing authorisation application (EMA) filed: December 2015 CHMP opinion anticipated: 21st April 2017 Marketing authorisation anticipated: [redacted]
Indications and any restriction(s) as described in the summary of product characteristics[24]	Proposed indication: DMF (LAS41008) is indicated for the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.
Method of administration and dosage	DMF is for oral use as gastro-resistant tablets. To improve tolerability, it is recommended to begin treatment with a low initial dose with subsequent gradual increases. In the first week, DMF 30 mg is taken once daily (1 tablet in the evening). In the second week, DMF 30 mg is taken twice daily (1 tablet in the morning and 1 in the evening). In the third week of treatment, DMF 30 mg is taken three times daily (1 tablet in the morning, 1 at midday, and 1 in the evening). From the fourth week of treatment, treatment is switched to only 1 tablet of DMF 120 mg in the evening. This dose is then increased by 1 DMF 120 mg tablet per week at different times of day for the subsequent 5 weeks. The maximum daily dose allowed is 720 mg (3 x 2 tablets of DMF 120 mg).

	If a particular dose increase is not tolerated, it may be temporarily reduced to the last tolerated dose. If treatment success is observed before the maximum dose is reached, no further increase of dose is necessary. After clinically relevant improvement of the skin lesions has been achieved, consideration should be given to careful reduction of the daily dose of DMF to the maintenance dose required by the individual. Dosage modifications may also be necessary if abnormalities in laboratory parameters are observed.

1.3 Summary of the clinical effectiveness analysis

The efficacy and safety of DMF (LAS41008) in adult patients with moderate to severe chronic plaque psoriasis is provided by a Phase 3 RCT, the BRIDGE study.[23] The study included a 4-week run-in period and a 16-week treatment period with up to one year off-treatment follow-up.

A total of 671 patients were randomised to receive either DMF (LAS41008), Fumaderm or placebo for 16 weeks. The coprimary endpoints were the percentage of patients achieving ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) and the percentage achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at week 16. The primary objectives were to demonstrate:

- Superiority of DMF (LAS41008) versus placebo based on the proportion of patients achieving PASI 75 (a 75% reduction in the PASI) at week 16 compared to baseline.
- Superiority of DMF (LAS41008) versus placebo based on the proportion of patients achieving a score of "clear" or "almost clear" in the PGA after 16 weeks of treatment.
- Non-inferiority of DMF (LAS41008) compared to Fumaderm regarding PASI 75 after 16 weeks of treatment.

Key secondary outcomes included:

- Superiority of DMF (LAS41008) versus placebo based on changes in PASI, PGA after 3 and 8 weeks and body surface area (BSA) after 3, 8 and 16 weeks.

- Non-inferiority of DMF (LAS41008) compared to Fumaderm regarding PASI 75 after 3 and 8 weeks of treatment.
- Assessment of the safety of DMF (LAS41008) compared to Fumaderm and placebo for both treatment periods (30/120mg DMF).

All three primary objectives of the study were met:

- Significantly more patients treated with DMF (LAS41008) achieved PASI 75 at week 16 compared with placebo. A PASI 75 was achieved by 37.5% of patients in the DMF (LAS41008) treatment group at Week 16 compared with 15.3% of patients in the placebo group, a risk difference of 22% ($p<0.0001$).
- DMF (LAS41008) was also shown to be non-inferior to Fumaderm in the proportion of patients who achieved PASI 75 at week 16 (37.5% vs. 40.3% DMF (LAS41008) vs. Fumaderm, $p<0.0003$).
- The proportion of patients achieving a PGA score of "clear" or "almost clear" at Week 16 was statistically greater in the DMF (LAS41008) group (33.0%) compared to placebo (13.0%; $p <0.0001$).

Treatment with DMF (LAS41008) led to continued improvement in PASI score over time compared with placebo. A significantly greater mean percentage change from baseline in the PASI total score was observed in the DMF (LAS41008) treatment group compared to the placebo group at Week 8 [redacted] and Week [redacted]

The percentage of involved body surface area (BSA) decreased from week 3 onwards in the DMF treatment group, with a significant reduction at week 8 compared with placebo ($p = 0.032$; 95% CI -2.93 to -0.13). By week 16, continuing improvements in BSA were reported, which were statistically significant vs. placebo for both DMF (LAS41008) ($p < 0.0001$; 95% CI -8.96 to -4.82) and Fumaderm ($p < 0.0001$; 95% CI -8.10 to -4.01).

DMF (LAS41008) treatment also significantly improved quality of life compared with placebo.

Subgroup analyses were undertaken in line with the decision problem. These supported the efficacy of DMF (LAS41008) over placebo [redacted]

[redacted] for the proportion of patients achieving PASI 75 at week 16 [redacted]

[redacted]

Extrapolation

The clinical response of psoriasis to treatment with Fumaderm is solely driven by the DMF content and therefore its efficacy, safety and tolerability can reasonably be extrapolated to products containing DMF alone; a point considered and accepted by the regulatory authorities.

On this basis it is appropriate to assume that the long-term safety and efficacy available for Fumaderm can be applied to DMF (LAS41008).

Key long term data for Fumaderm as used in the clinical setting are available from FUTURE,[25] a retrospective study in 984 patients with psoriasis treated for at least 24 months, with a mean duration of uninterrupted therapy of 44.1 months (max. 216 months). The study demonstrated sustained clinical efficacy of Fumaderm. The proportion of patients with PGA score of 'markedly improved or clear' increased from 67% at six months to 82% after 36 months, with over 80% patients remaining on treatment. Improvement in symptoms was independent of disease severity prior to treatment. The study demonstrated a favourable safety profile for long-term use. Changes in laboratory parameters were usually minor and did not require treatment modification in over 90% of cases.[25]

Network Meta-analysis (NMA)

In order to compare DMF (LAS41008) with the other comparators included in the decision problem, and in the absence of direct head-to-head trials, a network meta-analysis (NMA) was conducted. The NMA demonstrated that DMF (LAS41008) shows superior efficacy compared with placebo and inferior efficacy when compared with biologics, apremilast and Fumaderm. Although the direction of treatment effect is the same, the results from the NMA and BRIDGE study when comparing DMF and Fumaderm are different. The difference in efficacy seen between Fumaderm and DMF (LAS4100) in the NMA is a result of the different methodology used in the analysis.

In line with methods recommended by NICE, the NMA followed an ordered categorical model, whereby patients moved from one category (PASI 50, 75 and 90) to the next. Analysis used a multi-categorical response variable with estimates of treatment effect vs placebo and distance between categories.

In light of this, a conservative approach was taken in the health economic modelling, and scenario analyses were conducted to ensure the robustness of the approach.

Adverse events

The safety profile of DMF (LAS41008) closely matched that of Fumaderm and no new safety issues were identified.

Common adverse events (AEs) with DMF (LAS41008) were gastrointestinal disorders such as diarrhoea, abdominal pain and nausea, flushing, and blood disorders such as leukopenia, lymphopenia and eosinophilia. The changes in haematology values observed in the DMF group were comparable to those in the Fumaderm group and as reported in association with Fumaderm. In this limited dataset, no clear relationship between blood disorders such as leukopenia and lymphocytopenia and the onset of infections could be found.

The majority of TEAEs were of mild to moderate intensity with a low level of TEAEs of severe intensity. The number of patients who experienced at least one TEAE (during treatment or within 30 days after last study medication intake) leading to study withdrawal in the DMF (LAS41008) group was comparable to that in the Fumaderm group.

1.4 Summary of the cost-effectiveness analysis

A cost-effectiveness evaluation was conducted from the perspective of the National Health Service (NHS) and Personal Social Service to compare treatment sequences with and without DMF (LAS41008) in adults with moderate to severe plaque psoriasis who have failed to respond to or who have a contraindication to, or are intolerant to other systemic non-biologic therapies.

The objective was to determine whether the addition of DMF (LAS41008) as an additional non-biologic treatment option in the treatment pathway for psoriasis represents a cost-effective use of NHS resources.

The analysis was based on a Markov state-transition cohort model with a 14-day cycle length and a 10-year time horizon.

The base case cost-effectiveness analysis evaluated DMF (LAS41008) as an additional line of therapy before biologic therapy followed by a biologic therapy sequence and best supportive care (BSC):

Treatment sequence: DMF → adalimumab → ustekinumab → BSC

Comparator sequence: adalimumab → ustekinumab → BSC

The health states in the model comprised a trial period and a maintenance period for each treatment option. After a treatment specific trial period (10-16 weeks, depending on the indication) patients that achieved response, i.e. PASI75, continued on treatment. Responders were assumed to continue treatment until they discontinued use.

After failing or discontinuing all treatment in the selected treatment sequence patients were assumed to receive BSC as the last line of treatment.

Direct medical costs including treatment costs and costs related to drug administration, hospitalisations, outpatient visits and routine patient monitoring were included in line with previous submissions to NICE and published cost-effectiveness studies.

Health effects were measured in QALYs. EQ-5D utilities from previous NICE technology appraisals were used for each PASI response category and PASI response rates from the network meta-analysis (NMA) were applied.

In the base case, cost per patient was [redacted] for the treatment sequence (with DMF (LAS41008) and [redacted] for the comparator sequence, representing a [redacted] per patient for the treatment sequence. Discounted QALYs gained per patient were [redacted] for the treatment sequence compared with the comparator sequence [redacted]. The introduction of DMF (LAS41008) before [redacted]

The cost-effectiveness result was robust to a number of scenario analyses demonstrating that for all scenarios tested the introduction of DMF (LAS41008) as an additional non-biologic systemic treatment option in moderate to severe psoriasis patients is cost-effective at the £20,000 per QALY threshold.

One-way and probabilistic results demonstrate the robustness of the conclusion that DMF (LAS41008) as part of the treatment sequence is the cost-effective option.

Conclusion

DMF (LAS41008) is a clinically and cost-effective option for the treatment of moderate to severe psoriasis in patients whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference.

In clinical practice DMF (LAS41008) will be the first licensed fumaric acid ester (FAE) for use in psoriasis in the UK.

Table 3: Incremental cost-effectiveness results

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)	Incremental analysis
DMF-Ada-Ust-BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A
Ada-Ust-BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years								

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; Ada adalimumab; Ust ustekinumab; BSC best supportive care

2 The technology

2.1 Description of the technology

Brand name: Skilarence®▼

UK approved name: Dimethyl fumarate

Therapeutic class: not yet assigned

Brief overview of the mechanism of action:

Psoriasis is a chronic inflammatory disorder characterised by abnormal epidermal proliferation in the involved area of skin. Evidence indicates that altered local and systemic cytokine regulation play an important role in the pathogenesis of psoriasis.[26] An altered balance between the T helper Type (Th) cells, Th1 and Th2, may play a critical role in the psoriatic lesions,[26,27] leading to a predominance of Th1-cell cytokines over the Th2-cell cytokines.[28] The clinical appearance of plaque psoriasis reflects the infiltration of inflammatory cells, including dendritic cells and lymphocytes, into the skin and the hyperproliferation and abnormal differentiation of keratinocytes.[29]

DMF (LAS41008) and its active metabolite monomethyl fumarate, to which it is rapidly converted after oral intake, have anti-inflammatory and immunomodulatory effects which are not fully elucidated.[24] The main activity is considered to be an immunomodulatory effect mainly due to interaction with intracellular reduced glutathione of cells directly involved in the pathogenesis of psoriasis.[24] There is a shift in T cell phenotype from the Th1 and Th17 profile to a Th2 profile,[24] inflammatory cytokine production is reduced, with a resulting reduction in events such as keratinocyte proliferation and infiltration of inflammatory cells within psoriatic plaques.[24]

DMF inhibits certain functions of skin cells, namely, differentiation, proliferation and migration, as well as affecting the immune system and proliferating cells in general.[30,31]

DMF (LAS41008) will be the first fumaric acid ester (FAE) licensed in the UK for treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy. In clinical practice, DMF will offer patients and clinicians an

additional systemic, non-biologic treatment option. It will be used in patients for whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference. This submission will focus on this position and subgroup of patients.

FAEs have been used in Germany since 1959[20] and on a licensed basis since 1994 and are subject to unlicensed use in other markets including the UK where they have been imported and used since 1999.[21] The British Association of Dermatologists Biologic Interventions Register (BADBIR) data indicate that 7.6% of patients receiving conventional systemic therapy are currently receiving unlicensed FAEs.[22] In Scotland FAEs are recommended by the Scottish Intercollegiate Guidelines Network (SIGN) as an alternative maintenance therapy in patients who have failed or are not suitable for other systemic therapies.[32]

DMF (LAS41008) will be the first licensed FAE for use in the UK and will offer an additional licensed option increasing patient and clinician treatment choice for adults requiring systemic therapy. Currently available systemic treatments are not effective or suitable in all patients. Individual treatment responses vary and the choice of treatment needs to reflect individual patient considerations (e.g. planning to have a family, interactions with treatments for co-morbid conditions or alcohol) and the potential for adverse effects that require treatment discontinuation or limit long-term use.[17,18,19]

2.2 Marketing authorisation/CE marking and health technology assessment

Marketing authorisation application filed with the EMA: December 2015

CHMP opinion anticipated: 21st April 2017

Marketing authorisation anticipated: [redacted]

The proposed indication is for the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.[24]

A copy of the proposed Summary of Product Characteristics (SmPC)[24] is provided in Appendix 1. A copy of the draft EPAR will be provided when available.

The main issues raised during the regulatory process related to:

[redacted]

Regulatory approvals outside of the UK

None planned

Health Technology Assessments

A submission will be made to the Scottish Medicines Consortium (SMC) in June 2017. A submission to the National Centre for Pharmacoeconomics (NCPE) in the Republic of Ireland is also planned for 2017.

2.3 Administration and costs of the technology

Details of the administration of DMF (LAS41008) are provided in Table 4.

Table 4: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Gastro-resistant, film-coated tablet	SmPC[24]
Acquisition cost (excluding VAT) *	[redacted]	List Price
Method of administration	Oral	
Doses	30 mg and 120 mg	
Dosing frequency	Three times daily once maintenance dose is reached. To improve tolerability, it is recommended to begin treatment with a low initial dose with subsequent gradual increases. In the first week, DMF 30 mg is taken once daily (1 tablet in the evening). In the second week, DMF 30 mg is taken twice daily (1 tablet in the morning and 1 in the evening). In the third week of treatment, DMF 30 mg is taken three times daily (1 tablet in the morning, 1 at midday, and 1 in the evening). From the fourth week of treatment, treatment is switched to only 1 tablet of DMF 120 mg in the evening. This dose is then increased by 1 DMF 120 mg tablet per week at different times of day for the subsequent 5 weeks The maximum daily dose allowed is 720 mg (3 x 2 tablets of DMF 120 mg). If treatment success is observed before the maximum dose is reached, no further increase of dose is necessary.	SmPC[24]
Average length of a course of treatment	24 months. It is expected that the long-term efficacy of DMF (LAS41008) will be comparable to DMF-containing products where extensive clinical	SmPC[24]

	experience has shown the potential for improvement in efficacy over time and maintenance of benefit for at least 24 months of treatment.	
Average cost of a course of treatment	[redacted]	List price per tablet
Anticipated average interval between courses of treatments	Not applicable – repeated courses not anticipated	
Anticipated number of repeat courses of treatments	Not applicable – repeated courses not anticipated	
Dose adjustments	During treatment initiation if a particular dose increase is not tolerated, it may be temporarily reduced to the last tolerated dose. After clinically relevant improvement of the skin lesions has been achieved, consideration should be given to careful reduction of the daily dose of DMF to the maintenance dose required by the individual. Dosage modifications may be necessary if abnormalities in laboratory parameters are observed	SmPC[24]
Anticipated care setting	It is anticipated that treatment will be initiated in the secondary care setting by a dermatologist. Thereafter treatment may be continued in the community setting with regular monitoring.	SmPC[24]

2.4 Changes in service provision and management

DMF (LAS41008) represents a further treatment option alongside current standard options for the treatment of moderate to severe psoriasis, and no significant change to current practice is anticipated.

There are no additional tests or investigations required for selection of patients suitable for DMF (LAS41008) treatment above those required for currently available treatments. Prior to initiating therapy a current complete blood count (including differential blood count and platelet count) should be performed. Treatment should not be initiated if leukopenia below 3.0 $x10^9$/L or lymphopenia below 1.0 x 10^9/L or

other pathological results are identified. During treatment a complete blood count with differential should be performed every three months with treatment discontinued in the event the white blood cell count falls below $3.0x10^9$/L or the lymphocyte count drops below $0.8x10^9$/L or any pathological results occur.[24]

Renal and hepatic function should be checked prior to initiation of treatment and every three months thereafter.[24] If abnormalities arise in blood, liver or renal function tests, discontinuation or dose reduction is advised in the SmPC but no specific concomitant therapies are required. Other systemic therapies (e.g. methotrexate, acitretin) also require monitoring of liver and/or renal function / blood tests during therapy so it is anticipated that the existing infrastructure and resources will be utilised for DMF.

DMF is an oral therapy and dose reduction or discontinuation can be managed remotely.

2.5 Innovation

DMF (LAS41008) will be the first FAE licensed in the UK for treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.

As stated above FAEs have been used in Germany on a licensed basis since 1994, but in the UK are subject to unlicensed use only. Recent British Association of Dermatologist Biologic Interventions Register (BADBIR) data indicate that 7.6% of patients receiving conventional systemic therapy are receiving unlicensed FAEs.[22] DMF (LAS41008) represents an opportunity for all patients receiving FAEs to receive a licensed treatment.

3 Health condition and position of the technology in the treatment pathway

3.1 Overview of psoriasis

Psoriasis is an inflammatory skin condition which follows a relapsing and remitting course. It is a chronic, painful, disfiguring and disabling disease for which there is no cure.[1]

Plaque psoriasis is the most common form, accounting for around 90% of cases.[3] It is characterised by well-deliniated red, scaly plaques that vary in extent from a few localised patches to generalised involvement.[3] Lesions cause itching, stinging and pain.[1]

Aetiology

Psoriasis is characterised by abnormal epidermal proliferation in the involved area of skin. Evidence indicates that altered local and systemic cytokine regulation play an important role in the pathogenesis of this disease.[26] The clinical appearance of plaque psoriasis reflects the infiltration of inflammatory cells, including dendritic cells and lymphocytes, into the skin and the hyperproliferation and abnormal differentiation of keratinocytes.[29]

Psoriasis can occur at any age, the majority of cases occur before the age of 35 years.[3] Men and women are equally likely to be affected.[33] The diagnosis is clinical, there are no laboratory findings specific for psoriasis.[34]

Psoriasis is by nature a chronic, incurable disease with an unpredictable course of symptoms and triggers.[1] It is thought to be caused by a combination of genetic and environmental risk factors.[2] Although it has a strong genetic component, environmental factors such as infections can play an important role in the presentation of disease.[35] Both external and systemic factors can trigger psoriasis in genetically predisposed individuals. In about a quarter of people with psoriasis, lesions are provoked by injury to the skin.[4]

Psoriasis is generally graded as mild, moderate or severe, an assessment which takes into account the extent of the area affected and severity of the lesions.

Psoriasis affecting ‘difficult to treat sites’ namely the face, flexures, genitalia, scalp, palms and soles may have an especially high impact, may result in functional

impairment, require particular care when prescribing topical therapy and can be resistant to treatment.[3]

3.2 Effects of psoriasis on patients, carers and society

Impact on patients

Death directly due to psoriasis is rare but the associated morbidity is significant.[3] Psoriasis is associated with a physical, emotional and social burden.[1,5] Even people with minimal involvement (less than the equivalent of three palm areas) state that psoriasis has a major effect on their life.[5]

Depending on the severity and location of skin lesions, individuals may experience significant physical discomfort and disability. Itching and pain can interfere with basic functions, such as self-care and sleep.[4] Skin lesions on the hands can prevent individuals from working at certain occupations, engaging in sports and caring for family members at home.[4] There are also problems related to the treatments used (mess, odour, inconvenience and time), and the effect of living with a highly visible, disfiguring skin disease (difficulties with relationships, difficulties with securing employment and poor self-esteem).[5]

Psoriasis is also associated with a number of comorbidities. In a significant proportion of patients, joints may be affected (psoriatic arthritis).[3] One study reported joint disease in 13.8% patients.[36] A number of studies have also suggested severe psoriasis may be associated with increased levels of cardiovascular disease[3,6,7] and an increased risk of major adverse cardiac events[8] which may eventually increase the risk of overall mortality. Studies have suggested that people with psoriasis, particularly severe disease, may also be at increased risk of lymphoma and non-melanoma skin cancer.[3]

Psoriasis can also have a profound impact on mental health. About a third of people with psoriasis experience major psychological distress,[5] patients with psoriasis have an increased risk of depression, anxiety, and suicidality.[9] It has been estimated that in the UK in excess of 10,400 diagnoses of depression, 7,100 diagnoses of anxiety, and 350 diagnoses of suicidality may be attributable to psoriasis annually.[9]

Impact on society

Disruptions caused by psoriasis treatment, the comorbidities, associated stigma and lack of confidence can have a cumulative impact throughout a person's lifetime and influence major life-changing decisions, alter the course of patients' lives e.g. attainment of life goals, chosen career, desired educational level, and impact social and personal relationships.[10] Psoriasis may reduce an individual's ability to work and negatively impact income levels.[11] Predictions suggest that four million working days are lost in the UK per year due to moderate to severe psoriasis alone, at a cost of almost £0.5 billion to the economy.[37]

Impact on the NHS

Psoriasis also has a significant impact on the NHS. Psoriasis represents between 1.7 and 5% of the 13 million GP consultations for skin disease each year (i.e. 221,000 - 650,000 consultations per annum).[12] In 2014/15 there were 12,441 hospital admissions for psoriasis (any type) equating to 13,034 finished consultant episodes and 13,358 bed days. Although the type of psoriasis was not specified for all admissions, 1,253 were specifically attributed to psoriasis vulgaris equating to 1,341 finished consultant episodes and 3,727 bed days.[13]

Prevalence and incidence in the UK

The estimated overall UK prevalence of psoriasis is approximately 2%[2] with around 1% of people having severe disease.[30]

3.3 Clinical pathway of care

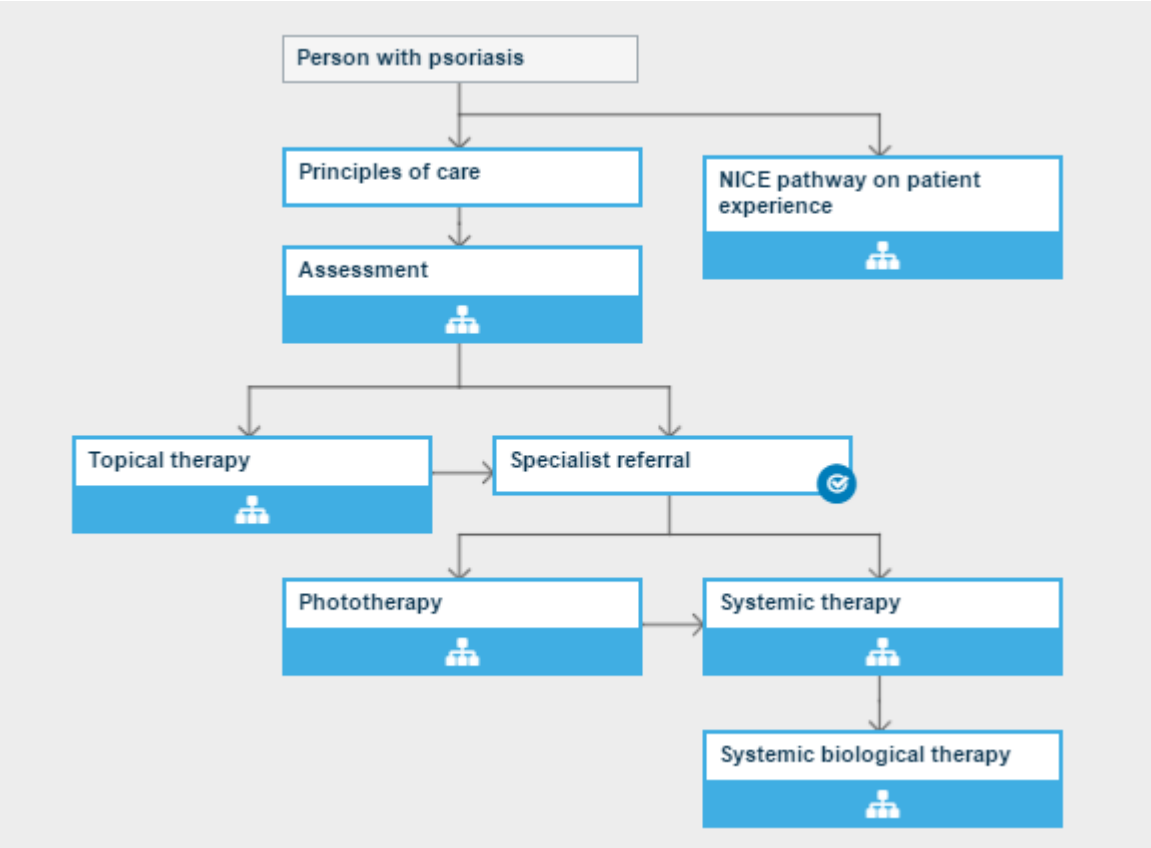
Clinical Guidance and Guidelines

NICE Pathway and Clinical Guideline

A NICE pathway for psoriasis based on the NICE Clinical Guideline CG153 Psoriasis: assessment and management (Oct 2012)[5] and recommendations from subsequent NICE technology appraisals is available[38] (Figure 1).

Current clinical practice in England and Wales reflects this pathway.

Figure 1: NICE psoriasis - clinical pathway



NICE techology appraisal guidance

Details of individual technology appraisals are provided in Table 5.

Table 5: NICE technology appraisal guidance

Date guidance issued	TA no.	Technology	Recommendation
November 2016	TA419[16]	Apremilast for treating moderate to severe plaque psoriasis	Apremilast is recommended as an option for treating chronic plaque psoriasis in adults whose disease has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA, or when these treatments are contraindicated or not tolerated, only if: the disease is severe (PASI >10) and DLQI >10); treatment is stopped if the psoriasis has not responded adequately at 16 weeks and the company provides apremilast with; the discount agreed in the patient access scheme.
July 2015	TA350[39]	Secukinumab for treating moderate to severe plaque psoriasis	Secukinumab is recommended, within its marketing authorisation, as an option for treating adults with plaque psoriasis only when: the disease is severe (PASI >10 and DLQI>10); the disease has failed to respond to standard systemic therapies (e.g. ciclosporin, methotrexate and PUVA), or these treatments are

			contraindicated or the person cannot tolerate them; the company provides secukinumab with the discount agreed in the patient access scheme. Secukinumab treatment should be stopped in people whose psoriasis has not responded adequately at 12 weeks
September 2009	TA180[40]	Ustekinumab for the treatment of adults with moderate to severe psoriasis	Ustekinumab is recommended as a possible treatment for people with plaque psoriasis if: standard assessments show that their psoriasis is severe and is affecting their quality of life and their psoriasis has not improved with other treatments including ciclosporin, methotrexate and PUVA, or they have had side effects with these treatments in the past or there is a medical reason why they should not be given them. The manufacturer provides ustekinumab according to the patient access scheme. Ustekinumab is stopped if psoriasis has not clearly improved after 16 weeks.
June 2008	TA146[41]	Adalimumab for the treatment of adults with psoriasis	Adalimumab is recommended as a possible treatment for adults with plaque psoriasis only if: their condition is severe and has not improved with other treatments such as ciclosporin, methotrexate and PUVA, or they have had side effects with these in the past or there is a medical reason why they should not be given these treatments. Adalimumab is continued beyond 16 weeks only if the psoriasis has clearly improved within this time.
January 2008	TA134[42]	Infliximab for the treatment of adults with psoriasis	Infliximab is recommended as a treatment option for adults with plaque psoriasis only when: the disease is very severe (PASI≥20 and DLQI>18. The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA, or the person is intolerant to or has a contraindication to these treatments. Infliximab is continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks
July 2006	TA103[43]	Etanercept and efalizumab for the treatment of adults with psoriasis	Etanercept, at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when: the disease is severe (PASI≥10 and DLQI>10); psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant to, or has a contraindication to, these treatments; etanercept is discontinued in patients whose psoriasis has not responded adequately at 12 weeks. NICE guidance on efalizumab has been withdrawn

At the time of this submission an appraisal of Ixekizumab for treating moderate to severe chronic plaque psoriasis [ID904] is ongoing with guidance anticipated April 2017.

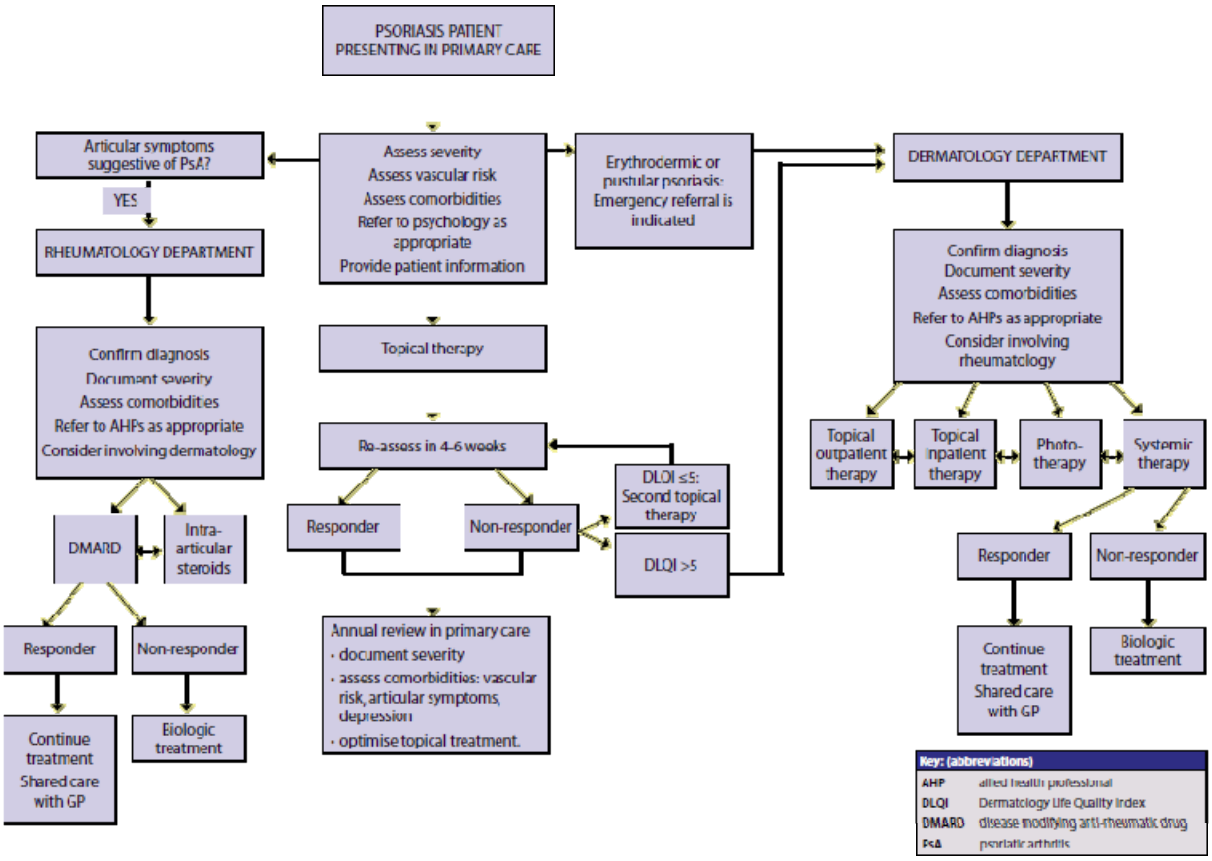
Additional guidelines

In addition to the NICE CG153 Psoriasis: assessment and management other relevant guidelines include:

- SIGN 121: Diagnosis and management of psoriasis and psoriatic arthritis in adults.

  The overall pathway for SIGN 121 is shown in Figure 2 with patients sequencing from topical to non-biological systemic treatments and then to biological systemic therapies as determined by clinical need. However, although FAEs are unlicensed in the UK, for patients requiring non-biological systemic therapies SIGN 121 recommends that FAEs can be considered as an alternative maintenance therapy for patients who are not suitable for other systemic therapies or have failed other therapies.[32]

Figure 2: SIGN 121: Diagnosis and management of psoriasis and psoriatic arthritis in adults.



European and German guidelines

The 2015 European S3-Guidelines on the systemic treatment of psoriasis vulgaris and the German S3-guideline on the treatment of psoriasis vulgaris both recommend the use of FAEs for induction and long-term treatment.[44,45]

Current treatment pathway

There is no cure for psoriasis and the approach to therapy is largely governed by the extent and severity of disease.[3] The aim of treatment is to minimize the extent and severity of the disease to the point at which it no longer disrupts substantially the patient's quality of life.[14] Treatment and care should take into account patients' needs and preferences and therefore it is important to ensure treatment strategy is developed to meet the person's health goals.[5]

In clinical practice feedback from clinicians confirms that the treatment pathway as set out in the NICE guideline is generally applied.[15]

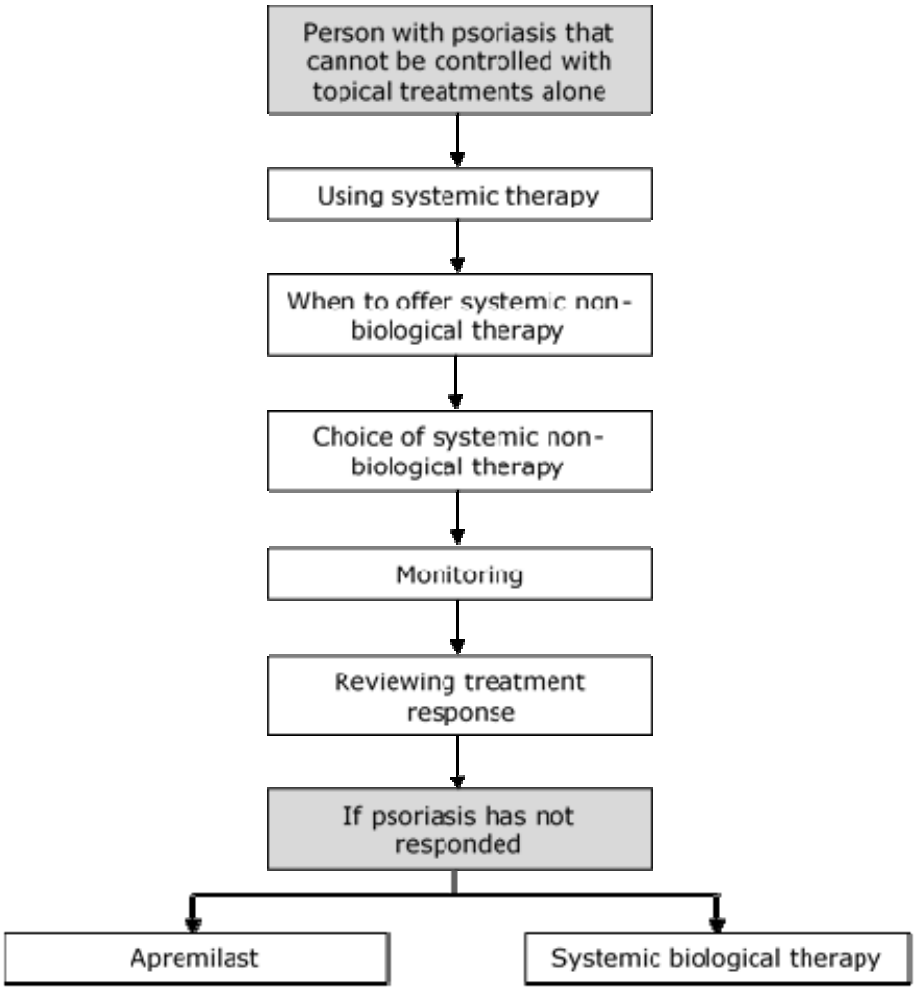
A number of treatment options are currently available for the treatment of psoriasis including topical therapy, phototherapy and systemic therapy (which includes conventional non-biologic agents and biologic agents). Individual responses to treatment vary. Patients sequence through available therapies depending on clinical need and personal preference. Choice of treatment is based on severity of psoriasis, extent of body surface affected and response to prior treatment.[5] In addition, treatment should be tailored to the individual with consideration of age, co-morbidities and current treatments, personal circumstances (e.g. family planning, alcohol use) and preferences, and risks and benefits of available treatment options.[5]

In general, topical therapies are recommended as first-line therapy for milder forms of psoriasis, with phototherapy being recommended as second-line therapy, or for more extensive disease. Conventional non-biologic systemic therapies are recommended in patients with psoriasis that cannot be controlled with topical treatments alone. Biologic therapies are generally recommended for severe disease in patients who have failed to respond to standard systemic therapies and PUVA; or where the person is intolerant to, or has a contraindication to, these treatments.

The current clinical pathway of care using systemic therapies according to published NICE clinical guidelines and technology appraisals can be seen in Figure 3. It is

important to note that as stated previously FAEs are used on an unlicensed basis within this pathway for patients who are not suitable for currently licensed systemic therapies (methotrexate, ciclosporin and acitretin).[14]

Figure 3: Psoriasis treatment pathway



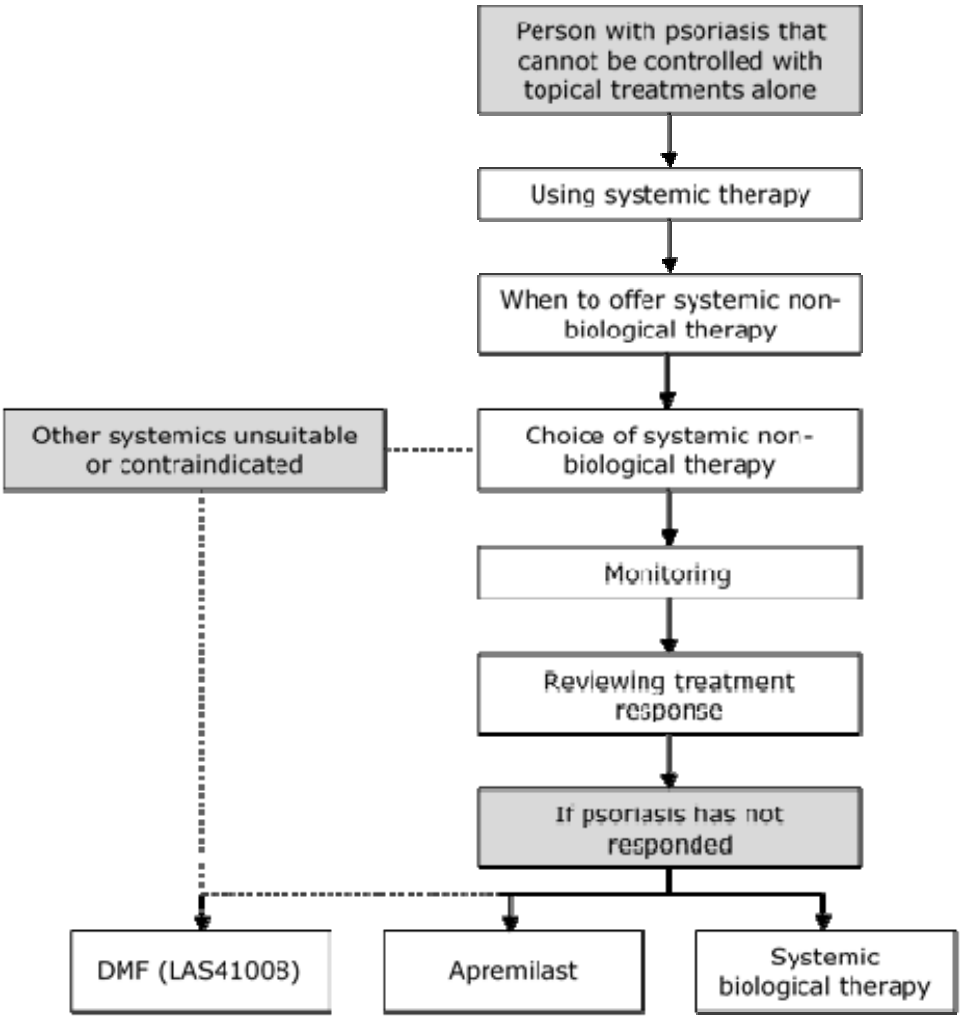
Once patients have sequenced through all available treatment options they progress to best supportive care However, even with the development of more efficacious treatments for psoriasis, patients may not reach high-level responses or lose efficacy over time, which means there is still an unmet need for new treatment options.

Place of DMF (LAS41008) in the existing treatment pathway

It is anticipated that in clinical practice DMF (LAS41008) will offer an additional treatment option for patients in whom other oral systemic therapies (methotrexate, ciclosporin and acitretin) are clinically inappropriate through lack of efficacy, contraindications, tolerability and/or toxicity issues, or patient preference. In clinical practice and as validated with clinical experts DMF (LAS41008) will provide clinicians

and patients with an oral licensed FAE.[14] The position of DMF (LAS41008) in the current treatment pathway is provided in Figure 4. DMF (LAS41008) will be used as an alternative to current systemic non-biological treatments and in common with other oral systemic therapies use is anticipated prior to biologics.

Figure 4: Anticipated place of DMF (LAS41008) in treatment pathway



3.4 Issues relating to current practice

Non-biological systemic therapies are not effective or suitable in all patients. Individual treatment responses vary and there may be contraindications, adverse effects that require treatment discontinuation or limit continual long-term use, or therapies may be unsuitable when taken with treatments for co-morbid conditions.[17,18,19] There is a need for further effective non-biological systemic treatments and oral FAEs are currently being used on an unlicensed basis to meet

this need. Recent British Association of Dermatologists Biologic Interventions Register (BADBIR) data indicate that 7.6% of patients receiving conventional systemic therapy are currently receiving unlicensed FAEs.[22]

The use of FAEs to treat psoriasis to meet this need is supported by clinical evidence. FAEs have been used successfully to treat psoriasis for over 30 years.[46] A licensed product for psoriasis (Fumaderm®) was made available in Germany in 1994[20] and is the most commonly prescribed oral systemic non-biological therapy.[47] In light of this evidence and despite being unlicensed in the UK, FAEs are recommended in SIGN guideline 121 as an additional therapeutic option for systemic therapy.[31]

DMF (LAS41008) will provide clinicians and patients with an oral licensed FAE and provide a treatment option for patients in whom other oral systemic therapies (methotrexate, ciclosporin and acitretin) are clinically inappropriate through lack of efficacy, contraindications, tolerability and/or toxicity issues, or patient preference.

3.5 Assessment of equality issues

As stated previously FAEs have been used in Germany on a licensed basis since 1994, but in the UK are subject to unlicensed use only. DMF (LAS41008) represents a potentially licensed alternative to current unlicensed FAEs and an opportunity for all patients receiving FAEs to receive a licensed treatment

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

A systematic literature review to identify randomised controlled trials of DMF (LAS41008) and systemic treatment options, including phototherapy in patients with moderate to severe psoriasis was performed between September 2015 and June 2016 with an update performed in October 2016.

Full details of the search criteria are provided in Section 4.10.

The review was conducted from a global perspective and therefore a number of comparators were included which are not relevant to the scope or decision problem for this appraisal.

Evidence identified for DMF (LAS41008) is presented in Sections 4.2 to 4.8 and 4.12. Sources which present data for comparator agents are only utilised in network meta-analyses (NMA) and presented in Section 4.10.

4.2 List of relevant randomised controlled trials

The efficacy and safety of DMF (LAS41008) in adult patients with moderate to severe chronic plaque psoriasis is provided by a Phase 3 RCT, the BRIDGE study; see Table 6.

BRIDGE directly compared LAS41008 (gastro-resistant DMF tablets) with placebo and an active comparator Fumaderm®. Fumaderm is an FAE product licensed in Germany. It contains a mix of DMF and the zinc, calcium and magnesium salts of monoethylfumarate and, as stated previously, is used on an unlicensed basis in the UK.

No head-to-head data are available comparing DMF(LAS41008) with apremilast, etanercept, adalimumab, secukinumab, ustekinumab or ixekizumab and a NMA was performed to estimate comparative efficacy (see Section 4.10).

Table 6: Relevant RCT

Trial name (NCT number)	Population	Intervention	Comparators	Primary study references
BRIDGE NCT01726933	Adults with moderate to severe chronic plaque psoriasis	DMF (LAS41008)	Placebo Fumaderm	Mrowietz et al. 2016[23] Clinical Study Report M41008 -1102. June 2016[48]

4.3 Summary of methodology of the relevant randomised controlled trials

The efficacy and safety of DMF (LAS41008) in adult patients with moderate to severe chronic plaque psoriasis is provided by a Phase 3 RCT, the BRIDGE study. The study included a 4-week run-in period and a 16-week treatment period with up to one year off-treatment follow-up.

A total of 671 patients were randomised to receive either DMF (LAS41008), Fumaderm or placebo for 16 weeks. The coprimary endpoints were the percentage of patients achieving ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) and the percentage achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at week 16. The primary objectives were to demonstrate:

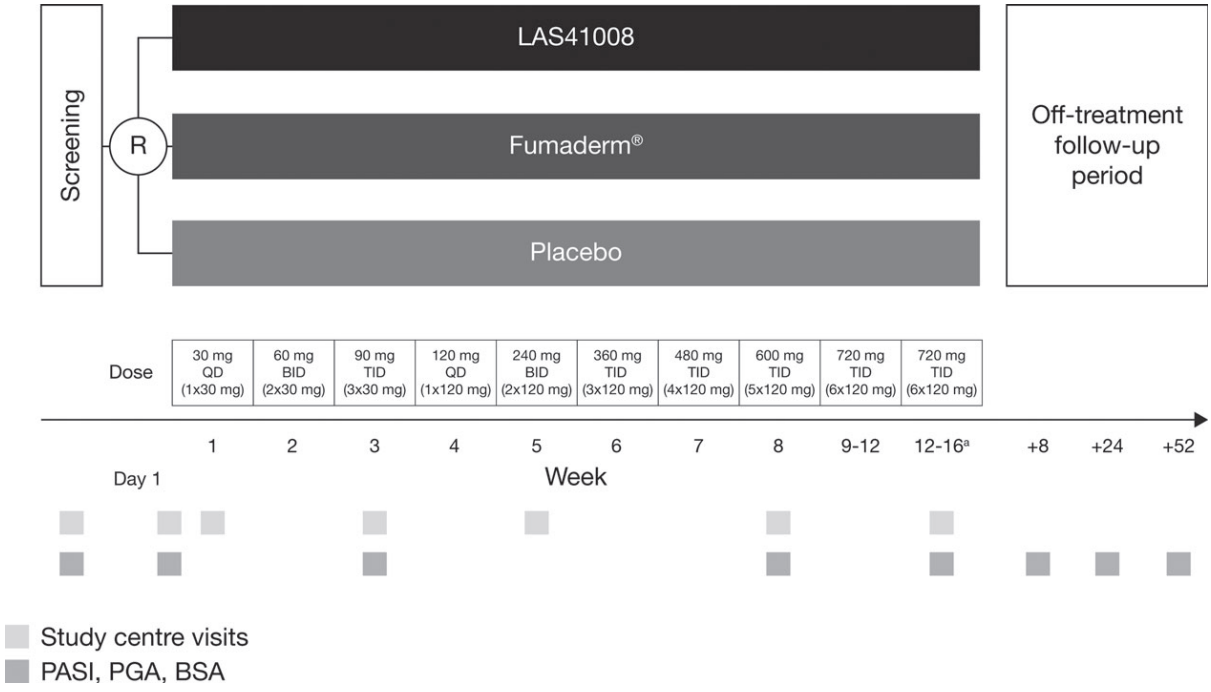
- Superiority of DMF (LAS41008) versus placebo based on the proportion of patients achieving PASI 75 (a 75% reduction in the PASI) at week 16 compared to baseline.
- Superiority of DMF (LAS41008) versus placebo based on the proportion of patients achieving a score of "clear" or "almost clear" in the PGA after 16 weeks of treatment.
- Non-inferiority of DMF (LAS41008) compared to Fumaderm regarding PASI 75 after 16 weeks of treatment.

During the treatment period the patients visited the study centre at baseline (Day 1, Visit 1) and at Weeks 1 (Visit 2), 3 (Visit 3), 5 (Visit 4), 8 (Visit 5), 12 (Visit 6) and 16 (Visit 7). After the 16 week visit, treatment was stopped and the patients were

followed up for a further 12 months, including 3 visits after 2, 6 and 12 months (F1, F2 and F3, respectively). In case of relapse and a need for new systemic therapy during the follow-up period, a final follow-up visit was conducted prior to initiation of the therapy.

A summary of the trial design is provided in Figure 5 with further details provided in Table 7.

Figure 5: Schematic of the BRIDGE trial



Key; BID, twice daily; QD, once daily; R, randomisation; TID, three times daily

Source: Mrowietz et al. 2016[23]

Table 7: Summary of the BRIDGE Trial

	BRIDGE
Study objectives	To investigate the efficacy and safety of systemic treatment with DMF (LAS41008) up to a total daily dose of 720 mg in patients with moderate to severe chronic plaque psoriasis. Primary Objectives: • Superiority of DMF (LAS41008) versus placebo based on the proportion of patients achieving PASI 75 (≥ 75% reduction in the PASI) at week 16 compared to baseline. • Superiority of DMF (LAS41008) versus placebo based on the proportion of patients achieving a score of "clear" or "almost clear" in the PGA after 16 weeks of treatment. • Non-inferiority of DMF (LAS41008) compared to Fumaderm regarding PASI 75 after 16 weeks of treatment. Secondary Objectives • Superiority of DMF (LAS41008) versus placebo based on changes in PASI, PGA after 3 and 8 weeks and body surface area (BSA) after 3, 8 and 16 weeks. • Non-inferiority of DMF (LAS41008) compared to Fumaderm regarding PASI 75 after 3 and 8 weeks of treatment. • Assessment of the safety of DMF (LAS41008) compared to Fumaderm and placebo for both treatment periods (30/120mg DMF). • Assessment of the safety and efficacy of DMF (LAS41008) and Fumaderm when administered concomitantly with medicines known to have potential nephrotoxic effects, e.g. angiotensin-converting enzyme inhibitors, angiotensin II inhibitors and statins.
Location	A total of 704 patients were randomised in four countries across 57 sites (Austria = 7, Germany = 36, Poland = 12, and the Netherlands = 2). Of these 699 patients received at least one dose of study medication and were included in the safety analysis set and 671 in the full analysis set.
Trial design	Phase 3, multicentre, 2:2:1 randomised, double-blind, three-arm study. Patients were randomised to receive either DMF (LAS41008), Fumaderm (active comparator) or placebo in a randomisation schedule of 2:2:1 for a 16-week treatment phase with a subsequent off-treatment follow up of 12 months.
Eligibility criteria for participants	Inclusion criteria • Male and female patients aged 18 years or older with a diagnosis of chronic plaque psoriasis for at least 12 months before enrolment in the study • No diagnosis of guttate, erythrodermic or pustular psoriasis • Severity of psoriasis defined as moderate to severe, as reflected in meeting all the following criteria: o PASI >10 o Body surface area (BSA) >10 % o PGA moderate to severe (score of 3 = moderate, 4 = moderate to severe; or 5 = severe) • Prior therapy with systemic drugs for psoriasis that was discontinued e.g. due to an adverse event (AE) or insufficient effect, or naïve to

	systemic treatment but identified as a candidate for systemic treatment • With a complete record of at least 12 months of other previous topical and systemic treatments, if any. • Not on systemic therapy with drugs that may have interfered with the investigational products taken within the defined wash-out period <u>Key exclusion criteria</u> • Patients with a diagnosis of guttate, erythrodermic or pustular psoriasis • Patients suffering from significant gastrointestinal problems (ulcers, diarrhoea, etc.) • Patients with active infectious disease • Patients with known HIV positive status or suffering from other immunosuppression • Patients with haematological abnormalities • Patients with severe liver or kidney disease • Previous failed therapy with fumaric acid esters either due to inadequate efficacy or lack of tolerability A list of all inclusion and exclusion criteria is provided in Appendix 2.
Setting and locations where the data was collected	The study was conducted in hospitals and outpatient clinics.
Duration of the study	Date study initiated (first informed consent): 7January 2013 Date last patient completed the 12 month treatment-free follow-up period: 19 October 2015
Trial drugs (n=number treated)	DMF (LAS41008) n=279 Fumaderm n=283 Placebo n=137
Method of randomisation	Patients were randomly assigned (2:2:1) to receive either DMF (LAS41008), Fumaderm or placebo. Randomisation was performed using a web-based interactive-web response system (IWRS). The randomisation sequence was kept concealed from the investigators during the trial.
Dose titration	Treatment was up-titrated over the first 9 weeks, with placebo or up to a maximum daily dose of 720 mg DMF in the DMF (LAS41008) or Fumaderm groups as per clinical practice. After week 4, a reduction to the last tolerated dose was permitted in case of intolerability. Details of the dosing schedule are provided in Table 8 Depending on the treatment group to which patients were randomised, they took 1 of the following combinations in the first 3 weeks, increasing the number of tablets weekly • **DMF (LAS41008)**: DMF gastro-resistant tablets of 30 mg and the same number of placebo tablets for Fumaderm Initial • **Fumaderm group**: Fumaderm Initial 30 mg tablets and the same number of placebo tablets for DMF (LAS41008) 30 mg

<table>
<tr><td></td><td>

- **Placebo group**: placebo tablets for DMF gastro-resistant 30 mg and the same number of placebo tablets for Fumaderm Initial

</td></tr>
<tr><td>Permitted and disallowed concomitant medications</td><td>

Disallowed medications

<table>
<tr><th>Treatment</th><th>Wash-out period</th></tr>
<tr><td colspan="2">Topical Treatment</td></tr>
<tr><td>Corticosteroids
Vitamin A analogues
Vitamin D analogues
Anthracene derivatives
Tar
Salicylic acid preparations</td><td>2 weeks</td></tr>
<tr><td colspan="2">Systemic treatment</td></tr>
<tr><td>Biologics with antipsoriatic activity</td><td>3 months</td></tr>
<tr><td>Conventional systemic antipsoriatic drugs and phototherapy</td><td>1 month</td></tr>
<tr><td>Immunosuppressive medication (If not covered by any of the above treatments)
Cytostatics</td><td>6 months</td></tr>
</table>

</td></tr>
<tr><td>Discontinuation of study drugs</td><td>

Patients withdrew from the study for the following reasons:

- Unacceptable toxicity
- Pregnancy
- Protocol deviation
- Patient choice to withdraw consent
- Withdrawal of patient consent

</td></tr>
<tr><td>Primary outcomes</td><td>

Primary efficacy endpoints

- PASI 75 at Week 16
- Proportion of patients achieving a score of “clear” = 0 or “almost clear” = 1 in the PGA at Week 16

Both these endpoints were tested to show superiority of DMF (LAS41008) over placebo but only PASI 75 was tested to show non-inferiority of DMF (LAS41008) versus Fumaderm

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<tr><td>Secondary outcomes</td><td>

Secondary efficacy endpoints

- Proportion of patients achieving PASI 75 at Week 3 and 8
- Proportion of patients achieving PASI 50 and PASI 90 at Week 3, 8, and 16
- Proportion of patients achieving a score of “clear” = 0 or “almost clear” = 1 in the PGA at Week 3 and 8
- Percent change in PASI at Week 3, 8, 16 and F1
- PGA score at Week 3, 8, 16 and F1
- Body surface area (BSA) at Week 3, 8, and 16
- Treatment success rate at Week 3, 8, and 16
- Treatment success was defined as patients achieving either a “clear”

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</table>

	or “almost clear” score in the PGA and/or PASI 90. • Remission rate at Week 3, 8, and 16 - Remission was defined as a score of “clear” in the PGA. • Time to relapse - Relapse was defined as the event when the achieved maximal improvement from baseline was subsequently reduced by ≥50% based on PASI. Two time-to-relapse analyses were conducted: a) relapse occurring at any time during the study duration (on-treatment + 12 months off treatment) and b) relapse occurring within 2 months after last study drug intake. • Time to rebound - Rebound was defined as a worsening of psoriasis over baseline value (PASI≥125%) <u>Health-related quality of life</u> • Patient Benefit Index (PBI) based on the Patient Need Questionnaire (PNQ) and Patient Benefit Questionnaire (PBQ) at Week 16 and at the 2 month follow-up visit (F1) • Dermatology Life Quality Index [DLQI] score after 16 weeks of treatment and at the 2 month follow-up visit (F1). Further information on PASI, PGA, PBI and DLQI are provided in Appendix 3.
Safety outcomes	• Adverse events • Physical examination • Vital signs • Laboratory assessments (blood and urine analysis) • Clinical chemistry parameters: Creatinine, total bilirubin, aspartate amino transferase (AST), Alanine amino transferase (ALT), gamma-glutamyl-transferase (gamma-GT), alkaline phosphatase (ALP) • Haematology parameters: Haemoglobin, red blood cell count (erythrocytes), haematocrit, platelet count (thrombocytes), total white blood cells (WBC) count (leucocytes), neutrophils, granulocytes, lymphocytes, monocytes, eosinophils, basophils • Urinalysis (dipstick) parameters: pH, blood (leukocytes and erythrocytes), protein, glucose, ketones, nitrite
Pre-planned subgroups	Subgroup analyses were carried out to consider the consistency of the study endpoints. These included subgroup analyses for: • Pre-treatment with systemic therapies • Baseline severity • Age
Sources: Mrowietz et al 2016[23], LAS41008 Clinical Study Report 1102[48] Key: PASI, Psoriasis Area and Severity Index; PGA, Physicians Global Assessment	

Table 8: Dosing schedule of DMF

Week	Number of tablets			Total daily dose of DMF (mg)
	Morning	Noon	Evening	
	30 mg DMF per tablet, double-dummy			
1	0	0	2 (1 active, 1 placebo)	30
2	2 (1 active, 1 placebo)	0	2 (1 active, 1 placebo)	60
3	2 (1 active, 1 placebo)	2 (1 active, 1 placebo)	2 (1 active, 1 placebo)	90
	120 mg DMF per tablet			
4	0	0	1	120
5	1	0	1	240
6	1	1	1	360
7	1	1	2	480
8	2	1	2	600
9-16	2	2	2	720

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Sample size

The multiple primary hypotheses were to be tested each on a 5% significance level based on the testing procedure. A power of 90% was required in the sample size calculation. The ratio between DMF (LAS41008) and placebo patients was 2:1. For PASI 75, a difference of 40% between DMF (LAS41008) versus placebo was assumed, based on a DMF response rate of 50% and a placebo response rate of 10%. This would have required a sample size of 44 patients for the DMF (LAS41008) and 22 patients for the placebo group.

For the proportion of patients achieving a score of “clear” or “almost clear” in the PGA, a difference of 30% between DMF (LAS41008) versus placebo was assumed based on a DMF response rate of 40% and a placebo response rate of 10%. This

would have required a sample size of 70 patients for the DMF (LAS41008) and 35 patients for the placebo group.

For the non-inferiority for DMF (LAS41008) compared to Fumaderm regarding PASI 75 after 16 weeks of treatment a non-inferiority margin of 15% was set in line with scientific advice from the regulators. This margin was well within the effect size compared to placebo but was also considered a reasonable maximal difference that was judged to be not clinically relevant. Based on a proportion of patients achieving PASI 75 of 50% for DMF (LAS41008), an expected difference to Fumaderm of 0, a power of 90% and a significance level of 5%, this would have given a sample size of 234 patients per treatment group.

A sample size of 234 + 234 + 117 (2:1 ratio between active and placebo groups) of 585 patients was necessary. Based on an estimated drop-out rate of 15% during the treatment phase, a total sample size of 690 patients was set. 276 patients were to be enrolled in each of both treatment groups with active ingredient and 138 patients in the placebo group.

The study was planned as an adaptive design with one planned interim analysis.

Interim analysis

This interim analysis was performed after data for the two primary efficacy variables from 230 evaluable patients, were available, in order to address the implications of continuing with the original sample size and to check if there were any safety concerns.

The sample size in BRIDGE was based on published data which had an inherent variability and thus an adaptive design was invoked, as an appropriate method to fulfil regulatory aspects as well as ethical considerations, by allowing for the option of adjusting the final number of patients that might be required to reach the primary objective. Consequently, an interim analysis was planned and agreed with the European Medicines Agency (EMA) in 2011, and subsequently performed, to address whether the study should be stopped due to futility, or continued with a potentially adapted sample size. After having considered the results of the interim analysis, the decision was taken not to make any adjustments in sample size. The

threshold for statistical significance was adjusted to be ≤0.0038, because the sample size was not modified.

Populations analysed

Details of the populations defined for statistical analysis are provided in Table 9. All statistical analyses were based on the full analysis set (FAS) and the per protocol set (PPS). As the results of both were consistent, only data for the FAS set are presented within this submission document.

Table 9: Analysis sets

Analysis set	Definition
Safety analysis set (SAS)	All patients who were randomised and received at least one dose of study medication DMF (LAS41008) n= 279, Fumaderm n=283, placebo n=137
Full analysis set (FAS)	All patients of the safety analysis set with at least one measurement of the primary variable PASI and PGA after Week 0 DMF (LAS41008) n= 267, Fumaderm n=273, placebo n=131
Per protocol set (PPS)	All patients of the FAS for whom no relevant protocol deviations were documented DMF (LAS41008) n= 246, Fumaderm n=253, placebo n=127

Statistical analysis

Primary endpoint

One-sided p-values (for further use in the adaptive interim analysis) for the superiority testing were calculated. The decision was based on the one-sided p-values for superiority at Week 16 comparing DMF (LAS41008) and placebo.

For the non-inferiority testing, one-sided p-values for the test decision were calculated comparing Fumaderm and DMF (LAS41008).

Additional descriptive CIs with adjusted confidence level were calculated. The CIs and p-values were calculated based on an asymptotic Wald test.

A hierarchical approach was used to deal with multiple comparisons. The non-inferiority testing for PASI 75 was ordered hierarchically after the two primary superiority endpoints, i.e., only if both superiority comparisons led to a rejection of the null hypothesis (in the FAS and PPS population), non-inferiority for PASI 75 was

to be tested (a priori-order of hypotheses). As long as the first two primary hypotheses could be rejected, this non-inferiority testing could be done at a 5% significance level.

This approach was combined and integrated into the adaptive design concept. The Bauer P. and Köhne method[49] based on the Fisher's combination test, was used to combine the results of each of the two stages. The statistical significance threshold was set to 0.00380 according to this method. This was a conservative approach as no penalty was needed as no adaptation of sample size was done.

Secondary efficacy endpoints

Secondary efficacy endpoints were analysed with descriptive statistics per visit and treatment group. The following statistical tests were used to test for differences between DMF (LAS41008) and placebo and DMF (LAS41008) and Fumaderm:

The proportions of patients with PASI 50, PASI 75, PASI 90 and the proportion of patients achieving a score of “clear” or “almost clear” in the PGA were analysed using an asymptotic Wald test for risk differences, calculating two-sided 95% confidence intervals (CIs).

Percent change from baseline in PASI, BSA, and change from baseline in BSA were analysed using an ANCOVA with factors treatment and centre and the corresponding baseline values as covariable.

Time to relapse and time to rebound was analysed using Kaplan-Meier estimates.

Results of the PNQ and PBQ were summarized with descriptive statistics per treatment group and each questionnaire item was tabulated with counts and percentages.

Health-related quality of life

Results of the DLQI questionnaire were analysed descriptively. Statistical comparisons between treatment groups were performed using the Cochran-Mantel-Haenszel test for categorical data. The DLQI score was analysed by means of an ANOVA model with treatment and centre as factor.

The PBI score was analysed using an ANOVA with factors treatment and centre. The distribution of PGA, the treatment success rate and remission rate was analysed

using the Cochran-Mantel-Haenszel test to obtain descriptive two-sided p-values. The treatment success and remission rate was stratified by centre.

Safety analysis

Safety parameters were analysed descriptively.

Subgroup analysis

Pre-planned

Subgroup analyses were conducted to evaluate the consistency of the DMF (LAS41008) effect over placebo on the primary efficacy endpoints and the DLQI total score at Week 16. Analyses were performed in the following subgroups: gender, age (≤35, > 35 to ≤ 55years and > 55 years old), race (Caucasian, Black or African American, Asian and Other), PASI severity (moderate: PASI >10 to ≤20%; severe: PASI >20%) and PGA severity (moderate = 3; severe = grouping of the categories moderate to severe [PGA score 4] with severe [PGA score 5]). Analyses were based on the FAS. The analysis of co-primary efficacy endpoints was performed by a linear binomial regression including treatment, subgroup variable and treatment-by-subgroup interaction. The risk difference and the corresponding 95% CIs for the individual subgroups were derived from the binomial regression model. The p-values corresponding to the between-treatment group difference (active vs. placebo) are presented.

The analysis of DLQI total score at Week 16 was carried out using an ANCOVA model with baseline DLQI score, treatment group, subgroup variable, centre and treatment-by-subgroup category. Least square (LS) means estimates and their corresponding standard error (SE) and 95% CI were derived using the appropriate contrasts in the model specified above.

The p-value of the treatment-by-subgroup interaction for active vs. placebo comparison was used to evaluate the homogeneity of the treatment effect between DMF and placebo across subgroup categories. The statistical significance was set to 10%.

The statistical methods for the subgroup analysis were consistent with those used for the full analysis.

Post-Hoc

In order to evaluate the efficacy of DMF as first-line systemic therapy, post-hoc analyses based on LOCF were performed on the FAS for the subgroups of patients who were receiving systemic therapy for the first time compared to those who had previous experience of other systemic agents.

Data management, patient withdrawals

In case of drop-outs, for all efficacy analyses derived from PASI and PGA assessments, the last assessment prior to withdrawal was carried forward for the subsequent (missing) assessments (last observation-carried-forward [LOCF]).

If the last visit (excluding the follow-up visits) was done more than 7 days after last intake, then assessments for the primary efficacy parameters, PASI and PGA, from such visits were not used for the analysis of on-treatment study visits. LOCF up to Week 16 was applied using the last on-treatment assessment or assessment where the visit took place ≤7 days after the last intake of study medication.

For the primary efficacy analysis of responders, an alternative approach for handling missing data was applied, setting patients with missing examinations as non-responders (sensitivity analysis). Additionally, analyses of the total PASI score (continuous data) and the percent change from baseline and the PGA were performed based on observed cases.

Analysis of other efficacy variables was done on observed cases approach, i.e. no imputation technique was applied for missing observations.

4.5 Participant flow in the relevant randomised controlled trials

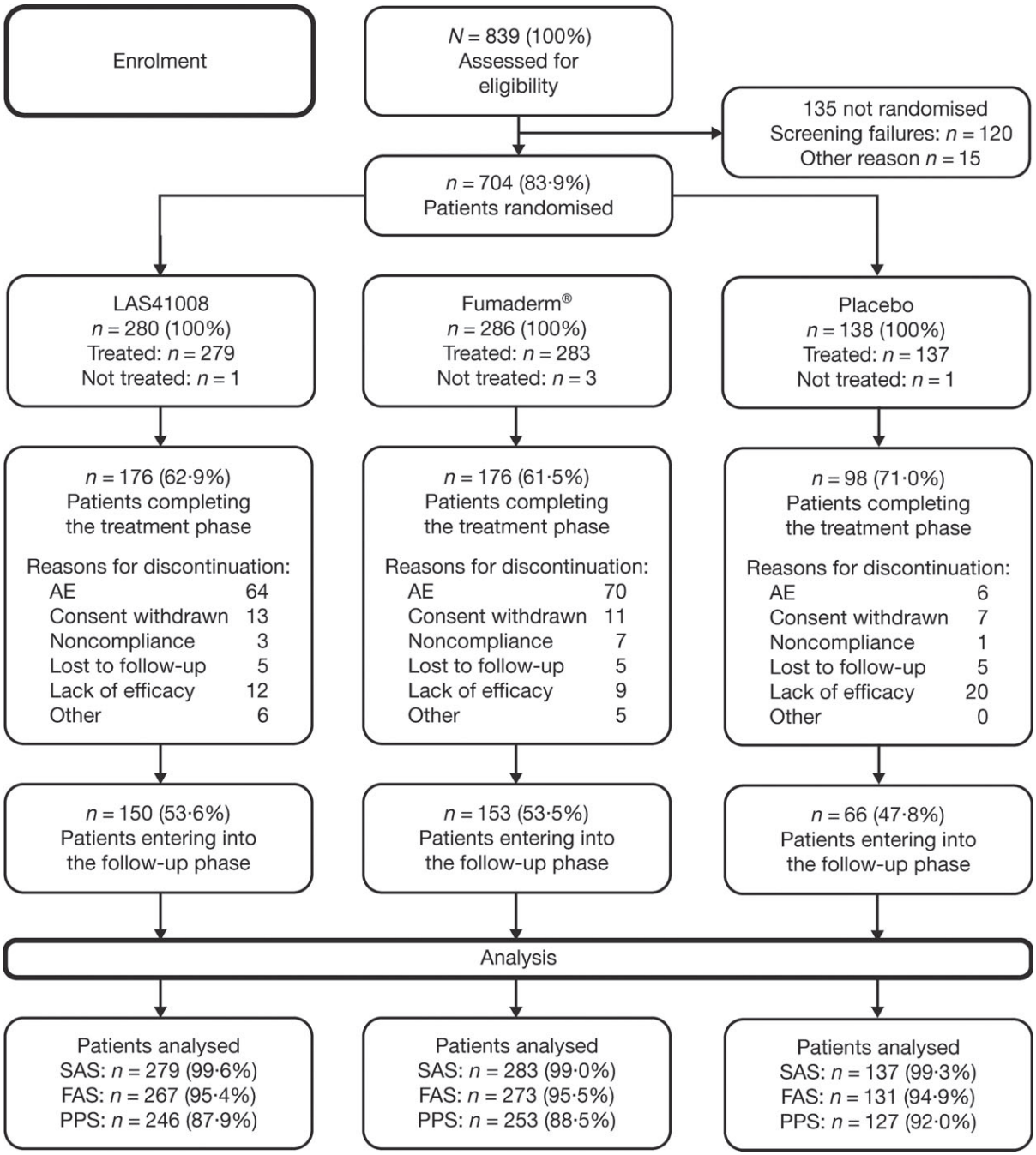
Participant flow

Participant flow is presented in Figure 6. Overall 839 patients were screened with 699 receiving a least one dose of study medication and were included in the SAS and 671 (DMF n=267, Fumaderm n=273 and placebo n=131) in the FAS.

The proportion of patients who did not complete treatment was not significantly different between the DMF and Fumaderm treatment groups. The most frequently recorded reason for premature termination in the DMF and Fumaderm treatment groups was the occurrence of an AE, as observed in 62.1% and 65.4% of the patients who withdrew early during the treatment phase, respectively (Figure 6). Lack of efficacy was the most frequently recorded reason in the placebo group, as observed in 51.3% of the patients who withdrew early during the treatment phase in this group (Figure 6).

A total of 369 patients entered into the follow up phase of which 110 completed all follow up visits (F1, F2 and F3). Details of patients who entered and completed the follow up phase are provided in (Table 10). Common reasons for premature study termination after completion of the treatment phase were: lack of efficacy, withdrawal of consent for personal reasons, and reasons within the category “other” (Table 10).

Figure 6: CONSORT diagram of participant flow in BRIDGE



Source: Mrowietz et al 2016[23]

Table 10: Number of patients who completed the follow-up phase and reason for study termination

	DMF (LAS41008) n-279	Fumaderm n=283	Placebo n=137	Total n=699
	N (%)			
Number entered into the follow up phase	150 (53.6%)	153 (53.5%)	98 (71.0%)	450 (100%)
Number of patients who completed the follow up phase	42 (23.9)	51 (29.0)	17 (17.3)	110 (24.4)
Main reason for study termination				
Withdrawal of consent	27 (20.1)	29 (23.2)	22 (27.2)	78 (22.9)
Lack of efficacy	34 (25.4)	40 (32.0)	28 (34.6)	102 (30.0)
Lost to follow up	18 (13.4)	21 (16.8)	12 (14.8)	51 (15.0)
Adverse event	2 (1.5)	1)0.8)	0 (0.0)	3 (0.9)
Non-compliance with study protocol	3 (2.2)	1 (0.8)	0 (0.0)	4 (1.2)
Other	50 (37.3)	33 (26.4)	19 (23.5)	102 (30.0)

Source: LAS41008 CSR M41008-1102 June 2016[48]

Patient characteristics

Baseline characteristics are provided in Table 11.

The baseline characteristics were well balanced between the treatment arms and were representative of the population of patients with moderate to severe psoriasis who will be treated with DMF in clinical practice. The demographic and baseline characteristics were well balanced between the treatment groups (Table 11).

Of the 699 patients included in the safety analysis set, most were Caucasian (99%) and male (65%), and the mean age was 44 years (Table 11). Most patients had moderate psoriasis based on Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA) scores at baseline: the mean PASI score at baseline was 16.35 and 60% of patients scored as moderate on the PGA.

The baseline characteristics of the 671 patients included in the full analysis set were comparable to those for the SAS (Table 11).

Table 11: Baseline demographics and clinical characteristics (SAS and FAS)

	Safety analysis set (SAS)			Full analysis set (FAS)		
	DMF (n = 279)	Fumaderm (n = 283)	Placebo (n = 137)	DMF (n = 267)	Fumaderm (n = 273)	Placebo (n = 131)
Male, n (%)	174 (62.4)	185 (65.4)	93 (67.9)	[redacted]	[redacted]	[redacted]
Age (years)						
Mean ± SD	44.0 ± 15.2	45.0 ± 13.8	44.0 ± 14.3	[redacted]	[redacted]	[redacted]
Range	18-80	18-87	18-78			
Race, n (%)						
White	275 (98.6)	280 (98.9)	137 (100.0)	[redacted]	[redacted]	[redacted]
Black/African American	1 (0.4)	0	0			
Asian	1 (0.4)	3 (1.1)	0			
Other	2 (0.7)	0	0			
PASI total score, mean ± SD	16.3 ± 5.7	16.4 ± 6.79	16.2 ± 4.9	[redacted]	[redacted]	[redacted]
PGA group, n (%)[a]						
Moderate	162 (60.7)	164 (60.1)	79 (60.3)	[redacted]	[redacted]	[redacted]
Moderate to severe	93 (34.8)	94 (34.4)	49 (37.4)			
Severe	12 (4.5)	15 (5.5)	3 (2.3)			
Body surface area (%), mean ± SD	21.9 ± 11.6	21.3 ± 12.5	21.9 ± 12.3	[redacted]	[redacted]	[redacted]
Prior conventional systemic therapy, n (%)						
Methotrexate	20 (7.2)	39 (13.8)	14 (10.2)	[redacted]	[redacted]	[redacted]
Ciclosporin	12 (4.3)	8 (2.8)	8 (5.8)			
Fumaderm®	9 (3.2)	11 (3.9)	4 (2.9)			
Acitretin	8 (2.9)	15 (5.3)	9 (6.6)			
Apremilast	1 (0.4)	1 (0.4)	0			
Prior biological therapy, n (%)						
Interleukin inhibitors[b]	7 (2.5)	4 (1.4)	3 (2.2)	[redacted]	[redacted]	[redacted]
TNF-a inhibitors[c]	1 (0.4)	6 (2.1)	0			
Prior nondrug therapy including phototherapy, n %	75 (26.9)	86 (30.4)	43 (31.4)	[redacted]	[redacted]	[redacted]

Key: PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; TNF, tumour necrosis factor. [a]The PGA scale was defined as: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, moderate to severe; 5, severe. [b]Including secukinumab, ustekinumab and brodalumab. [c]Including adalimumab and etanercept.
Source: Mrowietz et al 2016 (SAS)[23], Almirall Data on File (FAS)[50]

4.6 Quality assessment of the relevant randomised controlled trials

BRIDGE was conducted in compliance with Good Clinical Practice (GCP) and the Declaration of Helsinki. Outcome assessments were all conducted in accordance with trial validated methodology.

Selection bias

Patients were randomly assigned (2:2:1) to receive either DMF (LAS41008), Fumaderm or placebo. Randomisation was performed using a web-based interactive-web response system (IWRS). The randomisation sequence was kept concealed from the investigators during the trial.

Drop outs

The drop-out rate in the study was higher than expected (36-37% in the study versus 18% used to determine the sample size). This is likely to be due to the rigid titration period which did not allow clinicians and/or patients to individualise dosing. The drop-out and discontinuation rates were comparable between the DMF (LAS41008) and Fumaderm treatment groups (Figure 6).

Analysis

Quality assessment in accordance with the NICE recommended checklist for RCT assessment of bias is provided in Table 12. Full details are provided in Appendix 4.

Table 12: Quality Assessment – BRIDGE study

	BRIDGE
Was randomisation carried out appropriately	Yes. Patients were randomised 2:2:1 ratio to receive DMF (LAS41008), Fumaderm or placebo
Was concealment of treatment allocation adequate?	Yes. Treatment allocation was concealed using a double dummy design and IWRS
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No imbalances between the treatment groups. The drop-out rate in the study was higher than expected. This is likely to be due to the rigid titration period which did not allow clinicians and/or patients to individualise dosing. However the drop-out and discontinuation rates were

	comparable between the DMF (LAS41008) and Fumaderm treatment groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so was this appropriate and were appropriate methods used to account for missing data?	Yes
How closely do the RCT(s) reflect routine clinical practice?	The baseline characteristics of patients in the trial reflect those patients likely to receive DMF (LAS41008) in clinical practice. The outcomes measured are relevant to clinical practice.
Source: Mrowietz et al 2016[23]	

4.7 Clinical effectiveness results of the relevant randomised controlled trials

The following endpoints of the BRIDGE study relevant to the decision problem are presented in this section. All p values cited are taken from the CSR and it should be noted that due to p value conventions applied by the British Journal of Dermatology (BJD) the CSR p-values vary from those cited in the key publication Mrowietz et al 2016.[23] The BJD 'Guidelines for statistical reporting in the British Journal of Dermatology' state that in submitted articles '*The smallest P value that need be reported is P <0.001, save in studies of genetic associations*'.

Coprimary endpoints

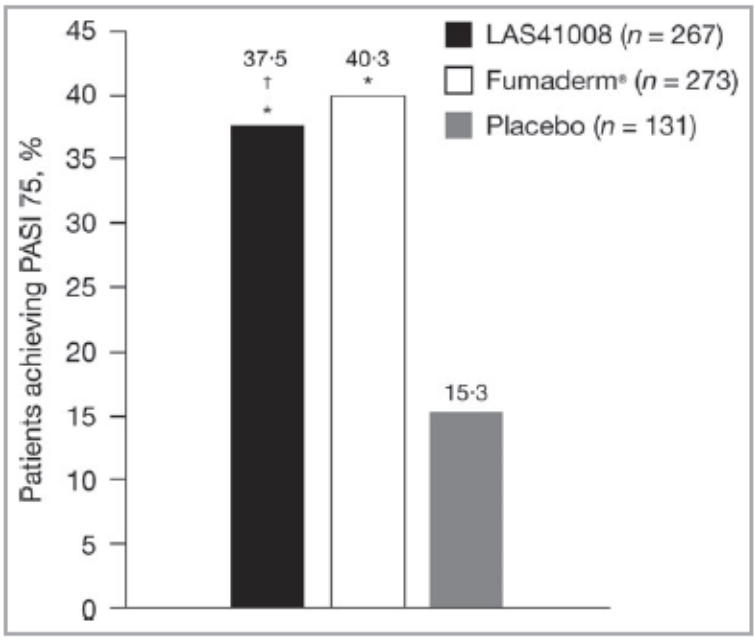
All three primary objectives of the study as stated in Section 4.3 were met.

PASI 75

Significantly more patients treated with DMF (LAS41008) achieved PASI 75 at week 16 compared with placebo. A PASI 75 was achieved by 37.5% of patients in the DMF (LAS41008) treatment group at Week 16 compared with 15.3% of patients in the placebo group, a risk difference of 22% ($p<0.0001$) (Figure 7).

DMF (LAS41008) was also shown to be non-inferior to Fumaderm in the proportion of patients who achieved PASI 75 at week 16 (37.5% vs. 40.3% DMF (LAS41008) vs. Fumaderm, $p<0.0003$) (Figure 7).

Figure 7: Percentage of patients achieving ≥75% improvement on PASI at week 16 (FAS, LOCF)

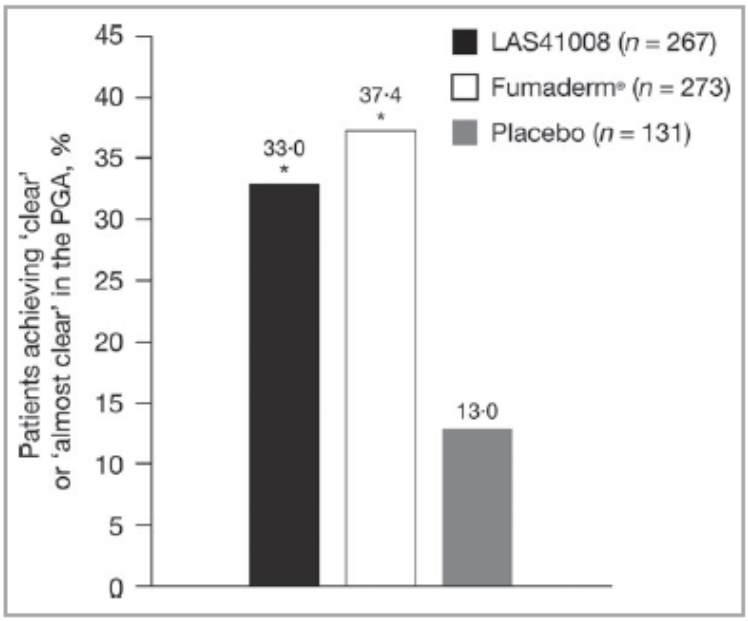


*p<0.0001 vs. Placebo, †p<0.0001 non-inferiority vs. Fumaderm (p values taken from CSR)
Source: Mrowietz et al 2016,[23] LAS41008 CSR M41008-1102 June 2016[48]

PGA

The proportion of patients achieving a PGA score of "clear" or "almost clear" at Week 16 was statistically greater in the DMF (LAS41008) group (33.0%) compared to placebo (13.0%; p <0.0001) (Figure 8).

Figure 8: Percentage of patients achieving a score of 'clear' or 'almost clear' in the PGA at week 16 (FAS, LOCF)



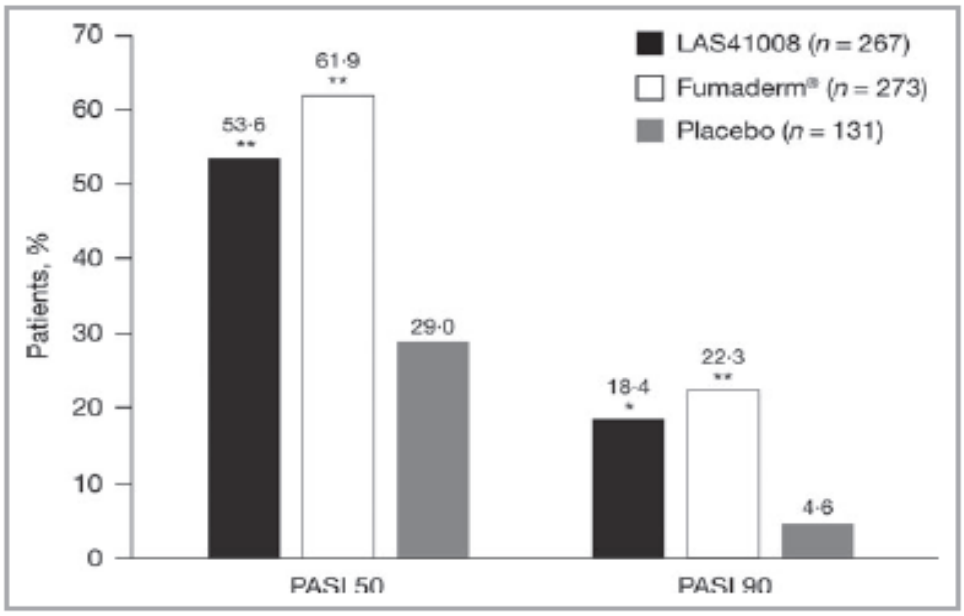
*p<0.0001 vs. Placebo(p value taken from CSR)
Source: Mrowietz et al 2016,[23] LAS41008 CSR M41008-1102 June 2016[48]

Key secondary endpoints

PASI 50 and 90

A significantly higher proportion of patients in the DMF (LAS41008) treatment group compared to the placebo group achieved PASI 50 (53.6% vs. 29.0%, p <0.001) and PASI 90 (18.4% vs. 4.6%, p <0.001) at Week 16 (Figure 9). No significant differences were observed between DMF (LAS41008) and Fumaderm.

Figure 9: Percentage of patients achieving PASI 50 and PASI 90 at week 16 (FAS, LOCF)



*p<0.001 vs. placebo, **p<0.001 vs. placebo (p values taken from CSR)
Source: Mrowietz et al 2016,[23] LAS41008 CSR M41008-1102 June 2016[48]

Percentage change in PASI at weeks 3, 8, and 16

Treatment with DMF (LAS41008) led to continued improvement in PASI score over time compared with placebo (Table 13). A significantly greater mean percentage change from baseline in the PASI total score was observed in the DMF (LAS41008) treatment group compared to the placebo group at Week 8 [redacted], Week 16 [redacted]. No significant difference was observed between DMF (LAS41008) and Fumaderm at any visit.

Table 13: PASI total score, percentage change from baseline (FAS, LOCF)

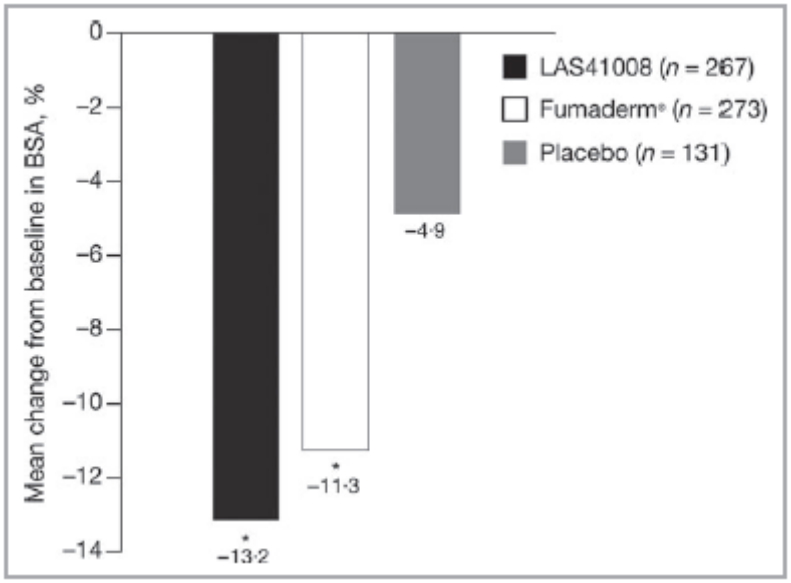
Visit	DMF(LAS41008) n=267	Fumaderm n=273	Placebo n=131	DMF_Placebo difference in LS means/p-value	DMF_Fumaderm difference in LS means/p-value
	Mean % change from baseline (SD)				
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: LAS41008 CSR M41008-1102 June 2016[48]

Body surface area (BSA)

The percentage of involved BSA decreased from week 3 onwards in the DMF treatment group, with a significant reduction at week 8 compared with placebo (p = 0.032; 95% CI -2.93 to -0.13) (Table 14). By week 16, continuing improvements in BSA were reported, which were statistically significant vs. placebo for both DMF (LAS41008) (p < 0.0001; 95% CI -8.96 to -4.82) and Fumaderm (p < 0.0001; 95% CI -8.10 to -4.01) (Figure 10). No statistically significant differences were observed between the DMF (LAS41008) and Fumaderm treatment groups.

Figure 10: Mean change from baseline in BSA score at week 16 (FAS)



*p<0.0001 vs. placebo
Source: Mrowietz et al 2016,[23] LAS41008 CSR M41008-1102 June 2016[48]

Table 14: Change from baseline in BSA (FAS)

Week	DMF (LAS41008) n=267	Fumaderm n=273	Placebo n=131	DMF – Placebo, difference in LS means / p- value
	Mean change from baseline (SD)			
8	- 4.1 (7.56)	-3.5 (6.2)	-2.3 (7.59)	-1.53, p = 0.0324
16	-13.2 (12.07)	-11.3 (10.25)	-4.9 (10.76)	-6.86, p <0.0001

Sources: Mrowietz et al 2016,[23] LAS41008 CSR M41008-1102 June 2016[48]

Proportion of patients achieving a score of 'clear' or 'almost clear in PGA at weeks 3 and 8

In the FAS population, [redacted] in the DMF (LAS41008) group achieved a score of "clear" or "almost clear" in the PGA at Week 3. There was no significant difference between the DMF and placebo group and between the DMF and the Fumaderm group.

At Week 8, [redacted] and [redacted] of the patients in the DMF (LAS41008) and Fumaderm group, respectively, achieved a score of "clear" or "almost clear" in the PGA, compared to [redacted] of the patients in the placebo group. There was no significant difference between the DMF (LAS41008) and placebo group or between the DMF and Fumaderm group.

Treatment success rate

Treatment success was defined as patients achieving either a "clear" or "almost clear" score in the PGA and/or PASI 90. At Week 16, a significantly higher treatment success rate was observed in the DMF (LAS41008) group (33.3%) compared to the placebo group (13%) at Week 16 (p <0.001) (Table 15).

There was no significant difference between the DMF (LAS41008) and the Fumaderm treatment groups.

Table 15: Treatment Success Rate, FAS

Week	DMF (LAS41008) n=267	Fumaderm n=273	Placebo n=131	p value DMF – placebo, p-value	p value DMF – placebo, p-value
	n (%)				
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	88 (33.3)	104 (38.1)	17 (13.0)	<0.001	0.218

Source: Mrowietz et al 2016,[23] LAS41008 CSR M41008-1102 June 2016[48]

Remission rate

Remission rate was defined as a score of "clear" in the PGA. A significant difference between DMF and placebo was observed in the remission rate at Week 16 [redacted] (Table 16). No significant differences in the remission rates were observed between DMF and Fumaderm.

Table 16: Remission rate (FAS)

Week	DMF (LAS41008) N=267	Fumaderm N=273	Placebo N=131	p-value DMF-Placebo	p-value DMF-Fumaderm
	n (%)				
Week 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: NA: not applicable
Source: LAS41008 CSR M41008-1102 June 2016[48]

Time to relapse

Relapse was defined as the event when the achieved maximal improvement from baseline was subsequently reduced by ≥50% based on PASI. Two time-to-relapse analyses were conducted: a) relapse occurring at any time during the study duration (on-treatment +12 months off treatment [F3]) and b) relapse occurring within 2 months after last study drug intake.

Relapse during the study duration (up to the 12 months follow up visit [F3])

In the FAS population, [redacted] in the DMF (LAS41008) group [redacted], [redacted] patients in the Fumaderm group [redacted], and [redacted]% patients in the placebo group

[redacted] had a relapse during treatment or within the 2 months after end of treatment. The median time to relapse was [redacted] days in the DMF (LAS41008) group, [redacted] in the Fumaderm group and [redacted] days in the placebo group.

The mean time to relapse in the DMF (LAS41008) and Fumaderm group was [redacted] (standard error [SE]: [redacted]) and [redacted] (SE: [redacted]) days, respectively, compared to [redacted] (SE: [redacted]) days in the placebo group.

The Kaplan-Meier curve is presented in Figure 11.

Figure 11: Kaplan-Meier Curve: Time to relapse during the study (FAS)

Time to relapse within 2 months of stopping therapy

Relapse within 2 months of stopping therapy was observed in [redacted]% of patients in the DMF (LAS41008) group [redacted] and [redacted]% of patients in the Fumaderm group [redacted] compared to a more than two-fold increased proportion of relapsing patients, [redacted]% of patients, observed in the placebo group [redacted]. The mean time to relapse was [redacted] (SE: [redacted]) and 65.0 (SE: [redacted]) days in the DMF (LAS41008) and Fumaderm groups, respectively, and [redacted] (SE: [redacted]) days in the placebo group. The

Kaplan-Meier curve for time to relapse within 2 months of stopping therapy is presented in Figure 12.

Figure 12: Kaplan-Meier Curve: Time to relapse within 2 months of stopping therapy (FAS)

Time to Rebound

Rebound defined as a worsening of psoriasis over baseline value (PASI≥125%) was documented for very few patients in either the DMF (LAS41008) or the Fumaderm group, whereas the proportion of patients fulfilling the criteria for rebound was higher in the placebo group. In the FAS population, 2 (1.13%) of 177 patients in the DMF (LAS41008) group, 4 (2.19%) of 183 patients in the Fumaderm group, and 7 (9.33%) of 75 patients in the placebo patients had a rebound.

The mean time to rebound was [redacted] (SE: [redacted]) days and [redacted] (SE: [redacted]) days in the DMF (LAS41008) and Fumaderm groups, respectively, and [redacted] (SE: [redacted]) days in the placebo group.

Quality of life – Dermatology Quality of Life Index

The mean DLQI index was significantly lower in the DMF (LAS41008) treatment group compared to the placebo group at Week 16 (5.4 vs. 8.5, p-value<0.0001) (Table 17). Treatment with DMF (LAS41008) improved mean DLQI scores by 52% compared with an improvement of 22% with placebo. No difference in the mean DLQI at week 16 was observed between DMF (LAS41008) and Fumaderm (5.4 vs. 6.0) (Table 17).

A significantly lower mean DLQI was also observed in the DMF (LAS41008) treatment group (4.8) compared to placebo (7.8) after two months off treatment. Quality of life benefit was not seen after 6 and 12 months off treatment.

Table 17: DLQI scores (FAS)

Visit	DLQI score	DMF (LAS41008) N = 267	Fumaderm N = 272	Placebo N = 131	DMF-Placebo p-value LS means 2-sided 95% CI	DMF-Fumaderm p-value LS means 2-sided 95% CI
Screening	Mean (SD)	11.3 (6.26)	12.0 (7.04)	10.9 (6.49)	0.5932 0.37 (-1.00, 1.75)	0.2362 -0.67 (-1.79,0.44)
Week 16	Mean (SD)	5.4 (6.07)	6.1 (7.18)	8.5 (6.88)	<0.001 -3.24 (-4.70, -1.78)	0.2429 -0.69 (-1.84, 0.47)
F1 at 2 months off treatment	Mean (SD)	4.8 (5.57)	5.4 (6.12)	7.8 (5.98)	0.0016 -3.02 (-4.86, 1.16)	0.3415 -0.69 (-2.12, 0.74)
F2 at 6 months off treatment	Mean (SD)	5.8 (6.66)	6.6 (5.77)	7.6 (6.33)	0.1064 -2.47 (-5.47, 0.54)	0.3746 -0.95 (-3.05, 1.16)
F3 at 12 months off treatment	Mean (SD)	7.8 (6.63)	8.0 (5.66)	7.0 (5.96)	0.6918 0.61 (-2.40, 3.61)	0.9242 -0.10 (-2.27, 2.06)

Source: LAS41008 CSR M41008-1102 June 2016,[48] Van De Kerkhof et al 2016[51]

Patient benefit index (PBI)

The mean PBI was significantly higher in the DMF (LAS41008) treatment group compared to the placebo group at Week 16 (2.1 vs. 1.3; p-value<0.0001) and at the 2 months follow-up visit (2.4 vs. 1.5; p-value<0.0001) (Table 18).

As with DLQI no significant differences in the mean PBI were observed between DMF (LAS41008) and Fumaderm.

Table 18: Mean PBI (FAS)

Visit	DMF (LAS41008) n=254	Fumaderm n=260	Placebo n=119	DMF – Placebo p-value LS means 2-sided 95% CI	DMF – Fumaderm p-value LS means 2-sided 95% CI
	Mean (SD)				
Week 16	2.1 (1.25)	[redacted]	1.3 (1.10)	<0.0001 [redacted]	[redacted]
F1 (2 months post treatment)	2.4 (1.05)	[redacted]	1.5 (1.17)	<0.0001 [redacted]	[redacted]
F1 (6 months post treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F1 (12 months post treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: LAS41008 CSR M41008-1102 June 2016,[48] Van der Kerhof et al 2016[51]

4.8 Subgroup analyses

Pre-planned and post-hoc sub group analyses were planned. Pre-planned analyses included subgroup analysis according to severity of psoriasis and post-hoc analyses according to previous use of systemic non-biological therapy.

Pre-planned subgroup analyses

In accordance with the International Conference on Harmonisation requirements, subgroup analyses were conducted to evaluate the consistency of the DMF (LAS41008) gastro-resistant tablets' effect over placebo on the primary efficacy endpoints and the DLQI index total score at Week 16. Analyses were based on the FAS and were performed in the following subgroups: gender, age and severity of psoriasis based on PASI and PGA at baseline to assess the consistency of the effect of DMF (LAS41008) versus placebo on the co-primary endpoints (PASI 75 and PGA at week 16) and DLQI at week 16.

Results

Subgroup analysis results for change in PASI and PGA are presented in [redacted]

The treatment effect between DMF and placebo observed in the subgroups was generally similar to those seen for the overall FAS population, [redacted] Greater treatment differences were seen in [redacted] at baseline.

There were no statistically significant subgroup differences when the DLQI scores were analysed in subgroups by age, gender, or severity of psoriasis based on PASI and PGA at baseline.

Age

Patients in the age groups [redacted]

Compared with placebo [redacted] treated with DMF (LAS41008) achieved:

- PASI 75 at Week 16 (Table 19).
- A score of “clear” or “almost clear” in the PGA at Week 16 (Table 19)

In the age group [redacted] the placebo effect was higher than observed in the other age groups leading to a smaller treatment effect of DMF (LAS41008).

Compared with Fumaderm the non-inferiority of DMF (LAS41008) to Fumaderm in the proportion of patients achieving PASI 75 at Week 16 was achieved in the age groups [redacted] (Table 20).

Table 19: Superiority of DMF (LAS41008) vs. Placebo in primary efficacy variable by age group (FAS)

	DMF n (%)	Placebo n (%)	DMF – Placebo difference p-value CI (significance level 99.24%)
Age ≤ 35 years			
Proportion of patients with PASI 75 at Week 16	[redacted]	[redacted]	[redacted]
Proportion of patients with a ‘clear’ or ‘almost clear’ score in PGA at week 16	[redacted]	[redacted]	[redacted]
Age > 35 years and ≤ 55 years			
Proportion of patients with PASI 75 at Week 16	[redacted]	[redacted]	[redacted]
Proportion of patients with a ‘clear’ or ‘almost clear’ score in PGA at week 16	[redacted]	[redacted]	[redacted]
Age > 55 years			
Proportion of patients with PASI 75 at Week 16	[redacted]	[redacted]	[redacted]
Proportion of patients with a ‘clear’ or ‘almost clear’ score in PGA at week 16	[redacted]	[redacted]	[redacted]

Source: LAS41008 CSR M41008-1102 June 2016[48]

Table 20: Statistical test for non-inferiority of DMF (LAS41008) vs. Fumaderm in PASI 75 at week 16 (FAS)

	DMF (LAS41008) n (%)	Fumaderm n (%)	DMF – Fumaderm difference p-value for superiority CI (significance level 99.24%)
Age ≤ 35 years			
Proportion of patients with PASI 75 at Week 16	[redacted]	[redacted]	[redacted]
Age > 35 years and ≤ 55 years			
Proportion of patients with PASI 75 at Week 16	[redacted]	[redacted]	[redacted]
Age > 55 years			
Proportion of patients with PASI 75 at Week 16	[redacted]	[redacted]	[redacted]

Source: LAS41008 CSR M41008-1102 June 2016[48]

Severity

While patients whose baseline PASI was moderate at baseline behaved similarly to the overall FAS population, [redacted]

Figure 13: Subgroup analysis: Number of patients with PASI 75 by week 16

Figure 14: Subgroup analysis: Number of patients with clear or almost clear PGA by week 16

Additional post-hoc subgroup *analyses - Pre-treatment with systemic therapies*

At the request of the European Medicines Agency during evaluation of the dossier post-hoc analyses were performed on the FAS for the subgroups of patients who were receiving systemic therapy or PUVA for the first time [redacted] compared to those who had previous experience of other systemic agents such as methotrexate or ciclosporin [redacted] This analysis showed that the baseline demographics were comparable between these groups (Table 21).

Table 21: Demographic characteristics and baseline severity for systemic-naive patients and patients pre-treated with systemics (FAS population, LOCF; N=671)

	Systemic naïve n=538			Pre-treated with systemic n=133		
	DMF (LAS41008)	**Fumaderm**	**Placebo**	**DMF (LAS41008)**	**Fumaderm**	**Placebo**
Gender						
Male (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caucasian (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI						
Moderate (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA						
Moderate (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSA						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: PASI: Moderate: >10-≤20, Severe: >20. PGA: Moderate: 3, Severe: 4-5

BSA: body surface area; DLQI: Dermatology Life Quality Index; FAS: full analysis set; LOCF: last observation carried forward; N: number of patients; PASI: Psoriasis Area Severity Index; PGA: Physician's Global Assessment; SD: standard deviation

Source: Almirall Data on File: Regulatory submission: Summary of clinical efficacy[52]

The results for the co-primary endpoints are given in Table 22 and Table 23. [redacted]

[redacted]

Table 22: Percent of patients achieving PASI 75 at week 16 for systemic-naive and for patients pre-treated with systemics (FAS population, LOCF; N=671)

Treatment group			Number (%) of patients			
	Systemic-Naive Patients (N=538)			Patients Pretreated with Systemics (N=133)		
DMF(LAS41008)	n=223	Yes	[redacted]	n=44	Yes	[redacted]
		No	[redacted]		No	[redacted]
Fumaderm	n=214	Yes	[redacted]	n=59	Yes	[redacted]
		No	[redacted]		No	[redacted]
Placebo	n=101	Yes	[redacted]	n=30	Yes	[redacted]
		No	[redacted]		No	[redacted]
	Treatment comparisons RD, 95% CI, p-value				Treatment comparisons RD, 95% CI, p-value[a]	
DMF (LAS41008) vs. Placebo	[redacted]				[redacted]	
Fumaderm vs. Placebo	[redacted]				[redacted]	
DMF (LAS41008)vs. Fumaderm	[redacted]				[redacted]	

[a] The large range of the 95% CI is due to the small sample size.

Key: CI, confidence interval: FAS, full analysis set; LOCF, last observation carried forward; RD,risk difference, p-value from test for superiority

Source: Almirall Data on File: Regulatory submission: Summary of clinical efficacy[52]

Table 23: Percent of patients achieving a PGA of clear or almost clear at week 16 for systemic-naive patients and for patients pre-treated with systemics (FAS population, LOCF; N=671)

Treatment group			Number (%) of patients			
	Systemic-Naive Patients (N=538)			Patients Pretreated with Systemics (N=133)		
DMF (LAS41008)	n=223	Yes	[redacted]	n=44	Yes	[redacted]
		No	[redacted]		No	[redacted]
Fumaderm	n=214	Yes	[redacted]	n=59	Yes	[redacted]
		No	[redacted]		No	[redacted]
Placebo	n=101	Yes	[redacted]	n=30	Yes	[redacted]
		No	[redacted]		no	[redacted]
	Treatment comparisons RD, 95% CI, p-value			Treatment comparisons RD, 95% CI, p-value[a]		
DMF (LAS41008)vs. Placebo	[redacted]			[redacted]		
Fumaderm vs. Placebo	[redacted]			[redacted]		
DMF (LAS41008) vs. Fumaderm	[redacted]			[redacted]		

[a] The large range of the 95% CI is due to the small sample size

Key: CI, confidence interval: FAS, full analysis set; LOCF, last observation carried forward; RD,risk difference, p-value from test for superiority

Source: Almirall Data on File: Regulatory submission: Summary of clinical efficacy[52]

4.9 Meta-analysis

Not applicable. The evidence supporting the efficacy and safety of DMF (LAS41008) for the treatment of moderate to severe psoriasis is provided by the BRIDGE study.

4.10 Indirect and mixed treatment comparisons

In the absence of head-to-head trials an NMA was conducted to compare DMF (LAS41008) with the comparators relevant to the decision problem: Fumaderm, apremilast and standard systemic biologic therapies as used in clinical practice as per the NICE treatment pathway (adalimumab, etanercept, secukinumab, ustekinumab). Ixekizumab was also included in order that inputs could be generated for inclusion in the economic model (See Section 5.2) in the event that ixekizumab is recommended by NICE and is being used in clinical practice at the time DMF (LAS41008) is considered by the appraisal committee.

NMAs have been presented as an extension of traditional meta-analysis (where all included studies compare the same intervention with the same comparator) by including multiple pair-wise comparisons across a range of different interventions.[53,54,55] The key value of a NMA is that the efficacy of a particular intervention versus competing interventions can be obtained in the absence of head-to-head comparisons; indirect treatment comparison (ITC) of two interventions is made via a common comparator.

4.10.1 Systematic literature review (SLR)

Study identification

A systematic literature review (SLR) following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[56] was performed to identify published RCTs on DMF (LAS41008) and recommended systemic treatment options, including phototherapy in patients with moderate to severe plaque psoriasis. The review was conducted from a global perspective and consequently included additional comparator treatments not specified in the decision problem.

This SLR was originally performed between September 2015 and June 2016 and was updated in October 2016.

Search Strategies

Electronic literature searches were performed on 17 October 2016 using the following relevant bibliographic databases

The databases of interest were:

- MEDLINE
- MEDLINE In-Process
- EMBASE
- Cochrane Database of Systematic Reviews
- Cochrane Central Register for Controlled Trials (Ovid®)

All databases were searched using the Ovid® platform.

Additionally, two trial registries were manually searched:

- Clinicaltrials.gov – United States (US) National institute of Health
- World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP)

Furthermore, the following conference websites were searched for 2014-2016:

- American Academy of Dermatology (AAD)
- European Academy of Dermatology and Venereology (EADV)
- World Congress of Dermatology

For the AAD and EADV abstracts from 2016 were hand-searched and added to the findings. For the World Congress of Dermatology no conferences occurred in 2016.

Appendix 5 presents the search strategies for all databases searched, including the number of hits.

A search strategy was implemented combining disease terms with study design terms and specific interventions. Validated search filters by Cochrane were used to identify randomised and other controlled trials in MEDLINE or EMBASE. Although search filters were only applied in the database they were designed for, the individual database searches were combined in the end to facilitate the removal of duplicates and study designs not of interest (case studies, editorials, comments etc.).

The search was performed without a time cut-off point. Conference abstracts published before 2013 were excluded. It was assumed that studies presented before as an abstract were available as a full text publication within this time-frame.

The search was restricted to the English and German language and where possible, studies were limited to ‘human’ and ‘adult’. The German language was initially included since Fumaderm® is currently approved only in Germany, where it is the most commonly prescribed oral therapy for the treatment of psoriasis.

Reference lists from relevant and recent systematic reviews were found through the database searches and were scanned to identify further studies for consideration.

Selection was performed by two researchers independently. Any discrepancies between researchers were resolved by discussing the discrepancy with both

researchers and including a third researcher to make the final decision. For the abstracts that met the selection criteria, available publications were obtained and evaluated using the full-text selection criteria. The selected citations were grouped per study as many studies have been published in several sources such as conference abstracts and full text articles (Appendix 6). Only studies reporting the required outcomes of interest were selected for the analysis.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were the same for both the original and updated SLR . Details are shown below (Table 24). The relevance of each identified citation was based on title and abstract according to predefined patient population, intervention, comparator, outcome and study design (PICOS) selection criteria.

While the SLR protocol was developed to support a potential submission in Germany (thus German language was included) during the full text screening stage the decision was made to exclude German articles. The reason for this was that this SLR has been tailored to this appraisal and the decision problem. During screening one article was excluded based on the German language.

Key outcome measures included were those within the BRIDGE trial. Outcomes were recorded for 8, 12, 16 and 24 weeks (all with a margin of +/- 2 weeks) and induction time. Induction time is the time point at which the primary endpoint was measured in the pivotal studies of the medicine.

Table 24. PICOS criteria SLR

Criteria		Inclusion	Exclusion
STUDY DESIGN	**Abstract and full-text selection**	Phase II, III, IV randomised controlled trials (Crossover up to time of crossover)	Phase I clinical trials Case-control studies, case reports and retrospective analyses Methodology studies or protocols Pharmaco-economic studies Pharmacokinetics, Pharmacodynamics Reviews, letter, report, expert opinion Genetics studies Biomarkers studies Observational studies Guidelines SLR, meta-analyses and NMA* Pooled, post-hoc, sub- analysis**
POPULATION	**Abstract selection**	Adult patients suffering from moderate to severe chronic plaque psoriasis (psoriasis vulgaris) requiring systemic therapy Both naïve patients and pre-treated patients.	Patients with scalp or nail psoriasis Studies focussed solely on targeting patients with psoriatic arthritis (PsA) Healthy patients/controls Immunosuppressed patients
	Full-text selection	Adult (18+) patients (males and females) suffering from moderate to severe chronic plaque psoriasis (psoriasis vulgaris) requiring systemic therapy Both naïve patients and pre-treated patients. Children and adult outcomes reported separately Patients with different diseases, outcomes for plaque psoriasis reported separately. Moderate to severe is defined as PASI>10%, BSA>10%, PGA score of 3, 4 or 5	
TREATMENT / INTERVENTION	**Abstract and full-text selection**	The following treatments were included: • DMF (LAS41008) • Fumaderm • Adalimumab • Etanercept • Infliximab • Secukinumab • Ustekinumab	Any other intervention not listed under inclusion and combination therapies of the treatments listed under inclusion or other combinations (such as intervention of interest + topical treatment) Phototherapy vs phototherapy without any systemic therapy arm or placebo arm *Non approved dosages of interventions listed under inclusion*

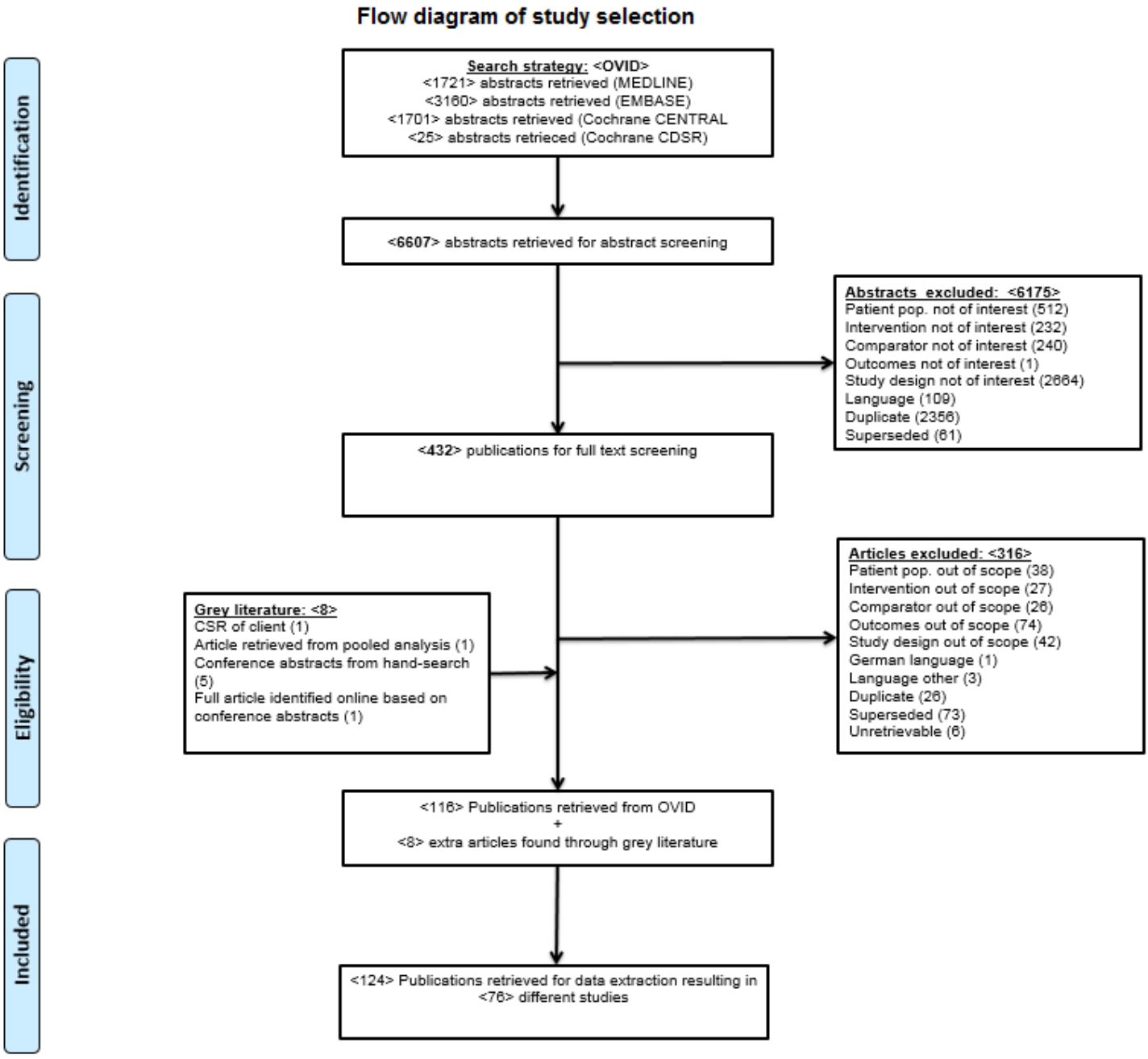
		• Ixekizumab • Apremilast • Ciclosporin • Methotrexate • Acitretin • Phototherapy	
COMPARATOR	**Abstract and full-text selection**	Interventions above compared to each other or to placebo	Any other intervention not listed under inclusion, and combination therapies of the treatments listed under inclusion. If multiple arms, at least two arms need to be of interest.
OUTCOMES	**Abstract selection**	No selection on outcomes	No selection on outcomes
	Full-text selection	Efficacy • PASI 50,75,90 • PASI continuous • Physician Global Assessment (PGA) • PGA clear and almost clear • Body Surface Area (BSA) • Relapse and rebound Safety • Adverse events (AEs) • Serious AEs • Withdrawal due to AEs, SAE, Lack of efficacy HRQoL • Dermatological Life Quality Index (DLQI)	Any outcomes not listed under inclusion
TIME POINTS	**Abstract and full-text selection**	• 8 weeks (+/- 2 weeks) • 12 weeks (+/- 2 weeks) • 16 weeks (+/- 2 weeks) • 24 weeks (+/- 4 weeks) • Induction phase (drug dependent)	
Language	**Abstract and full-text selection**	• The search will be restricted to the English language	

*** Pooled analysis were excluded; however we cross-checked that the original studies had been captured in the search. If these had not been captured, we identified them and added them. This was done transparently and made clear in the PRISMA diagram.**
****Reviews and meta-analysis were excluded from data extraction since the pooled results cannot be used in our analysis. However, good quality meta-analysis and systematic reviews (i.e. Cochrane reviews, up to 5) were used for cross-checking of references.**
HRQoL = Health-related quality of life; SLR = Systematic literature review; NMA = Network meta-analysis

Results of the SLR

A PRISMA flowchart detailing the number of studies included and excluded at each stage of the review is shown in Figure 15.

Figure 15. Flow diagram of study selection



4.10.2 Network meta-analysis

Identification of studies

The SLR described in Section 4.10.1 was used to identify all potential studies that may have been relevant for indirect comparison of DMF (LAS41008) with the comparators relevant to the decision problem. Based on the evidence retrieved in the SLR, the feasibility of an NMA was assessed.

Treatments to be compared

The interventions and doses of interest in the base case analysis are presented in Table 25. The NMA focuses on the comparators relevant to the decision problem: Fumaderm, apremilast and standard systemic biologic therapies (adalimumab, etanercept, secukinumab, ustekinumab). Ixekizumab was also included in order that inputs could be generated for the economic model (See Section 5.2) in the event that ixekizumab is recommended by NICE and being used in clinical practice at the time DMF is considered by the appraisal committee.

Doses included

The usual recommended dose for etanercept is 25 mg twice a week or 50 mg once a week. Treatment with 50 mg twice a week can also be used during the first 12 weeks of treatment for plaque psoriasis.[57] It was assumed that 25 mg twice a week and 50 mg once a week have an identical clinical efficacy, and these two dosages were therefore pooled together in the ‘etanercept low dose’ treatment arm. The etanercept dose of 50 mg twice a week was used in the ‘etanercept high dose’ treatment arm.

The usual approved dose for ustekinumab in adults is 45 mg at 0 weeks and 4 weeks, followed by the same dose every 12 weeks. Patients weighing over 100 kg receive a dose of 90 mg at the same time points. For the NMA ustekinumab has been split into three different treatment arms: ustekinumab low dose (patients receiving 45 mg), ustekinumab high-dose (patients receiving 90 mg) and the ustekinumab mixed (mixed group of patients receiving 45 mg or 90 mg).

Infliximab is excluded from the base case since it is not a comparator within the NICE scope or decision problem.

Table 25. Approved dosing schedules and included studies for the treatments included in the base case analysis

	Induction Phase Dose	Maintenance Phase Dose	Included Studies
DMF (LAS41008)	30 mg, followed by 120 mg according to a standard progressive dosage regimen		BRIDGE[23,51,58-60]
Fumaderm	30 mg, followed by 120 mg according to a standard progressive dosage regimen		BRIDGE[23,51,58-60]
Apremilast	Week 0-1 increase daily from 10 mg twice daily to 30 mg twice daily	30 mg twice daily from week 1 onwards	ESTEEM 1,[61-65] ESTEEM 2,[61-64,66-69] Papp 2012,[70,71] LIBERATE,[72-76] Ohtsuki 2016[77]
Adalimumab	80 mg week 0	40 mg starting at week 1 followed every 2 weeks	Asahina 2010,[78] CHAMPION,[79,80] X-PLORE[81]
Secukinumab	300 mg (given as 2 injections of 150 mg) at weeks 0, 1, 2 and 3	300 mg starting at week 4, administration monthly.	CLEAR,[82-85] ERASURE,[86,87] FEATURE,[88,89] FIXTURE,[86] JUNCTURE[89,90]
Etanercept (low-dose)	25 mg twice weekly or 50 mg weekly for 12 weeks.		Gottlieb 2003,[91,92] LIBERATE,[72-76] Leonardi 2003,[92-94] Papp 2005,[92,95,96] PRISTINE,[97,98] Van de Kerkhof 2008,[99,100] PRESTA,[101.102] CRYSTEL[103,104]
Etanercept (high-dose)	50 mg bi-weekly for 12 weeks		ACCEPT,[105] Bachelez 2015,[106,107] Bagel 2012,[108] FIXTURE,[86] Gottlieb 2011,[109] Leonardi 2003,[92-94] Papp 2005,[92,95,96] PRESTA,[101,102] PRISTINE,[97,98] Strober 2011,[110] UNCOVER -2,[111-113] UNCOVER -3,[111,114] Tyring 2006,[115,116] CRYSTEL[103,104]
Ustekinumab (low-dose)	45 mg	45 mg every 12 weeks	ACCEPT,[105] LOTUS,[117] PEARL,[118,119] PHOENIX 1,[120,121] PHOENIX 2,[122-124] The Japanese Ustekinumab Study Group[125,126]
Ustekinumab (high-dose)	90 mg	90 mg every 12 weeks	ACCEPT,[104] PHOENIX 1,[119,120] PHOENIX 2,[121-123] The Japanese Ustekinumab Study Group[125,126]
Ustekinumab (mixed)	45 mg/ 90 mg (if body weight >100 kg) weeks 0 and 4	45 mg (or 90 mg if body weight >100 kg) every 12 weeks	AMAGINE-2,[127,128] AMAGINE-3,[128,129] CLEAR[82-85]
Ixekizumab	160 mg	80 mg every 2 weeks up to 12 weeks followed by 80 mg every 4 weeks	UNCOVER -2,[111-113] UNCOVER -3,[111,114] UNCOVER-1[130,131]

Inclusion/exclusion criteria for studies included in the NMA

As described in section 4.10.1, a number of exclusion/inclusion criteria were used to identify potential relevant studies for the NMA.

Table 26 provides details of the PICOS criteria for the selection of trials for the NMA.

Table 26. PICOS criteria NMA

Criteria		Inclusion	Exclusion
STUDY DESIGN	**Abstract and full-text selection**	Phase II, III, IV randomised controlled trials (Crossover up to time of crossover)	Phase I clinical trials Case-control studies, case reports and retrospective analyses Methodology studies or protocols Pharmaco-economic studies Pharmacokinetics, Pharmacodynamics Reviews, letter, report, expert opinion Genetics studies Biomarkers studies Observational studies Guidelines SLR, meta-analyses and NMA* Pooled, post-hoc, sub- analysis**
POPULATION	**Abstract selection**	Adult patients suffering from moderate to severe chronic plaque psoriasis (psoriasis vulgaris) requiring systemic therapy Both naïve patients and pre-treated patients.	Patients with scalp or nail psoriasis Studies focussed solely on targeting patients with psoriatic arthritis (PsA) Healthy patients/controls Immunosuppressed patients
	Full-text selection	Adult (18+) patients (males and females) suffering from moderate to severe chronic plaque psoriasis (psoriasis vulgaris) requiring systemic therapy Both naïve patients and pre-treated patients. Children and adult outcomes reported separately Patients with different diseases, outcomes for plaque psoriasis reported separately. Moderate to severe is defined as PASI>10%, BSA>10%, PGA score of 3, 4 or 5	
TREATMENT / INTERVENTION	**Abstract and full-text selection**	<u>Biologics and second-line systemic therapies</u> including: • Adalimumab (80mg starting dose, 40mg eow); • Secukinumab (300mg); • Etanercept low dose (25mg biw or 50mg ow); • Etanercept high dose (50mg biw); • Ustekinumab low dose (45mg); • Ustekinumab high dose (90mg); • Ustekinumab mixed (45/90mg depending on	Any other intervention not listed under inclusion and combination therapies of the treatments listed under inclusion or other combinations (such as intervention of interest + topical treatment) Phototherapy vs phototherapy without any systemic therapy arm or placebo arm *Non approved dosages of interventions listed under inclusion*

		weight); • Ixekizumab (160mg followed by 80mg every 2 weeks up to 12 weeks followed by 80mg every 4 weeks); • Apremilast (30mg); • Fumaderm (30-720mg);	
COMPARATOR	**Abstract and full-text selection**	Interventions above compared to each other or to placebo	Any other intervention not listed under inclusion, and combination therapies of the treatments listed under inclusion. If multiple arms, at least two arms need to be of interest.
OUTCOMES	**Abstract selection**	No selection on outcomes	No selection on outcomes
	Full-text selection	Efficacy • PASI 50,75,90 (PASI response)	Any outcomes not listed under inclusion
TIME POINTS	**Abstract and full-text selection**	• 16 weeks (+/- 2 weeks) • Induction phase (drug dependent)	
Language	**Abstract and full-text selection**	• The search will be restricted to the English language	

*** Pooled analysis will be excluded; however we will cross-check that the original studies have been captured in the search. If these have not been captured, we will identify them and add them. This will be done transparently and made clear in the PRISMA diagram.**
****Reviews and meta-analysis are excluded from data extraction since the pooled results cannot be used in our analysis. However, good quality meta-analysis and systematic reviews (i.e. Cochrane reviews, up to 5) will be used for cross-checking of references.**
HRQoL = Health-related quality of life; SLR = Systematic literature review; NMA = Network meta-analysis

Details of the excluded studies are provided in (Table 27):

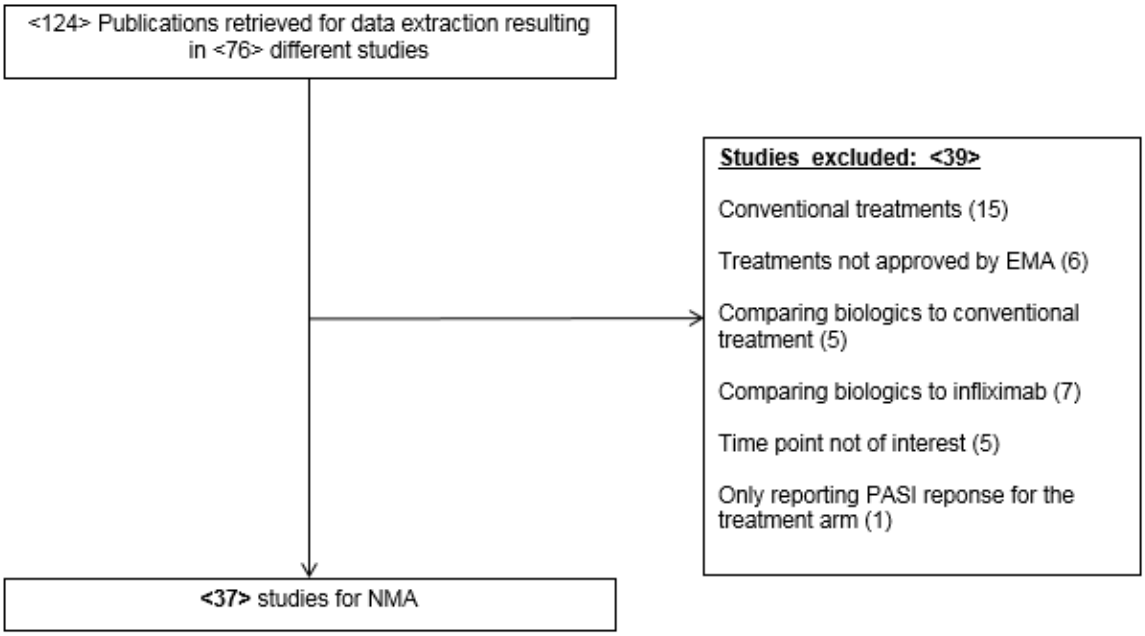
Table 27. Excluded studies

Study	Reason for exclusion
STATURE[132], Sandhu 2003[133], Reich 2014[134], Krueger 2007[135], Hueber 2010[136] and Leonardi 2012[137]	Studies not comparing licensed drugs with recommended doses by European Medicines Authority (EMA)
Aditya 1989[143,144], Dogra 2013[145], Akcali 2014[146], Shupack 1997[147], Meffert 1997[148], Laburte 1994[149], Ellis 1991[150], Ho 2009[151], Heydendael 2003[152], Flytström 2008[153], Dogra 2012[154], Caca-Biljanovska 2002[155], Fallah Arani 2011[156], METOP[157], Thaci 2002[158]	Studies comparing conventional treatment arms to each other or placebo
RESTORE 1[138], Caproni 2009[139], Antiga 2010[140], Gisondi 2008[141] and Lee 2016[142]	Studies comparing conventional treatments with a biologic or approved second-line systemic therapies
Cai 2016[159], Gordon 2006[160,161], EXPRESS[162-164], Maari 2014[165] and Zhang 2015[166]	Studies reporting outcomes only on other time points than 16 weeks or induction time*
Menter 2008[167, 168]	Studies reporting outcomes at 16 weeks, but only for the treatment arm and not for the placebo arm
(Chaudhari 2001[169], EXPRESS II[170,171], PIECE[172], SPIRIT[94,173,174], The Japanese Infliximab Study[175], Yang 2012[176] and De Vries 2013[177]	Studies comparing infliximab to another biologic treatment or placebo

* Induction time is the time point at which the primary endpoint was measured in the pivotal studies of the medicine: 12 weeks for secukinumab, etanercept, ustekinumab, and ixekizumab and 16 weeks for adalimumab, apremilast, Fumaderm and DMF (LAS41008).

A flow diagram of study selection is provided in (Figure 16). 37 studies were identified for inclusion within the NMA

Figure 16. Flow diagram of study selection NMA



4.10.3 Methods and outcomes of included studies

Feasibility assessment

Based on the identified evidence, the feasibility of an evidence synthesis by means of a NMA involving the following steps was conducted

1. The data extraction results were examined to determine whether a network of interlinked studies could be constructed. The treatment arms of each RCT were classified under one category. Each treatment category reflected one treatment strategy that could be expected to have the same results (up to sampling error) in terms of efficacy and safety if the same population had been treated. Pooling of different dosages of the same treatment was performed enabling one global network to be drawn. Assuming availability of the data on each outcome of interest, this global network gave a summary of all possible comparisons that were undertaken by the NMA. Details of the studies selected are provided in Section 4.10.2.

2. The study design and patient characteristics of each RCT were investigated to detect any differences across studies that could affect the relative treatment effects. This step reflects the exploration of the similarity assumption that is posed in the analysis.
3. For each outcome, the availability and the comparability (e.g. if different measurement tools or definitions have been used) of the data reported across the studies was assessed. This step reflects the exploration of the transitivity assumption of the analysis. The placebo response rates were investigated and other baseline risk values. The network was then amended to reflect the possible comparisons that could be included in the NMA per outcome. The network diagram for the base case analysis is presented in Figure 23.
4. Taking into consideration all the specificities of the evidence base identified, scenario analyses were defined.

Outcomes assessed in the NMA

The NMA results presented in this submission focus on the most relevant efficacy parameter in the moderate to severe psoriasis therapy area: PASI response rates. PASI response rates were consistently reported across all studies and are the key efficacy parameter in the economic analysis. The PASI response rates which have been included are as follows:

- PASI 50 defined as a minimum of 50% improvement of PASI score from baseline
- PASI75 defined as a minimum of 75% improvement of PASI score from baseline
- PASI 90 defined as a minimum of 90% improvement of PASI score from baseline

The use of PASI response rates as the primary outcome measure is consistent with the outcomes in the BRIDGE study, previous NICE STA psoriasis submissions and, as stated, also aligns with the efficacy inputs used to inform the cost-effectiveness model.

Results are reported based on the preferred multinomial model (probit link) which takes into account that the treatment effect is the same regardless of the cut-off. This

model is recommended by the NICE Decision Support Unit for binary PASI outcomes. The model pools the outcomes of PASI50, PASI75 and PASI90 at 16 weeks and induction time. The input-data is reported separately per PASI outcome. Since the PASI50, PASI75 and PASI90 are pooled together in the multinomial, the generic term of: *PASI response* is used for these outcomes from this point forward.

The NMA for safety outcomes - adverse events and serious adverse events - was not feasible (a) due to the high diversity in definitions for AE and SAE (for example some trials reported treatment-emergent AE whilst others reported any AE) and (b) due to the variety in trial durations (from 8 to 64 weeks) and (c) due to crossover design in many of the RCTs.

Patient populations of trials included in the NMA

Table 28 provides an overview of the patient characteristics of each trial. Patients' age ranged from 39 to 50 years and 53% to 89% were male of the studies reporting this information. For most studies the majority of the patients were Caucasian, however for four studies the population was entirely Asian (PEARL,[118,119] The Japanese Ustekinumab Study Group,[125,126] LOTUS,[117] and Ohtsuki 2016[77]). Duration of psoriasis ranged from 12 to 23 years and most trials did not report comorbidity of psoriatic arthritis or a relatively low percentage. In terms of prior therapy, a majority of the trials did not report this clearly and for the trials that did report this there was some diversity. Table 29 provides an overview of the disease characteristics of each trial. PASI score at baseline ranged from 15 to 30, BSA at baseline from 15% to 50% and DLQI at baseline ranged from 10 to 16.

Table 28. Patient demographics and baseline characteristics of studies included in the base-case NMA

Trial name	Treatment name	ITT	Age mean (SD)	Sex: male (%)	Caucasian (%)	Asian (%)	Psoriasis years mean (SD)	PsA (%)	Treatment -naïve (%)	Biologic-experienced (%)	Conventional -experienced (%)
BRIDGE[23,51,58-60]	DMF (LAS41008) 30-720mg oral	279	44 (15.2)	62	99	0	NR	NR	NR	NR	NR
	Fumaderm 30-720mg oral	283	45 (13.8)	65	99	1	NR	NR	NR	NR	NR
	Placebo	137	44 (14.3)	68	100	0	NR	NR	NR	NR	NR
BRIDGE – Subgroup[23,51,58-60*]	DMF (LAS41008) 30-720mg oral	279	44 (15.2)	62	99	0	NR	NR	NR	NR	NR
	Fumaderm 30-720mg oral	283	45 (13.8)	65	99	1	NR	NR	NR	NR	NR
	Placebo	137	44 (14.3)	68	100	0	NR	NR	NR	NR	NR
CHAMPION[79,80]	Adalimumab 40mg SC eow - 80mg at week 0	108	43 (12.6)	65	95	3	18 (10.1)	21	NR	NR	NR
	Placebo	53	41 (11.4)	66	93	4	19 (8.7)	21	NR	NR	NR
JUNCTURE[89,90]	Secukinumab 300mg SC ow (week 1-4) followed by every 4 weeks	60	47 (14.2)	77	93	NR	21 (13.5)	23	NR	25	50
	Placebo	61	44 (12.7)	62	97	NR	20 (12.2)	20	NR	21	48
ERASURE[86,87]	Secukinumab 300mg SC ow (week 1-4) followed by every 4 weeks	245	45 (13.5)	69	70	21	17 (11.1)	23	NR	29	52
	Placebo	248	45 (12.6)	69	71	19	17 (12.4)	27	NR	29	44
FEATURE[88,89]	Secukinumab 300mg SC ow (week 1-4) followed by every 4 weeks	59	45 (12.6)	64	92	NR	18 (11.9)	NR	NR	39	34
	Placebo	59	47 (14.1)	66	97	NR	20 (14.2)	NR	NR	44	49
FIXTURE[86]	Secukinumab 300mg SC ow (week 1-4) followed by every 4 weeks	327	45 (13.2)	69	69	22	16 (12.3)	15	NR	12	60
	Etanercept 50mg SC bid	326	44 (13.0)	71	67	23	16 (12.0)	14	NR	14	63
	Placebo	326	44 (12.6)	73	67	22	17 (11.6)	15	NR	11	61
Gottlieb 2003[91,92]	Etanercept 25mg SC bid	57	48 (NR)	58	89	NR	23 (1.6)	28	0%	NR	NR
	Placebo	55	47 (NR)	67	95	NR	20 (1.7)	35	0%	NR	NR
Papp 2005[92,95,]	Etanercept 25mg SC bid	196	45 (12.0)	65	92	NR	22 (NR)	28	11%	NR	NR

Trial name	Treatment name	ITT	Age mean (SD)	Sex: male (%)	Caucasian (%)	Asian (%)	Psoriasis years mean (SD)	PsA (%)	Treatment -naïve (%)	Biologic-experienced (%)	Conventional -experienced (%)
[96]	Etanercept 50mg SC bid	194	45 (12.4)	67	89	NR	20 (NR)	26	12%	NR	NR
	Placebo	193	45 (11.3)	64	91	NR	19 (NR)	26	11%	NR	NR
CRYSTEL[103,104]	Etanercept 25mg SC bid	352	45 (11.8)	72	NR	NR	22 (10.9)	NR	NR	NR	NR
	Etanercept 50mg SC bid	359	45 (11.9)	72	NR	NR	22 (11.3)	NR	NR	NR	NR
Leonardi 2003[92-94]	Etanercept 25mg SC bid	160	44 (0.9)	74	85	NR	19 (0.9)	22	NR	NR	NR
	Etanercept 25mg SC bid	162	45 (1.0)	67	85	NR	19 (0.9)	22	NR	NR	NR
	Etanercept 50mg SC bid	164	45 (0.8)	65	87	NR	19 (0.9)	22	NR	NR	NR
	Placebo	166	46 (1.0)	63	90	NR	18 (0.9)	22	NR	NR	NR
Tyring 2006[115,116]	Etanercept 50mg SC bid	311	46 (12.8)	65	90	NR	20 (12.3)	35	NR	NR	NR
	Placebo	307	46 (12.1)	70	88	NR	20 (11.4)	33	NR	NR	NR
Strober 2011[110]	Etanercept 50mg SC bid	139	45 (14.8)	61	91	NR	15 (12.1)	33	NR	8	32
	Placebo	72	45 (13.9)	64	93	NR	16 (11.7)	21	NR	4	28
Bagel 2012[108]	Etanercept 50mg SC bid	62	39§ (NR)	53	69	5%	18§ (NR)	NR	NR	NR	NR
	Placebo	62	42§ (NR)	58	76	3%	12§ (NR)	NR	NR	NR	NR
Gottlieb 2011[109]	Etanercept 50mg SC bid	141	43 (12.5)	70	90	NR	17 (12.7)	23	NR	14	26
	Placebo	68	44 (13.6)	69	96	NR	19 (13.2)	21	NR	15	28
PRESTA[101,102]	Etanercept 50mg BIW	314	45 (13.0)	65	93	NR	19 (11.7)	28	NR	14	NR
	Etanercept 50mg QW	207	44 (12.5)	69	91	NR	18 (10.8)	26	NR	13	NR
Bachelez 2015[106,107]	Etanercept 50mg SC bid	335	42§ (NR)	70	87	6	18§ (NR)	21	NR	11	NR
	Placebo	107	46§ (NR)	66	84	7	17§ (NR)	24	NR	11	NR
UNCOVER - 2[111-113]	Etanercept 50mg SC bid	358	45 (13.0)	66	94	2	19 (12.0)	NR	NR	21	48
	Ixekizumab biw	351	45 (13.0)	63	94	3	18 (12.0)	NR	NR	24	51
	Ixekizumab every four weeks	347	45 (14.0)	70	92	3	19 (13.0)	NR	NR	36	51
	Placebo	168	45 (12.0)	71	89	4	19 (13.0)	NR	NR	26	48
UNCOVER - 3[111,114]	Etanercept 50mg SC bid	382	46 (14.0)	70	92	3	18 (12.0)	NR	NR	16	48
	Ixekizumab biw	385	46 (13.0)	66	94	3	18 (12.0)	NR	NR	15	44
	Ixekizumab every four weeks	386	46 (13.0)	67	93	3	18 (12.0)	NR	NR	15	47

Trial name	Treatment name	ITT	Age mean (SD)	Sex: male (%)	Caucasian (%)	Asian (%)	Psoriasis years mean (SD)	PsA (%)	Treatment -naïve (%)	Biologic-experienced (%)	Conventional -experienced (%)
	Placebo	193	46 (12.0)	71	91	4	18 (13.0)	NR	NR	17	43
PRISTINE[97,98]	Etanercept 50mg SC bid	137	44 (12.7)	74	63	24	17 (10.7)	29%	NR	NR	NR
	Etanercept 50mg SC bid	136	44 (12.7)	65	65	23	18 (10.4)	33%	NR	NR	NR
Van de Kerkhof 2008[99,100]	Etanercept 50mg SC bid	96	46 (12.8)	62	NR	NR	19 (11.3)	16%	NR	NR	NR
	Placebo	46	44 (12.6)	54	NR	NR	17 (8.2)	11%	NR	NR	NR
Asahina 2010[78]	Adalimumab 40mg SC eow	38	48 (12.8)	84	NR	NR	14 (9.3)	NR	NR	NR	NR
	Adalimumab + loading dose 40mg SC eow - 80mg at week 0	43	44 (14.3)	81	NR	NR	14 (7.4)	NR	NR	NR	NR
	Placebo	46	44 (10.8)	89	NR	NR	16 (8.8)	NR	NR	NR	NR
X-PLORE[81]	Adalimumab 40mg SC eow - 80mg at week 0	43	50§ (NR)	70	91	NR	19 (12.8)	26	NR	61	40
	Placebo	42	46.5§ (NR)	67	93	NR	18 (13.3)	29	NR	36	50
PHOENIX 2[122-124]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks	409	45 (12.1)	69	91	NR	19 (11.7)	26	NR	38	55
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks	411	47 (12.1)	67	91	NR	20 (12.3)	23	NR	37	55
	Placebo	410	47 (12.5)	69	93	NR	21 (12.2)	26	NR	39	59
PHOENIX 1[120,121]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks	255	45 (12.5)	69	96	NR	20 (11.7)	29	NR	53	55
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks	256	46 (11.3)	68	93	NR	20 (11.1)	37	NR	51	55
	Placebo	255	45 (11.3)	72	92	NR	20 (11.7)	35	NR	50	56
ACCEPT[105]	Etanercept	347	46 (13.4)	71	91	NR	19 (12.1)	27	NR	12	57
	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks	209	45 (12.6)	64	92	NR	19 (11.8)	30	NR	12	62
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks	347	45 (12.3)	67	89	NR	19 (11.8)	27	NR	10	52
LOTUS[117]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks	162	40 (12.4)	78	NR	100	15 (8.9)	9	NR	12	39
	Placebo	160	39 (12.2)	76	NR	100	14 (8.6)	9	NR	7	43

Trial name	Treatment name	ITT	Age mean (SD)	Sex: male (%)	Caucasian (%)	Asian (%)	Psoriasis years mean (SD)	PsA (%)	Treatment -naïve (%)	Biologic-experienced (%)	Conventional -experienced (%)
The Japanese Ustekinumab Study Group[125,126]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks	64	47 (12.5)	83	NR	100	16 (8.2)	9	NR	2	NR
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks	62	47 (12.8)	76	NR	100	17 (10.7)	11	NR	0	NR
	Placebo	32	49 (12.7)	84	NR	100	16 (11.2)	3	NR	0	NR
PEARL[118,119]	Ustekinumab 45mg SC weeks 0, 4, 16	61	41 (12.7)	82	NR	100	12 (7.5)	16	NR	21	71
	Placebo	60	40 (10.1)	88	NR	100	14 (7.3)	12	NR	15	72
CLEAR[82-85]	Secukinumab 300mg SC ow (weeks 1-4) followed by 4-weekly	337	45 (14.0)	68	89	NR	20 (12.9)	21	NR	14	65
	Ustekinumab 45mg (<100kg) - 90mg (>100kg) SC weeks 0,4, every 12 weeks	339	45 (13.7)	74	85	NR	16 (11.2)	16	NR	13	66
AMAGINE-2[127,128]	Ustekinumab 45mg (<100kg) - 90mg (>100kg) SC	300	45 (13.0)	68	90	NR	19 (13.0)	17	NR	28	NR
	Placebo	309	44 (13.0)	71	88	NR	18 (12.0)	17	NR	29	NR
AMAGINE-3[128,129]	Ustekinumab 45mg (<100kg) - 90mg (>100kg) SC	313	45 (13.0)	68	90	NR	18 (12.0)	20	NR	24	NR
	Placebo	315	44 (13.0)	66	93	NR	18 (12.0)	19	NR	24	NR
UNCOVER-1[130,131]	Ixekizumab 80mg SC every 2 weeks	433	45 (12)	67	93	NR	20 (12)	NR	NR	40	57
	Ixekizumab 80 mg SC every 4 weeks	432	46 (13)	67	92	NR	19 (12)	NR	NR	39	49
	Placebo	431	46 (13)	70	93	NR	20 (12)	NR	NR	42	52
Ohtsuki 2016[77]	Apremilast 20 mg twice a day	85	NR	NR	0	100	NR	NR	NR	NR	NR
	Apremilast 30 mg twice a day	85	NR	NR	0	100	NR	NR	NR	NR	NR
	Placebo	84	NR	NR	0	100	NR	NR	NR	NR	NR
LIBERATE[72-76]	Apremilast 30mg oral	83	46 (13.6)	59	95	0	20 (12.7)	NR	NR	NR	80
	Etanercept 50 mg SC	83	47 (14.1)	59	90	1	18 (11.7)	NR	NR	NR	70
	Placebo	84	43 (14.9)	70	95	2	17 (12.1)	NR	NR	NR	83
Papp 2012[70,71]	Apremilast 30mg oral bid	88	44 (14.7)	57	91	5	19 (12.0)	24	NR	53	NR

Trial name	Treatment name	ITT	Age mean (SD)	Sex: male (%)	Caucasian (%)	Asian (%)	Psoriasis years mean (SD)	PsA (%)	Treatment -naïve (%)	Biologic-experienced (%)	Conventional -experienced (%)
	Placebo	88	44 (13.7)	60	94	8	20 (11.6)	19	NR	44	NR
ESTEEM 1[61-65]	Apremilast 30mg oral bid	562	46 (13.1)	67	90	5	20 (13.0)	NR	NR	29	38
	Placebo	282	47 (12.7)	69	89	6	19 (12.4)	NR	NR	28	36
ESTEEM 2[61-64,66-69]	Apremilast 30mg oral bid	272	45 (13.1)	64†	91†	3†	18 (11.4)	NR	NR	NR	NR
	Placebo	136	46 (13.4)	73†	93†	4†	19 (12.1)	NR	NR	NR	NR

§ median; †calculated | bid: twice a day; biw: biweekly; eow: every other week; ITT: intention to treat; IV: intravenous; PsA: psoriatic arthritis; od: once daily; ow: once weekly; SC: subcutaneous
*BRIDGE subgroup consistsof patients experienced with prior systemic therapies or PUVA.

Table 29. Disease Characteristics of all included NMA trials

Trial name	Treatment name	ITT	PASI mean (SD)	BSA mean (SD)	DLQI mean (SD)	PGA definition	PGA mean (SD)	Moderate (%)	Moderate/ severe (%)	Severe (%)
BRIDGE[23,51,58-60]	DMF (LAS41008) 30-720mg oral	279	16 (5.7)	22 (11.6)	11 (6.3)	PGA 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=moderate-severe, 5=severe	NR	61	35	5
	Fumaderm 30-720mg oral	283	16 (6.8)	21 (12.5)	12 (7.0)		NR	60	34	6
	Placebo	137	16 (4.9)	22 (12.3)	11 (6.5)		NR	60	37	2
BRIDGE – Subgroup[23,51,58-60*]	DMF (LAS41008) 30-720mg oral eow	279	16 (5.7)	NR	11 (6.3)	PGA 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=moderate-severe, 5=severe	NR	61	35	5
	Fumaderm 30-720mg oral eow	283	16 (6.8)	NR	12 (7.0)		NR	60	34	6
	Placebo	137	16 (4.9)	NR	11 (6.5)		NR	60	37	2
CHAMPION[79,80]	Adalimumab 40mg SC eow - 80mg at week 0	108	20 (7.5)	34 (19.9)	12 (6.6)	PGA	NR	48	43	8
	Placebo	53	19 (6.9)	28 (16.1)	12 (7.0)		NR	38	59	4
Papp 2012[70,71]	Apremilast 30mg oral bid	88	19 (7.1)	31 (7.7)	11 (6.2)	NR	NR	NR	NR	NR
	Placebo	88	18 (5.7)	31 (6.7)	11 (6.7)		NR	NR	NR	NR
ESTEEM 1[61-65]	Apremilast 30mg oral bid	562	19 (7.2)	24 (14.7)	13 (7.1)	Static physicians global assessment	NR	71	NR	29
	Placebo	282	19 (7.4)	25 (14.6)	12 (6.7)		NR	68	NR	32
ESTEEM 2[61-64,66-69]	Apremilast 30mg oral bid	272	19 (7.1)	26 (15.4)	13 (7.1)	Static physicians global assessment	NR	NR	NR	27
	Placebo	136	20 (8.0)	28 (15.8)	13 (7.1)		NR	NR	NR	36
JUNCTURE[89,90]	Secukinumab 300mg SC ow (week 1-4) followed by every 4	60	19 (6.4)	26 (12.8)	NR	IGA mod 2011 score 3(moderate)	NR	65	NR	35

Trial name	Treatment name	ITT	PASI mean (SD)	BSA mean (SD)	DLQI mean (SD)	PGA definition	PGA mean (SD)	Moderate (%)	Moderate/ severe (%)	Severe (%)
	weeks					4(severe)				
	Placebo	61	19 (6.7)	26 (14.7)	NR		NR	62	NR	38
ERASURE[86,87]	Secukinumab 300mg SC ow (week 1-4) followed by every 4 weeks	245	23 (9.2)	33 (19.3)	14 (NR)	Modified investigator's global assessment score. 3=moderate, 4=severe	NR	63	NR	37
	Placebo	248	21 (9.1)	30 (15.9)	12 (NR)		NR	61	NR	39
FEATURE[88,89]	Secukinumab 300mg SC ow (week 1-4) followed by every 4 weeks	59	21 (8.0)	33 (18.0)	NR	IGA mod 2011 score 3=moderate, 4=severe	NR	68	NR	32
	Placebo	59	21 (8.5)	32 (17.4)	NR		NR	58	NR	42
FIXTURE[86]	Secukinumab 300mg SC ow (week 1-4) followed by every 4 weeks	327	24 (9.9)	34 (19.2)	13 (NR)	Modified investigator's global assessment score. 3=moderate, 4=severe	NR	62	NR	38
	Etanercept 50mg SC bid	326	23 (9.8)	34 (18.0)	13 (NR)		NR	60	NR	40
	Placebo	326	24 (10.5)	35 (19.1)	13 (NR)		NR	62	NR	38
Gottlieb 2003[91,92]	Etanercept 25mg SC bid	57	18 (1.1)	30 (2.3)	NR	NR	3 (0.1)	NR	NR	NR
	Placebo	55	20 (1.3)	34 (3.0)	NR		3 (0.1)	NR	NR	NR
Papp 2005[92,95,96]	Etanercept 25mg SC bid	196	19 (8.2)	29 (18.0)	12 (7.2)	NR	NR	NR	NR	NR
	Etanercept 50mg SC bid	194	20 (8.8)	29 (17.2)	11 (6.5)		NR	NR	NR	NR
	Placebo	193	19 (8.6)	27 (17.0)	12 (6.8)		NR	NR	NR	NR
CRYSTEL[103,104]	Etanercept 25mg SC bid	352	22 (10.3)	37 (21.9)	13 (7.3)	Marked or severe psoriasis assessed by physician (patients, %) PGA score 4 or 5	4 (0.7)	NR	52	NR
	Etanercept 50mg SC bid	359	23 (10.3)	40 (23.7)	14 (7.3)		4 (0.7)	NR	54	NR
Leonardi 2003[92-94]	Etanercept 25mg SC bid	160	18 (0.7)	28 (1.5)	12 (0.5)	IGA 0-5. Moderate-severe defined as 4-5	NR	NR	21	NR
	Etanercept 25mg SC bid	162	19 (0.7)	29 (1.6)	13 (0.5)		NR	NR	23	NR
	Etanercept 50mg SC bid	164	18 (0.7)	30 (1.6)	11 (0.5)		NR	NR	21	NR
	Placebo	166	18 (0.6)	29 (1.4)	13 (0.6)		NR	NR	23	NR
Tyring 2006[115,116]	Etanercept 50mg SC bid	311	18 (7.6)	27 (18.2)	12 (6.7)	NR	NR	NR	NR	NR
	Placebo	307	18 (7.4)	27 (17.2)	13 (6.7)		NR	NR	NR	NR
Strober 2011[110]	Etanercept 50mg SC bid	139	19 (6.0)	25 (13.9)	NR	Physician global	NR	50	NR	45

Trial name	Treatment name	ITT	PASI mean (SD)	BSA mean (SD)	DLQI mean (SD)	PGA definition	PGA mean (SD)	Moderate (%)	Moderate/ severe (%)	Severe (%)
	Placebo	72	18 (6.4)	22 (13.4)	NR	assessment moderate, severe, very severe	NR	47	NR	49
Bagel 2012[108]	Etanercept 50mg SC bid	62	16§ (NR)	16§ (NR)	NR	NR	NR	NR	NR	NR
	Placebo	62	15§ (NR)	15§ (NR)	NR		NR	NR	NR	NR
Gottlieb 2011[109]	Etanercept 50mg SC bid	141	19 (8.0)	24 (15.0)	NR	Physician global assessment moderate, severe, very severe	NR	51	NR	43
	Placebo	68	19 (6.9)	24 (15.5)	NR		NR	62	NR	35
PRESTA[101,102]	Etanercept 50mg BIW	314	20 (11.0)	31 (22.0)	12 (7.5)	NR	4 (0.7)	NR	NR	NR
	Etanercept 50mg QW	207	19 (10.0)	30 (22.0)	12 (7.5)		4 (0.7)	NR	NR	NR
Bachelez 2015[106,107]	Etanercept 50mg SC bid	335	19§ (NR)	25§ (NR)	12§ (NR)	PGA moderate, severe	NR	81	NR	18
	Placebo	107	20§ (NR)	26§ (NR)	12§ (NR)		NR	82	NR	15
UNCOVER - 2[111-113]	Etanercept 50mg SC bid	358	19 (7.0)	25 (16.0)	13 (7.0)	Static physicians global assessment	NR	NR	NR	48
	Ixekizumab biw	351	19 (7.0)	25 (16.0)	12 (7.0)		NR	NR	NR	49
	Ixekizumab every four weeks	347	20 (7.0)	27 (17.0)	12 (7.0)		NR	NR	NR	52
	Placebo	168	21 (8.0)	27 (18.0)	13 (7.0)		NR	NR	NR	49
UNCOVER - 3[111,114]	Etanercept 50mg SC bid	382	21 (8.0)	28 (17.0)	12 (7.0)	Static physicians global assessment	NR	NR	NR	50
	Ixekizumab biw	385	21 (8.0)	28 (17.0)	12 (7.0)		NR	NR	NR	46
	Ixekizumab every four weeks	386	21 (8.0)	28 (16.0)	12 (7.0)		NR	NR	NR	52
	Placebo	193	21 (8.0)	29 (17.0)	13 (7.0)		NR	NR	NR	46
PRISTINE[97,98]	Etanercept 50mg SC bid	137	21 (9.4)	33 (21.1)	15 (8.0)	NR	3 (0.8)	NR	NR	NR
	Etanercept 50mg SC bid	136	21 (9.4)	33 (19.4)	14 (7.3)		3 (0.7)	NR	NR	NR
Van de Kerkhof 2008[99,100]	Etanercept 50mg SC bid	96	21 (9.3)	27 (15.0)	13 (NR)	PGA marked (4) or severe(5)	NR	NR	55	NR
	Placebo	46	21 (8.7)	30 (17.8)	14 (NR)		NR	NR	46	NR
Asahina 2010[78]	Adalimumab 40mg SC eow	38	25 (9.0)	43 (19.4)	8 (NR)	Physician's Global Assessment	4 (0.6)	24	NR	76
	Adalimumab + loading dose 40mg SC eow - 80mg at week 0	43	30 (10.9)	48 (19.6)	9 (NR)		4 (0.7)	19	NR	81
	Placebo	46	29 (11.8)	47 (20.0)	8 (NR)		4 (0.7)	28	NR	72
X-PLORE[81]	Adalimumab 40mg SC eow - 80mg at week 0	43	20 (7.6)	27 (16.8)	NR	PGA 3=moderate, 4=marked, 5=severe	NR	56	NR	9

Trial name	Treatment name	ITT	PASI mean (SD)	BSA mean (SD)	DLQI mean (SD)	PGA definition	PGA mean (SD)	Moderate (%)	Moderate/ severe (%)	Severe (%)
	Placebo	42	22 (10.0)	28 (19.3)	NR		NR	52	NR	5
PHOENIX 2[122-124]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks	409	19 (6.8)	26 (15.5)	12 (7.1)	PGA marked (4) or severe(5)	NR	NR	41	NR
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks	411	20 (7.5)	27 (17.4)	13 (7.3)		NR	NR	39	NR
	Placebo	410	19 (7.5)	26 (17.4)	12 (6.9)		NR	NR	39	NR
PHOENIX 1[120,121]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks	255	21 (8.6)	27 (17.5)	11 (7.1)	PGA moderate (3) marked (4) or severe(5)	NR	49	93	6
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks	256	20 (7.6)	25 (15.0)	12 (6.9)		NR	52	95	5
	Placebo	255	20 (8.6)	28 (17.4)	12 (7.4)		NR	51	95	4
ACCEPT[105]	Etanercept	347	19 (6.2)	24 (13.9)	NR	NR	NR	NR	NR	NR
	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks	209	21 (9.2)	27 (17.8)	NR		NR	NR	NR	NR
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks	347	20 (8.4)	26 (17.6)	NR		NR	NR	NR	NR
LOTUS[117]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks	162	23 (9.5)	35 (18.5)	NR	NR	NR	NR	NR	NR
	Placebo	160	23 (9.5)	35 (19.6)	NR		NR	NR	NR	NR
The Japanese Ustekinumab Study Group[125,126]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks	64	30 (12.9)	47 (23.7)	11 (6.5)	PGA: 0=clear, 1=minimal;, 2=mild, 3=marked, 4=severe	4 (0.6)	NR	NR	NR
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks	62	29 (11.2)	47 (19.7)	11 (6.4)		4 (0.8)	NR	NR	NR
	Placebo	32	30 (11.8)	50 (22.5)	10 (6.2)		3 (0.6)	NR	NR	NR
PEARL[118,119]	Ustekinumab 45mg SC weeks 0, 4, 16	61	25 (11.9)	42 (24.4)	16 (6.1)	PGA >= 4 marked or severe	NR	NR	26	NR
	Placebo	60	23 (8.6)	36 (21.4)	15 (7.0)		NR	NR	33	NR
CLEAR[82-85]	Secukinumab 300mg SC ow (weeks 1-4) followed by 4-weekly	337	22 (8.5)	33 (17.8)	13 (7.6)	IGA mod 2011 score 4 (severe disease)	NR	61	NR	39
	Ustekinumab 45mg (<100kg) - 90mg (>100kg) SC weeks 0,4, every 12 weeks	339	22 (8.1)	32 (16.8)	13 (7.6)		NR	63	NR	37
AMAGINE-2[127,128]	Ustekinumab 45mg (<100kg) - 90mg (>100kg) SC	300	20 (8.2)	27 (19.0)	NR	Static physicians global assessment	NR	51	NR	44
	Placebo	309	20 (8.4)	28 (17.0)	NR		NR	54	NR	39

Trial name	Treatment name	ITT	PASI mean (SD)	BSA mean (SD)	DLQI mean (SD)	PGA definition	PGA mean (SD)	Moderate (%)	Moderate/ severe (%)	Severe (%)
AMAGINE-3[128,129]	Ustekinumab 45mg (<100kg) - 90mg (>100kg) SC	313	20 (8.4	28 (18.0)	NR	Static physicians global assessment	NR	61	NR	33
	Placebo	315	20 (8.7)	28 (17.0)	NR		NR	61	NR	36
UNCOVER-1[130,131]	Ixekizumab 80mg SC every 2 weeks	433	20 (8.0)	28 (18.0)	NR	Static-PGA	NR	NR	NR	47
	Ixekizumab 80 mg SC every 4 weeks	432	20 (7.0)	27 (16.0)	NR		NR	NR	NR	54
	Placebo	431	20 (9.0)	27 (18.0)	NR		NR	NR	NR	53
LIBERATE[72-76]	Apremilast 30mg oral	83	19 (7.0)	27 (15.6)	14 (6.7)		NR	NR	NR	21
	Etanercept 50 mg SC	83	20 (7.9)	28 (15.7)	13 (7.0)	Static-PGA	NR	NR	NR	16
	Placebo	84	19 (6.8)	27 (16.1)	11 (6.3)		NR	NR	NR	27
Papp 2012[70,71]	Apremilast 30mg oral bid	88	19 (7.1)	31 (7.7)	11 (6.2)	NR	NR	NR	NR	NR
	Placebo	88	18 (5.7)	31 (6.7)	11 (6.7)		NR	NR	NR	NR
ESTEEM 1[61-65]	Apremilast 30mg oral bid	562	19 (7.2)	24 (14.7)	13 (7.1)	Static physicians global assessment	NR	71	NR	29
	Placebo	282	19 (7.4)	25 (14.6)	12 (6.7)		NR	68	NR	32
ESTEEM 2[61-64,66-69]	Apremilast 30mg oral bid	272	19 (7.1)	26 (15.4)	13 (7.1)	Static physicians global assessment	NR	NR	NR	27
	Placebo	136	20 (8.0)	28 (15.8)	13 (7.1)		NR	NR	NR	36
Ohtsuki 2016[77]	Apremilast 20 mg twice a day	85	NR	NR	NR	NR	NR	NR	NR	NR
	Apremilast 30 mg twice a day	85	NR	NR	NR		NR	NR	NR	NR
	Placebo	84	NR	NR	NR		NR	NR	NR	NR

1. § median; †calculated| bid: twice a day; biw; biweekly; BSA: body surface area; DLQI: dermatology life quality index; eow: every other week; IGA: Investigator global assessment; ITT: intention to treat; IV: intravenous; od: once daily; ow: once weekly; PASI: psoriasis area and severity index; PGA: physician global assessment

*BRIDGE subgroup consists of patients experienced with prior systemic therapies or PUVA.

Differences in patient populations of trials included in the NMA

A key consideration for any NMA is whether the studies identified are suitably homogenous to facilitate a reliable comparison. This similarity comparison is achieved by comparing selected data from candidate studies (with covariates that act as treatment effect modifiers needing to be similar across trials).

All 37 trials were assessed for comparability in age, sex, duration of psoriasis, disease severity at baseline (PASI and BSA), comorbidity of psoriatic arthritis, race, prior use of systemic therapy and DLQI score at baseline. These characteristics were selected as potential treatment effect modifiers given that imbalances across the studies could introduce bias.

Age at baseline is presented in Figure 17 with values ranging from 41 to 48 years and no imbalances across studies.

Figure 17. Age at baseline

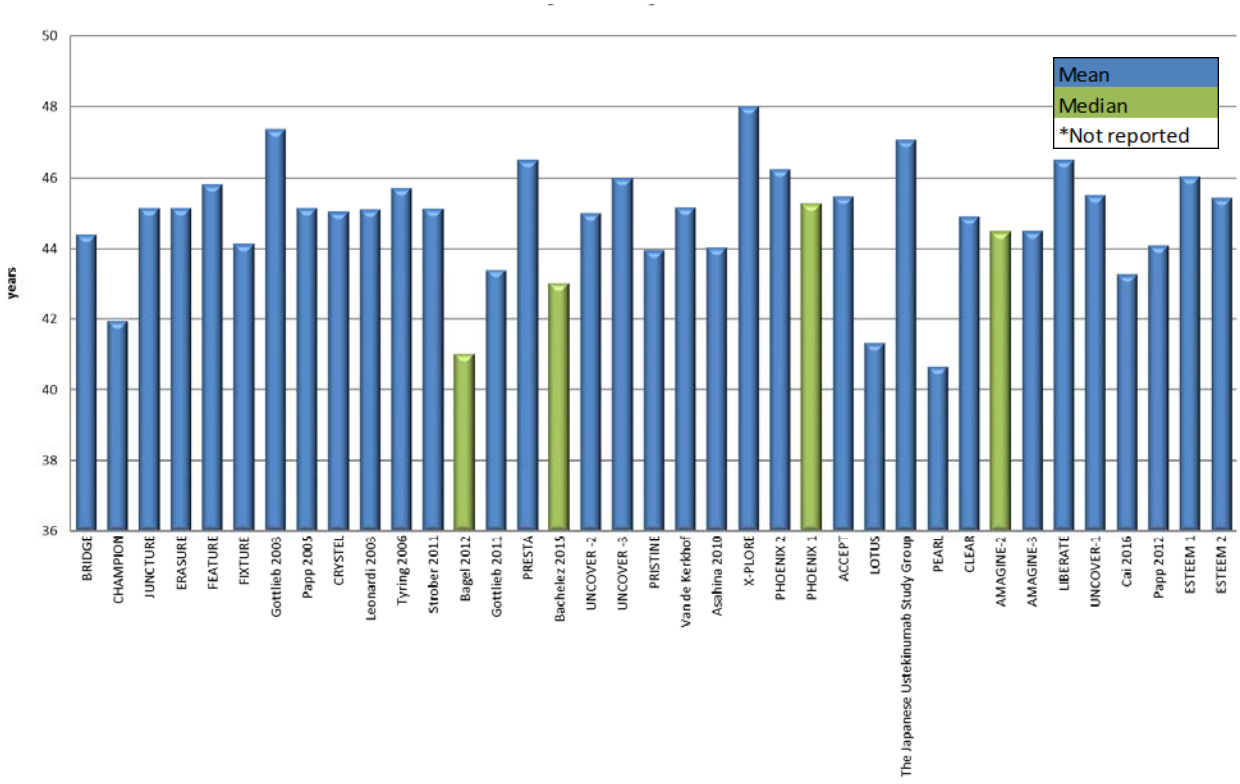
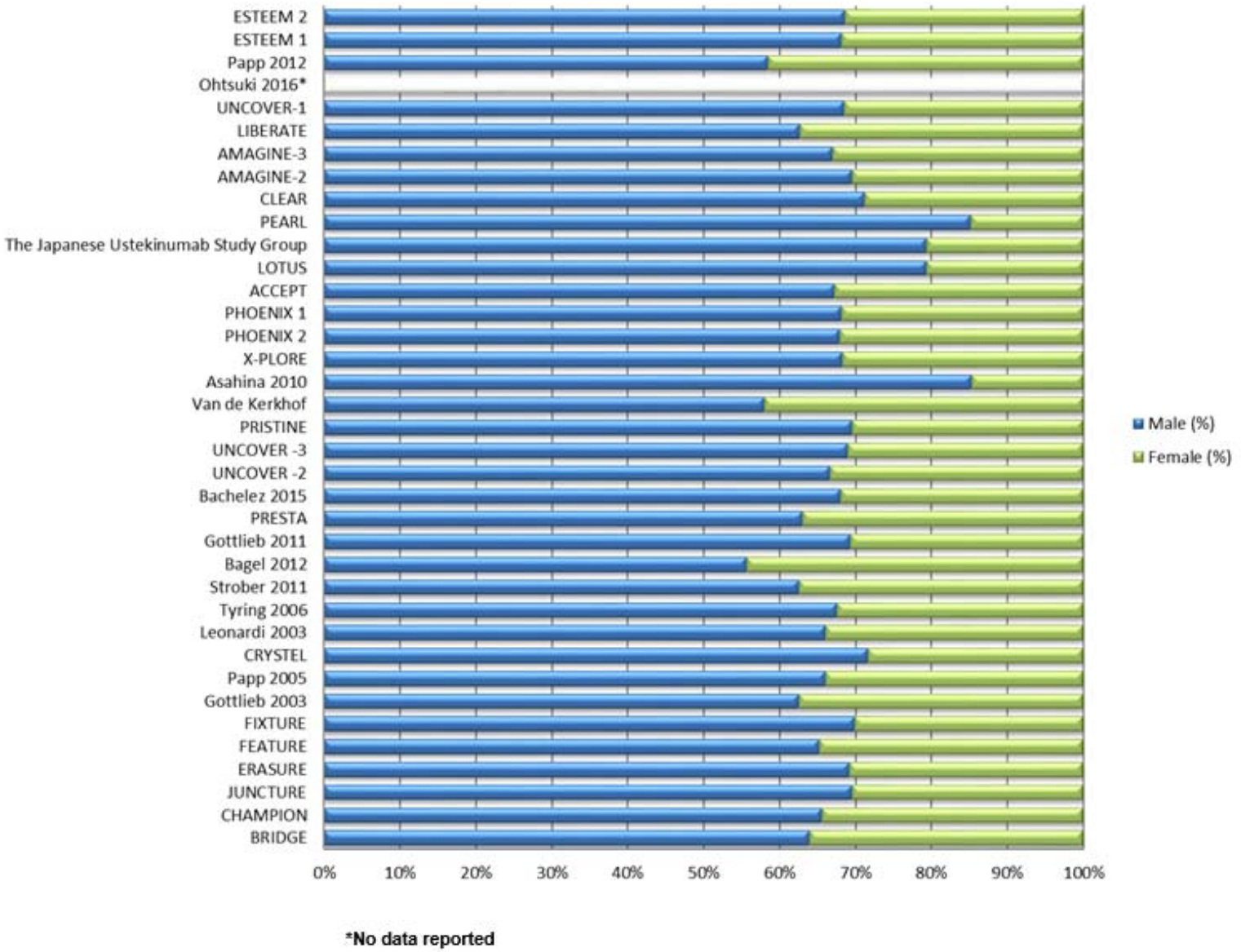


Figure 18 shows the percentage of males and females for all studies. Even though all studies reported a higher proportion of males when comparing the percentage of males across the studies, there was a high homogeneity with most trials including 60-70% of male patients (Figure 18). Therefore, the variation in male and female proportion was assumed to have no impact on study results overall.

Figure 18. Gender



*No data reported

Figure 19 shows the duration of psoriasis at baseline for each study. In the BRIDGE trial patients were required to have a diagnosis of plaque psoriasis for at least 12 months before enrolment and in the Ohtsuki 2016[77] trial at least 6 months, however for both trials no mean baseline values were reported. Disease duration varied from 13-22 years and no apparent variation is shown in the distribution of this characteristic.

Figure 19. Duration of psoriasis at baseline

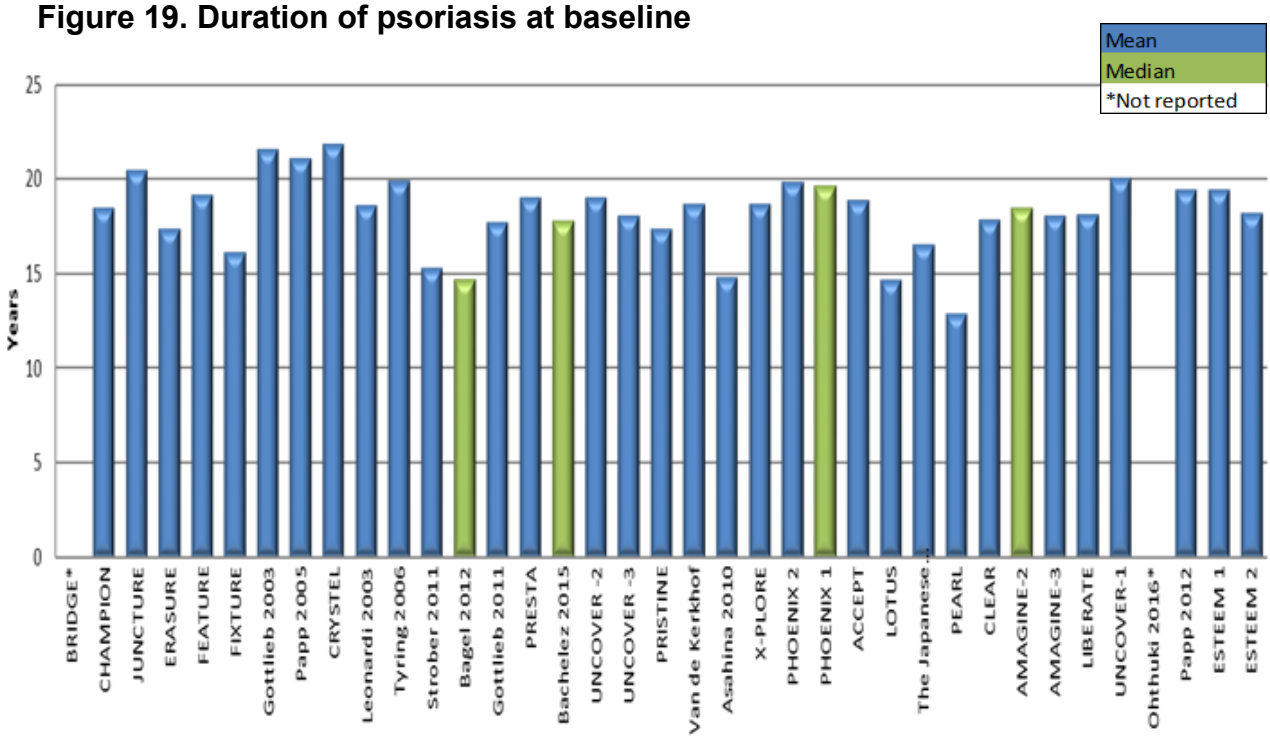


Figure 20 shows the comorbidity of psoriatic arthritis which ranged between 8% to 34% in the majority of trials.

Figure 20. Comorbidity of psoriatic arthritis

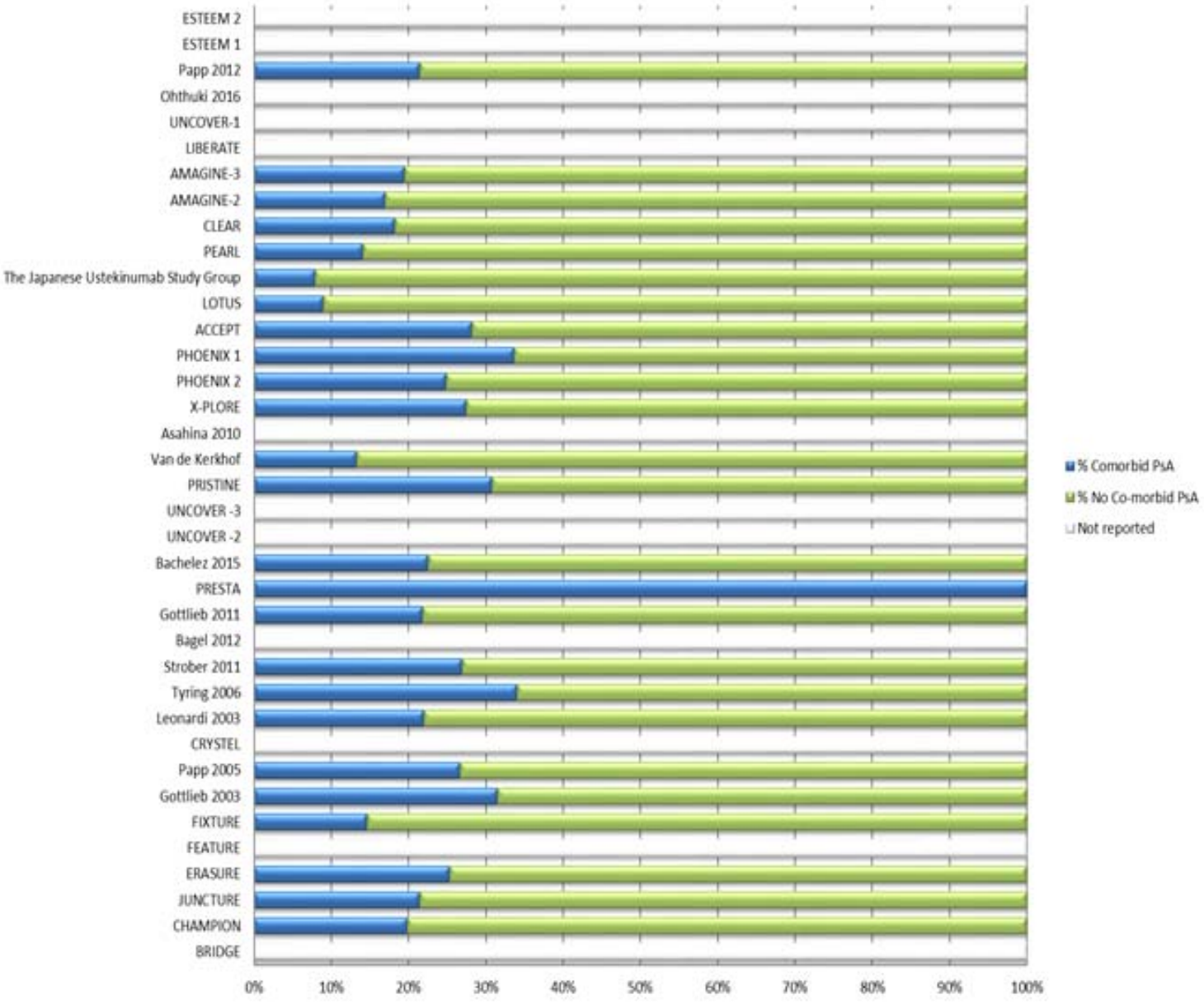


Figure 21 shows the distribution of race in each trial. In most trials the majority of the population is Caucasian. However, in four trials 100% of the population is Asian.[68,69,77,117,125,126]

Figure 21. Race

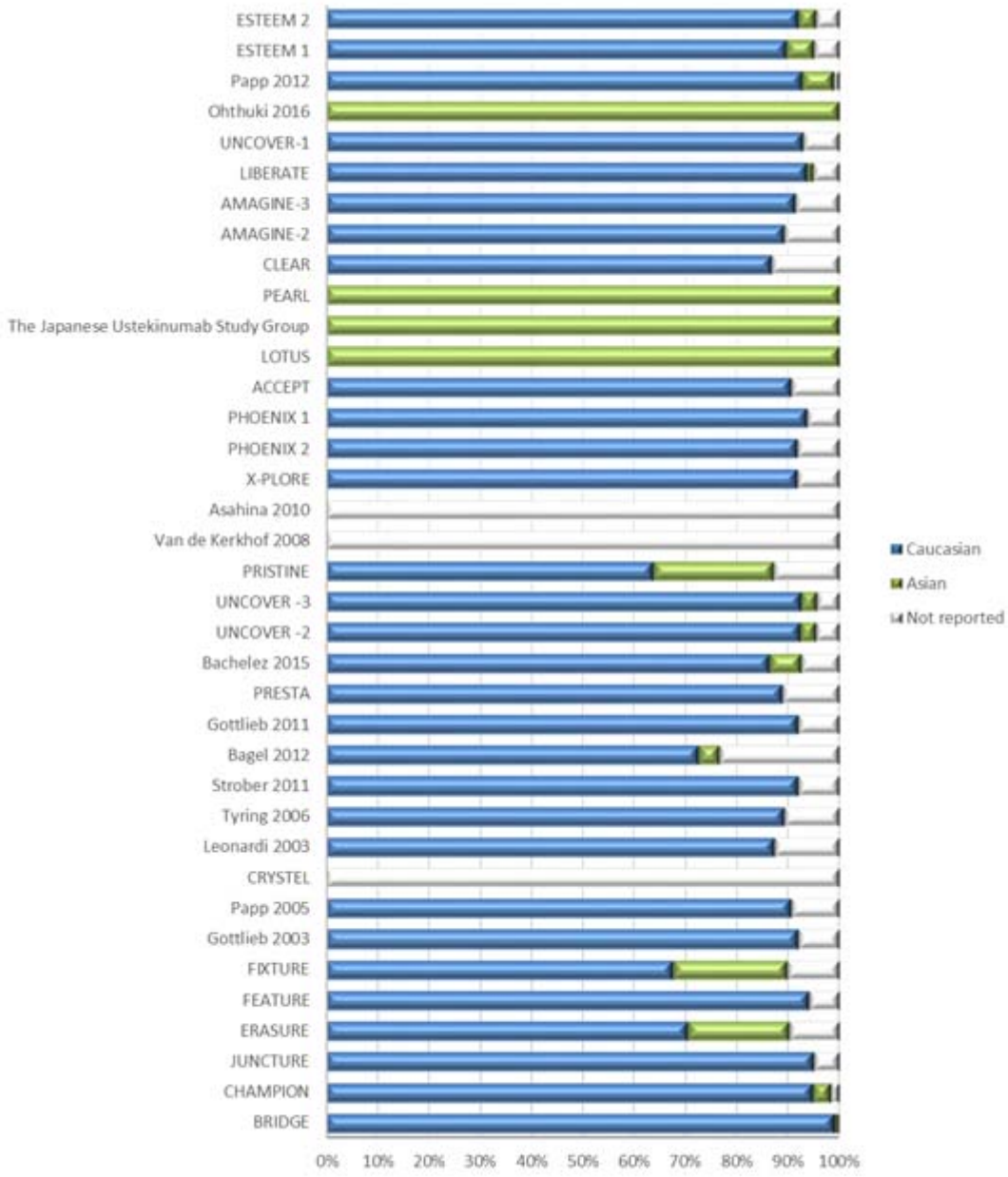
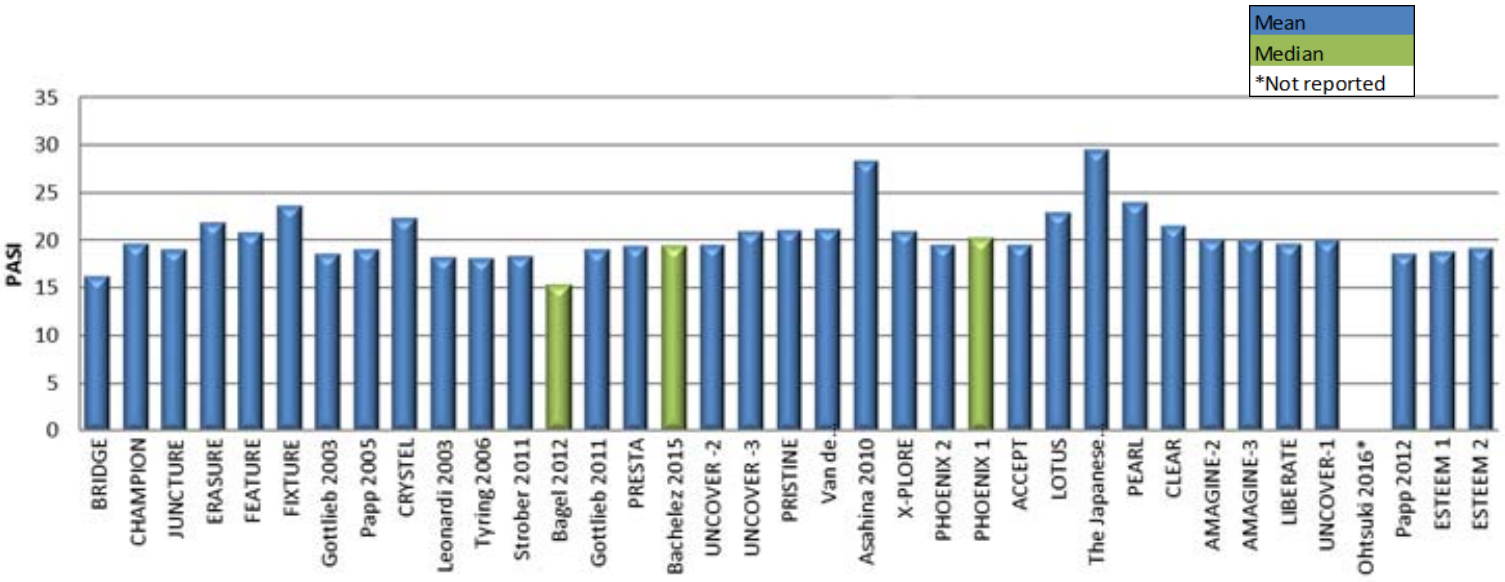


Figure 22 shows the PASI score at baseline. PASI scores at baseline varied from 15 to 30.

Figure 22. PASI at baseline



For all other possible effect modifiers not enough data were available to draw strong conclusions. The assumption was made that these would not impact on the outcomes of the NMA and, therefore, no additional scenarios based on the description of the characteristics at baseline were planned.

In summary, on inspection of the baseline characteristics across the included studies, no major imbalances which would impact on the outcomes of the NMA were noted.

Study quality assessment

Additionally, the NICE critical appraisal tool was used for each trial in order to assess the risk of bias.[178]

Ohtsuki 2016[77] was the only trial with an unclear or high risk of bias for all 7 questions, thus a scenario analysis was conducted excluding this study (see Scenario excluding Ohtsuki 2016 at 16 weeks and

Scenario excluding Ohtsuki 2016 at induction *time*). Appendix 7 shows a full assessment of each study.

Summary of planned analyses

Results will be reported based on the preferred multinomial model (probit link) which takes into account that the treatment effect is the same regardless of the cut-off. This model is suggested in the NICE DSU Technical Support Document 2[179] for PASI outcomes. The model pools the outcomes of PASI50, PASI75 and PASI90 at 16 weeks and induction time. The input-data is reported separately per PASI outcome in the data-availability tables. Since the PASI50, PASI75 and PASI90 are pooled together in the multinomial, the generic term for these outcomes of *PASI response is used*

Based on the assessment presented above, the NMA was deemed feasible and the following analyses were performed:

- Primary analyses:
    - PASI response at 16 weeks, and
    - PASI response at induction time

Induction time is the time point at which the primary endpoint was measured in the pivotal studies for each medicine mentioned: 12 weeks for secukinumab, etanercept, ustekinumab, and ixekizumab and 16 weeks for adalimumab, apremilast, Fumaderm and DMF (LAS41008).

The following scenario was defined and performed for the primary analyses:

- Exclusion of Ohtsuki 2016 based on quality appraisal.

In addition, one subgroup analysis for patients experienced with prior systemic therapies or PUVA in the network and for which a NICE recommendation is sought was conducted

This only included the subgroup data from the DMF (LAS41008) and Fumaderm of the BRIDGE trial. For all other trials, overall data was used due to lack of availability of this subgroup data.

Summary of trials included in the NMA

Network diagrams for the base-case NMA analysis and the scenario analysis are provided in Figure 23, Table 30 gives an overview of all included studies in the NMA.

Figure 24 shows the network for the scenario analysis excluding Ohtsuki 2016. The network for the subgroup analysis is the same as Figure 23.

A summary of the study design of each of the trials which were included in the base-case can be seen Table 31.

Figure 23. Network diagram for the NMA base case analysis

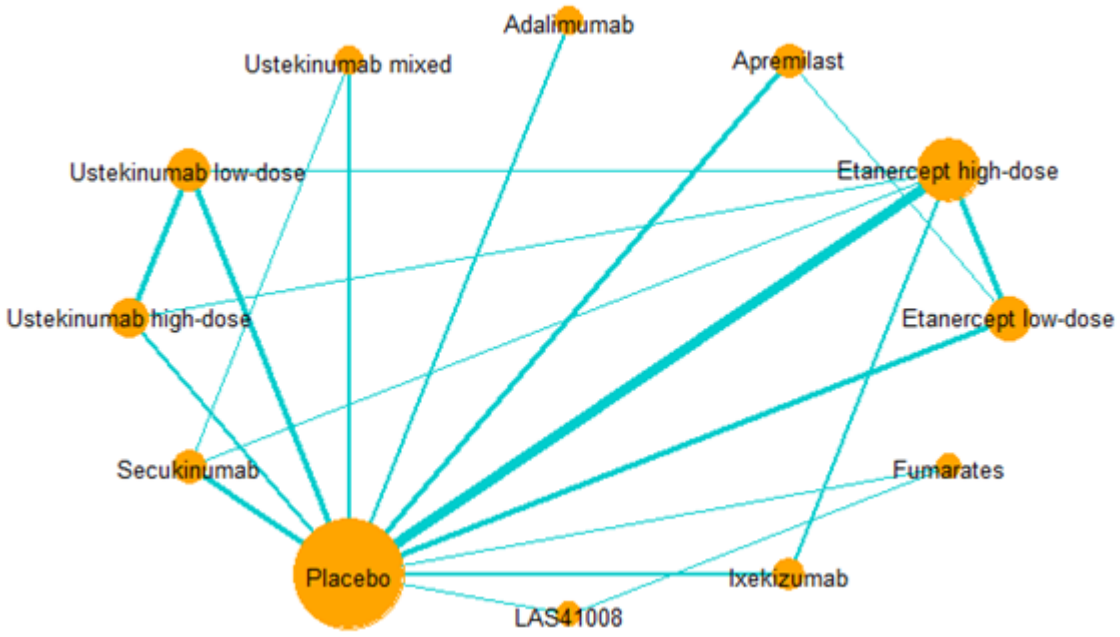


Table 30. Trials included in the evidence base

Trial name	Comparison
BRIDGE (subgroup*)[23,51,58-60]	LAS41008 vs Fumaderm vs Placebo
CHAMPION[79,80]	Adalimumab vs Placebo
JUNCTURE [89,90]	Secukinumab vs Placebo
ERASURE[86,87]	Secukinumab vs Placebo
FEATURE[88,89]	Secukinumab vs Placebo
FIXTURE[86]	Secukinumab vs Etanercept high-dose vs Placebo
Gottlieb 2003[91,92]	Etanercept low-dose vs Placebo
Papp 2005[92,95,96]	Etanercept low-dose vs Etanercept high-dose vs Placebo
CRYSTEL[103,104]	Etanercept low-dose vs Etanercept high-dose
Leonardi 2003[92-94]	Etanercept low-dose vs Etanercept high-dose vs Placebo

Tyring 2006[115,116]	Etanercept high-dose vs Placebo
Strober 2011[110]	Etanercept high-dose vs Placebo
Bagel 2012[108]	Etanercept high-dose vs Placebo
Gottlieb 2011[109]	Etanercept high-dose vs Placebo
PRESTA[101,102]	Etanercept high-dose vs Placebo
Bachelez 2015[106,107]	Etanercept high-dose vs Placebo
PRISTINE[82,83]	Etanercept low-dose vs Etanercept 50 biw
Van de Kerkhof 2008[99,100]	Etanercept low-dose vs Placebo
UNCOVER-2[111-113]	Etanercept high-dose vs Ixekizumab vs.Placebo
UNCOVER-3[111,114]	Etanercept high-dose vs Ixekizumab vs Placebo
UNCOVER-1[130,131]	Ixekizumab 80 mg vs Placebo
Asahina 2010[78]	Adalimumab vs Placebo
X-PLORE[81]	Adalimumab vs Placebo
PHOENIX 2[122-124]	Ustekinumab 45 mg vs Ustekinumab 90 mg vs Placebo
PHOENIX 1[120,121]	Ustekinumab 45 mg vs Ustekinumab 90 mg vs Placebo
ACCEPT[105]	Ustekinumab 45 mg vs Ustekinumab 90 mg vs. Etanercept high-dose
LOTUS[117]	Ustekinumab 45 mg vs Placebo mg
The Japanese Ustekinumab Study Group[125,126]	Ustekinumab 45 mg vs Ustekinumab 90 mg vs Placebo
PEARL[118,119]	Ustekinumab 45 mg vs Placebo
AMAGINE-2[127,128]	Ustekinumab 45/90 mg vs Placebo
AMAGINE-3[128,129]	Ustekinumab 45/90 mg vs Placebo
CLEAR[82,84,85]	Secukinumab vs Ustekinumab 45/90 mg
Papp 2012[70,71]	Apremilast 30 mg vs Placebo
ESTEEM 2[61-64,66-69]	Apremilast 30 mg vs Placebo
ESTEEM 1[61-65]	Apremilast 30 mg vs Placebo
Ohtsuki 2016†[77]	Apremilast 30 mg vs Placebo
LIBERATE[72-76]	Apremilast 30 mg vs Etanercept 50 mg eow vs Placebo

b.i.w, biweekly; eow, every other week

*BRIDGE subgroup consists of patients who have had prior systemic therapies or PUVA

† Excluded in a scenario analysis

Figure 24. Network of the scenario analysis excluding Ohtsuki 2016

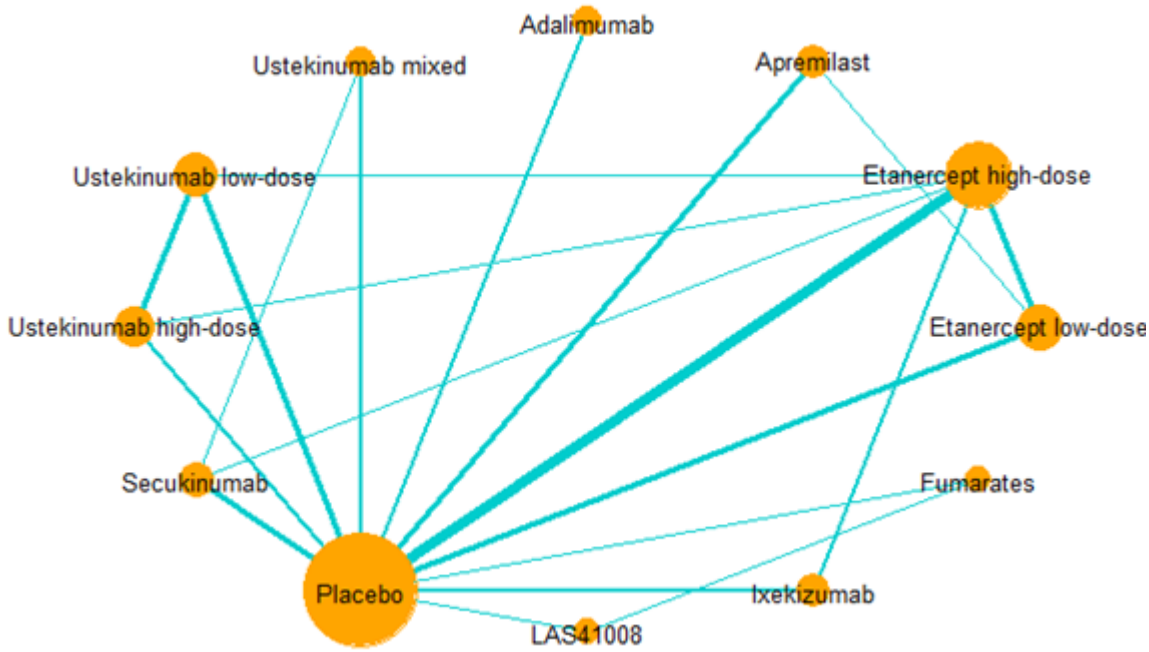


Table 31. Summary of trials used to conduct the base case NMA

Trial name	Treatment name	Study design	RCT duration	Primary endpoint	Main psoriasis inclusion criteria	Main prior treatment criteria
BRIDGE[23,51,58-60]	DMF (LAS41008) 30-720 mg oral Fumaderm 30-720 mg oral Placebo	RCT Phase 3 DB MC	16 Weeks	PASI75 and PGA0-1 at 16 weeks	Patients with moderate to severe chronic plaque psoriasis. PASI > 10, BSA>10, PGA moderate-severe	Prior therapy with systemic drugs for psoriasis that was discontinued e.g. due to an adverse event (AE) or insufficient effect, or naïve to systemic treatment but identified as a candidate for systemic treatment,
CHAMPION[79,80]	Adalimumab 40 mg SC eow – 80 mg at week 0 Methotrexate 7.5 to 5 mg oral ow Placebo	RCT Phase 3 DB MC	16 Weeks	PASI75 at week 16	Moderate-to-severe psoriasis, PASI≥10, BSA ≥10%	Patients were to have been candidates for systemic therapy or phototherapy and to have had active psoriasis despite treatment with topical agents. All patients were to have been naive to both TNF-antagonist therapy and methotrexate.
JUNCTURE[89,90]	Secukinumab 300 mg SC ow (week 1-4) followed by every 4 weeks Placebo	RCT Phase 3 DB MC	52 Weeks	PASI75 at week 12 PGA 0/1	Patients with moderate to severe plaque psoriasis. PASI ≥12. and IGA 3 (moderate) or 4 (severe)	Psoriasis poorly controlled by topical treatments, phototherapy, and/or previous systemic therapy.
ERASURE[86,87]	Secukinumab 300 mg SC ow (week 1-4) followed by every 4 weeks Placebo	RCT Phase 3 DB MC	52 Weeks	PGA 0/1 at week 12 PASI75 at week 12	Moderate-severe plaque psoriasis; BSA ≥10%, PASI ≥12	Psoriasis that was poorly controlled with topical treatments, phototherapy, systemic therapy, or a combination of these therapies
FEATURE[88,89]	Secukinumab 300 mg SC ow (week 1-4) followed by every 4 weeks Placebo	RCT Phase 3 DB MC	52 Weeks	PASI75 at week 12 IGA 0-1 at week 12	Moderate-severe plaque psoriasis; BSA ≥10%, PASI ≥12, PGA ≥3	Psoriasis inadequately controlled by topical treatments, phototherapy or previous systemic therapy.
FIXTURE[86]	Secukinumab 300 mg SC ow (week 1-4) followed by every 4 weeks Etanercept 50 mg SC bid Placebo	RCT Phase 3 DB MC	52 Weeks	PGA 0/1 at week 12 PASI75 at week 12	Moderate-severe plaque psoriasis; BSA ≥10%, PASI ≥12	Psoriasis that was poorly controlled with topical treatments, phototherapy, systemic therapy, or a combination of these therapies
Gottlieb 2003[91,92]	Etanercept 50 mg SC bid	RCT Phase 2 DB MC	24 Weeks	PASI75 at week 12	Active, stable plaque psoriasis involving 10% or more of BSA	All patients were to have had at least 1 previous systemic psoriasis therapy

Trial name	Treatment name	Study design	RCT duration	Primary endpoint	Main psoriasis inclusion criteria	Main prior treatment criteria
	Placebo					or phototherapy (such as methoxsalen plus UV-A, UV-B, oral retinoid, cyclosporine, or methotrexate).
Papp 2005[92,95,96]	Etanercept 25 mg SC bid Etanercept 50 mg SC bid Placebo	RCT Phase 3 DB MC	24 Weeks	PASI75 at week 12	Clinically stable, plaque psoriasis involving ≥10% BSA at screening	Patients were to have received at least one previous phototherapy or systemic therapy for psoriasis (or to have been a candidate to do so in the opinion of the investigator)
CRYSTEL[103,104]	Etanercept 25 mg SC bid Etanercept 50 mg SC bid	RCT OL MC	54 Weeks	PGA and PASI CFB at 54 weeks, CFB in Patient Satisfaction Survey	Active but clinically stable plaque psoriasis, BSA ≥10%, PGA ≥3	Patients had failed to respond to, or had a contraindication to or intolerance of, methotrexate, cyclosporin, psoralen plus UVA radiation (PUVA), or fumarates (where approved for psoriasis)
Leonardi 2003[92-94]	Etanercept 25mg SC bid Etanercept 25 mg SC bid Etanercept 50 mg SC bid Placebo	RCT Phase 3 DB MC	24 Weeks	PASI75 at week 12	Active but clinically stable plaque psoriasis ≥10% BSA and ≥10 PASI	Patients had previously received phototherapy or systemic psoriasis therapy at least once or been candidate for such therapy.
Tyring 2006[115,116]	Etanercept 50 mg SC bid Placebo	RCT DB MC	12 Weeks	PASI75 at week 12	Active but clinically stable plaque psoriasis ≥10% BSA and ≥10 PASI	Patients were required to have received at least one previous phototherapy or systemic therapy (or have been a candidate to do so in the opinion of the investigator).
Strober 2011[110]	Etanercept 50 mg SC bid Placebo	RCT Phase 3 DB MC	12 Weeks	PGA 0/1 at week 12 PASI75 at week 12	Chronic plaque psoriasis (≥ 6 months), stable for at least 2 months, ≥10% BSA, PGA≥3, PASI≥12.	NR
Bagel 2012[108]	Etanercept 50 mg SC bid Placebo	RCT DB MC	24 Weeks	PASI at 12 weeks	Stable moderate-severe plaque psoriasis covering ≥10% BSA and ≥10 PASI and 30%+ SSA affected with PSSI scores of 15 or higher.	Investigators considered patients candidates for phototherapy or systemic therapy.
Gottlieb 2011[109]	Etanercept 50 mg SC bid Placebo	RCT Phase 3 DB MC	12 Weeks	PGA 0/1 at week 12 PASI75 at week 12	Chronic plaque psoriasis for at least 6 months; stable plaque psoriasis for at least 2 months; BSA ≥10%, PGA ≥3, PASI ≥12	NR

Trial name	Treatment name	Study design	RCT duration	Primary endpoint	Main psoriasis inclusion criteria	Main prior treatment criteria
PRESTA[101,102]	Etanercept 50 mg BIW Etanercept 50 mg QW	RCT DB MC	24 Weeks	PGA 0/1 at week 12	Clinical stable plaque psoriasis; BSA ≥10%, PGA moderate-severe	Prohibited treatments included all forms of UVA+B within 28/14 days prior to baseline. Participants were not to have received systemic psoriasis treatment, ciclosporin or DMARDs within 28 days before starting, vit A or D. Use of any TNF-i at any time before enrolment was not permitted.
Bachelez 2015[106,107]	Etanercept 50 mg SC bid Placebo	RCT Phase 3 DB MC	12 Weeks	PASI75 at week 12 PGA 0/1 at week 12	Chronic (≥12 months) stable plaque psoriasis. BSA ≥10%, PASI ≥12.	Patients were candidates for systemic or phototherapy
UNCOVER-2[111-113]	Etanercept 50 mg SC bid Ixekizumab biw Ixekizumab every four weeks Placebo	RCT Phase 3 DB MC	12 Weeks	PASI75 at week 12 sPGA 0/1	Chronic plaque psoriasis at least 6 months before baseline. PASI≥12, BSA ≥10%, PGA 3+	Patients were candidates for phototherapy, systemic therapy, or both
UNCOVER-3[111, 114]	Etanercept 50 mg SC bid Ixekizumab biw Ixekizumab every four weeks Placebo	RCT Phase 3 DB MC	12 Weeks	PASI75 at week 12 sPGA 0/1	Chronic plaque psoriasis at least 6 months before baseline. PASI≥12, BSA ≥10%, PGA 3+	Patients were candidates for phototherapy, systemic therapy, or both
PRISTINE[97,98]	Etanercept 50 mg SC bid Etanercept 50 mg SC bid	RCT Phase 4 DB MC	24 Weeks	PASI75 at week 24	Chronic plaque psoriasis involving ≥10% BSA and ≥10 PASI	Patients failed, were intolerant of, had a contraindication for or otherwise were not candidates for one of the following: MTX, ciclosporin, PUVA.
Van de Kerkhof 2008[99,100]	Etanercept 50 mg SC bid Placebo	RCT Phase 3 DB MC	24 Weeks	PASI75 at week 12	Clinically stable plaque psoriasis; BSA ≥10%, PASI ≥12. Patients had failed to respond to, had a contra-indication for, or were intolerant of at least one systemic or phototherapy at any adequate dose of sufficient duration.	Patients had failed to respond to, had a contra-indication for, or were intolerant of at least one systemic or phototherapy at any adequate dose of sufficient duration.
Asahina 2010[78]	Adalimumab 40 mg SC eow Adalimumab + loading dose 40 mg SC eow – 80 mg at week 0	RCT Phase	24	PASI75	Moderate to severe chronic plaque	Patients were excluded if

Trial name	Treatment name	Study design	RCT duration	Primary endpoint	Main psoriasis inclusion criteria	Main prior treatment criteria
	Placebo	II/III DB MC	Weeks		psoriasis	they had been previously exposed to anti-TNF therapy
X-PLORE[81]	Adalimumab 40 mg SC eow – 80 mg at week 0 Placebo	RCT Phase 2 DB MC	40 Weeks	PGA 0/1 at week 16	Moderate to severe plaque psoriasis for 6 months or longer. BSA ≥10%, PASI ≥12, PGA ≥3	Patients could have received previous systemic treatment or phototherapy but were excluded if they had been previously exposed to adalimumab or guselkumab
PHOENIX 2[122-124]	Ustekinumab 45 mg SC weeks 0, 4 and every 12 weeks Ustekinumab 90 mg SC weeks 0, 4 and every 12 weeks Placebo	RCT Phase 3 DB MC	52 Weeks	PASI75 at week 12	Plaque psoriasis for at least 6 months, BSA ≥10%, PASI ≥12	Patients were candidates for phototherapy or systemic therapy.
PHOENIX 1[120, 121]	Ustekinumab 45 mg SC weeks 0, 4 and every 12 weeks Ustekinumab 90 mg SC weeks 0, 4 and every 12 weeks Placebo	RCT Phase 3 DB MC	40 Weeks	PASI75 at week 12	Plaque psoriasis for at least 6 months, BSA ≥10%, PASI ≥12	Patients were candidates for phototherapy or systemic therapy.
ACCEPT[105]	Etanercept Ustekinumab 45 mg SC weeks 0, 4 and every 12 weeks Ustekinumab 90 mg SC weeks 0, 4 and every 12 weeks	RCT Phase 3 OL MC	44 Weeks	PASI75 at week 12	Who had received a diagnosis of plaque psoriasis at least 6 months earlier	Patients were candidates for phototherapy or systemic therapy.
LOTUS[117]	Ustekinumab 45 mg SC weeks 0, 4 and every 12 weeks Placebo	RCT Phase 3 DB MC	28 Weeks	PASI75 at week 12	Plaque type psoriasis, PASI≥12, BSA ≥10%	NR
The Japanese Ustekinumab Study Group[125,126]	Ustekinumab 45 mg SC weeks 0, 4 and every 12 weeks Ustekinumab 90 mg SC weeks 0, 4 and every 12 weeks Placebo	RCT Phase 2/3 DB MC	64 Weeks	PASI75 at week 12	Moderate-to-severe plaque-type psoriasis at least 6 months prior to study entry, BSA ≥10%, PASI ≥12	Patients were candidates for phototherapy or systemic psoriasis therapy
PEARL[118,119]	Ustekinumab 45 mg SC weeks 0, 4, 16 Placebo	RCT Phase 3 DB MC	16 Weeks	PASI75 at week 12	Moderate-to-severe plaque psoriasis. BSA ≥10%, PASI ≥12	Patients were candidates for systemic or phototherapy
CLEAR[82-85]	Secukinumab 300 mg SC ow (weeks 1-4) followed by 4-weekly Ustekinumab 45 mg (<100kg) - 90mg (>100kg) SC weeks 0,4,	RCT Phase 3 DB MC	52 Weeks	PASI90 at week 16	Moderate-severe plaque psoriasis; BSA ≥10%, PASI ≥12 (same as FIXTURE)	Patients were inadequately controlled by topical treatments, phototherapy, and/or previous systemic therapy

Trial name	Treatment name	Study design	RCT duration	Primary endpoint	Main psoriasis inclusion criteria	Main prior treatment criteria
	every 12 weeks					
AMAGINE-2[127,128]	Ustekinumab 45 mg (<100 kg) – 90 mg (>100 kg) SC Placebo	RCT Phase 3 DB MC	52 Weeks	PASI at week 12 Physician Global Assessment	Moderate to severe plaque psoriasis	NR
AMAGINE-3[128,129]	Ustekinumab 45 mg (<100 kg) – 90 mg (>100 kg) SC Placebo	RCT Phase 3 DB MC	52 Weeks	PASI at week 12 PGA	Moderate to severe plaque psoriasis	NR
UNCOVER-1[130,131]	Ixekizumab 80 mg SC every 2 weeks Ixekizumab 80 mg SC every 4 weeks Placebo	RCT Phase 3 DB MC	12 weeks	PASI75 and PGA 0/1 at week 12	Moderate-severe plaque psoriasis at least 6 months before baseline. PASI≥12, BSA ≥10%, PGA 3+	Candidates for phototherapy or systemic psoriasis therapy
Papp 2012[70,71]	Apremilast 30 mg oral bid Placebo	RCT Phase 2 DB MC	24 Weeks	PASI75 at week 16	Moderate-severe plaque psoriasis; BSA ≥10%, PASI ≥12	Candidates for phototherapy or systemic therapy.
ESTEEM 1[61-65]	Apremilast 30 mg oral bid Placebo	RCT Phase 3 DB MC	52 Weeks	PASI-75 at week 16	PASI≥12, BSA ≥10%, PGA≥3, and were candidates for phototherapy/systemic therapy	Candidates for phototherapy or systemic therapy.
ESTEEM 2[61-64,66-69]	Apremilast 30mg oral bid Placebo	RCT Phase 3 DB	32 Weeks	NR	Moderate to severe psoriasis	Candidates for phototherapy or systemic therapy.
Ohtsuki 2016[77]	Apremilast 20 mg twice a day Apremilast 30 mg twice a day Placebo	RCT, DB	NR	PASI75	Chronic, stable plaque psoriasis for at least 6 months prior to screening as defined by: PASI score ≥ 12 and BSA ≥ 10%	NR
LIBERATE[72-76]	Apremilast 30 mg oral Placebo	RCT, DB	104 Weeks	PASI75	Chronic plaque psoriasis for ≥12 months (PASI score ≥12, BSA ≥10%, PGA score ≥3 [moderate to severe])	Had to have an inadequate response, intolerance, or contraindication to ≥1 conventional systemic agent for treatment of psoriasis

BSA: body surface area; DB: double-blind; eow: every other week; MC: multicenter; OL: open-label; PASI: psoriasis area and severity index; PGA: physician global assessment. RCT: randomised controlled trials; SC: single center; CFB: Change from baseline
*BRIDGE subgroup includes patients who had received prior systemic therapies or PUVA.

NMA methodology

The analyses followed the principles described in the NICE DSU technical support document 2[179] for ordered categorical data. For the PASI score, data were assumed to follow an underlying continuous distribution and were categorized using pre-defined cut-offs (PASI50/PASI75/PASI90). Assuming trial *i* and treatment *j*, where *j* = 0 is placebo/best supportive care, and *j = 1, 2,…,J* are the different therapies, the number of patients who achieved a minimum percentage improvement in PASI compared with the score at baseline were summarized into the following response categories:

- $PASI50_{ij}$ is at least a 50% change.
- $PASI75_{ij}$ is at least a 75% change.
- $PASI90_{ij}$ is at least a 90% change.

In order to make efficient use of the data, a coherent model that assumes the treatment effect is the same regardless of the cut-off was used.[179] The model also accounted for the fact that patients move from one category to the next in each trial, by using a multi-categorical response variable to analyse the data. An estimate of the treatment effect versus placebo and an estimate of the distance between the categories (50, 75 and 90) were obtained. Where, *rikj,* is a vector of the number of participants in arm *j* of trial *i* belonging to *k=1,..,4* mutually exclusive categories:

- $R_{ijk=1}$ *= Nij – PASI50ij (number of patients not achieving PASI50).*
- $R_{ijk=2}$ *= PASI50ij – PASI75ij (number of patients achieving PASI50, but not PASI75).*
- $R_{ijk=3}$ *= PASI75ij – PASI90ij (number of patients achieving PASI75, but not PASI90).*
- $R_{ijk=4}$ *= PASI90ij (number of patients achieving PASI90).*

The probability of a PASI50 response was then estimated based on the treatment effect, and the probability of PASI75 and PASI90 responses were estimated by adding the estimates of the distances between the respective categories to the probability of PASI50 response. The responses for each arm *j* of trial *i* in one of the four aforementioned categories were assumed to follow a multinomial distribution with a probit link function to map p_{ijk} – probability that a patient in arm *j* of trial *i* belongs to

category *k* - onto the real line values for linear predictors in binary response models. However, since the reported categories are different in different studies and overlap, it is helpful to re-write the multinomial likelihood as a series of conditional binomials.

In order not to influence the observed results based on the prior distribution, a common critique of the Bayesian approach, non-informative prior distributions can be used for the model parameter(s). By using 'flat' priors, it is assumed that any parameter value is 'equally' likely. As a consequence, posterior results are not influenced by the prior distribution but driven by the data as with a conventional frequentist meta-analysis. In Table 32, an overview of the prior distributions used in a Bayesian analysis is provided.

Table 32. Prior distributions for model parameters used for analysis in a Bayesian framework

Model parameters	*Distribution*	*Comment*
Nuisance parameters	$\mu_{ik} \sim \text{Normal}(0, 10\,000)$	μ is dependent upon the measurement scale and link function used
Treatment effect parameters	$d_{t_{ik}} \sim \text{Normal}(0, 10\,000)$	
Heterogeneity parameters	$\sigma \sim uniform(0, 2)$ $\sigma \sim uniform(0, 5)$	

Model critique

In order to identify the most appropriate model given the evidence base, the goodness-of-fit of model predictions to the observed data can be measured by calculating the posterior mean residual deviance, $\overline{D}$. The residual deviance reflects the difference between the deviance with the current model and the deviance with the saturated model. By comparing the posterior mean of $\overline{D}$ to the number of independent data points, the absolute model fit can be assessed to see whether each data point contributes approximately 1 to the posterior mean deviance as expected and therefore provides an adequate fit to the data. Although this approximation relates to a Normal distribution, this is expected to provide a useful overall measure of model fit.

The deviance information criterion (DIC) was used to compare the fixed and random effects model and provides a measure of model fit that penalises model complexity according to $DIC = \overline{D} + pD$, $pD = \overline{D} - \hat{D}$. pD is the 'effective number of parameters' and $\hat{D}$ is the deviance evaluated at the posterior mean of the model parameters. The model with the lowest DIC, and therefore the model providing the 'best' fit was considered the base-case model given the dataset used.[180] In section 4.10.4, only the results for the best model are presented.

In addition to comparing DIC values to decide which model fits 'best', diagnostic plots were explored in detail (see Section 4.10.4).

Assessment of convergence

In the analyses for multi-categorical data, two chains with 50,000 iterations from the OpenBUGS sampler were discarded as 'burn-in' and the inferences were based on 120,000 additional iterations, using a thinning of four for the fixed effects models and 10 for the random effects models.

History and density plots of the parameters were reviewed to confirm convergence. In addition, a check was performed ensuring that the Monte Carlo error was less than ≤5% of the posterior SD for the parameters examined.

Assessment of inconsistency

As opposed to the NMA models that assume the direct and indirect evidence to be consistent for any 'closed loops' in the evidence network, inconsistency models were performed in order to test the validity of the consistency assumption.[181] An inconsistency model was assessed each time that a closed loop was present in the network.

Software

The parameters of the different models were estimated within a Bayesian framework using a Markov Chain Monte Carlo (MCMC) method as implemented in the OpenBUGS software package.[182] R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) was used to prepare input files and plots. The WinBUGS code used to conduct the

network meta-analysis of the different outcomes was part of the NICE DSU technical support document 2[179] and is cited in the Appendix 8.

4.10.4 Results

For the analyses, the intention-to-treat (ITT) population which was reported in the majority of the studies along with the number of patients achieving a PASI response, was used. Outcomes from ERASURE were reported for fewer patients than the ITT population, however, it was not clear from the publication why patients were excluded. For each endpoint the results consist of probability tables that show a percentage and 95% CrI reflecting the probability of an intervention achieving a specific outcome (PASI 50/75/90) at a certain time point.

Summary

DMF (LAS41008) shows superior efficacy compared with placebo and inferior efficacy when compared with biologics, apremilast and Fumaderm. The difference in treatment effect becomes smaller with increasing stringency of PASI response.

These results were consistent for the base case (PASI response at 16 weeks) and for all further analyses:

- The scenario excluding Ohtsuki 2016[77] at 16 weeks
- PASI at induction time
- Subgroup of patients from the BRIDGE study who had received prior systemic therapies or phototherapy

Detailed results are provided below.

PASI response at 16 weeks

The results for the PASI response at 16 weeks are presented in Table 33 and Table 34. The treatment effects relative to placebo are all below zero suggesting that all treatments, including DMF (LAS41008), are better than placebo at increasing the probability of a reduction in symptoms. The absolute probabilities of achieving a

reduction of at least 75% in symptoms are higher for all competing interventions (except placebo) compared with DMF (LAS41008).

Table 33. Posterior mean, standard deviation (SD), median and (95% CrI) for PASI response at 16 weeks

Intervention	Mean	SD	Median (95% CrI)
$d_{DMF(LAS41008)}$	-0.72	0.19	-0.72 (-1.09, -0.34)
$d_{apremilast}$	-0.98	0.09	-0.99 (-1.16, -0.78)
$d_{Fumaderm}$	-0.89	0.19	-0.89 (-1.26, -0.51)
$d_{etanercept\ low\ dose}$	-1.22	0.17	-1.22 (-1.55, -0.88)
$d_{adalimumab}$	-1.96	0.12	-1.96 (-2.20, -1.72)

$d_{"treatment"}$: treatment effect relative to the reference treatment; SD: Standard deviation; CrI: Credible Interval

Table 34. Absolute probabilities of achieving at least 50, 70 or 90% relief in symptoms for PASI response at 16 weeks

Intervention	Mean	SD	Median (95% CrI)
Probability of achieving at least 50% relief in symptoms (PASI50)			
Placebo	0.22	0.01	0.22 (0.19, 0.24)
Adalimumab	0.88	0.02	0.88 (0.83, 0.92)
Etanercept low-dose	0.66	0.06	0.67 (0.54, 0.77)
Apremilast	0.58	0.04	0.58 (0.50, 0.64)
Fumaderm	0.54	0.07	0.54 (0.39, 0.69)
DMF (LAS41008)	0.47	0.07	0.47 (0.33, 0.62)
Probability of achieving at least 75% relief in symptoms (PASI75)			
Placebo	0.08	0.01	0.08 (0.07, 0.10)
Adalimumab	0.72	0.04	0.72 (0.64, 0.78)
Etanercept low-dose	0.43	0.06	0.43 (0.31, 0.56)
Apremilast	0.34	0.03	0.34 (0.28, 0.41)
Fumaderm	0.31	0.07	0.31 (0.19, 0.45)
DMF (LAS41008)	0.25	0.06	0.25 (0.15, 0.39)
Probability of achieving at least 90% relief in symptoms (PASI90)			
Placebo	0.02	0.00	0.02 (0.01, 0.02)
Adalimumab	0.45	0.04	0.45 (0.37, 0.54)
Etanercept low-dose	0.20	0.04	0.19 (0.12, 0.29)
Apremilast	0.14	0.02	0.14 (0.10, 0.18)
Fumaderm	0.12	0.04	0.12 (0.06, 0.21)
DMF (LAS41008)	0.09	0.03	0.09 (0.04, 0.16)

SD: Standard deviation; CrI: Credible Interval

Scenario excluding Ohtsuki 2016 at 16 weeks

The results for the PASI response at 16 weeks for the scenario analysis are consistent with the base case demonstrating that the exclusion of Ohtsuki has no significant impact Table 35 and Table 36.

Table 35. Posterior mean, standard deviation (SD), median and (95% CrI) for PASI response at 16 weeks – scenario analysis

Intervention	Mean	SD	Median (95% CrI)
$d_{DMF(LAS41008)}$	-0.71	0.21	-0.71 (-1.13, -0.30)
$d_{apremilast}$	-0.99	0.11	-0.99 (-1.19, -0.76)
$d_{Fumaderm}$	-0.89	0.21	-0.89 (-1.30, -0.48)
$d_{etanercept\ low\ dose}$	-1.22	0.18	-1.22 (-1.57, -0.86)
$d_{adalimumab}$	-1.96	0.13	-1.97 (-2.21, -1.70)

$d_{"treatment"}$: treatment effect relative to the reference treatment; SD: Standard deviation; CrI: Credible Interval

Table 36. Absolute probabilities of achieving at least 50, 70 or 90% relief in symptoms for PASI response at 16 weeks – scenario analysis

Intervention	Mean	SD	Median (95% CrI)
Probability of achieving at least 50% relief in symptoms (PASI50)			
Placebo	0.22	0.02	0.22 (0.19, 0.25)
Adalimumab	0.88	0.02	0.88 (0.83, 0.92)
Etanercept low-dose	0.67	0.06	0.67 (0.54, 0.78)
Apremilast	0.58	0.04	0.59 (0.50, 0.66)
Fumaderm	0.54	0.08	0.54 (0.39, 0.70)
DMF (LAS41008)	0.48	0.08	0.47 (0.32, 0.64)
Probability of achieving at least 75% relief in symptoms (PASI75)			
Placebo	0.08	0.01	0.08 (0.07, 0.10)
Adalimumab	0.72	0.04	0.72 (0.64, 0.79)
Etanercept low-dose	0.44	0.07	0.44 (0.31, 0.57)
Apremilast	0.35	0.04	0.35 (0.27, 0.43)
Fumaderm	0.32	0.07	0.31 (0.19, 0.47)
DMF (LAS41008)	0.26	0.07	0.25 (0.14, 0.40)
Probability of achieving at least 90% relief in symptoms (PASI90)			
Placebo	0.02	0.00	0.02 (0.01, 0.02)
Adalimumab	0.46	0.05	0.46 (0.37, 0.55)
Etanercept low-dose	0.20	0.05	0.20 (0.12, 0.30)
Apremilast	0.14	0.02	0.14 (0.10, 0.19)

Intervention	Mean	SD	Median (95% CrI)
Fumaderm	0.12	0.04	0.12 (0.06, 0.22)
DMF (LAS41008)	0.09	0.04	0.09 (0.04, 0.17)

SD: Standard deviation; CrI: Credible Interval

PASI response at induction time

The results for the PASI response at induction time are shown in Table 37 and Table 38. As for the base case, absolute probabilities of achieving a reduction of at least 75% in symptoms are higher for all competing interventions compared with DMF (LAS41008) with the exception of placebo.

Table 37. Posterior mean, standard deviation (SD), median and (95% CrI) for PASI response at induction time

Intervention	Mean	SD	Median (95% CrI)
$d_{DMF(LAS41008)}$	-0.72	0.13	-0.72 (-0.97, -0.47)
$d_{apremilast}$	-1.02	0.07	-1.02 (-1.16, -0.89)
$d_{Fumaderm}$	-0.89	0.13	-0.89 (-1.14, -0.64)
$d_{etanercept\ low\ dose}$	-1.31	0.06	-1.31 (-1.43, -1.19)
$d_{etanercept\ high\ dose}$	-1.73	0.04	-1.73 (-1.81, -1.65)
$d_{adalimumab}$	-1.98	0.09	-1.98 (-2.15, -1.81)
$d_{ustekinumab\ mixed}$	-2.06	0.07	-2.06 (-2.20, -1.92)
$d_{ustekinumab\ low\ dose}$	-2.23	0.06	-2.23 (-2.34, -2.13)
$d_{ustekinumab\ high\ dose}$	-2.37	0.06	-2.37 (-2.48, -2.25)
$d_{secukinumab}$	-2.59	0.07	-2.59 (-2.72, -2.47)
$d_{ixekizumab}$	-2.98	0.06	-2.98 (-3.10, -2.86)

$d_{"treatment"}$: treatment effect relative to the reference treatment; SD: Standard deviation; CrI: Credible Interval

Table 38. Absolute probabilities of achieving at least 50, 70 or 90% relief in symptoms for PASI response at induction time

Intervention	Mean	SD	Median (95% CrI)
Probability of achieving at least 50% relief in symptoms (PASI50)			
Placebo	0.16	0.01	0.16 (0.14, 0.17)
Ixekizumab	0.98	0.00	0.98 (0.97, 0.98)
Secukinumab	0.94	0.01	0.94 (0.93, 0.96)
Ustekinumab high-dose	0.91	0.01	0.91 (0.89, 0.93)
Ustekinumab low-dose	0.89	0.01	0.89 (0.87, 0.91)
Ustekinumab mixed	0.85	0.02	0.85 (0.82, 0.88)
Adalimumab	0.83	0.02	0.83 (0.79, 0.87)

Etanercept high-dose	0.76	0.01	0.76 (0.74, 0.78)
Etanercept low-dose	0.62	0.02	0.62 (0.57, 0.66)
Apremilast	0.50	0.03	0.50 (0.45, 0.56)
Fumaderm	0.45	0.05	0.45 (0.36, 0.55)
DMF (LAS41008)	0.38	0.05	0.38 (0.29, 0.48)
Probability of achieving at least 75% relief in symptoms (PASI75)			
Placebo	0.05	0.00	0.05 (0.05, 0.06)
Ixekizumab	0.91	0.01	0.91 (0.89, 0.93)
Secukinumab	0.83	0.02	0.83 (0.80, 0.86)
Ustekinumab high-dose	0.77	0.02	0.77 (0.74, 0.80)
Ustekinumab low-dose	0.73	0.02	0.73 (0.69, 0.76)
Ustekinumab mixed	0.67	0.03	0.67 (0.62, 0.71)
Adalimumab	0.64	0.03	0.64 (0.58, 0.70)
Etanercept high-dose	0.54	0.01	0.54 (0.51, 0.57)
Etanercept low-dose	0.38	0.02	0.38 (0.34, 0.42)
Apremilast	0.27	0.02	0.27 (0.23, 0.32)
Fumaderm	0.23	0.04	0.23 (0.16, 0.31)
DMF (LAS41008)	0.18	0.03	0.18 (0.12, 0.25)
Probability of achieving at least 90% relief in symptoms (PASI90)			
Placebo	0.01	0.00	0.01 (0.01, 0.01)
Ixekizumab	0.74	0.02	0.74 (0.71, 0.78)
Secukinumab	0.61	0.02	0.61 (0.56, 0.65)
Ustekinumab high-dose	0.52	0.02	0.52 (0.47, 0.56)
Ustekinumab low-dose	0.46	0.02	0.46 (0.42, 0.50)
Ustekinumab mixed	0.39	0.03	0.39 (0.34, 0.45)
Adalimumab	0.37	0.03	0.36 (0.31, 0.43)
Etanercept high-dose	0.28	0.01	0.28 (0.25, 0.30)
Etanercept low-dose	0.16	0.01	0.16 (0.13, 0.18)
Apremilast	0.10	0.01	0.10 (0.08, 0.12)
Fumaderm	0.08	0.02	0.08 (0.05, 0.12)
DMF (LAS41008)	0.06	0.01	0.05 (0.03, 0.09)

SD: Standard deviation; CrI: Credible Interval

Scenario excluding Ohtsuki 2016 at induction time

The results for the PASI response at induction time for the scenario excluding Ohtsuki 2016[77] are presented in Table 39 and Table 40 and are consistent with the base case.

Table 39. Posterior mean, standard deviation (SD), median and (95% CrI) for PASI response at induction time – scenario analysis

Intervention	Mean	SD	Median (95% CrI)
$d_{DMF(LAS41008)}$	-0.72	0.18	-0.72 (-1.07, -0.36)
$d_{apremilast}$	-1.00	0.10	-1.01 (-1.20, -0.80)
$d_{Fumaderm}$	-0.89	0.18	-0.89 (-1.24, -0.54)
$d_{etanercept\ low\ dose}$	-1.32	0.08	-1.32 (-1.49, -1.15)
$d_{etanercept\ high\ dose}$	-1.72	0.06	-1.72 (-1.83, -1.60)
$d_{adalimumab}$	-1.95	0.12	-1.95 (-2.18, -1.71)
$d_{ustekinumab\ mixed}$	-2.06	0.10	-2.06 (-2.26, -1.85)
$d_{ustekinumab\ low\ dose}$	-2.24	0.08	-2.24 (-2.40, -2.08)
$d_{ustekinumab\ high\ dose}$	-2.37	0.09	-2.37 (-2.54, -2.19)
$d_{secukinumab}$	-2.60	0.09	-2.60 (-2.79, -2.41)
$d_{ixekizumab}$	-2.97	0.09	-2.97 (-3.15, -2.78)

$d_{"treatment"}$: treatment effect relative to the reference treatment; SD: Standard deviation; CrI: Credible Interval

Table 40. Absolute probabilities of achieving at least 50, 70 or 90% relief in symptoms for PASI response at induction time – scenario analysis

Intervention	Mean	SD	Median (95% CrI)
Probability of achieving at least 50% relief in symptoms (PASI50)			
Placebo	0.16	0.01	0.16 (0.15, 0.18)
Ixekizumab	0.98	0.01	0.98 (0.96, 0.99)
Secukinumab	0.95	0.01	0.95 (0.93, 0.96)
Ustekinumab high-dose	0.92	0.01	0.92 (0.89, 0.94)
Ustekinumab low-dose	0.90	0.01	0.90 (0.87, 0.92)
Ustekinumab mixed	0.86	0.02	0.86 (0.81, 0.90)
Adalimumab	0.83	0.03	0.83 (0.77, 0.88)
Etanercept high-dose	0.77	0.02	0.77 (0.74, 0.80)
Etanercept low-dose	0.63	0.03	0.63 (0.57, 0.69)
Apremilast	0.51	0.04	0.51 (0.43, 0.59)
Fumaderm	0.47	0.07	0.47 (0.33, 0.61)
DMF (LAS41008)	0.40	0.07	0.40 (0.27, 0.54)
Probability of achieving at least 75% relief in symptoms (PASI75)			
Placebo	0.06	0.00	0.06 (0.05, 0.06)
Ixekizumab	0.91	0.01	0.92 (0.88, 0.94)
Secukinumab	0.84	0.02	0.84 (0.80, 0.88)
Ustekinumab high-dose	0.78	0.03	0.78 (0.73, 0.83)
Ustekinumab low-dose	0.74	0.02	0.74 (0.69, 0.79)
Ustekinumab mixed	0.68	0.04	0.68 (0.60, 0.75)

Adalimumab	0.64	0.04	0.64 (0.55, 0.72)
Etanercept high-dose	0.55	0.02	0.55 (0.51, 0.59)
Etanercept low-dose	0.39	0.03	0.39 (0.33, 0.45)
Apremilast	0.28	0.03	0.28 (0.22, 0.34)
Fumaderm	0.24	0.06	0.24 (0.15, 0.36)
DMF (LAS41008)	0.19	0.05	0.19 (0.11, 0.30)
Probability of achieving at least 90% relief in symptoms (PASI90)			
Placebo	0.01	0.00	0.01 (0.01, 0.01)
Ixekizumab	0.75	0.03	0.75 (0.69, 0.80)
Secukinumab	0.62	0.03	0.62 (0.55, 0.69)
Ustekinumab high-dose	0.53	0.03	0.53 (0.46, 0.60)
Ustekinumab low-dose	0.48	0.03	0.48 (0.42, 0.54)
Ustekinumab mixed	0.41	0.04	0.41 (0.33, 0.49)
Adalimumab	0.37	0.04	0.37 (0.28, 0.45)
Etanercept high-dose	0.28	0.02	0.28 (0.25, 0.32)
Etanercept low-dose	0.17	0.02	0.16 (0.13, 0.21)
Apremilast	0.10	0.02	0.10 (0.07, 0.14)
Fumaderm	0.08	0.03	0.08 (0.04, 0.15)
DMF (LAS41008)	0.06	0.02	0.06 (0.03, 0.11)

SD: Standard deviation; CrI: Credible Interval

Subgroup analysis – Prior systemic therapies or phototherapy

In this section results from a subgroup analysis from the BRIDGE trial including patients experienced with prior systemic therapies or PUVA are presented.

PASI response at 16 weeks

The results for the PASI response at 16 weeks for the subgroup of patients previously treated with systemic therapies or PUVA are shown in Table 41 and Table 42 and are consistent with the results seen in the base case.

Table 41. Posterior mean, standard deviation (SD), median and (95% CrI) for PASI response at 16 weeks

Intervention	Mean	SD	Median (95% CrI)
$d_{DMF(LAS41008)}$	-0.69	0.25	-0.69 (-1.18, -0.21)
$d_{apremilast}$	-1.00	0.10	-1.00 (-1.17, -0.80)
$d_{Fumaderm}$	-0.91	0.24	-0.91 (-1.39, -0.44)
$d_{etanercept\ low\ dose}$	-1.23	0.17	-1.23 (-1.57, -0.89)
$d_{adalimumab}$	-1.99	0.12	-1.99 (-2.22, -1.74)

$d_{"treatment"}$: treatment effect relative to the reference treatment; SD: Standard deviation; CrI: Credible Interval

Table 42. Absolute probabilities of achieving at least 50, 70 or 90% relief in symptoms for PASI response at 16 weeks

Intervention	Mean	SD	Median (95% CrI)
Probability of achieving at least 50% relief in symptoms (PASI50)			
Placebo	0.22	0.02	0.22 (0.19, 0.25)
Adalimumab	0.89	0.02	0.89 (0.84, 0.93)
Etanercept low-dose	0.68	0.06	0.68 (0.56, 0.78)
Apremilast	0.59	0.04	0.59 (0.52, 0.66)
Fumaderm	0.56	0.09	0.56 (0.38, 0.73)
DMF (LAS41008)	0.47	0.09	0.47 (0.29, 0.66)
Probability of achieving at least 75% relief in symptoms (PASI75)			
Placebo	0.08	0.01	0.08 (0.07, 0.10)
Adalimumab	0.72	0.04	0.72 (0.64, 0.79)
Etanercept low-dose	0.43	0.06	0.43 (0.31, 0.56)
Apremilast	0.34	0.03	0.34 (0.28, 0.41)
Fumaderm	0.32	0.08	0.31 (0.17, 0.49)
DMF (LAS41008)	0.25	0.08	0.24 (0.12, 0.41)
Probability of achieving at least 90% relief in symptoms (PASI90)			
Placebo	0.02	0.00	0.02 (0.01, 0.02)
Adalimumab	0.44	0.04	0.44 (0.36, 0.53)
Etanercept low-dose	0.19	0.04	0.19 (0.11, 0.28)
Apremilast	0.13	0.02	0.13 (0.09, 0.17)
Fumaderm	0.12	0.05	0.11 (0.05, 0.23)
DMF (LAS41008)	0.08	0.04	0.08 (0.03, 0.17)

SD: Standard deviation; CrI: Credible Interval

PASI response at induction time

The results for the PASI response at induction time for the subgroup of patients previously treated with systemic therapies or PUVA are shown in Table 43 and Table 44 which again show the same comparative efficacy as the base case.

Table 43. Posterior mean, standard deviation (SD), median and (95% CrI) for PASI response at induction time

Intervention	Mean	SD	Median (95% CrI)
$d_{DMF(LAS41008)}$	-0.69	0.23	-0.69 (-1.15, -0.23)
$d_{apremilast}$	-1.00	0.09	-1.00 (-1.18, -0.81)
$d_{Fumaderm}$	-0.90	0.23	-0.90 (-1.36, -0.45)
$d_{etanercept\ low\ dose}$	-1.32	0.08	-1.32 (-1.49, -1.16)
$d_{etanercept\ high\ dose}$	-1.72	0.06	-1.72 (-1.83, -1.61)

$d_{adalimumab}$	-1.95	0.12	-1.95 (-2.18, -1.72)
$d_{ustekinumab\ mixed}$	-2.06	0.10	-2.06 (-2.27, -1.86)
$d_{ustekinumab\ low\ dose}$	-2.25	0.08	-2.25 (-2.41, -2.09)
$d_{ustekinumab\ high\ dose}$	-2.38	0.09	-2.38 (-2.55, -2.20)
$d_{secukinumab}$	-2.60	0.09	-2.60 (-2.79, -2.42)
$d_{ixekizumab}$	-2.97	0.09	-2.97 (-3.16, -2.79)

$d_{"treatment"}$: treatment effect relative to the reference treatment; SD: Standard deviation; CrI: Credible Interval

Table 44. Absolute probabilities of achieving at least 50, 70 or 90% relief in symptoms for PASI response at induction time

Intervention	Mean	SD	Median (95% CrI)
Probability of achieving at least 50% relief in symptoms (PASI50)			
Placebo	0.16	0.01	0.16 (0.15, 0.17)
Ixekizumab	0.98	0.01	0.98 (0.96, 0.98)
Secukinumab	0.95	0.01	0.95 (0.92, 0.96)
Ustekinumab high-dose	0.92	0.01	0.92 (0.89, 0.94)
Ustekinumab low-dose	0.89	0.01	0.90 (0.86, 0.92)
Ustekinumab mixed	0.86	0.02	0.86 (0.81, 0.90)
Adalimumab	0.83	0.03	0.83 (0.77, 0.88)
Etanercept high-dose	0.77	0.02	0.77 (0.73, 0.80)
Etanercept low-dose	0.63	0.03	0.63 (0.57, 0.69)
Apremilast	0.50	0.04	0.50 (0.43, 0.57)
Fumaderm	0.46	0.09	0.46 (0.30, 0.64)
DMF (LAS41008)	0.38	0.09	0.38 (0.22, 0.56)
Probability of achieving at least 75% relief in symptoms (PASI75)			
Placebo	0.05	0.00	0.05 (0.05, 0.06)
Ixekizumab	0.91	0.01	0.91 (0.88, 0.94)
Secukinumab	0.83	0.02	0.84 (0.79, 0.88)
Ustekinumab high-dose	0.77	0.03	0.77 (0.72, 0.82)
Ustekinumab low-dose	0.73	0.03	0.73 (0.68, 0.78)
Ustekinumab mixed	0.67	0.04	0.67 (0.59, 0.74)
Adalimumab	0.63	0.04	0.63 (0.54, 0.71)
Etanercept high-dose	0.54	0.02	0.54 (0.50, 0.58)
Etanercept low-dose	0.38	0.03	0.38 (0.32, 0.44)
Apremilast	0.27	0.03	0.27 (0.21, 0.33)
Fumaderm	0.24	0.07	0.24 (0.12, 0.39)
DMF (LAS41008)	0.18	0.06	0.17 (0.08, 0.32)
Probability of achieving at least 90% relief in symptoms (PASI90)			
Placebo	0.01	0.00	0.01 (0.01, 0.01)
Ixekizumab	0.74	0.03	0.74 (0.68, 0.79)
Secukinumab	0.61	0.03	0.61 (0.54, 0.67)

Ustekinumab high-dose	0.52	0.03	0.52 (0.45, 0.59)
Ustekinumab low-dose	0.47	0.03	0.47 (0.41, 0.53)
Ustekinumab mixed	0.39	0.04	0.39 (0.32, 0.47)
Adalimumab	0.35	0.04	0.35 (0.27, 0.44)
Etanercept high-dose	0.27	0.02	0.27 (0.24, 0.31)
Etanercept low-dose	0.16	0.02	0.16 (0.12, 0.20)
Apremilast	0.09	0.02	0.09 (0.06, 0.12)
Fumaderm	0.08	0.03	0.08 (0.03, 0.16)
DMF (LAS41008)	0.05	0.03	0.05 (0.02, 0.12)

SD: Standard deviation; CrI: Credible Interval

Model selection

Di□erent modelling scenarios were assessed using criteria such as the deviance information criterion (DIC) statistic, convergence and autocorrelation graphs. These models included a fixed and a random-e□ects model. The model selected was the best fit and presented good convergence and no sign of autocorrelation. Since good convergence and no sign of autocorrelation were present for all the models considered, based on smallest DIC, the random effects model appeared to be the best fit for all analyses. For PASI response at 16 weeks, the fixed effect model had the lowest DIC, but the differences were small (less than 2 points), indicating no evidence of substantial heterogeneity. Hence, random effects models results are presented throughout the submission (see Section 4.10.4). DICs and parameter estimates for each outcome are presented in Table 45.

Table 45. Deviance Information Criteria for all random effects models

Model	Deviance	$Leverage_{Deviance}$	DIC
PASI response at 16 weeks	351.84	20.46	372.3*
PASI response at 16 weeks – scenario analysis	342.24	19.56	361.8†
PASI response at induction time	1136	50.01	1237
PASI response at induction time – scenario analysis	1092	62.44	1217
PASI response at 16 weeks – subgroup analysis	326.89	20.51	347.4††
PASI response at induction time – subgroup analysis	1076	63.59	1203

IT: Induction time; *Fixed effect model DIC: 371.3; †Fixed effect model DIC: 360.8; ††Fixed effect model DIC: 346.2

Consistency assessment

The consistency assumption of the NMA was evaluated by fitting and assessing an inconsistency model for the outcomes whose networks included “closed loops”. Comparison between a model fit diagnostic, i.e., DIC statistic of the consistency and the inconsistency model provides an “omnibus” test of consistency. For the consistency assumption to hold, the DIC of the consistency model should be lower than the one of the inconsistency model.

Table 46: DIC statistic for consistency and inconsistency model

Model	DIC consistency model	DIC inconsistency model
PASI response at 16 weeks	372.3	372.4
PASI response at 16 weeks – scenario analysis	361.8	361.9
PASI response at induction time	1237	1237
PASI response at induction time – scenario analysis	1217	1217
PASI response at 16 weeks – subgroup analysis	347.4	347.4
PASI response at induction time – subgroup analysis	1203	1203

As shown in Table 46, for all outcomes the DIC of the consistency model was lower or equal to the DIC of the inconsistency model, hence no apparent inconsistency was identified in the analyses.

Conclusion

The NMA compares the efficacy of DMF (LAS41008) with the comparators relevant to the decision problem: Fumaderm, apremilast and standard systemic biologic therapies (adalimumab, etanercept, secukinumab, ustekinumab) plus ixekizumab. The absolute probabilities of achieving a reduction of at least 50%, 75% and 90% in symptoms are higher for all the competing interventions compared with DMF (LAS41008) with the exception of placebo. The results obtained from the scenario analysis as well as the subgroup analysis, are consistent with the base case analysis.

4.11 Non-randomised and non-controlled evidence

Not applicable

4.12 Adverse reactions

Safety data are presented for the BRIDGE study. The safety profile of DMF gastro-resistant tablets was similar to that of Fumaderm (both groups receiving up to 720 mg of DMF per day).

Adverse events

The majority of adverse events were mild and did not lead to discontinuation of study treatment. The most common adverse reactions (>10%) were gastrointestinal (GI) events (such as nausea, diarrhoea, abdominal pain), flushing and lymphopenia. The only adverse reactions that led to discontinuation of treatment in >5% of patients were gastrointestinal reactions.

A total of 83.9% and 84.1% of patients in the DMF (LAS41008) and Fumaderm treatment groups, respectively, experienced at least one TEAE compared with 59.9% of patients in the placebo group (Table 47). TEAEs were defined as AEs with onset at or after the time of the first study drug administration. AEs that occurred more than 30 days after the last intake of study drugs were not considered an AE.

Treatment-related AEs were reported in 73.8% and 73.9% of the patients in the DMF (LAS41008) and Fumaderm group, respectively, and in 40.1% of the patients in the placebo group (Table 47).

A total of 24.0% and 24.4% of the patients in the DMF (LAS41008) and Fumaderm groups, respectively, experienced at least one TEAE leading to study drug withdrawal compared to 5.8% of the patients in the placebo group (Table 47).

Table 47: Adverse event overview (SAS)

	DMF (LAS41008) n=279	**Fumaderm n=283**	**Placebo n=137**
Total AEs	239 (85.7)	240 (84.8)	84 (61.3)
TEAEs	234 (83.9)	238 (84.1)	82 (59.9)
Treatment related AEs	206 (73.8)	209 (73.9)	55 (40.1)

TEAEs leading to withdrawal	67 (24.0)	69 (24.4)	8 (5.8)
Serious TEAEs	9 (3.2)	8 (2.8)	5 (3.6)
Treatment-related serious TEAEs	0 (0.0)	2 (0.7)	0 (0.0)
Serious AEs leading to death	0 (0.0)	1 (0.4)	0 (0.0)

Source: Mrowietz et al 2016, LAS41008 CSR M41008-1102 June 2016[23,48]

Treatment Emergent Adverse Events

The most frequently observed TEAEs in the DMF and Fumaderm groups were gastrointestinal disorders (DMF/Fumaderm vs. placebo, 62.7%/63.3% vs. [redacted]%), including diarrhoea (38.7%/39.9% vs. 16.8%), upper abdominal pain (20.1%/22.6% vs. 8.0%), abdominal pain (19.7%/15.9% vs. 5.1%), and nausea (10.8%/8.5% vs. 3.6%) (Table 48).

The majority of TEAEs were of mild to moderate intensity. In the DMF (LAS41008) and Fumaderm group, [redacted]% and [redacted]% of the patients, respectively, compared to [redacted]% of the patients in the placebo group experienced at least one TEAE of severe intensity.

TEAEs that occurred at higher frequencies in the DMF (LAS41008) and Fumaderm groups compared to the placebo group were vascular disorders ([redacted]%/[redacted]% vs. [redacted]%) including flushing (18.3%/16.3% vs. 1.5%), blood and lymphatic system disorders ([redacted]%/[redacted]% vs. [redacted]%) including lymphopenia (10.0%/10.6% vs. 0.0%) and eosinophilia (9.0%/6.0% vs. 0.0%) and skin and subcutaneous tissue disorders ([redacted]%/[redacted]% vs. [redacted]%) including erythema (9.7%/8.1% vs. 2.2%) and burning skin sensation (7.9%/7.1% vs. 2.2%).

TEAEs of special interest

TEAEs of special interest pertinent to DMF (LAS41008) gastro-resistant tablets were decreases in lymphocyte and leukocyte counts, flushing, gastrointestinal events, serious and opportunistic infections, malignancies, renal injury and proteinuria, and hepatic injury. This grouping of events was selected based on the risks known to be associated with Fumaderm treatment or potentially related to the immunological mode of action of DMF (LAS41008).

In the DMF (LAS41008) and Fumaderm groups, comparable changes in haematology values (increases in eosinophils and decreases in leukocytes and lymphocytes) were observed, as have been reported in association with Fumaderm. No clear relationship between blood disorders such as leukopenia and lymphocytopenia and the onset of infections could be found, although it should be interpreted with caution due to the low frequency of events. No trend in vital signs was observed.

Deaths

One patient in the Fumaderm group died subsequent to subendocardial ischaemia, which was assessed as 'not related' to the study drug.

Table 48: TEAEs occurring in more than 1% of all patients (SAS)

System Organ Class Preferred Term	DMF (LAS41008) n=279	Placebo n=137	Fumaderm n=283
Gastrointestinal disorders[2]	[redacted]	[redacted]	[redacted]
• Diarrhoea	108 (38.7)	22 (16.8)	113 (39.9)
• Abdominal pain upper	56 (20.1)	11 (8.0)	64 (22.6)
• Abdominal pain	55 (19.7)	7 (5.1)	45 (15.9)
• Nausea	30 (10.8)	5 (3.6)	24 (8.5)
• Flatulence	15 (5.4)	7 (5.1)	16 (5.7)
• Vomiting	13 (4.7)	2 (1.5)	19 (6.7)
Vascular disorders	[redacted]	[redacted]	[redacted]
• Flushing	51 (18.3)	2 (1.5)	46 (16.3)
• Hot flush	[redacted]	[redacted]	[redacted]
Blood and lymphatic disorders	[redacted]	[redacted]	[redacted]
• Lymphopenia	28 (10.0)	0 (0.0)	30 (10.6)
• Eosinophilia	25 (9.0)	0 (0.0)	17 (6.0)
• Leukocytosis	[redacted]	[redacted]	[redacted]
• Leukopenia			
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
• Pruritus	24 (8.6)	15 (10.9)	28 (9.9)
• Erythema	27 (9.7)	3 (2.2)	23 (8.1)
• Burning skin sensation	22 (7.9)	3 (2.2)	20 (7.1)

Source: Mrowietz et al 2016, LAS41008 CSR M41008-1102 June 2016[23,48]

4.13 Interpretation of clinical effectiveness and safety evidence

DMF (LAS41008, gastric resistant tablets) will be the first licensed FAE for use in the UK for the treatment of moderate to severe psoriasis. In clinical practice DMF (LAS41008) will be positioned where other oral systemic therapies (acitretin, methotrexate, and ciclosporin) are clinically inappropriate for patients through lack of efficacy, contraindications, tolerability and/or toxicity issues, or patient preference. In this position it will offer clinicians and patients access to a further oral systemic therapy.

The evidence base for DMF (LAS41008) consists of a single Phase 3, multicentre, randomised, double-blind, adaptive phase III study to evaluate the efficacy and safety of DMF (LAS41008) compared to Fumaderm and placebo in patients with moderate to severe chronic plaque psoriasis.

This clinical trial was designed, conducted and reported in accordance with the principles of good clinical practice.

The study population, which consisted of adult patients with chronic plaque psoriasis (64.7% male and 35.3% female patients aged between 18 and 87 years with a mean of 44.4 years) was representative of the population likely to receive DMF (LAS41008) in clinical practice.

The PASI and PGA endpoints were chosen as efficacy variables in accordance with the "Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis." (CHMP (2004). "Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis." CHMP/EWP/2454/02). Both are recognised and accepted endpoints in the assessment of psoriasis.

All three co-primary objectives of the study were met.

- PASI 75 was achieved by 37.5% of patients in the DMF (LAS41008) treatment group at Week 16 compared with 15.3% of patients in the placebo group, a risk difference of 22% ($p<0.0001$)
- DMF (LAS41008) was also shown to be non-inferior to Fumaderm in the proportion of patients who achieved PASI 75 at week 16 (37.5% vs. 40.3% DMF vs. Fumaderm, $p<0.0003$)

- The proportion of patients achieving a PGA score of “clear” or “almost clear” at Week 16 was statistically greater in the DMF (LAS41008) group (33.0%) compared to placebo (13.0%; p <0.0001)

A significant effect of DMF (LAS41008) over placebo was also observed in the proportion of patients achieving PASI 50 and PASI 90 after 16 weeks of treatment (p<0.001 for both PASI 50 and PASI 90).

Significantly greater mean changes from baseline were observed in PASI total and BSA in the DMF (LAS41008) group compared to the placebo group at week 16 (p<0.0001 for both PASI total and BSA).

The treatment success rate (defined as either a “clear” or “almost clear” score in the PGA and/or PASI 90) and remission rate (defined as a score of “clear” in the PGA) was significantly higher in the DMF (LAS41008) compared to the placebo group (p<0.0001 at week 16).

Rebound defined as a worsening of psoriasis over baseline value (PASI≥125%) was documented for very few patients in either the DMF (LAS41008) or the Fumaderm group, whereas the proportion of patients fulfilling the criteria for rebound was higher in the placebo group. In the FAS population, 2 (1.13%) of 177 patients in the DMF (LAS41008) group, 4 (2.19%) of 183 patients in the Fumaderm group, and 7 (9.33%) of 75 patients in the placebo group had a rebound.

Comparable effects were observed between DMF and Fumaderm for PASI 50 and PASI 90 at 16 weeks of treatment, with no statistically significant differences.

Quality of life

A significant effect in favour of DMF (LAS41008) vs. placebo was also detected in the PBI and the DLQI after 16 weeks of treatment (p < 0.0001).

No significant differences in the PBI and the DLQI were observed between DMF and Fumaderm after 16 weeks of treatment.

Side effect profile

The safety profile of DMF (LAS41008) closely matched that of Fumaderm and no new safety issues were identified.

Common AEs with DMF (LAS41008) were gastrointestinal disorders such as diarrhoea, abdominal pain and nausea, flushing, and blood disorders such as leukopenia, lymphopenia and eosinophilia. The changes in haematology values observed in the DMF group were comparable to those in the Fumaderm group and as reported in association with Fumaderm. In this limited dataset no clear relationship between blood disorders such as leukopenia and lymphocytopenia and the onset of infections could be found.

The majority of TEAEs were of mild to moderate intensity with a low level of TEAEs of severe intensity. The number of patients who experienced at least one TEAE (during treatment or within 30 days after last study medication intake) leading to study withdrawal in the DMF (LAS41008) group was comparable to that in the Fumaderm group.

As DMF (LAS41008) is an oral treatment, administration of doses is straightforward and it is anticipated that once the maximum required dose has been reached any dose modifications will be managed remotely. No change in current management arrangements or infrastructure is required.

Subgroups

The treatment effect between DMF (LAS41008) gastro-resistant tablets and placebo observed in the subgroups was generally similar to those seen for the overall FAS population, [redacted]

DMF (LAS41008) was [redacted] for the proportion of patients achieving PASI 75

at week 16 [redacted]

[redacted]

Indirect comparison data

In order to compare DMF (LAS41008) with the other comparators included in the decision problem, and in the absence of direct head-to-head trials, a network meta-analysis (NMA) was conducted. The NMA demonstrated that DMF (LAS41008) shows superior efficacy compared with placebo and inferior efficacy when compared with biologics, apremilast and Fumaderm. Although the direction of treatment effect is the same, the results from the NMA and BRIDGE study when comparing DMF and Fumaderm are different. The difference in efficacy seen between Fumaderm and DMF (LAS41008) in the NMA is a result of the different methodology used in the analysis.

In line with methods recommended by NICE, the NMA followed an ordered categorical model, whereby patients moved from one category (PASI 50, 75 and 90) to the next. Analysis used a multi-categorical response variable with estimates of treatment effect vs placebo and distance between categories.

In light of this, a conservative approach was taken in the health economic modelling, and scenario analyses were conducted to ensure the robustness of the approach.

Strengths and limitations of the clinical evidence base

Strengths

The trial is well designed with recognised and accepted endpoints.

The trial population is reflective of the patient population likely to receive DMF (LAS41008) in clinical practice.

Significant improvements across key efficacy points were demonstrated for DMF (LAS41008) compared with placebo and DMF (LAS41008) was demonstrated to be non-inferior to the active comparator, Fumaderm an FAE licensed for use in Germany.

Limitations

Trial duration

The primary efficacy end points were measured after only 16 weeks of treatment, of which up to 9 weeks was needed to titrate to the therapeutic dose. While the regulators agreed that the treatment duration of 16 weeks was adequate for demonstration of efficacy this relatively short treatment period may not allow provision of an estimate of the maximum efficacy, considering that the efficacy of FAEs is seen to improve over many months of treatment with a peak in efficacy around 6 to 12 months, and continues up to 24 months of treatment.[15,25]

High discontinuation rate

Discontinuation rates were relatively high, due mainly to the known side-effect profile of FAEs and also due to the rigid dose titration period which did not allow clinicians to individualise doses to the patient. The overall treatment discontinuation rate was around 36% which is higher than the 15% planned during the sample size estimation. Although the overall rate of patients completing treatment was lower (63.1%) in the DMF (LAS41008) group compared to placebo (71.5%), it was comparable to the completion rate in the active control, Fumaderm arm (62.2%).

Due to the relatively high drop-out rate observed, 'last observation carried forward' (LOCF) up to Week 16 was used for missing data from PASI and PGA assessments; in this context, the last observation-carried-forward approach may have diminished the reported treatment effect.

Extrapolating to Fumaderm

While specific data on the long-term efficacy and safety of DMF (LAS41008) are not currently available, bridging to the data available for Fumaderm provides this information. As stated previously in Section 4.2 Fumaderm contains a combination of both DMF and the zinc calcium and magnesium salts of MEF of which DMF is considered to be the active ingredient.[44] No clinically significant effect of MEF was demonstrated in a controlled clinical study comparing MEF at doses of up to 720mg per day to placebo in patients with psoriasis.[183]

Pharmacokinetic data support the fact that the MEF component of Fumaderm has no impact on exposure to the active ingredient DMF. DMF (LAS41008) demonstrates a similar plasma concentration-time profile of DMF to the DMF+MEF combination in Fumaderm, with no relevant differences in the rate and extent of absorption between the two products.[184,185]

In addition the BRIDGE study comparing DMF (LAS41008) with Fumaderm in moderate to severe psoriasis. (see Section 4.2 to 4.8 and 4.12) demonstrates:

- A statistically significant antipsoriatic effect of both products
- That at equivalent doses of DMF, the clinical efficacy of DMF (LAS41008) is non-inferior to Fumaderm with an equivalent safety and tolerability profile.
- Treatment with DMF (LAS41008) is not associated with any new side effects or any higher incidence of the well-established side effects of Fumaderm treatment

These trial results indicate that in the clinical setting the MEF component of Fumaderm does not contribute to efficacy or safety. The clinical response of psoriasis to treatment with Fumaderm is solely driven by the DMF content and therefore its efficacy, safety and tolerability can reasonably be extrapolated to products containing DMF alone; a point considered and accepted by the regulatory authorities.

On this basis it is appropriate to assume that the long-term safety and efficacy available for Fumaderm can be applied to DMF (LAS41008).

Key long term data for Fumaderm as used in the clinical setting are available from FUTURE,[25] a retrospective study in 984 patients with psoriasis treated for at least 24 months, with a mean duration of uninterrupted therapy of 44.1 months (max. 216 months). The study demonstrated sustained clinical efficacy of Fumaderm. The proportion of patients with PGA score of ‘markedly improved or clear’ increased from 67% at six months to 82% after 36 months, with over 80% patients remaining on treatment. Improvement in symptoms was independent of disease severity prior to treatment. The study demonstrated a favourable safety profile for long-term use. Changes in laboratory parameters were usually minor and did not require treatment modification in over 90% of cases.[25]

4.14 Ongoing studies

There are discussions ongoing with UK centres regarding possible phase 4 studies; however at this time, no studies are currently approved in the UK.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Published cost-effectiveness analysis (Review 1)

A systematic literature review was conducted to identify published evidence on the cost-effectiveness of DMF (LAS41008) for the treatment of psoriasis (Review 1).

Methods

Objective

The purpose of this section of the report was to review existing evidence on the cost-effectiveness of DMF (LAS41008 / Skilarence) for the treatment of psoriasis in adults.

- What evidence is available on the cost-effectiveness of DMF (LAS41008) for the treatment of psoriasis in adults?

Search strategy

The following electronic databases were searched: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); EMBASE (Ovid); EconLit, NHS EED, and Web of Science. A search filter was used to limit to cost-effectiveness and health economic studies. The searches were limited to English language. The search strategy is detailed in Appendix 9.

Supplementary searching included the review of conference abstracts from the following meetings from 2013 to Current:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- American Academy of Dermatology (AAD)
- British Association of Dermatology (BAD)
- European Academy of Dermatology and Venerology (EADV)

Eligibility criteria

The inclusion and exclusion criteria for the systematic review of economic evaluations are set out below.

Table 49: Summary of the eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	Plaque psoriasis	Psoriatic arthritis, scalp or nail psoriasis
Intervention(s)	DMF (LAS41008)	Any other intervention not listed and combination therapies of the treatment listed under inclusion criteria. Unlicensed dosages of the intervention listed under inclusion criteria.
Comparator(s)	Fumaderm (fumaric acid esters) Adalimumab Etanercept Infliximab Secukinumab Ustekinumab Ciclosporin Methotrexate Acitretin Apremilast Phototherapy Placebo Tofacitinib Brodalumab Ixekizumab **Biosimilars:** Biosimilars of the drugs reported above indicated for psoriasis in Phase III are of interest including but not limited to Inflectra (Infliximab), Rensima (Infliximab), GP2017 (adalimumab), and GP2015 (etanercept)	Any other comparator treatments not listed in inclusion criteria and combination therapies of the comparator treatments listed under inclusion criteria. Unlicensed dosages of comparator treatments listed under inclusion criteria.
Outcomes	Cost/QALY Cost/life-year gained	
Study design	Full economic evaluations: – cost-effectiveness analyses – cost-minimisation analyses – cost-utility analyses Systematic reviews of economic evaluations[a] will be included as sources of references	RCTs, observational studies, burden of illness studies, and budget impact assessments Publication types: editorial, letter, reviews (other than SRs)
Other	English language Countries in Europe, USA and Canada	Non-English language Countries other than those specified under inclusion criteria

Key: ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life year(s); SR = systematic review

Notes: (a) For the purpose of this review, a systematic review will be defined as one that has: a focused research question; explicit search criteria that are available to review, either in the document or on application; explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest; a critical appraisal of included studies, including consideration of internal and external validity of the research; and, a synthesis of the included evidence, whether narrative or quantitative.

Data abstraction strategy

Selection of studies:

Studies retrieved from the searches were selected for inclusion through a two-stage process according to the inclusion/exclusion criteria specified. First, titles and abstracts returned by the search strategy were screened for inclusion by two reviewers. Full texts of identified studies were obtained and screened in the same way.

Data extraction and quality appraisal:

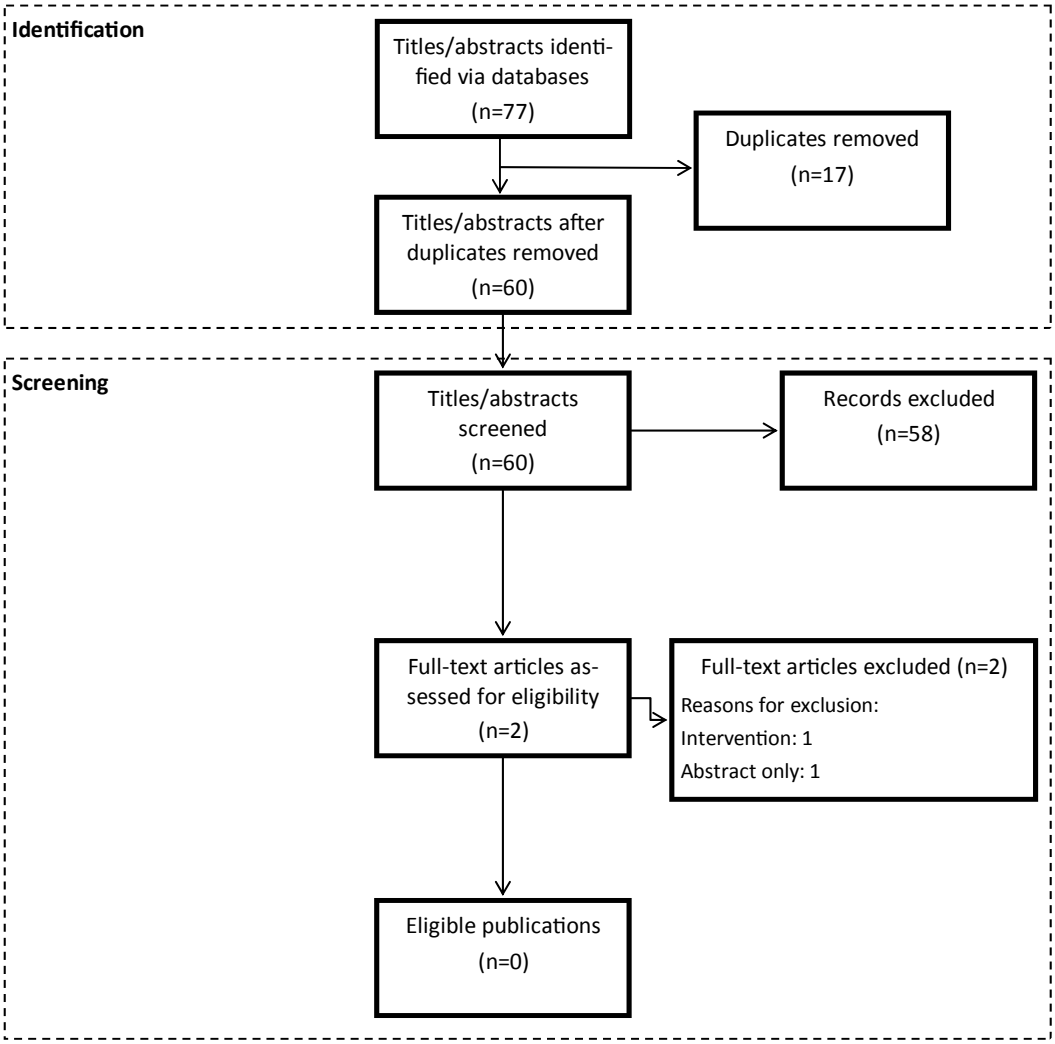
Data extraction was conducted using a standardised data specification form. Information extracted included: details on the country setting, model structure (summary), patient population, quality-adjusted life years (QALYs) (intervention vs. comparator), costs (currency; intervention vs. comparator), incremental cost-effectiveness ratio (ICER) (per QALY gained), and sensitivity analysis. These data are presented in summary tables. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

The quality of identified model-based cost-utility analyses was assessed using the checklist developed by Philips and colleagues (2006).[186]

Results

A total of 60 unique references identified by the searches and additional sources were screened for inclusion in the review. Two papers were retrieved for detailed consideration; both were excluded (see Appendix 10). The study selection process is outlined in Figure 25.

Figure 25. PRISMA flow chart for studies included and excluded from the cost-effectiveness review



No cost-utility studies for DMF (LAS41008) in the treatment of psoriasis were identified.

Update searches were conducted on 17 January 2017 (date limited 2016 to Current) (see Appendix 11). Eleven additional titles/abstract were retrieved by the searches of which five were duplicates. One of the records was eligible for full-text screening (Kuster et al., 2016);[187] however, it did not evaluate DMF (LAS41008) and was excluded. Thus, no cost-utility studies of DMF (LAS41008) in the treatment of psoriasis were identified.

5.1.2 Published cost-effectiveness analysis of regimens for the treatment of psoriasis in adults (Review 2)

In addition to the main search (Review 1; Section 5.1.1), to inform the development of the economic model, a second systematic literature review was conducted to identify published evidence exploring the cost-effectiveness of regimens for the treatment of psoriasis in adults (Review 2).

Methods

Objective

The purpose of this review was to identify existing evidence exploring the cost-effectiveness of regimens for the treatment of psoriasis in adults in order to inform the development of the economic model. The research question was: "What evidence is available on the cost-effectiveness of regimens for the treatment of psoriasis in adults?"

Search strategy

Scoping searches identified a good quality systematic review of cost-effectiveness analyses of existing treatment options for psoriasis, conducted by Zhang et al. (2015).[188] The Zhang review was used as the basis for the current review,[188] and it was assumed – given the broader approach in terms of the review objective, search strategy (population terms AND cost-effectiveness filter), and eligibility criteria – that Zhang et al. had identified relevant records published before 2013. Studies included in the Zhang review (n=53) were screened versus the eligibility criteria for the current review (no date limits were applied in screening).

For the update search, the search strategy was based on the strategy reported in the Zhang review. The difference was that intervention terms were combined with population terms and the cost-effectiveness filter using the Boolean operator AND. The following electronic databases were searched: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); EMBASE (Ovid), EconLit, NHS EED, and Web of Science. The searches were limited to English language, and limited to publications since 2013. The search strategy is detailed in Appendix 12.

Previous technology appraisals for psoriasis were identified by searching the NICE website and bibliographies were scrutinised for eligible studies. No date limits were applied. In addition, the bibliographies of systematic reviews of model-based economic evaluations identified in the searches were scrutinised for eligible studies (similarly no date restrictions were applied).

Eligibility criteria

The inclusion and exclusion criteria are set out below.

Table 50: Summary of the eligibility criteria

	Inclusion criteria	**Exclusion criteria**
Population	Adults suffering with moderate-to severe chronic plaque psoriasis.	Psoriatic arthritis, scalp or nail psoriasis
Interventions of interest	Fumaric acid esters (incl dimethyl fumarate; apremilast; etanercept; adalimumab; infliximab; ustekinumab; secukinumab; ciclosporin; methotrexate; phototherapy/PUVA; acitretin Tofacitinib; brodalumab; ixekizumab **Biosimilars:** Biosimilars of the drugs reported above indicated for psoriasis in Phase III are of interest including but not limited to Inflectra (Infliximab), Rensima (Infliximab), GP2017 (adalimumab), and GP2015 (etanercept)	Any other intervention not listed and combination therapies of the treatments listed under inclusion criteria. Unlicensed dosages of interventions listed under inclusion criteria.
Comparators	Interventions listed above should be compared with each other or with placebo	Any other comparator intervention not listed, and combination therapies of the treatments listed under inclusion criteria. Unlicensed dosages of interventions listed under inclusion criteria.
Outcomes	Cost/QALY Cost/life-year gained	
Study design	Full economic evaluations: – cost-effectiveness analyses – cost-utility analyses – cost minimisation analyses Systematic reviews of economic evaluations[a] will be included as sources of references	RCTs, observational studies, burden of illness studies, and budget impact assessments Publication types: editorial, letter, reviews (other than SRs)

	Inclusion criteria	Exclusion criteria
Other	English language UK models	Non-English language Countries other than UK

Key: PUVA = psoralen combined with ultraviolet A; QALYs = quality-adjusted life year(s); SRs = systematic reviews RCT – randomised controlled trial

Notes: (a) For the purpose of this review, a systematic review will be defined as one that has: a focused research question; explicit search criteria that are available to review, either in the document or on application; explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest; a critical appraisal of included studies, including consideration of internal and external validity of the research; and, a synthesis of the included evidence, whether narrative or quantitative

Data abstraction strategy

Selection of studies:

Studies retrieved from the searches were selected for inclusion through a two-stage process according to the inclusion/exclusion criteria specified (see Eligibility criteria, p143). First, abstracts and titles returned by the search strategy were screened for inclusion by two reviewers. Full texts of identified studies were obtained and screened in the same way. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Data extraction and quality appraisal:

Data extraction was conducted using a standardised data specification form. Information extracted included: details on the country setting, model structure (summary), patient population, QALYs (intervention vs. comparator), costs (currency; intervention vs. comparator), ICER (per QALY gained), and sensitivity analysis. Data were extracted and presented in summary tables.

The quality of identified model-based, cost-utility analyses was assessed using the checklist developed by Philips et al. (2006).[186]

Results

Studies identified

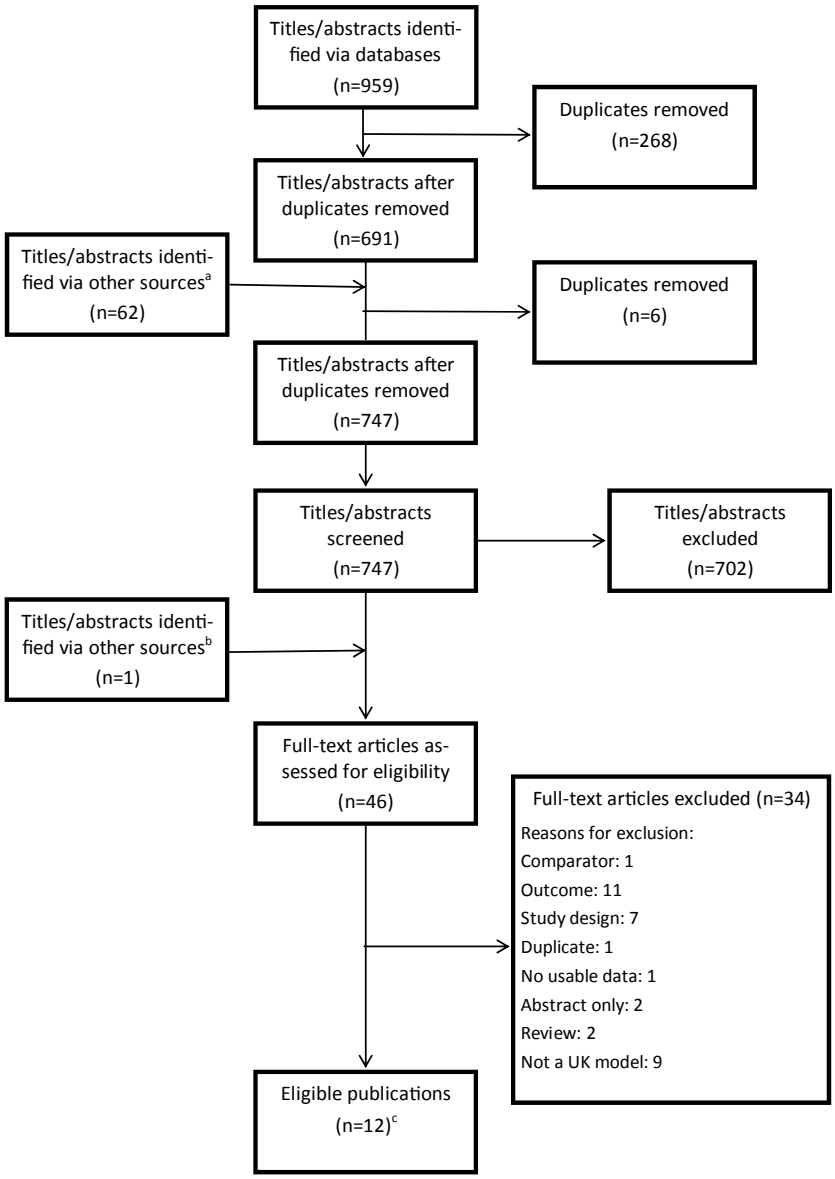
The included studies (n=53) from the Zhang review were screened versus the eligibility criteria for the current review. In addition, reports from previous NICE technology appraisals of psoriasis interventions (n=9) (identified via searching the NICE website)

were screened versus the eligibility criteria. Electronic database searches (2013 to current) yielded a total of 959 references. After de-duplication (electronic and manual), a total of 747 unique titles and abstracts were screened for inclusion in this review.

Bibliographies of relevant reviews identified by the searches but not considered eligible for inclusion in the current review (mainly because they did not appear to use systematic methodology as specified in the protocol for the current review) were also searched. This process identified one potentially relevant study (Loveman et al., 2009).[189]

A total of 46 full texts were retrieved for detailed consideration. Of these, 34 were excluded (a list of excluded studies by reason is provided in Appendix 13). Twelve publications (describing nine models) were considered eligible for inclusion in the review. The study selection process is outlined in Figure 26.

Figure 26. PRISMA flow chart for studies included and excluded from the cost-effectiveness review



Key: NICE = National Institute for Health and Care Excellence

Notes: (a) 53 studies included in the review conducted by Zhang et al., 2015[188] (identified in scoping searches) and nine NICE Technology Appraisals; (b) Papers identified via scrutiny of the bibliographies of identified systematic reviews; (c) A total of 12 publications were identified describing nine UK cost-utility models.

Update searches

Update searches were conducted on 17 January 2017 (date limited 2016 to Current) (see Appendix 14). Three hundred and ninety-six records were identified in the update searches; of these, 106 records were duplicates. Titles/abstracts were screened (n=290) and four were selected for full text screening.[190-193] In addition, one report from a previous NICE technology appraisal of psoriasis interventions was identified via searching the NICE website (TA419).[16] Of the five publications screened at full text, one was excluded[192] as it was only available as an abstract and could not be linked to a full text or TA report in line with eligibility criteria.

A total of four papers were therefore eligible for inclusion but all were linked to an existing model and no new models were identified: one was the Evidence Review Group (ERG) critique of the model presented in the NICE TA process;[193] one (TA419)[16] was a rapid review of TA 368[194] which included a patient access scheme (PAS) for apremilast and revisions to the model inputs to reflect the assumptions that the Appraisal Committee considered more plausible; i.e. source of efficacy and utility estimates; and, assumptions regarding best supportive care and apremilast wastage); two were abstracts[190,191] that are possibly linked to TA 419.[16]

In addition, one systematic review was identified in the searches;[195] the review was retrieved and the reference list was scrutinised; no additional models were identified.

Characteristics of included cost-utility studies

Nine UK cost-utility models (reported in 16 publications[16,39-43,189-191,193,194,196-200]) were identified assessing the cost-effectiveness of biologic therapies for moderate-to-severe psoriasis. Eight of the identified cost-utility models were reviewed in previous NICE technology appraisals (TAs): one multiple technology appraisal (MTA) of etanercept and efalizumab (TA 103),[43,196,200] and five single technology appraisals (STAs) of infliximab (TA 134),[42,189] adalimumab (TA 146),[41,197] ustekinumab (TA 180),[40] secukinumab (TA 350),[39] apremilast (TA 368[194,199] and TA 419[16,190,191]). NICE TA 419[16] was a rapid review of TA 368[194] and incorporated a PAS and a number of changes that were made to the model to reflect the assumptions that the Appraisal Committee considered most

plausible (i.e. source of efficacy and utility estimates and assumptions re BSC and apremilast wastage). No structural changes were made to the model. Changes that were made to specific inputs are noted in the data tables; however, in some cases data were highlighted as commercial in confidence and point estimates could not be extracted. Study characteristics for the included cost-utility models are summarised in Table 51. An overview of available evidence is presented below and detailed summaries are given in Appendix 15.

Table 51: Characteristics of included cost-effectiveness models

Model, Author [[multiple publications]]	Setting, perspective	Aim	Population	Regimens	Model approach	Cycle length Time horizon Discount rate	Sponsor
Woolacott et al., 2006[a196] [[NICE TA 103 (ETAN & EFALIZ), 2006[43]]]	UK UK NHS	To establish the most cost-effective sequence of therapies based on alternative threshold values for cost-effectiveness.	Moderate-to-severe psoriasis (definition unclear)	EFALIZ; ETAN 25 mg (intermittent); ETAN 25 mg (continuous); ETAN 50 mg; BSC	"York Model" (2 part: Decision Tree, trial period; Markov Model, Tx period) (PASI response 50/75/90)	1 yr 10 yrs 6% (costs) and 1.5% (health effects)	NIHR HTA Programme
Wyeth Model[b] [[NICE TA 103 (ETAN & EFALIZ[43]), 2006; Woolacott et al., 2006;[196] Lloyd et al., 2009[c200]]]	UK UK NHS	To assess the cost-effectiveness of ETAN 50 mg BIW, and to explore the characteristics of patients who benefited most from 50 mg dosing	Moderate-to-severe psoriasis (≥10% BSA; ≥10 PASI)	ETAN 50 mg BIW; ETAN 25 mg BIW; No Tx	The short-term (12-wk) analysis is based on patient-level data pooled across the registration trials, so no formal modelling is involved. Longer term extrapolation (ETAN [intermittent and continuous]) based on a model (time horizon 96 wks) (PASI response 50)	Unclear 96 wks 3.5% (costs and health effects)	Wyeth Pharmaceuticals Ltd
Serono Model[b] [[NICE TA 103 (ETAN & EFALIZ[43]), 2006; Woolacott et al., 2006[196]]]	UK UK NHS	To assess the cost-effectiveness of EFALIZ, and to explore the characteristics of patients who benefited most from 50 mg dosing	Moderate-to-severe psoriasis (definition unclear)	EFALIZ; No Tx	Decision tree - probability of continuation beyond 12 wks of therapy and adverse events. (PASI response 50)	NA (not a Markov model) 10 yrs 3.5% (costs and health effects)	Serono
NICE TA 134 (INFLIX),	UK UK NHS	To estimate the cost-effectiveness of INFLIX	Severe psoriasis (4th quartile	INFLIX 5 mg/kg; EFALIZ; ETAN	Based on "York Model" (2 part: Decision Tree,	1 yr 10 yrs	Schering-Plough

Model, Author [[multiple publications]]	Setting, perspective	Aim	Population	Regimens	Model approach	Cycle length Time horizon Discount rate	Sponsor
2008[a42] [STA] [[Loveman et al., 2009 (ERG critique)[189]]]		compared to current clinical practice (ETAN 25mg BIW (continuous)) in severe plaque psoriasis	DLQI; (≥10% BSA; ≥12 PASI)). (Moderate-to-severe psoriasis sensitivity analysis)	(various doses; Standard Tx (TNF/EFALIZ); BSC	trial period; Markov Model, Tx period) (PASI response 50/75/90)	3.5% (costs and health effects)	Ltd
Sizto et al., 2009[197] [[NICE TA 146 (ADALIM), 2008[a41]]]	UK UK NHS	To appraise the clinical and cost-effectiveness of adalimumab for moderate-to-severe chronic plaque psoriasis and determine the optimal treatment sequence	Moderate-to-severe psoriasis (≥10 PASI; DLQI >10)	BSC; MTX; CCS; EFALIZ; ETAN 50 mg (intermittently); ETAN; INFLIX; ADALIM; ETAN 25 mg (intermittently) [all Tx vs BSC and Biologics vs BSC]	Based on "York Model" (2 part: Decision Tree, trial period; Markov Model, Tx period) (PASI response 75 [50 in sensitivity analysis])	1 yr 10 yrs[e] 3.5% (Tx duration costs and health effects)	Abbott Laboratories Ltd
NICE TA 180 (USTEK), 2008[a40]	UK UK NHS	To appraise the clinical and cost effectiveness of USTEK within its licensed indication for the treatment of moderate-to-severe psoriasis	Moderate-to-severe psoriasis (PASI ≥10 and DLQI>10)	USTEK 45 mg / 90 mg; ADALIM; EFALIZ; ETAN; INFLIX; BSC	Based on "York Model" (2 part: Decision Tree, trial period; Markov Model, Tx period) (PASI response 75/90)	3 mths 10 yrs 3.5% (costs and health effects)	Janssen-Cilag Ltd
NICE TA 350 (SECUK), 2015[a39]	UK UK NHS	To appraise the clinical and cost effectiveness of SECUK within its licensed indication for treating moderate-to-severe plaque psoriasis	Adults with moderate-to-severe plaque psoriasis (PASI ≥12) [SG analysis with DLQI >10)	ETAN; ADALIM; INFLIX; SECUK; INFLIX	Based on "York Model" (2 part: Decision Tree, trial period; Markov Model, Tx period) (PASI response 75/90)	1 yr 10 yrs 3.5% (costs and health effects)	Novartis Pharmaceuticals Ltd
NICE TA 368 (APREM), 2015[a194] [Mughal et al., 2014[d199]] [TA 419[16,193]	UK UK NHS	To appraise the clinical and cost effectiveness of APREM within its licensed indication for treating moderate-to-	Adults with moderate-to-severe plaque psoriasis (PASI ≥10 and DLQI >10) not	APREM-ADALIM-ETAN-BSC vs ADALIM-ETAN-BSC	Based on "York Model" (2 part: Decision Tree, trial period; Markov Model, Tx period)	28 days 10 yrs 3.5% (costs and health effects)	Celgene UK

Model, Author [[multiple publications]]	Setting, perspective	Aim	Population	Regimens	Model approach	Cycle length Time horizon Discount rate	Sponsor
(APREM) rapid review of TA 368 with PAS model structure unchanged also reported in Mughal et al., 2016 a,b[190.191]		severe plaque psoriasis	responding or not eligible for other systemic non-biologic therapies		(PASI response 75/90)		
Sawyer et al., 2015[198]	UK UK NHS	To consider as far as evidence allows, the potential cost-effectiveness of sequential use of biologic therapies in patients for whom earlier biologic therapy has failed	Moderate-to-severe psoriasis (DLQI >10) who have previously received Tx with a biologic therapy	Biologic Tx (incl ADALIM, ETAN, INFLIX, USTEK); BSC	Based on "York Model" (2 part: Decision Tree, trial period; Markov Model, Tx period) (PASI response 75/90)	1 yr 10 yrs NR	NICE

Key: ADALIM = adalimumab; APREM = apremilast; BIW = twice weekly; BSC = best supportive care; CCS = ciclosporin; DLQI = dermatology life quality index; EFALIZ = efalizumab; ERG = Evidence Review Group; ETAN = etanercept; FAD = Final Appraisal Determination; HTA = health technology assessment; INFLIX = infliximab; MTX = methotrexate; Na = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NIHR = National Institute for Health Research; NR = not reported; PAS = patient access scheme; PASI = psoriasis area severity index; PUVA = psoralen combined with ultraviolet A; SECUK = secukinumab; TA = Technology Appraisal; Tx = treatment; UK = United Kingdom; USTEK = ustekinumab; wk(s) = week(s); yr(s) = year(s)

Notes: (a) Detail available in: Company Submission; ERG Report; and, FAD; (b) Company reports for TA 103 not identified on the NICE website, data extraction was from the information presented in the ERG report and Woolacott et al., 2006 publication; (c) Lloyd et al, conducted exploratory analysis to assess which subgroups would be most likely to benefit from the 50 mg dose (extension of analysis submitted in TA103); (d) TA 368 adapted for submission to Scottish Medicines Consortium (SMC), Scottish NHS perspective;[201] (e) Not explicitly reported but states "as per York model" in the company submission]

Table 52: Comparison of approach to best supportive care in the included models

Model, Author [[multiple publications]]	Base case resource use assumptions (per year unless stated otherwise)				Total cost per year as reported	Additional cost scenarios considered
	Tx included	Outpatient visits	Day centre care	Hospitalisations		
Woolacott et al., 2006[a196] [[NICE TA 103 (ETAN & EFALIZ), 2005[43]]]	NA	2	NA	See additional cost scenarios considered (right)	NA	Replacement of assumption around PASI 75 hospitalisation with 21 day stay for all BSC patients
Wyeth Model[b] [[NICE TA 103 (ETAN & EFALIZ[43]), 2005; Woolacott et al., 2006;[196] Lloyd et al., 2009[c200]]]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
Serono Model[b] [[NICE TA 103 (ETAN & EFALIZ[43]), 2005; Woolacott et al., 2006[196]]]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
NICE TA 134 (INFLIX), 2007[a42] [STA] [[Loveman et al., 2009 (ERG critique)[189]]]	NA?	2 for responders (PASI ≥75); 3 clinic visits per 6 weeks (non-responders PASI <75)	NA	Only 1 21-day hospital stay per year (non-responders PASI <75)	£130.04 (responders); £8534.88 (non-responders PASI <75)	Hospital admission for non-responders varied between 10 and 25 days; No additional clinical visits for non-responders
Sizto et al., 2009[197] [[NICE TA 146 (ADALIM), 2007[a41]]]	NA?	2	NA	Only 1 21-day hospital stay per year	£117 (cost with hospitalisation [or the unit cost] NR in the paper or in the TA report?	Sensitivity analysis varied days per hospital admission between 0, 16 and 39
NICE TA 180	NA	2	NA	Only 1 21-day hospital	£6209.54	Length of stay

Model, Author [[multiple publications]]	Base case resource use assumptions (per year unless stated otherwise)				Total cost per year as reported	Additional cost scenarios considered
	Tx included	Outpatient visits	Day centre care	Hospitalisations		
(USTEK), 2008[a40]				stay per year		adjusted to 17.5 and 27,5 days
NICE TA 350 (SECUK), 2015[a39]	45% of patients receive 15 mg oral MTX QW, 45% CCS 300 mg daily; UVB phototherapy at rates: 1.18 induction; 2.66 post induction Yr 1; 3.84 annual thereafter	Induction: 4; Post Induction Yr 1 3; Annual thereafter: 4	Day centre visit rates: Induction 1.54; Post induction Yr 1 3.46; Annual thereafter 5	10.7 days per year	Induction: £1433 (plus hosp if not PASI 75 £1232); Post Induction Yr 1: £2777 (plus hosp if not PASI 75 £4105); Annual for those remaining on Tx: £4210 (plus hosp if not PASI 75 £5337); Annual thereafter £3678 (plus hosp if PASI 75 £5337 and if not PASI 75 £5337)	Sensitivity analysis
NICE TA 368 (APREM), 2015[a194] [Mughal et al., 2014[d199]]	45% of patients receive MTX, 45% CCS continuously 16% have 24 sessions of NBUVB a yr	10% patients have 5 visits	All patients have 5 visits	82% of patients (high need) have 20.8 days hospitalised, 18% (very high need) have 53.04 days hospitalised. Average for all patients 26.6 days	£11,543 (£887.90 per 28-day cycle)	None
NICE TA 419[16,193] (APREM) Rapid Review of TA 368 also published in Mughal et al., 2016 a,b[190,191]	NR[e]	NR[e]	NR[e]	Average for all patients 6.49 days per year	NR[e] (£348.22 per 28-day cycle)	NR[e]
Sawyer et al., 2015[198]	45% of patients receive MTX, 45% CCS continuously (max 2 yrs), 16% have 24 sessions of PUVA	10% patients have 5 visits	All patients have 5 visits	82% of patients (high need) have 20.8 days hospitalised, 18% (very high need) have 53.04 days	£11436	Sensitivity analysis (variables associated with best supportive

Model, Author [[multiple publications]]	Base case resource use assumptions (per year unless stated otherwise)				Total cost per year as reported	Additional cost scenarios considered
	Tx included	Outpatient visits	Day centre care	Hospitalisations		
	a year			hospitalised		care (efficacy and resource use)
Other sources cited in the TAs for comparison						
Fonia et al., 2010[202]	Systemic drugs and supportive drugs; Pre intro. biologics 2.76 PUVA: Post intro biologics 0.26	Pre intro. biologics 3.22 Post intro. biologics 3.25	Pre intro. biologics 0.14 Post intro. biologics 0.16	Pre intro. biologics 1.55 Post intro. Biologics 6.49 days	Pre intro. biologics £4207 (£1252 drug costs + £2957 hospital use); post intro. biologics £11981 (£10707 drug costs + £1274 hospital use)	NA (retrospective cohort study [SEs reported])
NICE CG153[5,203]	45% of patients receive MTX, 45% CCS continuously (max 2 yrs), 16% have 24 sessions of NBUVB a yr	10% patients have 5 visits	All patients have 5 visits	82% of patients (high need) have 20.8 days hospitalised, 18% (very high need) have 53.04 days hospitalised	£10730	Extensive sensitivity analysis conducted, see Table 178 (p673) of GDG 153

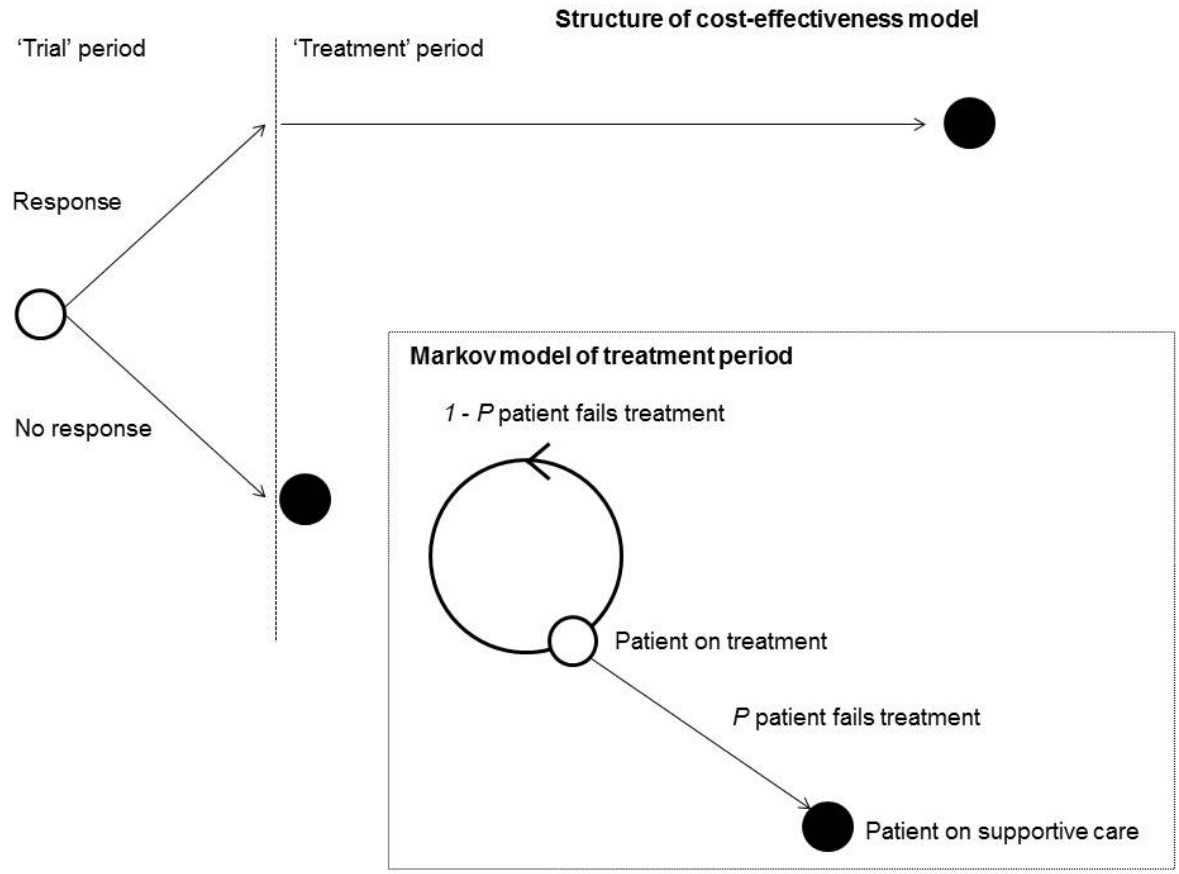
Key: ADALIM, adalimumab; APREM, apremilast; CCS, ciclosporin; CG, Clinical Guidelines; EFALIZ, efalizumab; ETAN, etanercept; hosp, hospitalisation; INFLIX, infliximab; intro., introduction; MTX, methotrexate; NA, not applicable; NBUVB Narrow band UVB; NICE, National Institute for Health and Care Excellence; NR, not reported; PASI =psoriasis area severity index; PUVA, psoralen and ultraviolet A; QW, once weekly; SE, standard error; SECUK, secukinumab; TA= technology appraisal; Tx= treatment; USTEK, ustekinumab; Yr(s), years(s)

Notes: (a) Detail available in: Company Submission; ERG Report; and, FAD; (b) Company reports for TA 103 not identified on the NICE website, data extraction was from the information presented in the ERG report and Woolacott et al., 2006 publication; (c) Lloyd et al, conducted exploratory analysis to assess which subgroups would be most likely to benefit from the 50 mg dose (extension of analysis submitted in TA103); (d) TA 368 adapted for submission to SMC, Scottish NHS perspective; (e) Assumptions re best supportive care in TA 419 assumed to be the same as in TA 368 apart from the number days of hospitalisation reduced to 6.49 days per cycle (20.8 days per year) meaning that the overall cost was £341.22 per 28-day cycle. In addition, assumptions re the efficacy of BSC were also assumed to be as per the National Clinical Guidelines Centre Model (CG 153)

The population considered in the included cost-effectiveness analyses were people with moderate-to-severe psoriasis. This was defined as psoriasis area severity index (PASI) ≥10 and dermatology life quality index (DLQI) >10 in the majority of included studies. In the adalimumab model[41,197] and the model reported by Sawyer et al. (2015)[198] the PASI score was not reported and the DLQI score (>10) was the only population descriptor given. Two of the identified models (TA 134 and TA 350)[39,42] used a definition of PASI ≥12 but conducted a subgroup analysis for a moderate-to-severe population (people with DLQI >10). In addition, while the majority of models considered a biologic naïve population the model reported by Sawyer et al. (2015)[198] considered patients previously treated with biologics.

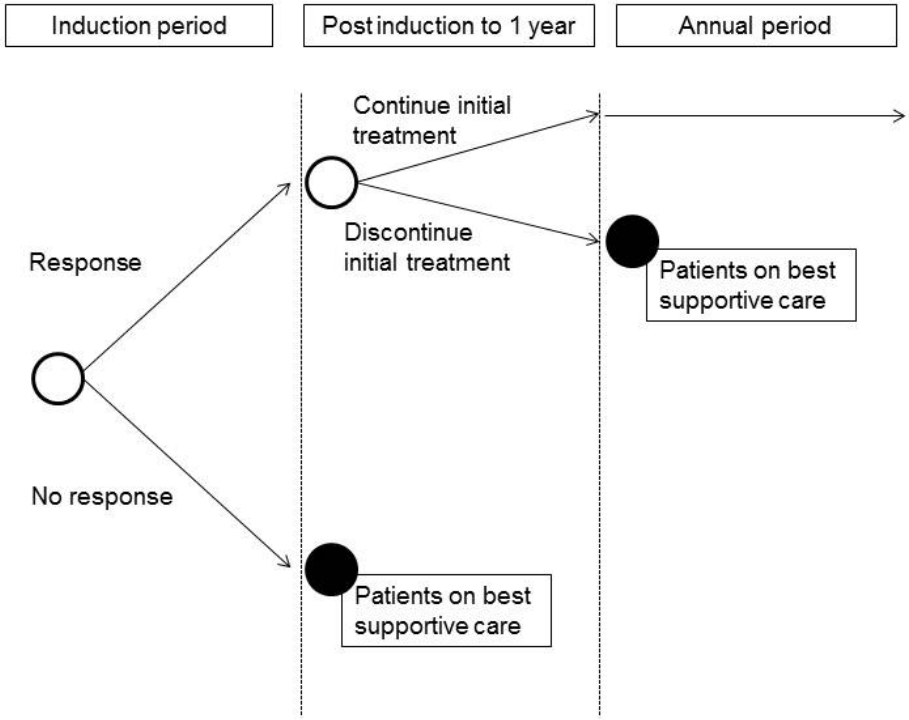
All of the included models were based on the "York model";[196] a Markov state transition cohort model (Figure 27). This was a two-part model comparing a "trial period" (decision-tree structure, based on the duration in the clinical trials for the included treatments, and a period of continued use (or "treatment period"). At the end of the "trial period", patients with a score of PASI 75 or more either remained on that line of treatment, or, in the event of inadequate response moved to best supportive care (BSC). During the "treatment period" patients were assumed to remain in the same health state unless they died or withdrew from treatment. Of note, the cost-utility model used to evaluate secukinumab (TA 350)[39] was a three-phase model (Figure 28); the decision tree structure was extended beyond the induction phase to Year 1. A more recent model (TA 368 2015; Figure 29) used to assess the cost-effectiveness of apremilast (TA 368[194] and TA 419[16,193]) was based on the structure used in the "York model" but adapted to allow comparison of a series of treatment sequences, with up to five lines of treatment.

Figure 27. Structure of the cost-effectiveness model in the "York model"



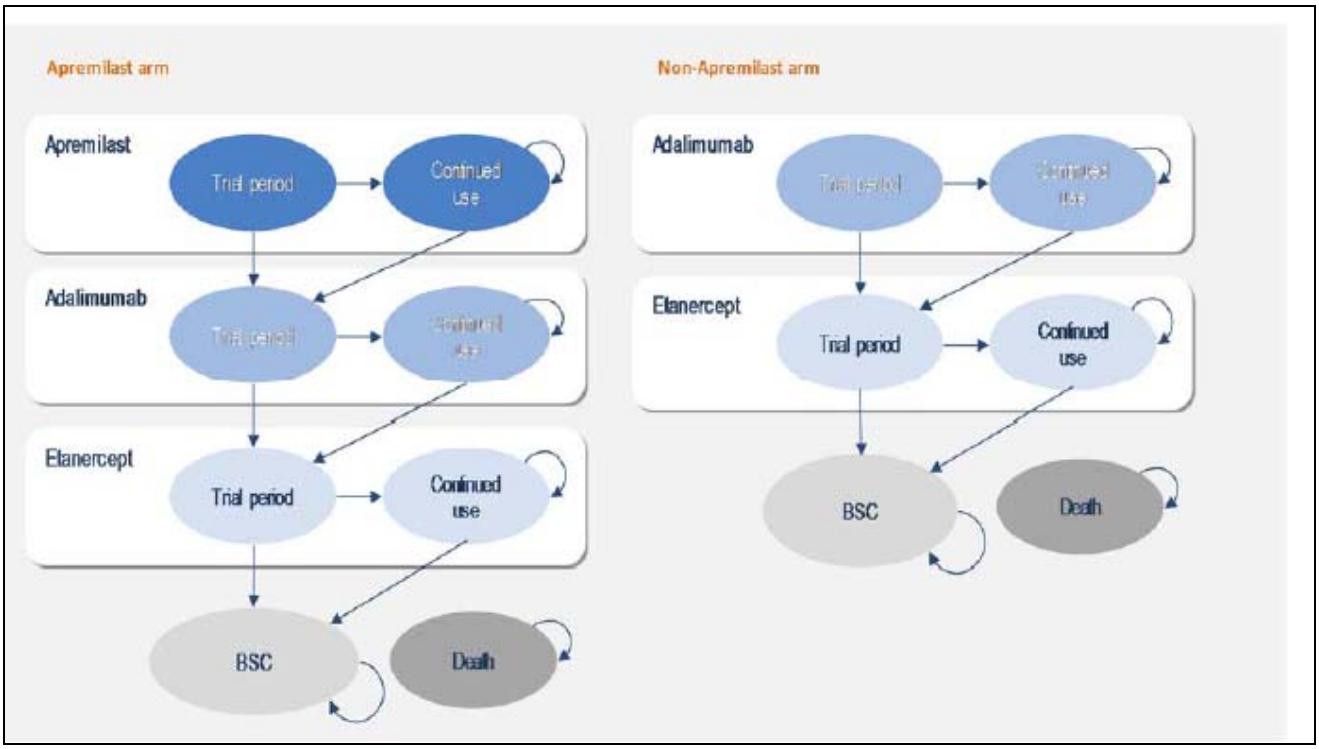
Source: Woolacott et al., Health Technol Assess, 2006 (Figure 3, p55 and Figure 4, p57)[196]

Figure 28. Model structure: NICE TA 350 (secukinumab)



Key: NICE = National Institute for Health and Care Excellence; TA = technology appraisal
Source: NICE TA 350 (secukinumab) company submission (Figure 28, p152)[39]

Figure 29. Model structure: NICE TA 368 (apremilast)



Key: BSC = best supportive care; NICE = National Institute for Health and Care Excellence; TA = technology appraisal

Notes: Transition to the death health state is allowed from all health states in the model (arrows not displayed in the figure)

Source: NICE TA 368 (apremilast) company submission (Figure 26, p33)[194] also NICE TA 419 (apremilast) rapid review of TA 368 with patient access scheme and revisions to the model to reflect the assumptions that the Appraisal Committee considered most plausible[16,193]

All models evaluated costs and effects over a 10-year time horizon and were conducted from a UK National Health Service (NHS) perspective. The adalimumab model (TA 146 and Sizto et al., 2009) also included lost productivity in a scenario analysis.[41,197]

Each of the models included the comparison of a biologic treatment with best supportive care or no treatment. The approach to BSC varied across the identified models (see Table 52, p152). The majority of included models also included comparison with alternative biologic treatments. The "York model", and the adalimumab model aimed to identify the most cost-effective sequence of treatment options conditional on a threshold of cost-effectiveness.[41,196,197] The cost-utility model evaluating apremilast (TA 368) assessed the cost effectiveness of placing apremilast before biologics for moderate-to-

severe plaque psoriasis,[194] and the cost-utility model reported in Sawyer et al. (2015) assessed the potential cost effectiveness of sequential biologic therapies.[198]

PASI response rates were used as the clinical effectiveness measure in all of the included models. Treatment effectiveness estimates were typically derived using methods of synthesis for efficacy evidence; e.g. meta-analysis, or network meta-analysis, or from pooled analysis of clinical trial data. Clinical effectiveness parameters are summarised in Appendix 16 for information.

QALYs were mostly generated with the help of EuroQol five dimensions questionnaire (EQ-5D), which was partly based on PASI and DLQI values (see Section 5.4) for discussion of identified utility values).

The costs considered in the analyses were direct costs only (adverse events not explicitly included), direct and indirect costs (adverse events not explicitly included), and direct costs and costs of adverse events. The exclusion of adverse events was considered a conservative approach. The main reason reported for the exclusion of adverse events was a lack of data on treatment pathways and resource use. In the model submitted in NICE TA 350 (secukinumab),[39] only the cost of serious adverse events that required hospitalisation were included in the model as it was assumed these could be cost drivers. The model incorporating indirect costs did so in a sensitivity analysis, and took into account costs of lost productivity during hospitalisation.[197] Direct costs considered in the included models were those incurred by the NHS including drug costs, administration costs, monitoring and the cost of outpatient visits, and of inpatient stays. Evidence sources for resource use typically referred to two sources: the NICE Clinical Guideline Centre 153[5,203] and Fonia et al., 2010.[202] Reference sources for costs included NHS Reference Costs, British National Formulary (BNF), NHS Trust data, Personal Social Services Research Unit (PSSRU), other published sources; e.g. National Clinical Guidelines Centre, previous TAs, and clinical opinion. Where cost data from published sources were used but not current, the PSSRU inflation index was used to inflate current costs. Costs input parameters are summarised in Appendix 17.

Base case results (and sensitivity analyses) for the included cost-utility studies are summarised in Appendix 18. The main drivers of cost effectiveness were target

population (as determined by DLQI and PASI score), the approach to best supportive care, treatment costs, efficacy estimates, utility values, rates in re-treatment, hospitalisation for non-responders, treatment withdrawal/discontinuation, dropout rates, and, lost productivity during hospitalisation.

Overall the quality of the included studies was moderate-to-good (see Appendix 19). There was some variability across the included models in the assessment of uncertainty and also in the methods used for model validation. Three studies (Mughal et al., 2014;[199] Mughal et al., 2016a,b[190,191]) were linked to the full model report; the abstracts were therefore not quality appraised separately. The majority of the included models appeared to have been funded by pharmaceutical companies (all as part of a NICE HTA assessment, and, as such although have the potential for bias have been independently critiqued (see Appendix 20). There were two exceptions, the "York model"[196] and the model by Sawyer et al. (2015)[198] which received funding from the NIHR HTA programme and NICE, respectively.

The purpose of this review was to identify UK model-based cost-utility analyses of regimens for the treatment of moderate-to-severe psoriasis. The review highlights that despite a number of models developed over the last 10 years there is ongoing uncertainty associated with key drivers of cost-effectiveness. In addition, this review indicates a move towards assessing sequential biologic therapies which itself presents new challenges and uncertainties specifically related to the assumptions surrounding treatment sequencing as well as assumptions related to the efficacy of a treatment contingent on its position in the treatment pathway. In the absence of models assessing the cost-effectiveness of DMF (LAS41008) (Review 1; Section 5.1.1), the information identified in this review was used to inform the development of a de novo model to assess the cost-effectiveness of DMF (LAS41008) for the treatment of moderate-to-severe psoriasis.

5.2 De novo analysis

5.2.1 Patient population

The target population is adults with moderate to severe plaque psoriasis who have failed to respond to or who have a contraindication to, or are intolerant to systemic non-biologic therapy. This population is representative of the patients assessed in the BRIDGE Study.

5.2.2 Model structure

A Markov state transition cohort model has been developed based on the model structure previously developed by the University of York Assessment Group Woolacott et al. (2006),[196] but adapted to allow a comparison of treatment sequences following NICE technology appraisal (TA) 368.[194] A Markov model was used to capture the chronic nature of psoriasis. Psoriasis is a lifelong condition with no known cure, the majority of cases occur before the age of 35 years.[3] Disease severity and treatment duration may vary among psoriasis patients. Furthermore, as patients may not respond or tolerate a particular therapy, several alternative treatments may be prescribed in current clinical practice. Treatment goals are to minimise the extent and severity of disease to the point at which it no longer disrupts substantially the patient's life.[14] Data suggest that patients cycle through multiple treatment options during their disease course. Thus, it is reasonable to assume that the assessment of the economic impact of using DMF (LAS41008) as an addition within a treatment sequence is more realistic and reflective of clinical practice than directly comparing the treatment to best supportive care (BSC) or biologic treatments. Figure 25 provides a depiction of the model. Recently apremilast has also been approved as part of the treatment sequence prior to the use of biologics (TA419).[16]

Each arm of the model allows the selection of up to four lines of treatment followed by BSC. In the base case DMF is considered as an addition to the standard sequence, adalimumab followed by ustekinumab followed by BSC. The intervention arm is DMF followed by adalimumab and then ustekinumab and BSC.

- Treatment sequence: DMF → adalimumab → ustekinumab → BSC
- Comparator sequence: adalimumab → ustekinumab → BSC

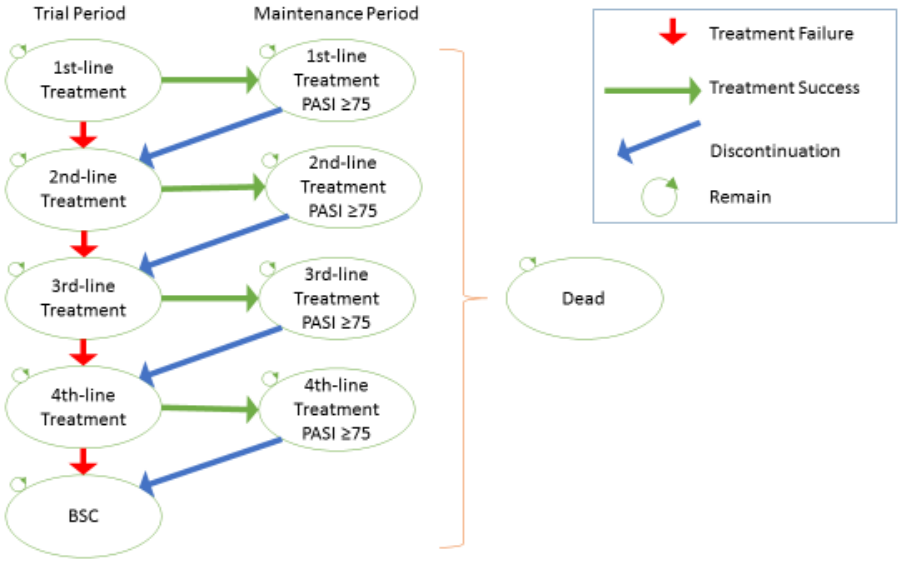
The model is flexible to the number of treatments selected in the treatment sequence and the treatments included. This allows DMF (LAS41008) to be considered for use at any point in the treatment sequence and to be compared directly to the other treatments in the model.

For each treatment, response is assessed after the recommended trial period, ranging from 10 to 16 weeks depending on the treatment (for more details on the dosing schedule and duration, see Table 54 and Section 5.2.3). Beyond the trial period, responders are assumed to continue treatment until they withdraw due to loss of efficacy or other causes. Non-responders and patients discontinuing during the continued-use period are assumed to move on to subsequent lines of treatment immediately.

As used in previous economic evaluations such as the study by Woolacott et al. (2006)[196] and by the National Clinical Guidelines Centre (in NICE Clinical Guideline CG153)[5,203], a 10-year time horizon is considered in the base case, but 20 year and lifetime horizons are also evaluated. To account for the different lengths of trial periods (i.e. 10, 12 or 16 weeks) a cycle length of 14 days is used in the model. A year is assumed to be composed of 26 cycles, each of 14 days.

Death from all causes is possible from any health state. No specific psoriasis-related mortality is included in the model because of the lack of evidence demonstrating that psoriasis is directly associated with increased mortality when compared with the general population.

Figure 30: Markov model structure



Abbreviations: BSC, best supportive care; PASI, psoriasis area severity index

Model health states

Model states are dependent on treatment states and the health states within each of the treatment states. The treatment states describe the treatment pathway and the health states describe the impact of treatments on the symptoms of psoriasis. For DMF (LAS41008) and each line of biologic therapy, two treatment states are described: a trial period and maintenance period (Figure 30). The trial period corresponds to initial treatment with an active therapy, at the end of which response is assessed according to whether a patient achieves a 75% reduction in the PASI score (i.e. PASI75). During the trial period patients are assumed to be in the no response health state and receive the baseline HRQoL. The maintenance period corresponds to treatment beyond the trial period in patients who achieve a PASI75 (Table 53). Patients in the maintenance period are assumed to maintain a PASI75 response until they discontinue. During the maintenance period patients are considered to be in health states PASI75-PASI90 or PASI>90 according to the NMA PASI response and receive the appropriate HRQoL for these health states.

Table 53: Model Health States

Treatment State	Health State	Definition
Trial Period	No response	10-16 weeks (depending on the treatment), after which treatment response is assessed for all patients
Maintenance Period	PASI75-PASI90 PASI>90	Continued use of treatment for patients having responded to treatment according to achievement of PASI75 response at the end of the trial period
BSC	PASI<50 PASI50-PASI<75 PASI75-PASI<90 PASI90	Last treatment strategy for patients having failed all other treatment options
None	Dead	Background mortality

The duration of the trial period is based on current recommendations regarding the period over which response is assessed for each treatment option (Table 54). The trial period is 10−16 weeks, depending on the therapy (16 weeks for DMF (LAS41008), adalimumab, apremilast, Fumaderm, ixekizumab and ustekinumab,12 weeks for etanercept and secukinumab and 10 weeks for infliximab), as specified in the NICE clinical guidelines. A 16-week trial period is used for DMF (LAS41008) as the primary endpoint response to treatment in the phase 3 clinical trials was evaluated at this time point. The sequential model was built with the flexibility to modify the trial periods, from 2 weeks up to a maximum of 16 weeks, for all treatments included in the analyses.

Table 54: Lengths of trial periods

Drug	Duration	Source
DMF	16 weeks	BRIDGE Study[23]
Apremilast	16 weeks	TA368[194]
Adalimumab	16 weeks	TA146[41]
Etanercept	12 weeks	TA103[43]
Fumaderm	16 weeks	BRIDGE Study[23]
Infliximab	10 weeks	TA134[42]
Ixekizumab	16 weeks	MIMS[204]
Secukinumab	12 weeks	TA350[39]
Ustekinumab	16 weeks	TA180[40]

Abbreviations: DMF, dimethyl fumarate; TA, technology appraisal

If treatments are found not to be effective, patients should receive supportive care, according to current guidelines. Thus, patients who fail all treatment options are assumed to receive BSC as the final line of treatment. BSC is assumed to be an absorbent treatment state, meaning that patients remain in this state for the remaining period of the analysis (i.e. up to 10 years in the base case) or until they die. Patients in BSC are split into four levels of PASI response according to the NMA placebo PASI response and receive the appropriate HRQoL for each of these health states.

Disease progression

The natural history of the disease is usually chronic with intermittent remissions and exacerbations (NICE CG153, 2012).[5,203] Disease severity and treatment duration may vary from patient to patient but there are limited data to suggest skin symptoms are progressive in nature.

No underlying disease progression is assumed within the model.

Key features of the analysis

The key features of the analysis are summarised in Table 55.

Table 55: Model structure and justifications

Factor	Chosen Value	Justification	Reference
Time horizon	10 years	The base case analysis is considered an appropriate timeframe to capture all relevant costs and effects and was used to match previous NICE analyses.	Woolacott et al. 2006[196] National Clinical Guidelines Centre 2012[5,203]
Cycle length	14 days	Used to account for the different lengths of trial periods.	
Half-cycle correction	Yes	As recommended in modelling guidelines	Siebert et al. 2012[205]
Health effects measured	QALYs	NICE reference case	NICE Methods Guide 2013[206]
Discount rate	3.5% for utilities and costs	NICE reference case	NICE Methods Guide 2013[206]
Perspective	NHS and PSS	NICE reference case	NICE Methods Guide 2013[206]

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; QALYs, quality-adjusted life years

5.2.3 Intervention technology and comparators

The intervention and comparators in the model are implemented according to their market authorization. The model also includes Fumaric Acid Esters (FAE). Use of FAEs is well supported by clinical evidence and although not licensed in the UK to treat psoriasis FAEs have been imported and used in the UK as an option for patients requiring systemic, non-biological therapies.[22] In the model it is assumed that FAEs are used the same as DMF (LAS41008).

DMF (LAS41008) is a tablet for oral use. To improve tolerability, it is recommended that treatment should begin with a low initial dose with subsequent gradual increases.

- Week one: 30 mg is taken once daily (1 tablet in the evening).
- Week two: 30 mg is taken twice daily (1 tablet in the morning and 1 in the evening).
- Week three: 30 mg is taken three times daily (1 tablet in the morning, at midday, and in the evening).
- Week four: treatment is switched to only 1 tablet of 120 mg in the evening.
- This dose is then increased by 1x120 mg tablet per week at different times of day for the subsequent 5 weeks, up to a maximum daily dose of 720 mg at week 9.

The maximum daily dose allowed is 720 mg (3x2 tablets of 120 mg)

If treatment success is observed before the maximum dose is reached, no further increase of dosage is necessary. After significant improvement of the skin lesions has been achieved, the daily intake of DMF (LAS41008) should be slowly reduced to an individually required maintenance dose. Dosage modifications may also be necessary in case of individual intolerability or abnormalities of laboratory parameters.

The model captures the increase in dosing as described above. In the model patients are treated with 720 mg at week 9 after which the dose is decreased to 624 mg, the average dose after 9 weeks in the BRIDGE study, for the remainder of the trial period. The average long-term dose is modelled as 360mg per day. This was the average long-term dose used in the FUTURE study.[25]

Dosages for the other treatments are modelled in line with their marketing authorisation and are presented below:

- Apremilast: 30 mg administered orally, twice daily;
- Etanercept: 50 mg once weekly, administered as a subcutaneous injection;
- Adalimumab: an initial 80mg subcutaneous injection, followed by a 40 mg dose given every other week;
- Infliximab: 5 mg per kg of body weight given as intravenous infusion on Weeks 0, 2 and 6 and every 8 weeks thereafter;
- Ixekizumab: 160 mg at week 0, 80 mg at weeks 2,4,6,8,10 and 12 and then 80 mg every 4 weeks;
- Secukunimab: 300mg subcutaneous injection every week for 4 weeks followed by one 300 mg injection every 4 weeks;
- Ustekinumab: an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter.

Clinical continuation rules

All comparator treatments have a clinical continuation rule as recommended by NICE. This rule states that treatment should be stopped for patients that do not achieve PASI75 within the trial period. As described previously, in the model only patients that achieve PASI75 during the trial period continue on treatment in the maintenance period. It is assumed that this continuation rule will also apply to DMF (LAS41008), therefore in the model, DMF (LAS41008) is only continued after the 16 week trial period if patients achieve PASI75.

5.3 Clinical parameters and variables

Clinical data from the BRIDGE study are combined with data from the literature to inform model inputs. Table 56 describes the data sources for the model.

Table 56: Data sources for the health economic model

Characteristic	Data	Source
Baseline patient characteristics	Age Weight	Reich et al.[25]
	Baseline HRQoL	Revicki et al.[80]
Efficacy	PASI50, PASI75 and PASI90 response rates	Section 4.10
	Length of trial period	NICE TA 368, 2015[194]
	Withdrawal rate	Woolacott et al., 2006[196]
Health-related quality-of-life	HRQoL improvements by PASI scores	Woolacott et al., 2006[196]

Abbreviations: HRQoL = health-related quality of life; NMA, network meta-analysis; PASI, psoriasis area severity index; TA, technology appraisal

Baseline patient characteristics

Baseline patient characteristics such as the mean age and weight are based on Reich et al.[25] The baseline age and sex distribution affect the life expectancy of patients in the model. The mean weight is used in the model to determine the dose and cost of infliximab.

Efficacy

PASI response rates

The network meta-analysis previously described was used to inform the effectiveness parameters, given the lack of head to head trials. In the model PASI75 response determines treatment continuation. Treatment response is assumed to occur at the end of the treatment specific trial period. To inform the HRQoL within the maintenance period PASI75 and PASI90 response are used.

PASI response for each treatment is reported in Table 57. DMF (LAS41008) and Fumaderm have the same response rates given that the BRIDGE study found that DMF (LAS41008) was non-inferior to Fumaderm. Previous analyses of Fumaderm have

reported higher response rates. In TA 108 Woolacott et al. (2006) found a PASI50 of 53%, a PASI75 of 27% and a PASI90 of 9%.[12]

Table 57. PASI Response

	PASI 50	PASI 75	PASI 90	Source
DMF	38%	18%	6%	NMA
Apremilast	50%	27%	10%	NMA
Adalimumab	83%	64%	37%	NMA
Etanercept	76%	54%	28%	NMA
Fumaderm	38%	18%	6%	Assumption
Infliximab	94%	82%	59%	Average of TA350 and TA419
Ixekizumab	98%	91%	74%	NMA
Secukinumab	94%	83%	61%	NMA
Ustekinumab	91%	77%	52%	NMA
Best supportive care	16%	5%	1%	NMA

Abbreviations: DMF, dimethyl fumarate

Withdrawal rates

In the maintenance phase of the model patients discontinued treatment at a constant rate of 20%. This rate has been used in previous NICE technology appraisals (NICE TA 368).[194] Due to the absence of long-term data pertaining to DMF (LAS41008) at the time of this analysis, the withdrawal probability for DMF (LAS41008) was assumed to be the same as for biologic treatments. In a 2016 analysis of drug survival rates and reasons for drug discontinuation in moderate-to-severe psoriasis it was found that 46% of patients continued FAE after 1 year and 25% of patients continued FAE after 5 years.[207] A 14% annual withdrawal rate was calculated between years 1 and 5, since much of the first year withdrawal is due to lack of efficacy, i.e. not achieving a 75% reduction in PASI. Data were also available for adalimumab, etanercept, infliximab and ustekinumab. Estimates of withdrawal from Arnold et al. (2016) were used in a sensitivity analysis.[207] The analysis assumed no withdrawals during the trial period.

Transition rates

Transition rates between health states are informed by the PASI response and withdrawal rates. Patients transition from the trial period to the maintenance period based on the PASI75 response. Patients transition from maintenance to a subsequent

trial period or BSC based on the withdrawal rates used in the model. Patients transition to the dead state based on age specific mortality rates. Only the mortality rates are time dependent. Response rates and withdrawal rates are assumed to be constant over time.

5.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

No EQ-5D data were collected in the DMF (LAS41008) trial. DLQI was collected in the BRIDGE study and multiple algorithms are available for mapping DLQI to EQ-5D. Using data from the BRIDGE study and a re-estimation of the Woolacott et al. algorithm from TA180 DLQI data were mapped to EQ-5D for DMF (LAS41008), Fumaderm and placebo arms of the BRIDGE Study. It was found that DMF (LAS41008) has higher expected HRQOL values in each PASI state compared to Fumaderm and placebo (Table 58).

Table 58: Improvements in HRQOL estimated from DLQI

PASI Response	DMF (LAS41008)	Fumaderm	placebo
<50	0.03	0.02	0.01
50-75	0.11	0.10	0.08
75-90	0.14	0.14	0.09
>90	0.19	0.16	0.18

Abbreviations: DLQI, dermatology life quality index; DMF, dimethyl fumarate; HRQoL, health-related quality of life

Mapping

The utility scores for the different PASI categories were taken from Woolacott et al. (2006)[196] to ensure consistency and comparability with previous NICE TAs in psoriasis. These data were estimated by mapping (using an ordinary least squares linear regression) the DLQI associated with PASI responses from etanercept trials to changes in EQ-5D utility using data from the Health Outcomes Data Repository (HODaR) database. HODaR contained 86 patient responses on DLQI and EQ-5D.

Several other studies have reported mapping algorithms linking change in DLQI to change in EQ-5D. These are detailed in Table 59.

Table 59: DLQI to EQ-5D mapping algorithms in the literature

Variable	Blome EQ-5D VAS[208]	Blome EQ-5D VAS[208]	Currie[209]	Heredi[210]	Heredi[210]	Norlin[211] PASI<10	Norlin[211] PASI≥10	Ustekinumab TA180 (MS),[40] re-estimation of Woolacott et al., 2006[196]	Ustekinumab TA180 (MS)[40]
R2	0.242	0.313	0.27	0.169	0.488	NR	NR	0.1315	NR
Constant	77.367	93.002	0.956	0.8	1.026	0.8781	0.8789	0.8554	0.908
DLQI	-1.493	-1.418	-0.2548	-0.02	-0.080	-0.0197	-0.0201	-0.0162	-0.016
PASI		-0.153							
active arthritis		-4.728			-0.134				
concomitant disease		-3.563							
light/laser therapy		2.252							
age		-0.256							
#psoriasis hospitalisations, year		-1.104			-0.104				
Gender (female)					-0.090				
Psoriasis duration					-0.004				
Chronic plaque psoriasis					-0.089				
Palmoplantar psoriasis					-0.347				
Scalp psoriasis					0.152				
#psoriasis GP visits, month					-0.160				
Use of home help					-0.139				

Abbreviations: DLQI, dermatology life quality index; EQ-5D, EuroQoL 5 Dimension; GP, general practitioner; MS, manufacturer submission; NR, not reported; PASI, psoriasis area severity index; VAS, visual analogue scale

Health-related quality-of-life studies

The comprehensive search described in Section 5.1; (Appendix 12 and 14) covers the search for relevant HRQoL/utilities. Parameter inputs used in existing cost-utility models are summarised in Table 60.

The majority of included models estimated utility values based on the proportion of patients in the different PASI categories and the change in utility from baseline associated with the different PASI response categories (and different baseline DLQI scores), and used a regression equation to map changes in EQ-5D utility. The most frequently referenced regression equation was that used in the "York model" (Woolacott et al., 2006).[196] These data were estimated by mapping (using an ordinary least squares linear regression) the DLQI associated with PASI responses from etanercept trials to changes in EQ-5D utility using data from the Health Outcomes Data Repository (HODaR) database. HODaR contained 86 patient responses on DLQI and EQ-5D.

Of note, in the model in TA 368 (apremilast)[16] EQ-5D data from the apremilast clinical trials were used in the DLQI ≤10 base-case (with a DLQI >10 scenario), but in the DLQI >10 base-case HRQoL decrements from Woolacott et al. (2006)[196] were applied to a baseline estimate reported in Revicki et al. (2008)[80] with the EQ-5D trial data used in sensitivity analysis. In line with the critique of TA 368,[193] the utility input parameters were updated and source data from the apremilast clinical trials were used in the analysis presented in TA 419.[16]

Three of the included models conducted analysis of EQ-5D data collected in clinical trials (TA 146 [adalimumab]; Sizto et al., 2009; TA 350 [secukinumab]).[39,41,197] In the model in TA 180 (ustekinumab),[40] observed patient-level SF-36 scores were converted into the SF-6D utility values and aggregated according to the PASI response categories; these estimates were used in a sensitivity analysis.

Two of the included models (TA 134 [infliximab];[42] Serono Model [TA 103][43]) used values reported in the literature (Woolacott et al., 2006 and Zug et al. 1995),[196,212] without conducting further analysis.

Table 60: Utility parameters from included cost-effectiveness models

Model, Author [[multiple publications]]	Utility	
	Source	Value
Woolacott et al., 2006[196] [[NICE TA 103 (ETAN & EFALIZ), 2005[43]]]	Utilities associated with Tx based on proportion of patients in the PASI categories and change in utility from BL per PASI response category. OLS linear regression analysis of DLQI and EQ-5D data from the HoDAR database to map changes in EQ-5D utility. Used mean for all patients regardless of BL QoL (base case) and for SG of patients with worst BL QoL (4th quartile DLQI).	Utility gain (all patients) PASI <50 0.05; PASI 50-75 0.17; PASI 75-90 0.19; PASI 90 0.21 ; (4th quartile DLQI) PASI <50 0.12; PASI 50-75 0.29; PASI 75-90 0.38; PASI 90 0.41
Wyeth Model [[NICE TA 103 (ETAN & EFALIZ[43]), 2005; Woolacott et al., 2006;[196] Lloyd et al., 2009[2--]]]	The 'mapping' of QoL (DLQI) and PASI to utility was based on a survey undertaken in Cardiff (Currie et al., 2007) QALYs were computed, for each patient, using AUC methods based on change in utility (predicted from DLQI) between BL and 12 and 24 wks.	NR[a]
Serono Model [[NICE TA 103 (ETAN & EFALIZ[43]), 2006; Woolacott et al., 2006[196]]]	Literature search identified Zug et al., 1995 which elicited utilities using TTO method	Non-response 0.59; Response 0.945; Mild psoriasis 0.89
NICE TA 134 (INFLIX), 2008[42] [STA] [[Loveman et al., 2009[189]]]	Woolacott et al., Health Technol Assess, 2006	Utility gain (4th quartile DLQI) PASI <50 0.12; PASI 50-75 0.29; PASI 75-90 0.38; PASI 90 0.41
Sizto et al., 2009[197] [[NICE TA 146 (ADALIM), 2008[41]]]	From analysis of EQ-5D data from CHAMPION and REVEAL trials; assessed using UK population weights; normal distribution	No response (PASI <50) 0.06 (0.03); Moderate response (PASI ≥50 to <90) 0.18 (0.02); Good response (PASI ≥90) 0.31 (0.03) [all mean change (SEM)]
NICE TA 180 (USTEK), 2008[40]	Estimated based on proportion of patients in each PASI category and the change in utility from BL, adjusted for BL DLQI. Estimated from an original analysis of patient-level data from 2 RCTs. The regression method used in Woolacott et al., 2006 was followed. A replicate mapping study was carried out to validate the methodology of mapping from DLQI onto the EQ-5D (German utility study NR])	PASI response <50, 0.04; ≥50 - <75, 0.17; ≥75 - <90, 0.22; ≥90, 0.25
NICE TA 350 (SECUK), 2015[39]	EQ-5D data across all time points and five trials was pooled in a complete case analysis. EQ-5D QoL changes from BL at a given timepoint as a function of PASI response at that timepoint multiplied by BL DLQI difference from the pooled mean BL DLQI. Impact of AEs captured through use of EQ-5D data	Baseline: 0.64; QoL impact: PASI <50 0.11; PASI 50-74 0.19; PASI 75-89 0.23; PASI >90 0.26; QoL PASI <50 0.75; PASI 50-74 0.84; PASI 75-89 0.87; PASI 90-100 0.91

Model, Author [[multiple publications]]	Utility	
	Source	Value
NICE TA 368 (APREM), 2015[194] [Mughal et al., 2014c[199];]	Applied utility gains for each PASI improvement category published in the "York model" (Woolacott et al., Health Technol Assess, 2006) and applied them to a BL score from Revicki et al., Br J Dermatol, 2008	Baseline (PASI 0): 0.7. Increments: PASI <50 0.05; PASI 50 0.17; PASI 75 0.19; PASI 90 0.21
NICE TA 419 (APREM), 2016[16] also reported in Mughal et al., 2016a,b[190,191]	Apremilast trials (in line with ERG critique of TA 368)	Baseline (PASI 0): 0.8. Increments: PASI <50 0.05; PASI 50 0.17; PASI 75 0.19; PASI 90 0.21
Sawyer et al., 2015[198]	Woolacott et al., Health Technol Assess, 2006	PASI <50 0.05; PASI 50-75: 0.17; PASI 75-90 0.19; PASI 90 0.21 (lowest BL DLQI subgroup: PASI <50 0.12; PASI 50-75: 0.29; PASI 75-90 0.38; PASI 90 0.41

Key: ADALIM = adalimumab; AEs = adverse events; APREM = apremilast; AUC = area under the curve; BL = baseline; EFALIZ = efalizumab; EQ-5D = EuroQol 5-dimension; DLQI = dermatology quality of life index; ETAN = etanercept; HoDAR = Health Outcomes Repository Database; INFLIX = infliximab; NA = not applicable; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; NR = not reported; OLS = ordinary least squares; PASI = psoriasis area severity index; Ph = Phase; QALYs = quality-adjusted life years; QoL = quality of life; SECUK = secukinumab; SG = subgroup; SMC = Scottish Medicines Consortium; TA = technology appraisal; TTO = time trade off; USTEK = ustekinumab; Wk(s) = week(s)

Notes: (a) Company reports for TA 103 not identified on the NICE website extraction was from the information presented in the ERG report and Woolacott et al., 2006 publication; (b) Lloyd et al, conducted exploratory analysis to assess which subgroups would be most likely to benefit from the 50 mg dose (extension of analysis submitted in TA103); (c) TA 368 adapted for submission to SMC, Scottish NHS perspective[201]

Adverse reactions

Adverse events were not explicitly considered in the model consistent with previous NICE technology assessments and the original York Assessment Group model (Woolacott et al. 2006).[196]

Health-related quality-of-life data used in cost-effectiveness analysis

The EQ-5D is the preferred measure of health-related quality-of-life (HRQoL) in the NICE reference case. However, no EQ-5D data were collected in the DMF (LAS41008) trial.

The health-related quality of life (HRQoL, sometimes called the utility) was modelled following the methods used in previous NICE submissions (Table 61). Patients in the first trial period were assumed to have a HRQoL of 0.70. In subsequent trial periods it was assumed that patients had a HRQOL of less than PASI75 response according to the response rate of the previous treatment. Patients in the maintenance period of treatment were assumed to have an improvement in HRQoL according to the PASI response achieved.

Table 61: Health-related quality of life by health state

Health State	HRQoL	Reference	Justification
Baseline	0.70	Revicki et al. 2008 [30]	To ensure consistency with previous NICE TAs
PASI response			
<50	0.75	Woolacott et al. 2006 [12]	To ensure consistency with previous NICE TAs
≥50-<75	0.87	Woolacott et al. 2006 [12]	
≥75-<90	0.89	Woolacott et al. 2006 [12]	
≥90	0.91	Woolacott et al. 2006 [12]	

Abbreviations: HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; PASI, psoriasis area severity index; TA, technology appraisal

To ensure consistency with previous NICE appraisals in psoriasis, the model uses baseline HRQoL score value taken from the study by Revicki et al. (2008)[80] and HRQoL scores for the different PASI categories were taken from Woolacott et al. (2006).[196] The baseline utility score was applied to patients in the first trial period. In subsequent trial periods utilities of PASI<50 and PASI≥50-PASI<75 are used. The distribution of PASI scores in the trial period is determined by the NMA results for the previous treatment. This reflects that patients in the trial period have recently discontinued treatment and have just started a new treatment that has not had time to improve their quality of life. Patients that respond to treatment and enter the maintenance phase receive the HRQoL associated with PASI75-PASI<90 or PASI90. As described above the PASI level in the maintenance phase is determined by the treatment specific NMA results. The HRQoL of patients receiving BSC is also determined by the PASI level from the NMA. For example, in the base case 17% are PASI50-PASI<75 and receive a HRQoL score of 0.87, 6% are PASI75-PASI<90 and receive a HRQoL score of 0.89 and 1% have a PASI90 and HRQoL of 0.91. The remaining patients on BSC have HRQoL of 0.75. The HRQoL of patients that have died is zero.

5.5 Cost and healthcare resource use identification, measurement and valuation

Costing analysis was undertaken from the NHS and Personal Social Service (PSS) perspective as required by the NICE methods guide.[206]

Resource identification, measurement and valuation studies

To maintain consistency with previous analyses (identified in the systematic search described in Section 5.1; (Appendix 12 and 14), the resource use inputs were taken from analysis published by the NICE Clinical Guideline Centre in 2012 and a 2012 cohort study providing evidence on the resource use of high-need psoriasis patients at a tertiary dermatology unit in the UK Fonia et al. (2010).[202]

The primary objective of Fonia et al. (2010)[202] was to compare resource use and associated costs in patients with plaque psoriasis for a period of 12 months before and for up to 12 months immediately after starting biologic therapy. A retrospective observational study of 76 patients with severe psoriasis was undertaken. Prior to initiation of biologic therapy 25% of patients were taking fumarates. The costs were estimated from an NHS perspective and used 2008 British pounds.

Results suggest that the length of inpatient days was reduced from 6.49 days prior to biologics to 1.55 days with biologics. Phototherapy sessions also decreased with the use of biologics from 2.76 to 0.26. However, there was a small increase in the probability of an A&E visit, 0.03 to 0.04, and outpatient attendances, 3.22 to 3.25, with biologics. Day ward admissions were more frequent upon initiation of biologic therapy 0.14 compared to 1.16.

In 2012 the National Clinical Guidelines Centre (NCGC) published a cost-effectiveness analysis to evaluate the cost-effectiveness of switching to a second biologic therapy compared to best supportive care for patients with moderate to severe chronic plaque psoriasis who have previously received treatment with a biologic therapy. A cost-utility analysis was undertaken in line with the methods of the NICE reference case. QALYs were calculated using utility weights from EQ-5D responses and UK public valuations. Costs were considered from a UK National Health Service and Personal Social Services perspective and expressed in 2011 UK sterling. Healthcare costs associated with starting and maintaining biologic therapy, as well as longer term costs of failing biologic therapy, were all included in the model. The model had a trial period and a treatment period similar to that described above and many of the model inputs were considered relevant to the current model.

Intervention and comparators' costs and resource use

In this analysis, in addition to the cost of the treatment, the trial period includes costs of administration, monitoring and outpatient visits. Patients were assumed to have full blood counts, liver function tests and urea and electrolyte tests, including serum creatinine. Only infliximab was associated with an additional administration cost which amounted to a regular day/night admission for an infusion. Subcutaneous treatments such as adalimumab, etanercept, secukinumab and ustekinumab were assumed to be self-administered by the patient, based on current practice in the UK and EMA guidelines. Therefore, no resource use and costs associated with drug administration were considered for the oral therapies including DMF (LAS41008), apremilast and Fumaderm or for subcutaneous injections. The frequencies of each of these monitoring tests for each biologic agent are presented in Table 62. It was assumed that DMF (LAS41008) would require monthly outpatient visits and tests during the trial period to manage the dosing.

Table 62: The number of monitoring tests and outpatient visits during the trial period

Resources	DMF (LAS41008)/ Fumaderm	Infliximab	Other biologics and apremilast	Reference
Outpatient Visits	4	1	2	NICE CG153 Appendix O[203]
Full Blood Count	4	3	2	
Liver Function Test	4	3	2	
Urea and Electrolytes	4	3	2	
Inpatient Days	0	3	0	

Abbreviations: CG, Clinical Guideline; DMF, dimethyl fumarate; NICE, National Institute for Health and Care Excellence

Resource Use during the Maintenance Period

During the maintenance period patients have the same visits and tests as described above. The frequency of these tests is also informed from the NICE Clinical Guidelines and Fonia et al. (2010).[5,202,203] During the maintenance period patients also have A&E visits, day ward admissions and phototherapy. In Fonia et al. (2010)[202] resource use is estimated for patients pre-biologic treatment and with biologic treatment. It was assumed that DMF and Fumaderm would have the resource use of a pre-biologic treatment and the biologic comparators in the model

would have the same resource use as the with-biologic use patients in the study (Table 63). The frequency of full blood count tests with DMF (LAS41008) is still being discussed with the regulatory authorities. For the purposes of the model we have assumed the more conservative approach as per EMA initial recommendations of 12 blood count tests per year. Following further discussions with the regulatory authorities it may be that this requirement will be less.

Table 63: Annual monitoring test and visits during the maintenance period

	DMF (LAS41008)/ Fumaderm	Infliximab	Other biologics and apremilast	Reference
Outpatient visits	6	4	4	NICE CG153 Appendix O[203]
Liver Function Test	5	4	4	
Full blood count	12	4	4	
Urea and electrolytes	5	4	4	
Inpatient Admissions	6.49	1.55	1.55	Fonia et al. (2010)[202]
A&E visits	0.03	0.04	0.04	
Day ward admissions	0.14	0.16	0.16	
Phototherapy	2.76	0.26	0.26	

Abbreviations: A&E, accident and emergency; CG, clinical guideline; NICE, National Institute for Health and Care Excellence

Unit Costs

Unit costs were updated to 2014/15 prices from the NICE Clinical Guideline 153 and Fonia et al. (2010)[5,202,203] using the Personal Social Services Research Unit (PSSRU) hospital and community health service price index[213] or from the national schedule of reference costs 2014/15.[214]

The cost of an outpatient visit for dermatology comes from the National Schedule of Reference Costs: 2014-2015.[214] Test costs come from the NICE Clinical Guideline (CG153) Appendix O and were updated to 2014/15 prices.[203] The unit costs of inpatient admissions, A&E visits, day ward admissions and phototherapy come from Fonia et al. (2010) and were updated from 2010 prices.[202]

Non-Responder Costs

The evidence review group (ERG) for NICE's technology assessment of apremilast (TA 419)[16] determined that the use of Fonia et al. (2010)[202] to estimate the non-

responder cost was uncertain. The ERG estimated the non-response cost was £225 per cycle and recommended a range between £45.04 and £348.22 per cycle.[193]

Drug acquisition costs

The cost of each treatment is estimated from the recommended daily dose and the acquisition costs as listed on the British National Formulary. The cost of DMF (LAS41008) and Fumaderm® were provided by Almirall. The per tablet cost of Fumaderm is £2.52. This was estimated from the list price of Fumaderm in Germany €2.43 for a 120 mg tablet and a 22% import charge, using an exchange rate of €1=£0.85 (January 2017). Clinical experts report that the actual cost of Fumaderm to UK centres varies depending on volume bought and local agreements. Prices between £4 and £7 per 120 mg tablet of Fumaderm seem to be quite common. It is therefore expected that a cost of £2.52 per tablet is very conservative. [redacted] Given that the patients on DMF (LAS41008) start on 30mg and increase their daily dose weekly the trial period cost of DMF (LAS41008) was calculated accordingly. This results in a cost of treatment for DMF (LAS41008) slightly higher than if patients took 360 mg daily for the full trial period. The weekly cost of DMF (LAS41008) during the trial period is [redacted] compared to a weekly cost of [redacted] during the maintenance phase when patients are assumed to be taking [redacted] The weekly costs of each treatment are reported in Table 64.

The prices of apremilast, adalimumab, infliximab and ustekinumab come from British National Formulary (BNF) 71, 2016.[215] The price of the biosimilar for etanercept according to MIMS[204] was used in the model, 4x50mg for £656 compared to the BNF 71 brand price of 4x50mg for £715.[215]

Given that infliximab also has a biosimilar the generic price of infliximab was used, £377.66 for 100 mg compared to the brand price of £419.62 for 100mg. The cost of infliximab was calculated assuming patients receive 5mg/kg at weeks 0, 2, 6 and then every 8 weeks and that they weigh 77.8kg. Also, the cost of infliximab is based on the assumption that dose sharing is possible. Accounting for vial wastage costs would increase the cost of infliximab.

The average weekly cost of secukinumab was calculated using the cost of 2x150mg vials at £1218.78 from MIMS.[204] Patients are recommended to be treated with

300mg every week for the first four weeks and then monthly after week 4. This means patients will receive 6 treatments of 300mg over the 12 week trial period. This gives an average weekly cost of £609.39 during the trial period. During the maintenance period patients continue receiving treatment monthly giving an average weekly cost of £304.70.

The list prices of secukinumab and apremilast are used in the model although a patient access scheme has been negotiated with the Department of Health for each of these treatments. Discounts, of 25%, were applied to secukinumab and apremilast in sensitivity analyses.

Patients receiving ustekinumab have an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose in 4 weeks, and then every 12 weeks thereafter. For patients with a body weight greater than 100 kg, the dose increases from 45 mg to 90 mg. The dose does not affect the price in the model because the manufacturer has agreed to provide the higher dose needed for people who weigh more than 100kg at the same total cost as the lower dose (NICE, TA180).[40]

Table 64: Weekly drug costs (based on BNF, MIMS costs, SmPC data for dosages and data on file)

Treatment	Weekly cost during the trial period	Weekly cost during the maintenance period
DMF (LAS41008)	[redacted]	[redacted]
Apremilast	£137.50	£137.50
Adalimumab	£220.09	£176.07
Etanercept	£164.00	£164.00
Fumaderm	£66.90	£52.92
Infliximab	£440.73	£183.64
Ixekizumab	£750.00	£281.25
Secukinumab	£609.39	£304.70
Ustekinumab	£268.38	£178.92

Abbreviations: BNF, British National Formulary; DMF, dimethyl fumarate; SMPC, summary of product characteristics

Health-state unit costs and resource use

Patients on BSC are assumed to get the same costs as those patients in Fonia et al. (2010) pre-biologic.[202] This takes into account the non-progressive nature of the disease. This means that patients pre-biologics have the same BSC as patients that have failed all lines of biologics. This was an assumption from the evidence review

group for apremilast that was accepted by the NICE technology appraisal committee.[193]

The costs reported in Fonia et al. (2010)[202] includes £1249.40 per annum of pre-biologic systemic treatments, £1.14 of other supportive drugs, and £2956.70 of inpatient visits, outpatient visits, A&E visits, day ward admissions and phototherapy. The total cost of pre-biologic treatment was reported to be £4207, £4798 inflated to 2014/15 prices.

Adverse reaction unit costs and resource use

Adverse events were not explicitly considered in the model consistent with previous NICE technology assessments and the original York Assessment Group model (Woolacott et al. 2006).[196]

Miscellaneous unit costs and resource use

No additional unit costs or resource use were included in the model.

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

A number of model assumptions have been specified in Table 65. Each of these assumptions has been tested in the sensitivity analysis.

Assumptions

Table 65. Base Case Model Assumptions and Justifications

No.	Assumption	Justification
1	Patients discontinue all treatments at a rate of 20% annually.	No long-term evidence currently available for DMF discontinuation.
2	Patients costs of BSC are the same prior to biologic use and after biologic use.	Psoriasis is not a disease that progresses.
3	Patients on DMF follow the recommended dosing pattern.	Physicians will adhere to guidelines
4	Treatment effects are constant regardless of the line of therapy for which it is used.	Treatment sequences contain treatments with different modes of action.

Sensitivity Analyses

In order to assess the uncertainty around the value of inputs in the model, one-way sensitivity analyses were undertaken as described in Table 66. Probabilistic analysis was undertaken to assess the effect of uncertainty on the mean. Probabilistic inputs are reported in Table 66.

Table 66. One-way sensitivity analysis parameters

Variable	Base Case	Lower Value	Upper Value
Time Horizon	10 Years	20 Years	Lifetime
Discount Rate	3.5%	1.5%	5.0%
Percent Female	50%	0%	100%
Age	50 years	35 years	65 years
Withdrawal Rate DMF	20%	10%	30%
Withdrawal Rate Biologics	20%	10%	30%
Baseline HRQoL	0.7	0.6	0.8
HRQoL changes	0.05 0.17 0.19 0.21	0.03 0.15 0.17 0.19	0.07 0.19 0.21 0.23
GP visits and tests	6	-	12
Non-responder costs	£250	£0, £45.04	£348.22
Cost of tablet	[redacted]	[redacted]	[redacted]
Dosing	624 mg	Decrease 120mg weekly	-
NMA Results	Base case NMA results Table 57	Subgroup analysis of patients with previous systemic treatments Table 44	Subgroup analysis excluding low quality studies Table 40

Abbreviations: DMF, dimethyl fumarate; GP, general practitioner; HRQoL, health-related quality of life; PASI, psoriasis area severity index

Table 67. Probabilistic Inputs

Variables		Mean	SE	α	β	Distribution
PASI Response						
DMF (LAS41008)	PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	Beta
apremilast	PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	Beta
adalimumab	PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet

Variables		Mean	SE	α	β	Distribution
	PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	Beta
etanercept	PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	Beta
Fumaderm	PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	Beta
infliximab	PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	Beta
secukinumab	PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	Beta
ustekinumab	PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	Beta
ixekizumab	PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	Beta
BSC	PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
Health-Related Quality-of-Life						
PASI response	≥90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	≥75-<90	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	≥50-<75	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
	<50	[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
Baseline		[redacted]	[redacted]	[redacted]	[redacted]	Dirichlet
Resource Use						
Trial Period DMF (LAS41008) and Fumaderm	Outpatient visits	4.00	2.00	4.00	1.00	Gamma
	Liver Function Test	4.00	2.00	4.00	1.00	Gamma
	Full blood count	4.00	2.00	4.00	1.00	Gamma
	Urea and electrolytes	4.00	2.00	4.00	1.00	Gamma
	Inpatient Days	0	0	0	0	Gamma
	A&E visits	0	0	0	0	Gamma
	Day ward admissions	0	0	0	0	Gamma

Variables		Mean	SE	α	β	Distribution
	Phototherapy	0	0	0	0	Gamma
Maintenance Period DMF (LAS41008) and Fumaderm	Outpatient visits	6.00	3	4	1.5	Gamma
	Liver Function Test	5.00	2.5	4	1.25	Gamma
	Full blood count	12.00	6	4	3	Gamma
	Urea and electrolytes	5.00	2.5	4	1.25	Gamma
	PIIINP	0.00	0	0	0	Gamma
	Glomerular Filtration rate	0.00	0	0	0	Gamma
	Liver Biopsy	0.00	0	0	0	Gamma
	Inpatient Days	6.49	3.245	4	1.62	Gamma
	A&E visits	0.03	0.01314	4	0.007	Gamma
	Day ward admissions	0.14	0.072336	4	0.036	Gamma
	Phototherapy	2.76	1.38	4	0.69	Gamma
Trial Period biologics and apremilast	Outpatient visits	2.00	1.00	4.00	0.5	Gamma
	Liver Function Test	2.00	1.00	4.00	0.5	Gamma
	Full blood count	2.00	1.00	4.00	0.5	Gamma
	Urea and electrolytes	2.00	1.00	4.00	0.5	Gamma
	Inpatient Days	0	0	0	0	Gamma
	A&E visits	0	0	0	0	Gamma
	Day ward admissions	0	0	0	0	Gamma
	Phototherapy	0	0	0	0	Gamma
Maintenance Period biologics and apremilast	Outpatient visits	4.00	2.00	4.00	1.00	Gamma
	Liver Function Test	4.00	2.00	4.00	1.00	Gamma
	Full blood count	4.00	2.00	4.00	1.00	Gamma
	Urea and electrolytes	4.00	2.00	4.00	1.00	Gamma
	PIIINP	0.00	0	0	0	Gamma
	Glomerular Filtration rate	0.00	0	0	0	Gamma
	Liver Biopsy	0.00	0	0	0	Gamma
	Inpatient Days	1.55	0.78	4.00	0.39	Gamma
	A&E visits	0.04	0.02	4.00	0.01	Gamma
	Day ward admissions	1.16	0.58	4.00	0.29	Gamma
	Phototherapy	0.26	0.13	4.00	0.07	Gamma
BSC	Annual Cost	4797.94	781.30	37.71	127.23	Gamma
Non-Responder Costs		225.00	112.50	4	56.25	Gamma

Abbreviations: BSC, best supportive care; DMF, dimethyl fumarate; PASI, psoriasis are severity index; SE, standard error

5.7 Base-case results

Base-case incremental cost effectiveness analysis results

The base case results describe the costs and QALYs for the following treatment sequence. Further treatment sequences are tested and reported in Table 76.

- Treatment sequence: DMF (LAS41008) → adalimumab → ustekinumab → BSC
- Comparator sequence: adalimumab → ustekinumab → BSC

Abbreviations: BSC, best supportive care; DMF, dimethyl fumarate

The base case model results suggest that the DMF (LAS41008) sequence dominates the no-DMF (LAS41008) sequence (Table 68). The treatment sequence (with DMF (LAS41008)) has [redacted] per patient compared to [redacted] per patient for the comparator sequence. The costs of the treatment sequence are lower than the comparator sequence [redacted] compared to [redacted]. This suggests the DMF (LAS41008) sequence is [redacted] and [redacted] meaning that the comparator sequence is dominated and the treatment sequence (with DMF (LAS41008)) is the cost-effective option.

Table 68: Deterministic results

	QALYs	Costs	ICER (Cost/QALY)
Treatment Sequence	[redacted]	[redacted]	
Comparator Sequence	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

At the end of 10 years only 2% of patients are still taking DMF (LAS41008) (Table 69). In the treatment sequence at 10 years 4% more patients are taking biologics (either adalimumab or ustekinumab in the base case scenario) and 6% fewer patients are on BSC compared to the comparator sequence. The same number of patients have died in each sequence since there is no treatment effect on mortality.

Table 69. Percent of patients on treatments at 10 years

	DMF (LAS41008)	Biologics	BSC	Dead
Treatment Sequence	2%	27%	67%	4%
Comparator Sequence	0%	23%	73%	4%

Abbreviations: BSC, best supportive care; DMF, dimethyl fumarate

Clinical outcomes from the model

No other clinical outcomes other than QALYs are captured in the model.

Disaggregated results of the base case incremental cost effectiveness analysis

[redacted] Patients in the DMF (LAS41008) sequence are have [redacted] DMF (LAS41008) costs but [redacted] costs of the other treatments.

Table 70. Summary of QALY gain by health state

Health state	QALY intervention (X)	QALY comparator (Y)	Increment	Absolute increment	% absolute increment
On DMF (LAS41008)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year;

**No discounting or half cycle correction has been applied to these totals*

Table 71. Summary of costs by health state

Health state	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
On DMF (LAS41008)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

**No discounting or half cycle correction has been applied to these totals*

Table 72. Summary of predicted resource use by category of cost

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Cost of DMF (LAS41008)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of adalimumab and ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of Tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs of Visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Analysis at 5 years to match the budget impact analysis

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

The probabilistic analysis demonstrates that the results are robust to the uncertainty in the model. The mean of the simulations results in higher QALYs and lower costs for the treatment sequence (with DMF) and the probability of the treatment sequence being cost-effective is 0.968 using a cost-effectiveness threshold of £20,000 per QALY (Table 73).

Figure 31 shows a scatter plot of the 1000 simulations for the treatment and comparator sequences. This demonstrates the variability in the simulations and the high degree of overlap.

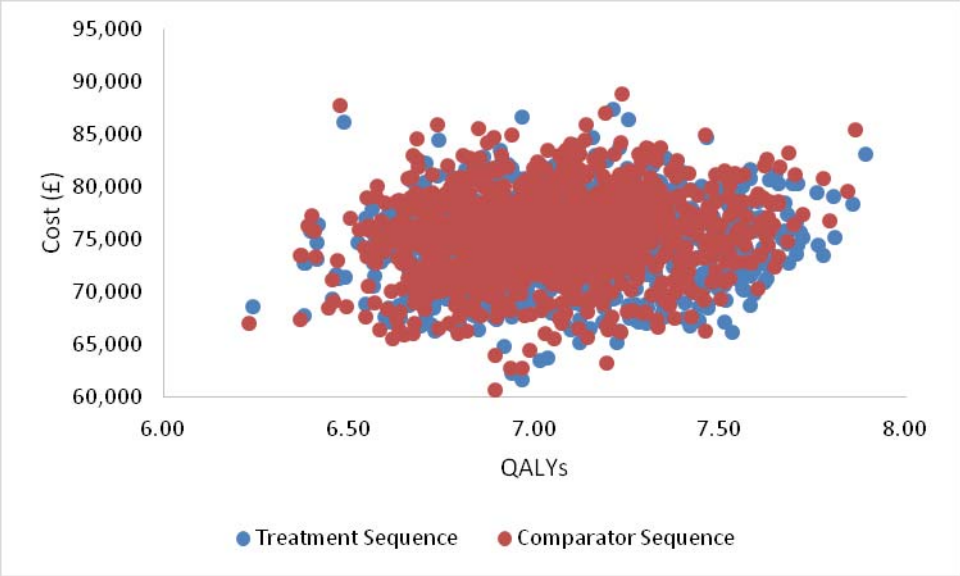
The cost-effectiveness acceptability curve shows that the treatment sequence is the cost-effective option at all cost-effectiveness thresholds up to £100,000 per QALY (Figure 32).

Table 73: Probabilistic results

	QALYs	Costs	ICER (Cost/QALY)	Probability of cost-effectiveness
Treatment Sequence	[redacted]	[redacted]		0.968
Comparator Sequence	[redacted]	[redacted]	Dominated	0.032

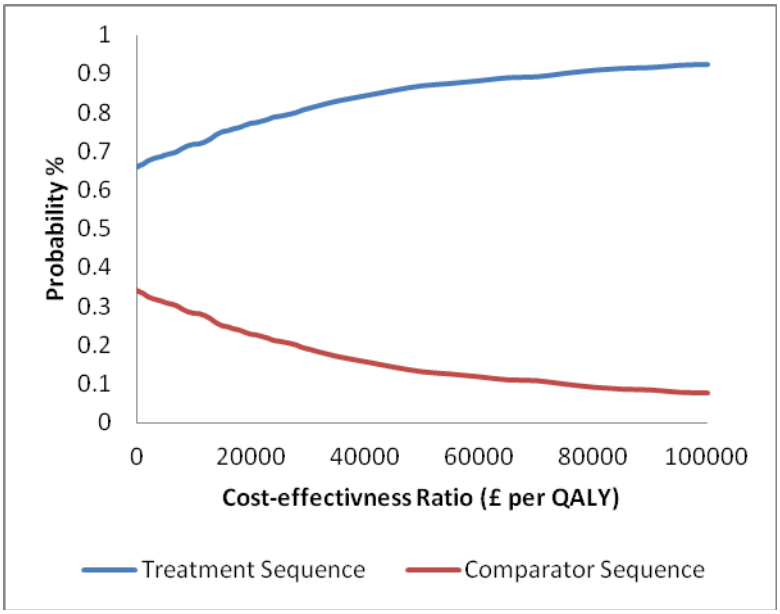
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Figure 31. Cost and QALYs of 1,000 simulations



Abbreviations: QALYs, quality-adjusted life years

Figure 32. Cost-effectiveness acceptability curve



Abbreviations: QALY, quality-adjusted life year

Deterministic sensitivity analysis

All sensitivity analyses report deterministic results unless otherwise specified. The variables described in Table 66 were tested and are reported in Table 74. The sensitivity analysis shows that the cost-effectiveness of the treatment sequence (with DMF) is robust to the uncertainty in the model parameters. Scenario analyses testing different time horizons demonstrate the long-term cost-effectiveness of the treatment sequence. As the time horizon increases QALYs and costs in both sequences increase, but the treatment sequence remains cost-effective at the £20,000 per QALY threshold. The discount rate was also varied, but did not affect the conclusion. Testing male and female populations separately demonstrated that males have fewer QALYs due to higher mortality rate, but that the treatment sequence was the cost-effective option for males and females. Conclusions were also robust to differences in the starting age of the population.

Table 74. One-Way Sensitivity Results

Scenario		QALYs	Costs	ICER (Cost/QALY)
Base Case	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
20-Year Results	Treatment Sequence	[redacted]	[redacted]	£12,898
	Comparator Sequence	[redacted]	[redacted]	
Lifetime Results	Treatment Sequence	[redacted]	[redacted]	£15,476
	Comparator Sequence	[redacted]	[redacted]	
1.5% Discount Rate	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
5.0% Discount Rate	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
100% Male	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
100% Female	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
Age 35 years	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
Age 65 years	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
Withdrawal rate DMF 10%	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
Withdrawal rate DMF 30%	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated

Scenario		QALYs	Costs	ICER (Cost/QALY)
Withdrawal Rate for adalimumab and ustekinumab 10%	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
Withdrawal Rate for adalimumab and ustekinumab 30%	Treatment Sequence	[redacted]	[redacted]	£8,499
	Comparator Sequence	[redacted]	[redacted]	
Withdrawal Rate from Arnold et al.	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	£438,546
Baseline HRQoL 0.6	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
Baseline HRQoL 0.8	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
Lower HRQoL changes	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
Higher HRQoL changes	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated

Abbreviations: DMF, dimethyl fumarate; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

An absolute decrease or increase of 10% to the withdrawal rate of DMF (LAS41008) did not affect the conclusions although a threshold analysis showed that the treatment sequence was no longer the cost-effective option if the withdrawal rate of DMF (LAS41008) is [redacted] An absolute decrease or increase of 10% to the biologics in each sequence resulted in the treatment sequence still being the cost-effective option although a higher withdrawal rate of the biologics made the treatment sequence more expensive than the comparator sequence.

Changes to the HRQoL did not change the cost-effectiveness conclusions and the treatment sequence remained the dominant strategy.

Additional scenario analyses are demonstrated in Table **75**. In all scenarios the treatment sequence remained the cost-effective strategy. The scenario analysis of patients that had experienced systemics demonstrates the same per patient QALYs and a decrease in per patient cost, suggesting that the treatment sequence is even more cost-saving in this patient population.

Table 75. Scenario analyses

Scenario		QALYs	Costs	ICER (Cost/QALY)
Base Case	Treatment Sequence	[redacted]	[redacted]	

Scenario		QALYs	Costs	ICER (Cost/QALY)
	Comparator Sequence	[redacted]	[redacted]	Dominated
Monthly GP visits and tests	Treatment Sequence	[redacted]	[redacted]	£547
	Comparator Sequence	[redacted]	[redacted]	
No non-responder costs	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
£0.88 increase in the cost of each tablet	Treatment Sequence	[redacted]	[redacted]	£19,853
	Comparator Sequence	[redacted]	[redacted]	
Slow decrease in dosing	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
Non-responder costs £45.04	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
Non-responder costs £348.22	Treatment Sequence	[redacted]	[redacted]	£13,804
	Comparator Sequence	[redacted]	[redacted]	
Subgroup of patients experienced with systemics or PUVA	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated
NMA scenario analysis	Treatment Sequence	[redacted]	[redacted]	
	Comparator Sequence	[redacted]	[redacted]	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio, QALY. Quality-adjusted life year

The model allows for a treatment sequence that has 4 choices of 10 treatments which results in more than 5,000 possible treatment sequences. However, not all treatment sequences are used given that some treatments have the same mode of action. Selected treatment sequences were chosen to demonstrate the use of DMF (LAS41008) in different sequences. Of most interest is the base case analysis which is the current most likely use of DMF (LAS41008). In the base case and in other comparisons where DMF (LAS41008) is added prior to a sequence of biologics the treatment sequence with DMF (LAS41008) is more effective and less costly and dominates the comparator. This is the case because DMF (LAS41008) is less expensive and more effective to BSC and adding DMF (LAS41008) to the beginning of a sequence results in fewer patients using BSC.

Recently apremilast has been approved by NICE for use prior to other biologics. In direct comparisons to apremilast, DMF (LAS41008) is less costly and less expensive and is considered the cost-effective option at an ICER of £30,000 per QALY. However, these analyses are based on the BNF list price for apremilast since the PAS is unknown. Threshold analysis was undertaken to determine the percent discount for apremilast to be the cost-effective option compared to DMF (LAS41008).

This analysis shows that the discount of apremilast must be greater than [redacted] of the BNF price for apremilast to be the cost-effective option compared to DMF (LAS41008).

Where DMF (LAS41008) is compared directly to a biologic or a sequence of the biologics the biologic sequence is found to be more effective and more costly, but DMF (LAS41008) remains the cost-effective option. This supports findings from TA108 that stated "the York Model found that it would only be cost effective to use etanercept and efalizumab in a sequence after methotrexate, ciclosporin and Fumaderm."[196]

In the base case analysis it is assumed that Fumaderm is equally effective as DMF (LAS41008). This results in Fumaderm having the same effectiveness and higher costs and being dominated by DMF (LAS41008). [redacted] This resulted in Fumaderm being more expensive and more effective than DMF (LAS41008) with an ICER of £31,887.

Table 76. Scenario analyses of sequences

Treatment Sequence	QALYs	Costs	ICER (Cost/QALY)
DMF-Ada-Ust-BSC	[redacted]	[redacted]	
Ada-Ust-BSC	[redacted]	[redacted]	Dominated
DMF-Etn-Ada-Ust-BSC	[redacted]	[redacted]	
Etn-Ada-Ust-BSC	[redacted]	[redacted]	Dominated
DMF-Ada-Sec-BSC	[redacted]	[redacted]	
Ada-Sec-BSC	[redacted]	[redacted]	Dominated
DMF-Ada-Ust-BSC	[redacted]	[redacted]	
Apr- Ada-Ust-BSC	[redacted]	[redacted]	£122,505
DMF-Ada-Sec-BSC	[redacted]	[redacted]	
Apr- Ada-Sec-BSC	[redacted]	[redacted]	£98,829
DMF-BSC	[redacted]	[redacted]	
Apr-BSC	[redacted]	[redacted]	£96,093
DMF-BSC	[redacted]	[redacted]	£35,256
BSC	[redacted]	[redacted]	
DMF-BSC	[redacted]	[redacted]	
Ada-BSC	[redacted]	[redacted]	£68,054
DMF-BSC	[redacted]	[redacted]	
Etn-BSC	[redacted]	[redacted]	£57,079
DMF-BSC	[redacted]	[redacted]	

Inf-BSC	[redacted]	[redacted]	£65,951
DMF-BSC	[redacted]	[redacted]	
Sec-BSC	[redacted]	[redacted]	£129,811
DMF-BSC	[redacted]	[redacted]	
Ust-BSC	[redacted]	[redacted]	£65,748
DMF-BSC	[redacted]	[redacted]	
Ixe-BSC	[redacted]	[redacted]	£130,627
DMF-BSC	[redacted]	[redacted]	
Fumaderm-BSC	[redacted]	[redacted]	Dominated
DMF-BSC	[redacted]	[redacted]	
Fumaderm (NMA)-BSC	[redacted]	[redacted]	£31,887
DMF-Ada-Ust-BSC	[redacted]	[redacted]	
Ada-Ust-DMF-BSC	[redacted]	[redacted]	£86,324

Abbreviations: Ada, adalimumab; Apr, apremilast; BSC, best supportive care; DMF, dimethyl fumarate; Etn, etanercept; ICER, incremental cost-effectiveness ratio; Inf, infliximab; Ixe, ixekizumab; QALY, quality-adjusted life year; Sec, secukinumab; Ust, ustekinumab

Summary of sensitivity analyses results

The probabilistic analysis demonstrates that the results are robust to the uncertainty in the model. The mean of the simulations results in higher QALYs and lower costs for the treatment sequence (with DMF (LAS41008)) and the probability of the treatment sequence being cost-effective is 0.968 using a cost-effectiveness threshold of £20,000 per QALY (Table 73).

A number of one-way and scenario analyses were undertaken. The sensitivity analysis shows that the cost-effectiveness of the treatment sequence (with DMF (LAS41008)) is robust to the uncertainty in the model parameters. Scenario analyses testing different time horizons, discount rates, sex distributions and starting ages demonstrate the cost-effectiveness of the treatment sequence (Table 74).

Alternative comparator sequences were tested. All sequences tested for which DMF (LAS41008) was added to a sequence found that the DMF (LAS41008) sequence dominated. In direct comparisons versus DMF (LAS410008), DMF (LAS41008) was less expensive and less effective and the cost-effective option at £20,000 per QALY (Table 76).

5.9 Subgroup analysis

A subgroup analysis was undertaken considering patients that had experienced use with prior systemic therapies and PUVA. Data for this analysis were from a network

meta-analysis including patients from the BRIDGE trial who had experienced prior systemic therapies (see Section 4.10). These patients were found to have a similar probability of achieving PASI50, PASI75 and PASI90 as the ITT population. The probabilities of achieving PASI50 and PASI75 are the same as the base case analysis. The probabilities of achieving PASI90 decreased from 6% to 5%.

Using the subgroup NMA results in the cost-effectiveness model resulted in the treatment sequence having the same QALYs, [redacted] and costs decreasing from [redacted]. This resulted in the treatment sequence with DMF (LAS41008) being cost-effective and dominating the comparator sequence.

5.10 Validation

Validation of de novo cost-effectiveness analysis

The model was reviewed by a second health economist with experience undertaking single technology assessments and multiple technology assessments for NICE. The programming of the model was thoroughly checked and the assumptions of the model reviewed.

The results of the model were compared to TA 368. In TA 368 a sequence of apremilast-adalimumab-etanercept-BSC was compared to adalimumab-etanercept-BSC. Using the de novo model developed these sequences were tested and compared to TA 368 in Table 77. The results for TA 368 show a very similar difference in QALYs and higher incremental costs. This is because the TA 368 base case analysis used higher BSC costs and a different price year. In a scenario where the BSC costs from TA 368 were used in the de novo model results were very similar and incremental cost-effectiveness ratios (ICER) suggest the no apremilast sequence is dominated.

Table 77: A comparison to the results of TA 368

Source	Sequence	Inc QALYs	Inc Costs	ICER (cost/QALY)
TA 368	Apremilast	-	-	-
	No Apremilast	[redacted]	[redacted]	dominated
De novo model	Apremilast	[redacted]	[redacted]	-

	No Apremilast	[redacted]	[redacted]	£55,654
De novo model with BSC costs from TA 368	Apremilast	[redacted]	[redacted]	-
	No Apremilast	[redacted]	[redacted]	dominated

Abbreviations: BSC, best supportive care; Inc., incremental; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal

Further comparison was made to the results of TA 350. Percent differences in QALYs ranged from 1% to 2%; percent differences in costs were higher ranging from 4% to 30%. These differences are mainly due to the differences in costs of BSC.

Table 78: Comparison to TA350

	Current Analysis		TA 350 ERG report		Percent Difference	
	QALY	Costs	QALY	Costs	QALY	Costs
BSC	[redacted]	[redacted]	6.44	£ 28,357	2%	30%
Etn	[redacted]	[redacted]	6.596	£ 37,255	1%	28%
Ada	[redacted]	[redacted]	6.688	£ 41,748	1%	22%
Ust	[redacted]	[redacted]	6.798	£ 48,457	1%	4%
Inf	[redacted]	[redacted]	6.824	£ 62,176	1%	11%
Sec	[redacted]	[redacted]	6.829	£ 76,361	2%	30%

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year; TA, technology appraisal; Ada, adalimumab; Etn, etanercept; nf, infliximab; Sec, secukinumab

5.11 Interpretation and conclusions of economic evidence

A cost-effectiveness evaluation was conducted from the perspective of the National Health Service (NHS) and Personal Social Service to compare treatment sequences with and without DMF (LAS41008) in adults with moderate to severe plaque psoriasis who have failed to respond to or who have a contraindication to, or are intolerant to other systemic non-biologic therapies.

The objective was to determine whether the addition of DMF (LAS41008) as an additional non-biologic systemic treatment option in the treatment pathway for psoriasis represents a cost-effective use of NHS resources.

The analysis was based on a Markov state-transition cohort model with a 14-day cycle length and a 10-year time horizon.

The base case cost-effectiveness analysis evaluated DMF (LAS41008) as an additional line of therapy before biologic therapy followed by a biologic therapy sequence and best standard care (BSC),

Treatment sequence: DMF → adalimumab → ustekinumab → BSC

Comparator sequence: adalimumab → ustekinumab → BSC

The health states in the model comprised a trial period and a maintenance period for each treatment option. After a treatment specific trial period (10-16 weeks, depending on the indication) patients that achieved response, i.e. PASI75, continued on treatment. Responders were assumed to continue treatment until they discontinued use.

After failing or discontinuing all treatment in the selected treatment sequence patients were assumed to receive BSC as the last line of treatment.

Direct medical costs including treatment costs and, costs related to drug administration, hospitalisations, outpatient visits and routine patient monitoring were included in line with previous submissions to NICE and published cost-effectiveness studies.

Health effects were measured in QALYs. EQ-5D utilities from previous NICE technology appraisals were used for each PASI response category and PASI response rates from the network meta-analysis (NMA) were applied.

In the base case, cost per patient was [redacted] for the DMF (LAS41008) sequence and [redacted] for the comparator sequence, representing a cost saving of [redacted] per patient for the DMF (LAS41008) sequence. Discounted QALYs gained per patient were greater for the DMF (LAS41008) sequence compared with the comparator sequence [redacted] The introduction of DMF (LAS41008) before [redacted].

The cost-effectiveness result was robust to a number of scenario analyses demonstrating that for all scenarios tested the introduction of DMF (LAS41008) as an additional non-biologic systemic treatment option in moderate to severe psoriasis patients is cost-effective at the £20,000 per QALY threshold.

One-way and probabilistic results demonstrate the robustness of the conclusion that DMF (LAS41008) as part of the treatment sequence is the cost-effective option.

6 Assessment of factors relevant to the NHS and other parties

Population: people eligible for treatment

The target population for the use of DMF (LAS41008) is the prevalent moderate to severe psoriasis patients aged 18 years or older in England and Wales. The adult population size in England and Wales is calculated from the mid-2015 by the Official National Statistics (ONS, 2016).[216] The prevalence of psoriasis in the UK is estimated to be 1.52%[217] of which 20% are estimated to be moderate to severe patients.[218] The estimates of moderate-to-severe psoriasis patients eligible for DMF (LAS41008) over the next 5 years are reported in Table 79. The prevalence of psoriasis and the percent moderate or severe are assumed to stay constant and the population to increase at 0.08% annually. No specific subgroups were analysed separately.

Table 79: The Prevalence of Moderate to Severe Psoriasis

	2017	2018	2019	2020	2021
Adults in England and Wales	45,616,133	45,652,626	45,689,148	45,725,699	45,762,280
Patients with Psoriasis	693,439	693,994	694,549	695,105	695,661
Patients with Moderate or Severe Psoriasis	138,688	138,799	138,910	139,021	139,132

Costs included

The following costs were taken into account within budget impact calculations:

- Technology costs
- Monitoring costs
- Resource utilisation

Details of unit costs for the above are presented in Table 72.

Resource savings

The budget impact analysis suggests resources will be saved that would have been spent on biologic treatment and BSC. The overall savings from using DMF (LAS41008) will be approximately [redacted]

Budget impact

It is assumed that DMF (LAS41008) use [redacted] in the first year increasing up to [redacted] at [redacted] years, however, this variable is flexible in the budget impact model. This means in the first year [redacted] patients will begin treatment with DMF (LAS41008). Those that did not achieve response will go on to subsequent treatment as specified in the chosen treatment sequence for DMF (LAS41008). In the base case it is assumed that patients that fail DMF (LAS41008) will go onto adalimumab followed by ustekinumab followed by BSC (as in the CEA base case). The [redacted] of patients that do not start DMF (LAS41008) will have the same costs and treatment effects of the comparator sequence i.e. adalimumab followed by ustekinumab and then BSC.

Table 80: Uptake of DMF (LAS41008)

	2017	2018	2019	2020	2021
Percent Uptake (% increase of those previously not using DMF (LAS41008))	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients on DMF (LAS41008)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DMF, dimethyl fumarate

Treatment costs included in the budget impact model include the cost of DMF (LAS41008), the cost of biologics, the cost of non-response (hospital and physician visits), costs of tests, costs of visits, costs of phototherapy and costs of BSC. Each cost is estimated based on the number of patients in the DMF sequence or the comparator sequence and the number of patients that remain on each treatment based on the withdrawal rate used in the model.

The number of patients treated with DMF (LAS41008) are estimated for 1-5 years (Table 81).

Table 81: 1 Year Per Patient Costs

	DMF (LAS41008) **sequence**	**No DMF** (LAS41008) **sequence**
Cost of DMF (LAS41008)	[redacted]	[redacted]
Cost of Biologics	[redacted]	[redacted]
Cost of non-Response	[redacted]	[redacted]
Cost of Tests	[redacted]	[redacted]
Cost of Visits	[redacted]	[redacted]
Cost of Phototherapy	[redacted]	[redacted]
Cost of BSC	[redacted]	[redacted]
Total Cost	[redacted]	[redacted]
Difference	[redacted]	

Abbreviations: BSC, best supportive care; DMF, dimethyl lfumarate

The per patient costs demonstrate that the DMF sequence has [redacted] of those patients that do not use DMF (LAS41008) in the sequence (Table 81). The five year population cost is presented in Table 82.

Table 82: 1 Year Population Costs

	DMF (LAS41008) **sequence (millions £)**	**No DMF** (LAS41008) **sequence (millions £)**
Cost of DMF (LAS41008)	[redacted]	[redacted]
Cost of Biologics	[redacted]	[redacted]
Cost of non-Response	[redacted]	[redacted]
Cost of Tests	[redacted]	[redacted]
Cost of Visits	[redacted]	[redacted]
Cost of Phototherapy	[redacted]	[redacted]
Cost of BSC	[redacted]	[redacted]
Total Cost	[redacted]	[redacted]
Difference	[redacted]	

Abbreviations: Bec, best supportive care; DMF, dimethyl fumarate

When [redacted] moderate to severe psoriasis patients are treated without DMF (LAS41008) for 5 years the total cost is estimated to be [redacted]. With an uptake of [redacted] patients are treated with DMF (LAS41008) this offers an [redacted]. These costs are driven by the costs of the treatment as well as all of the inputs in the cost-effectiveness model

Additional factors not included in the analysis

There are no additional factors that have not been included in the analysis.

Interpretation and conclusion

The budget impact analysis suggests that the treatment sequence with DMF (LAS41008) is cost-saving compared to the treatment sequence without DMF (LAS41008). This is due to reduced use of other psoriasis drug treatments and reduced use of best supportive care. However, the use of DMF (LAS41008) will require additional testing, physician visits and phototherapy. Overall, a [redacted] in the use of DMF (LAS41008) has the [redacted].

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8 Appendices

The following appendices have been provided in a separate document:

- Appendix 1: Draft SmPC provided in response to EMA Day180 report
- Appendix 2: BRIDGE study inclusion / exclusion criteria
- Appendix 3: BRIDGE study information on PASI, PGA, PBI and DLQI
- Appendix 4: BRIDGE study quality assessment
- Appendix 5: NMA: literature review search strategy
- Appendix 6: NMA: grouping of studies
- Appendix 7: NMA: study quality assessment
- Appendix 8: NMA: WinBUGS code
- Appendix 9: Cost effectiveness analysis 1: search strategy
- Appendix 10: Cost effectiveness analysis 1: excluded studies
- Appendix 11: Cost effectiveness analysis 1: update search strategies
- Appendix 12: Cost-effectiveness analysis 2: search strategy
- Appendix 13: Cost effectiveness analysis 2: excluded studies
- Appendix 14: Cost effectiveness analysis 2: update search strategies
- Appendix 15: Detailed summary of included cost-effectiveness studies
- Appendix 16: Clinical effectiveness parameters
- Appendix 17: Cost input parameters from included cost-effectiveness models
- Appendix 18: Results of included cost effectiveness studies
- Appendix 19: Quality appraisal of cost utility studies
- Appendix 20: Summaries of ERG critique of evidence submitted for NICE TAs

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Single technology appraisal

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

Dear [redacted],

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on Wednesday 15th March 2017 from Almirall Limited. In general, they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at the end of the letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by the end of **Wednesday 19th April 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sharlene Ting, Technical Lead (Sharlene.Ting@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Technical Adviser – Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on clinical effectiveness data

Licensed indication

A1. PRIORITY QUESTION. Company submission (CS), section 2.2, bullet point 3 (page 25). The main issues raised during the regulatory process related to: "the proposed indication of first-line systemic therapy".

- Please clarify the anticipated licensed indication for dimethyl fumarate (DMF).
- Please clarify the company's intended position for DMF in the treatment pathway.

Decision problem

A2. PRIORITY QUESTION. CS, section 1.1, table 1 (pages 12-14). The company's decision problem is narrowly defined compared to the proposed licensed indication (CS, section 1.2, table 2, page 15) and the NICE scope.

- Please provide further justification for the difference given that the majority of the population in the BRIDGE trial was treatment naïve.
- Please explain why a *post-hoc* analysis was used.
- Please include the omitted non-biological systemic agents as comparators in the systematic review and network meta-analysis (NMA), as per the scope. Alternatively, please provide a full justification for omitting potentially relevant information about DMF and its comparators.

BRIDGE trial

Analysis sets

A3. PRIORITY QUESTION. CS, section 4.4, table 9 (page 48); CS, section 4.6, table 12 (page 57) and Appendix 4 (page 10).

- Please clarify the definition of full analysis set (FAS) used, as it differs between table 9 (CS, page 48) and Appendix 4 (page 10).
- Please clarify how the FAS (defined as "all patients who were randomised and received at least one dose of study medication, with at least one measurement of the primary variable PASI and PGA after Week 0") meets internationally accepted definitions of an intention-to-treat population.

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A4. CS, section 4.7, Time to relapse within 2 months of stopping therapy (page 63). Please explain which analysis set the sample sizes refer to, that is, [redacted] and [redacted] in the DMF, Fumaderm and placebo groups respectively.

A5. CS, section 4.8, figures 13 and 14 (page 71). Please clarify which analysis set the total sample size of [redacted] in Figures 13 and 14 refers to.

A6. CS, section 4.7, table 7 (page 66).

- Table 7 caption states that a FAS was used for DLQI scores. However, CS, section 4.4, "Data management, patient withdrawals" (page 51) states that an observed case approach was used for missing data for efficacy variables other than PASI/PGA.
    - Please clarify which approach was used.
    - If an observed case approach was used, please provide the patient numbers for each group.
- Table 7 (CS, page 66) first row of data states "screening". However, Appendix 3 (page 9) states that the DLQI was measured at baseline.
    - Please clarify whether the first row of data is assessed at screening or baseline.
    - If the data in the first row of Table 7 is not at baseline, please confirm the number of weeks before baseline that screening occurred and provide the baseline values for DLQI.

Participant flow

A7. PRIORITY QUESTION. CS, section 4.5, figure 6 and table 10 (pages 52-54).

- The numbers provided for patients analysed in the safety analysis set (SAS) and FAS in Figure 6 indicate that 12, 10 and 6 treated participants in the LAS41008 (DMF), Fumaderm and placebo groups respectively did not have at least 1 PASI/PGA assessment (CS, page 53).
    - Please provide the reasons for the lack of assessments in these 28 participants.
    - Please clarify where these 28 participants fit in Figure 6.
- In Figure 6 (CS, page 53), 176, 176 and 98 participants completed the treatment phase in the LAS41008, Fumaderm and placebo groups respectively. Please describe what happened to the participants who completed the treatment phase but did not enter the follow-up phase.

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- Table 10 (CS, page 54) states that 98 participants in the placebo group entered the follow-up phase, whereas Figure 6 (CS, page 53) states 66 participants. Please clarify the number of participants in the placebo group entering the follow-up phase.

A8. Table 10 (CS, page 54) lists "Other" as the main reason for study termination in 50, 33 and 19 participants in the DMF, Fumaderm and placebo groups respectively. Please provide details of the "other" reasons.

Participant characteristics

A9. CS, section 4.5, table 11 (page 55) and CS, section 4.8, table 21 (page 73).

- CS, section 4.10.3, Table 28 (page 90) suggests that "treatment naïve/biologic experienced/conventional experienced" are not reported by BRIDGE. However, this contradicts information in Tables 11 and 21. Please clarify.

- The following data in Table 11 (CS, page 55) are either duplicated or seem incorrect for the SAS or FAS. Please confirm whether the data are accurate, and if not, provide the correct data for:

    - PASI total score
    - PGA group
    - Body surface area
    - Prior conventional systemic therapy (placebo arm of FAS)

- Please provide the number of participants in all 3 groups for both systemic naïve and pre-treated with systemic subgroups in Table 21 (CS, page 73).

A10. CS, section 4.10.3, tables 28 and 29 (pages 90 and 94). The data for the participant and disease characteristics for BRIDGE and BRIDGE – subgroups are identical. Please confirm whether these data are correct.

Dosing data

A11. PRIORITY QUESTION. CS, section 4.3, figure 5 (page 41).

- Please provide the following weekly dosing data separately for the DMF and Fumaderm arms (2 tables).

Week	N on treatment	N tablets total	Mean N tablets/week/pp
1	n=???	n=???	μ=???
2	n=???	n=???	μ=???
…	…	…	…
15	n=???	n=???	μ=???

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16	n=???	n=???	μ=???

- The treatment protocol outlined in Figure 5 suggests dosing of 720 mg daily from week 9 to 16. If the mean observed dose is less than 720 mg for these weeks,
    - please provide reasons for this deviation and
    - a breakdown by arm, of the number of patients receiving 1, 2, 3, 4, 5 and 6 tablets separately for each relevant week.

Clinical effectiveness results

A12. PRIORITY QUESTION. CS, section 4.7, Co-primary endpoints (pages 57-58).

- Please provide the results of the co-primary outcomes for the SAS.
- Please provide the PASI continuous scores for the FAS and SAS at week 16 and final follow up at 12 months.

A13. PRIORITY QUESTION. CS, section 4.7, Figure 11 (page 63).

- Please provide the Kaplan Meier data that underlie Figure 11 (Time to relapse during the study [FAS]) in the following format for all 3 arms. This should also be provided in an Excel workbook (3 tables).

Time	N Events	N Censored	S(t)
0	0	0	100%
…	…	…	…
…	…	…	…
…	…	…	…

A14. CS, section 4.7, Figures 11 and 12 (pages 63 and 64).

- Please explain the terms ‘reference’ and ‘test’ in the legends of Figures 11 and 12, and the patient numbers.
- Please provide statistical comparisons for the Kaplan-Meier curves in Figures 11 and 12.

A15. CS, section 4.7, PASI 75 (pages 57-58).

For all 3 groups, please state:

- the number (and proportion) of participants contributing data to the PASI 75 response estimates evaluated at week 16.
- the number (and proportion) of participants contributing data to the PASI 75 response estimates assessed using the last observation carried forward (LOCF) approach. Please tabulate the durations of the LOCF for each arm. For example, a patient with a last measurement at week 10 would have a LOCF duration of 6 weeks (1 table).

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LOCF for	DMF	Fumaderm	Placebo
16 weeks	n=???	n=???	n=???
15 weeks	n=???	n=???	n=???
14 weeks	n=???	n=???	n=???
…	…	…	…

Safety data

A16. CS, section 4.12, Adverse reactions (pages 128-130).

- Please clarify whether there are any longer-term data on adverse events of DMF, even in other indications.
    - If available, please provide these data.

A17. PRIORITY QUESTION. CS, section 4.13, Extrapolating to Fumaderm (page 136).

- Please provide further details of the reported adverse events in the FUTURE retrospective study on Fumaderm, if available.

Systematic review and network meta-analysis (NMA)

Excluded studies

A18. PRIORITY QUESTION. A Cochrane review on oral fumaric acid esters for psoriasis identified 6 relevant studies (Altmeyer et al. 1994; Fallah Arani et al. 2011; Langner et al. 2004; Mrowietz et al. 2006; Nugteren-Huying et al. 1990; Peeters et al. 1992).

- Please clarify why these studies were not included in the NMA for the Fumaderm comparison.

- Please clarify whether these studies are of relevance to the assessment of adverse effects.

A19. CS, section 4.10.1, Systematic literature review (SLR) (page 78). "During screening one article was excluded based on the German language."

- Please provide summary details of the German language study that was excluded from the systematic review.

- Please describe in what way the German language study does not fit the inclusion criteria of the systematic review and/or NMA.

- If the German language study was excluded because of language only, please explore the impact of excluding this study.

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Ranking of effectiveness in the NMA

A20. PRIORITY QUESTION. CS, section 4.10.4, Results (pages 117-127). Please provide a ranked list comparing the effectiveness of the different interventions examined in the NMA for all outcomes.

Section B: Clarification on cost-effectiveness data

Best supportive care

B1. PRIORITY QUESTION. CS, section 5.2, *De novo* analysis (page 161). Please explain what is included as part of best supportive care (BSC) used in the model.

Drug doses and costs

B2. CS, section 5.2.3, Intervention technology and comparators (page 166). The stated mean dose of DMF in the BRIDGE trial at 9 weeks was 624 mg. However, the suggested maintenance dose for DMF is 360 mg based on the retrospective FUTURE study on Fumaderm.

- Please clarify whether there are any data from longer-term follow up of the participants in BRIDGE.

- Please clarify whether there are any data suggesting what the maintenance dose is likely to be in the UK.

B3. PRIORITY QUESTION. CS, section 4.3, figure 5 (page 41).
FUTURE reported a mean Fumaderm dosing regimen ranging from 2.58 to 3.72 tablets/day depending on weight (Reich et al. 2009).

- Please explain why the same dosing regimen was applied to Fumaderm as for DMF in the BRIDGE trial.

- Please provide the duration of the treatment period prior to maintenance therapy in FUTURE.

- Please clarify the effect of applying the dosing regimen reported in FUTURE on the weekly dose and cost of Fumaderm during the BRIDGE trial period.

    - Please explore the associated effect on the cost-effectiveness estimates for DMF followed by BSC compared to Fumaderm compared to BSC.

B4. CS, section 5.5, Drug acquisition costs (page 179).

- Please explain why there is an import charge for Fumaderm tablets in the model.

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- Please clarify the dose and pack sizes of Fumaderm initial and Fumaderm.
- Please clarify whether Fumaderm initial and Fumaderm are licensed in other EU countries for use in plaque psoriasis.
- If Fumaderm initial and Fumaderm are licensed elsewhere, please state the prices in each country.
- Please clarify the unit cost and dosing assumed for ixekizumab for the trial period and the maintenance period.

Health-related quality of life data

B5. PRIORITY QUESTION. CS, section 5.4, table 58 (page 170).

- Please provide the source data for Table 58.
- Please clarify the computation undertaken to derive the values in Table 58. Are calculations for each PASI/treatment category based on estimating each patient's baseline DLQI and change in DLQI to derive each patient's quality of life increment and then averaging the resulting mapped individual patient's quality of life increments?
- What are the baseline quality of life values implied in each of the 3 treatments when the mapping function is applied?

Resource use and costs

B6. CS, section 5.5, Health-state unit costs and resource use (pages 180-181).

- For the pre-biologics, biologics and BSC, please tabulate each element of resource use derived from Fonia et al. (2010) separately and include
    - the unit cost applied to these elements
    - any inflation indexing
    - the implied annual cost for each of the pre-biologics, the biologics and BSC. Please provide an account of any discrepancies between the three annual totals.
- Please clarify what index and which two index values have been used to inflate the costs reported in Fonia et al. (2010).

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Excel model

B7. PRIORITY QUESTION. Please confirm whether Cells F8:J26 of the *Effectiveness* worksheet of the economic model are drawn from Table 38 (CS, page 120) of the clinical effectiveness section.

- If this is the case, please outline why the PASI response at induction is to be preferred to the PASI response at 16 weeks and why these estimates differ.

- If this is not the case, please outline how cells F8:J26 of the *Effectiveness* worksheet of the economic model have been derived. Please clarify the impact of using the 16-week PASI response estimates.

B8. PRIORITY QUESTION. CS, section 5.9, Subgroup analysis (page 194). The ERG cannot identify how to implement the subgroup analysis in the submitted model. Please outline how to arrive at the cost-effectiveness estimates outlined in section 5.9 in the submitted Excel model.

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Almirall response to ERG clarification questions – 19 April 2017

Single technology appraisal: **Dimethyl fumarate for treating moderate to severe plaque psoriasis [ID776]**

Section A: Clarification on clinical effectiveness data

Licensed indication

A1. PRIORITY QUESTION. Company submission (CS), section 2.2, bullet point 3 (page 25). The main issues raised during the regulatory process related to: [redacted]

- Please clarify the anticipated licensed indication for dimethyl fumarate (DMF).
- Please clarify the company's intended position for DMF in the treatment pathway.

Response:

Anticipated indication

DMF (LAS41008) [redacted]

Intended position for DMF (LAS41008) in the treatment pathway

In clinical practice and in line with our submission DMF (LAS41008) will be used in a specific subgroup of patients: those for whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference.

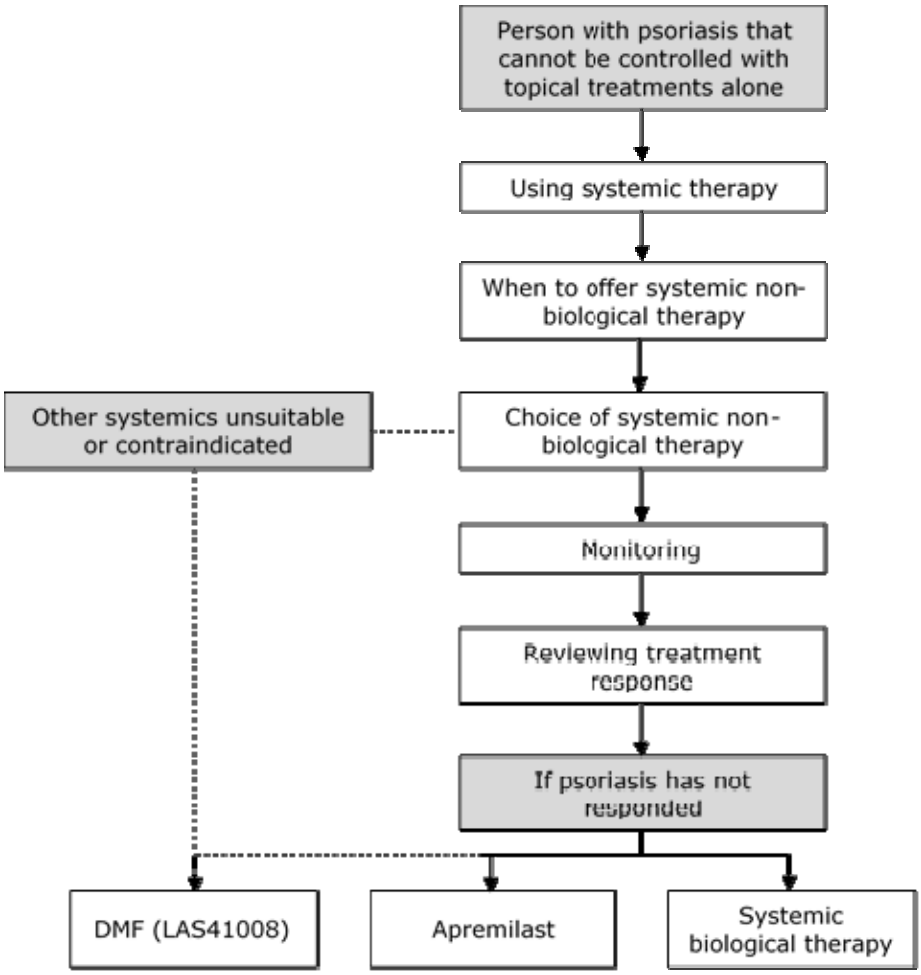
In clinical practice DMF (LAS41008) will be used as an alternative to current systemic non-biologic treatments and in common with other oral systemic therapies use is anticipated prior to biologics. In addition DMF (LAS41008) will be the first fumaric acid ester (FAE) licensed in the UK for treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy. In the UK FAEs are currently subject to unlicensed use where they have been imported and used since 1999.

In general and based on feedback from UK dermatologists using FAEs in clinical practice, the profile of the typical patient treated with FAEs, is a patient who is:

- pre-biologic (i.e. has not reached the NICE recommended criteria for treatment with a biologic agent)
- with relatively stable disease, not acute or severe disease
- in need of longer term maintenance
- and who failed on other systemic treatments or are contraindicated or intolerant to methotrexate, and ciclosporin

Figure 4 from our submission document illustrating the anticipated place of DMF (LAS41008) in the treatment pathway is provided below.

Figure 1: Anticipated place of DMF (LAS41008) in treatment pathway (as per Figure 4 in the Almirall submission)



Decision problem

A2. PRIORITY QUESTION. CS, section 1.1, table 1 (pages 12-14). The company's decision problem is narrowly defined compared to the proposed licensed indication (CS, section 1.2, table 2, page 15) and the NICE scope.

- Please provide further justification for the difference given that the majority of the population in the BRIDGE trial was treatment naïve.

Response: As stated above it is anticipated that, in clinical practice, DMF (LAS41008) will be used in patients for whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference. The submission document focuses on this subgroup as per the Decision Problem.

In order to provide results for this specific subgroup a post-hoc analysis of the BRIDGE study was performed. The results of this analysis (see pages 72 to 75, Almirall submission) demonstrated that the efficacy in the population who had previous systemic therapy in the BRIDGE trial was not significantly different from that seen in systemic-naïve patients. The baseline characteristics of the two groups were comparable.

- Please explain why a *post-hoc* analysis was used.

Response: A post-hoc analysis was used as analysis of this specific subgroup was not included within the original statistical analysis plan of the BRIDGE trial. The subgroup analysis was run to respond to questions received during the regulatory process.

- Please include the omitted non-biological systemic agents as comparators in the systematic review and network meta-analysis (NMA), as per the scope. Alternatively, please provide a full justification for omitting potentially relevant information about DMF and its comparators.

Response: Non-biological systemic agents are not appropriate comparators for this appraisal and hence data comparing DMF (LAS41008) with these agents is not provided.

In clinical practice DMF (LAS41008) is likely to be positioned where other oral systemic therapies (acitretin, methotrexate, and ciclosporin) are clinically inappropriate for patients through lack of efficacy, contraindications, tolerability and/or toxicity issues, or patient preference. The non-biologic systemic agents acitretin, methotrexate, and ciclosporin are therefore not relevant comparators. Phototherapy is also not a relevant comparator as its use is usually before systemic therapies which are recommended when phototherapy has been ineffective, cannot be used or has resulted in rapid relapse.

In line with the anticipated positioning of DMF (LAS41008) the only appropriate comparators as discussed and agreed with NICE at the Decision Problem meeting are:

- Fumaric acid esters
- Apremilast
- Systemic biological therapies (including etanercept, adalimumab, secukinumab, ustekinumab and ixekizumab)
- Best supportive care (for people in whom biologic therapies are not tolerated or contraindicated).

BRIDGE trial

Analysis sets

A3. PRIORITY QUESTION. CS, section 4.4, table 9 (page 48); CS, section 4.6, table 12 (page 57) and Appendix 4 (page 10).

- Please clarify the definition of full analysis set (FAS) used, as it differs between table 9 (CS, page 48) and Appendix 4 (page 10).

Response: The definition of FAS is as per Table 9 and includes all patients from the safety analysis set with at least one measurement of the primary variable PASI and PGA after Week 0. The definition in Appendix 4 is incorrect in referring to the SAS population

- Please clarify how the FAS (defined as “all patients who were randomised and received at least one dose of study medication, with at least one measurement of the primary variable PASI and PGA after Week 0”) meets internationally accepted definitions of an intention-to-treat population.

Response: In line with ICH Harmonised Tripartite Guidelines: Statistical Principles for Clinical Trials (February 1998)[1] FAS, as per the BRIDGE study, describes the analysis set which is as complete as possible and as close as possible to the intention-to-treat population. The relevant extract from these principles is provided below with a copy of the full document provided alongside this response.

'5.2.1 Full Analysis Set

The intention-to-treat (see Glossary) principle implies that the primary analysis should include all randomised subjects. Compliance with this principle would necessitate complete follow-up of all randomised subjects for study outcomes. In practice this ideal may be difficult to achieve, for reasons to be described. In this document the term 'full analysis set' is used to describe the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomised subjects. Preservation of the initial randomisation in analysis is important in preventing bias and in providing a secure foundation for statistical tests. In many clinical trials the use of the full analysis set provides a conservative strategy. Under many circumstances it may also provide estimates of treatment effects which are more likely to mirror those observed in subsequent practice.'

A4. CS, section 4.7, Time to relapse within 2 months of stopping therapy (page 63). Please explain which analysis set the sample sizes refer to, that is, [redacted] and [redacted] in the DMF, Fumaderm and placebo groups respectively.

Response: The sample sizes are a subset of the FAS. The reason for using these sample sizes is that the analysis set considered for measurement of time to relapse within 2 months of stopping therapy, took into account those patients who completed the treatments at week 16 and entered into the follow up phase of the trial, which differs from the whole FAS.

A5. CS, section 4.8, figures 13 and 14 (page 71). Please clarify which analysis set the total sample size of [redacted] in Figures 13 and 14 refers to.

Response: The sample size of [redacted] refers to the FAS.

A6. CS, section 4.7, table 7 (page 66). Table 7 caption states that a FAS was used for DLQI scores. However, CS, section 4.4, "Data management, patient withdrawals" (page 51) states that an observed case approach was used for missing data for efficacy variables other than PASI/PGA.

- Please clarify which approach was used.

Response: Please note that the table on page 66 of the Almirall submission is Table 17 not Table 7.

The DLQI scores are based on the FAS with the observed case approach used. For DLQI 'observed cases' refers to the final assessment available so data analysed as 'Week 16' comprised data collected at Week 16 supplemented by the data collected at the end-of-treatment visit for those patients who withdrew from the study before Week 16.

- If an observed case approach was used, please provide the patient numbers for each group.

Response: Patient numbers for each group are provided in Table 1.

Table 1: Patient numbers for each group

	DMF (LAS41008)	Fumaderm	Placebo
Baseline	[redacted]	[redacted]	[redacted]
Week 16/ET	[redacted]	[redacted]	[redacted]
FU 1 – 2 months	[redacted]	[redacted]	[redacted]
FU 2 – 6 months	[redacted]	[redacted]	[redacted]
FU 3 – 12 months	[redacted]	[redacted]	[redacted]

Source: LAS41008 CSR M40118-1102 June 2016 .Table 14.7.2

- Table 7 (CS, page 66) first row of data states "screening". However, Appendix 3 (page 9) states that the DLQI was measured at baseline. Please clarify whether the first row of data is assessed at screening or baseline.

Response: The first row in Table 17 reports data from the baseline visit not the screening visit. Please note that within the CSR, for DLQI data screening refers to baseline.

- If the data in the first row of Table 7 is not at baseline, please confirm the number of weeks before baseline that screening occurred and provide the baseline values for DLQI.

Response: Not applicable see above response.

Participant flow

A7. PRIORITY QUESTION. CS, section 4.5, figure 6 and table 10 (pages 52-54). The numbers provided for patients analysed in the safety analysis set (SAS) and FAS in Figure 6 indicate that 12, 10 and 6 treated participants in the LAS41008 (DMF), Fumaderm and placebo groups respectively did not have at least 1 PASI/PGA assessment (CS, page 53).

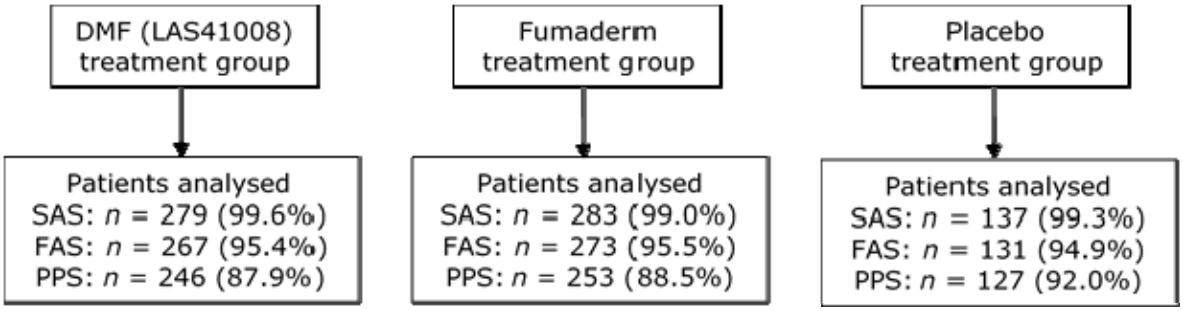
- Please provide the reasons for the lack of assessments in these 28 participants.
- Please clarify where these 28 participants fit in Figure 6.

Response: Of the 28 patients [redacted]

The decision to exclude the data from [redacted] Of the remaining patients without a PASI/PGA assessment on treatment, [redacted] had already either withdrawn from the study before the first on-treatment PASI/PGA assessment at Week 3, while for the remainder [redacted]

In Figure 6 of the Almirall submission document, these 28 patients are accounted for by the difference between the SAS and the FAS populations see Figure 2 i.e. 12 patients in the DMF (LAS41008) treatment group, 10 in the Fumaderm treatment group and 6 in the placebo group treatment group.

Figure 2: Details of the number of patients analysed in each data set (Taken from Figure 6, Almirall submission)



- In Figure 6 (CS, page 53), 176, 176 and 98 participants completed the treatment phase in the LAS41008, Fumaderm and placebo groups respectively. Please describe what happened to the participants who completed the treatment phase but did not enter the follow-up phase.

Response: Information on patients who did not enter into follow up was not collected, as their participation in the study (due to their choice) and study consent had formally ended.

However, from information provided on the Study Closure Form and from comments recorded in the Case Report Form text describing 'other' causes, provided in response to A8 below, in many cases the decision was to start an alternative treatment, with Fumaderm if available or with alternative antipsoriatic medication.

- Table 10 (CS, page 54) states that 98 participants in the placebo group entered the follow-up phase, whereas Figure 6 (CS, page 53) states 66 participants. Please clarify the number of participants in the placebo group entering the follow-up phase.

Response: We can confirm that Figure 6 is correct and 66 (47.8%) participants entered the follow-up phase.

A8. Table 10 (CS, page 54) lists "Other" as the main reason for study termination in 50, 33 and 19 participants in the DMF, Fumaderm and placebo groups respectively. Please provide details of the "other" reasons.

Response: The eCRF recorded more detail in respect of the category 'other' for reasons for study termination. Listings are provided in the accompanying file 'ID776_Almirall response to ERG clarification question A8_AIC'.

The reported reasons are comparable across the three treatment arms and mainly relate to a worsening of the underlying disease and / or a need for a new treatment, with patients in a number of cases explicitly reported as being transferred onto Fumaderm and so continuing on fumaric acid ester treatment.

Participant characteristics

A9. CS, section 4.5, table 11 (page 55) and CS, section 4.8, table 21 (page 73).

- CS, section 4.10.3, Table 28 (page 90) suggests that “treatment naïve/biologic experienced/conventional experienced” are not reported by BRIDGE. However, this contradicts information in Tables 11 and 21. Please clarify.

Response: This was an error and the amended data for the BRIDGE subgroup is provided, in bold, in Table 2.

Table 2. Patient demographics and baseline characteristics of studies included in the base-case NMA – Amended data for BRIDGE subgroup (provided in bold)

Trial name	Treatment name	ITT	Age mean (SD)	Sex: male (%)	Caucasian (%)	Asian (%)	Psoriasis years mean (SD)	PsA (%)	Treatment -naïve (%)	Biologic-experienced (%)	Conventional-experienced (%)
BRIDGE	DMF (LAS41008) 30-720mg oral	279	44 (15.2)	62	99	0	NR	NR	NR	NR	NR
	Fumaderm 30-720mg oral	283	45 (13.8)	65	99	1	NR	NR	NR	NR	NR
	Placebo	137	44 (14.3)	68	100	0	NR	NR	NR	NR	NR
BRIDGE – Subgroup	DMF (LAS41008) 30-720mg oral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Fumaderm 30-720mg oral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- The following data in Table 11 (CS, page 55) are either duplicated or seem incorrect for the SAS or FAS. Please confirm whether the data are accurate, and if not, provide the correct data for:
    - PASI total score
    - PGA group
    - Body surface area
    - Prior conventional systemic therapy (placebo arm of FAS)

Response: We can confirm the numbers in Table 11 are correct.

- Please provide the number of participants in all 3 groups for both systemic naïve and pre-treated with systemic subgroups in Table 21 (CS, page 73).

Response: The number of participants in each group are provided in Table 3:

Table 3: Number of patients in the systemic naïve and pre-treated with systemic subgroups

	Systemic naïve n=538			**Pre-treated with systemic n=133**		
	DMF (LAS41008) [redacted]	**Fumaderm** [redacted]	**Placebo** [redacted]	**DMF (LAS41008)** [redacted]	**Fumaderm** [redacted]	**Placebo** [redacted]

A10. CS, section 4.10.3, tables 28 and 29 (pages 90 and 94). The data for the participant and disease characteristics for BRIDGE and BRIDGE – subgroups are identical. Please confirm whether these data are correct.

Response: This was an error and the amended data for Table 28 is provided above in Table 2. Amended data for the BRIDGE subgroup in Table 29 are provided in bold in Table 4 below.

Table 4: Disease Characteristics of all included NMA trials. Amended data for BRIDGE subgroup (provided in bold)

Trial name	Treatment name	ITT	PASI mean (SD)	BSA mean (SD)	DLQI mean (SD)	PGA definition	PGA mean (SD)	Moderate (%)	Moderate/ severe (%)	Severe (%)
BRIDGE	DMF (LAS41008) 30-720mg oral	279	16 (5.7)	22 (11.6)	11 (6.3)	PGA 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=moderate-severe, 5=severe	NR	61	35	5
	Fumaderm 30-720mg oral	283	16 (6.8)	21 (12.5)	12 (7.0)		NR	60	34	6
	Placebo	137	16 (4.9)	22 (12.3)	11 (6.5)		NR	60	37	2
BRIDGE – Subgroup	DMF (LAS41008) 30-720mg oral eow	[redacted]	[redacted]	[redacted]	[redacted]	PGA 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=moderate-severe, 5=severe	[redacted]	[redacted]	[redacted]	[redacted]
	Fumaderm 30-720mg oral eow	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]

Key: eow, every other week

Dosing data

A11. PRIORITY QUESTION. CS, section 4.3, figure 5 (page 41).

- Please provide the following weekly dosing data separately for the DMF and Fumaderm arms (2 tables).

Week	N on treatment	N tablets total	Mean N tablets/week/pp
1	n=???	n=???	μ=???
2	n=???	n=???	μ=???
…	…	…	…
15	n=???	n=???	μ=???
16	n=???	n=???	μ=???

Response: The requested weekly dosing data is provided below in Table 5 (DMF) and Table 6 (Fumaderm).

Table 5: Weekly dosing data DMF treatment arm (SAS)

Week	**Number of patients on treatment**	**Total number of tablets**	**Mean number of tablets/day/per patient**	**Mean number tablets/week/per patient**
1*	[redacted]	[redacted]	[redacted]	[redacted]
2*	[redacted]	[redacted]	[redacted]	[redacted]
3*	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]

* For weeks 1 to 3 tablets included 30 mg DMF per tablet. For weeks 4 to 16 tablets included 120 mg DMF per tablet

Source: Almirall Data on File. April 2017.

Table 6: Weekly dosing data Fumaderm treatment arm (SAS)

Week	Number of patient on treatment	Total number of tablets	Mean number of tablets/day/per patient	Mean number tablets/week/per patient
1*	[redacted]	[redacted]	[redacted]	[redacted]
2*	[redacted]	[redacted]	[redacted]	[redacted]
3*	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]

*For weeks 1 to 3 tablets included 30 mg DMF per tablet. For weeks 4 to 16 tablets included 120 mg DMF per tablet

Source: Almirall Data on File. April 2017.

- The treatment protocol outlined in Figure 5 suggests dosing of 720 mg daily from week 9 to 16. If the mean observed dose is less than 720 mg for these weeks,
    - please provide reasons for this deviation and
    - a breakdown by arm, of the number of patients receiving 1, 2, 3, 4, 5 and 6 tablets separately for each relevant week.

Response:

Reasons for deviation

The treatment regimen outlined in the BRIDGE study protocol stated that if treatment success was observed before the maximum dose of 720 mg/day of DMF was reached, no further increase of dosage was necessary and then the dosage had to be steadily reduced to an individual maintenance dose. The same dosing schedule was used in each treatment group, details of this are provided in Table 8, page 46 of the Almirall submission.

Breakdown of patient numbers

Tables providing a breakdown by arm, of the number of patients receiving 1, 2, 3, 4, 5 and 6 tablets separately for each relevant week are provided on an academic in confidence basis in the accompanying word document file name ‘ID776_Almirall response to ERG clarification question A11_AIC’.

Clinical effectiveness results

A12. PRIORITY QUESTION. CS, section 4.7, Co-primary endpoints (pages 57-58).

- Please provide the results of the co-primary outcomes for the SAS.

Response: The results for the co-primary outcomes PASI 75 at week 16 and the proportion of patients achieving a score of 'clear'=0 or 'almost clear' = 1 in the PGA at Week 16 are provide in Table 7 and Table 8 respectively.

Table 7: Proportion of patients with PASI 75 at week 16 (SAS)

Effect	N		n	(%)	RD	Confidence Interval	Significance level of CI	p-value	Non inferiority Limit
Treatments:									
Placebo	137	[redacted]	[redacted]	[redacted]					
DMF (LAS41008)	279	[redacted]	[redacted]	[redacted]					
Fumaderm	283	[redacted]	[redacted]	[redacted]					
Treatment comparisons									
DMF (LAS41008) vs Fumaderm					[redacted]	[redacted]	[redacted]	[redacted]	-15%
DMF (LAS41008) vs Placebo					[redacted]	[redacted]	[redacted]	[redacted]	
Fumaderm vs Placebo					[redacted]	[redacted]	[redacted]	[redacted]	

Key: RD, risk difference

One-sided p-value for superiority for DMF (LAS41008) vs Placebo and Fumaderm vs Placebo treatment comparisons. One-sided p-value for non-inferiority for DMF (LAS41008) vs Fumaderm comparison.

Confidence Interval (lower limit, upper limit) for the risk difference, only for descriptive purposes.

Source: Almirall Data on File. December 2016

Table 8: Proportion of patients with score (almost) clear in PGA at week 16 (SAS):

Effect	N		n	(%)	RD	Confidence Interval	Significance level of CI	p-value	Non inferiority Limit
Treatments:									
Placebo	137	[redacted]	[redacted]	[redacted]					
DMF(LAS41008)	279	[redacted]	[redacted]	[redacted]					
Fumaderm	283	[redacted]	[redacted]	[redacted]					
Treatment comparisons									
DMF (LAS41008) vs Fumaderm					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DMF (LAS41008) vs Placebo					[redacted]	[redacted]	[redacted]	[redacted]	
Fumaderm vs Placebo					[redacted]	[redacted]	[redacted]	[redacted]	

Key: RD, risk difference
One-sided p-value for superiority for DMF (LAS41008) vs Placebo and Fumaderm vs Placebo treatment comparisons. One-sided p-value for non-inferiority for DMF (LAS41008) vs Fumaderm comparison.
Confidence Interval (lower limit, upper limit) for the risk difference, only for descriptive purposes.
Source: Almirall Data on File. December 2016

- Please provide the PASI continuous scores for the FAS and SAS at week 16 and final follow up at 12 months.

Response: The PASI continuous scores for the FAS and SAS at week 16 and final follow up at 12 months are provided below.

Table 9: PASI continuous scores for the FAS and SAS at week 16 and final follow up at 12 months

	Mean Total PASI score (absolute values)(SD), 95% CI			
	DMF (LAS41008)	**Fumaderm**	**Placebo**	**Total**
SAS				
	N=279	**N=283**	**N=137**	**N=699**
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Follow up (F3) 12 months	[redacted]	[redacted]	[redacted]	[redacted]
FAS				
	N=267	**N=273**	**N=131**	**N= 671**
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Follow up (F3) 12 months	[redacted]	[redacted]	[redacted]	[redacted]

A13. PRIORITY QUESTION. CS, section 4.7, Figure 11 (page 63).

- Please provide the Kaplan Meier data that underlie Figure 11 (Time to relapse during the study [FAS]) in the following format for all 3 arms. This should also be provided in an Excel workbook (3 tables).

Time	N Events	N Censored	S(t)
0	0	0	100%
…	…	…	…
…	…	…	…
…	…	…	…

Response: Information is provided below in Table 10, Table 11 and Table 12.
and also in the accompanying Excel workbook ID776_Almirall response to ERG clarification question A13_AIC.

Table 10: Time to relapse in PASI 75 for DMF (LAS 41008)

Time (days)	N Censored	N Events	S(t)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]

Table 11: Time to relapse in PASI 75 for Fumaderm

Time (days)	N Censored	N Events	S(t)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 12: Time to relapse in PASI 75 for placebo

Time (days)	N Censored	N Events	S(t)
[redacted]			

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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A14. CS, section 4.7, Figures 11 and 12 (pages 63 and 64).

- Please explain the terms 'reference' and 'test' in the legends of Figures 11 and 12, and the patient numbers.

Response: 'Reference' refers to Fumaderm and 'Test' to DMF (LAS41008). Patient numbers are Fumaderm n=237, DMF (LAS41008) n=267 and placebo n=132

- Please provide statistical comparisons for the Kaplan-Meier curves in Figures 11 and 12.

Response: The statistical comparisons for the Kaplan-Meier curves in Figures 11 and 12 are provided below in Table 13 and Table 14.

Table 13: Figure 11 statistical comparison

Test	Chi - Square	DF	Pr > Chi-Square
Log-Rank	[redacted]	[redacted]	[redacted]

Key: DF, degrees of freedom (from the chi-squared distribution; Pr, probability (p-value)
Source: Almirall Data on File. April 2017

Table 14: Figure 12 statistical comparison

Test	Chi - Square	DF	Pr > Chi-Square
Log-Rank	[redacted]	[redacted]	[redacted]

Key: DF, degrees of freedom (from the chi-squared distribution); Pr, probability (p-value)
Source: Almirall Data on File. April 2017

A15. CS, section 4.7, PASI 75 (pages 57-58).

For all 3 groups, please state:

- the number (and proportion) of participants contributing data to the PASI 75 response estimates evaluated at week 16.

Response: The number (and proportion) of participants contributing data to the PASI 75 response estimates evaluated at week 16 are provided in Table 15.

Table 15: Number (and proportion) of participants contributing data to the PASI 75 (FAS)

	DMF (LAS41008) N=267	**Fumaderm N=273**	**Placebo N=131**	**Total N=671**
No N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Yes N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]

Source: Almirall Data on File. April 2017

- the number (and proportion) of participants contributing data to the PASI 75 response estimates assessed using the last observation carried forward (LOCF) approach. Please tabulate the durations of the LOCF for each arm. For example, a patient with a last measurement at week 10 would have a LOCF duration of 6 weeks (1 table).

LOCF for	DMF	Fumaderm	Placebo
16 weeks	n=???	n=???	n=???
15 weeks	n=???	n=???	n=???
14 weeks	n=???	n=???	n=???

Response: Details on the number (and proportion) of participants contributing data to the PASI 75 response estimates assessed using the last observation carried forward (LOCF) approach are provided in Table 16.

Table 16: Number (and proportion) of participants contributing data to the PASI 75

Proportion of subjects with PAS 75 at week 16	DMF (LAS41008) N=267	Fumaderm N=273	Placebo N=131
Final			
Yes n (%)	[redacted]	[redacted]	[redacted]
No n (%)	[redacted]	[redacted]	[redacted]

Source: Almirall CSR Table 14.3.1.1

Since PASI was only collected at baseline, Week 3, Week 8 and Week 16 the requested durations of the LOCF for each arm are not possible. The information available is provided in Table 17.

Table 17: Number of subjects with LOCF in 1, 2 or 3 visits

LOCF for:	DMF (LAS41008) N=267 N(%)	Fumaderm N=273 N(%)	Placebo N=131 N(%)
2 visits (from Week 3 to Week 16)	[redacted]	[redacted]	[redacted]
1 visit (from Week 8 to Week 16	[redacted]	[redacted]	[redacted]
0 visits	[redacted]	[redacted]	[redacted]

Safety data

A16. CS, section 4.12, Adverse reactions (pages 128-130).

- Please clarify whether there are any longer-term data on adverse events of DMF, even in other indications.
    - If available, please provide these data.

Response: While DMF (Trade name: Tecfidera) is also approved for multiple sclerosis (MS), the formulation, dosage and dosing regimen are different to DMF used to treat psoriasis and it is not possible to compare from one indication to another.

For MS the patient population for which DMF (Tecfidera) is licensed has a different risk-benefit situation compared with the psoriasis population. In addition MS patients may be at a higher risk of developing Progressive Multifocal Leukoencephalopathy (PML) because of their underlying neurological condition and the previous or concomitant use of other drugs which have also been linked to PML.

For these reasons the safety data from other indications including MS cannot be extrapolated to psoriasis.

A17. PRIORITY QUESTION. CS, section 4.13, Extrapolating to Fumaderm (page 136).

- Please provide further details of the reported adverse events in the FUTURE retrospective study on Fumaderm, if available.

Response: Please note that Almirall do not have access to data for the FUTURE study beyond what is published. Information on adverse events from the key publication[2] is provided below.

The FUTURE study collected data on the safety and efficacy of fumaric acid esters (FAE; Fumaderm) in the long-term treatment of psoriasis. 984 Patients were included at 163 dermatological centres if they either had been treated continuously with FAE for at least 24 months, or for 36 months with interruptions of no longer than 6 months. Safety parameters were monitored and the severity of skin symptoms was assessed by PGA and PASI. This study did not report details of adverse events, only whether therapy was changed due to adverse events. A therapy change occurred during the FAE treatment in 171 (17.4 %) of patients. Reasons for the therapy change were documented in 103 of the patients. A side effect was stated as reason for the therapy change in 18 patients (1.8 % of 984 patients).

Safety Results

- Data was collected from baseline, after 3, 6, 12, 24, and 36 or more months of therapy.
- The maximum incidence of lymphopenia was seen at 24 months - 41 % of patients
- The maximum incidence of leukopenia was seen at 24 months - 12% of patients
- The maximum incidence of elevation of liver enzymes (GT, ALAT or ASAT) was seen at 3 months - 13 % of patients
- The maximum incidence of an elevation of the creatinine level was seen at 24 months - 6 % of patients
- Abnormal blood counts or serum parameters were documented in 9 % and 7 % of patients, respectively, even before initiation of therapy.
- During the entire observation period 94.2 % of patients required no therapeutic measures (e. g. dose adjustment or discontinuation of therapy)
- For patients with altered blood counts or hepatic or renal parameters, 96.1 % required no therapeutic measures.
- Among those patients whose laboratory alterations made a therapeutic change necessary, in most cases therapy could be continued after a dose reduction.
- Therapy was discontinued after more than 2 years of treatment in only 16 and 9 patients respectively, due to alterations of blood count or hepatic or renal parameters

Systematic review and network meta-analysis (NMA)

Excluded studies

A18. PRIORITY QUESTION. A Cochrane review on oral fumaric acid esters for psoriasis identified 6 relevant studies (Altmeyer et al. 1994; Fallah Arani et al. 2011; Langner et al. 2004; Mrowietz et al. 2006; Nugteren-Huying et al. 1990; Peeters et al. 1992).

- Please clarify why these studies were not included in the NMA for the Fumaderm comparison.

Response: The reasons for the exclusion of the 6 studies (Altmeyer et al. 1994[3]; Fallah Arani 2011[4]; Langner et al. 2004[5]; Mrowietz et al. 2006[6]; Nugteren-Huying et al. 1990[7]; Peeters et al. 1992[8]) identified in the Cochrane review on oral fumaric acid esters for psoriasis[9] are outlined in Table 18 below.

Table 18. Overview excluded articles from Cochrane review

Study	Reason for exclusion
Altmeyer et al. 1994[3]	This study reports on a mixed population of plaque, guttate, pustular and erythroderma psoriasis. Results are not reported separately for plaque psoriasis patients.
Fallah Arani 2011[4]	This study compares a conventional treatment arm (methotrexate) to fumarates, and was excluded during the feasibility assessment (see Table 27 in the original submission).
Langner et al. 2004[5]	This is a conference abstract published before 2013, and has been excluded in line with the inclusion/exclusion criteria for the systematic review.
Mrowietz et al. 2006[6]	This is a conference abstract published before 2013, and has been excluded in line with the inclusion/exclusion criteria for the systematic review.
Nugteren-Huying et al. 1990[7]	This article is a brief communication, and has been excluded in line with the inclusion/exclusion criteria for the systematic review.
Peeters et al. 1992[8]	This study focused on patients with psoriatic arthritis and not psoriasis.

- Please clarify whether these studies are of relevance to the assessment of adverse effects.

Response: The excluded studies are not of relevance to the assessment of adverse events as for the same reasons the studies were excluded from the NMA. The studies do not include information relevant to the appraisal including the anticipated patient population.

A19. CS, section 4.10.1, Systematic literature review (SLR) (page 78). "During screening one article was excluded based on the German language."

- Please provide summary details of the German language study that was excluded from the systematic review.

- Please describe in what way the German language study does not fit the inclusion criteria of the systematic review and/or NMA.

- If the German language study was excluded because of language only, please explore the impact of excluding this study.

Response: During full-text screening one article, Angsten and Schopf 2007[10], was excluded based on the German language. This study compared infliximab (n=6) to etanercept low-dose (n=6) in male psoriasis vulgaris patients. In terms of efficacy outcomes, only overall PASI score was reported at induction time for both arms. Our NMA focussed on PASI response (PASI50/75/90) at 16 weeks and induction time and therefore the outcomes reported in Angsten and Schopf 2007 are not relevant.

Ranking of effectiveness in the NMA

A20. PRIORITY QUESTION. CS, section 4.10.4, Results (pages 117-127). Please provide a ranked list comparing the effectiveness of the different interventions examined in the NMA for all outcomes.

Response: Based on the posterior distributions of each intervention relative to one reference treatment of choice, the probability that each treatment is ranked at a certain position out of all different interventions compared is calculated and presented with rankograms. In addition, the expected rank is reported. An additional numerical summary to supplement the rankograms is to estimate the surface under the cumulative ranking (SUCRA) line for each treatment; SUCRA is equal to 1 (or 100%) when a treatment is certain to be the best among all the available treatments and 0 (or 0%) when it is certain to be the worst.[11]

PASI response at 16 weeks

Regarding the ranking output, a rankogram of all competing treatments is presented in Figure 3. DMF (LAS41008) (red line) showed the highest probability of ranking fifth, whilst Fumaderm and apremilast showed the highest probability of ranking fourth and third, respectively. In addition, median rank and SUCRA values were calculated for all treatments (Table 19) DMF (LAS41008), Fumaderm and apremilast showed SUCRA values equal to [redacted] and [redacted] respectively.

Figure 3. Rankogram for PASI response at 16 weeks - base case

Table 19. Ranking outcomes for PASI response at 16 weeks - base case

Intervention	Median rank (95% CrI)	SUCRA
Adalimumab	[redacted]	[redacted]
Etanercept low-dose	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Fumarates	[redacted]	[redacted]
LAS41008	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

CrI: Credible interval; SUCRA: Surface under the cumulative ranking

PASI response at induction time

Regarding the ranking output, a rankogram of all competing treatments is presented in Figure 4. DMF (LAS41008) (red line) showed the highest probability of ranking eleventh, whilst Fumaderm and apremilast showed the highest probability of ranking tenth and ninth, respectively. In addition, median rank and SUCRA values were calculated for all treatments (Table 20). DMF (LAS41008), Fumaderm and apremilast showed SUCRA values equal to [redacted] and [redacted] respectively.

Figure 4. Rankogram for PASI response at induction time - base case

[redacted]

Table 20. Ranking outcomes for PASI response at induction time - base case

Intervention	Median rank (95% CrI)	SUCRA
Ixekizumab	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]
Ustekinumab high-dose	[redacted]	[redacted]
Ustekinumab low-dose	[redacted]	[redacted]
Ustekinumab mixed	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]
Etanercept high-dose	[redacted]	[redacted]
Etanercept low-dose	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Fumaderm	[redacted]	[redacted]
DMF (LAS41008)	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

CrI: Credible interval; SUCRA: Surface under the cumulative ranking

PASI response at 16 weeks - Scenario excluding Ohtsuki 2016

Regarding the ranking output, a rankogram of all competing treatments is presented in Figure 5. DMF (LAS41008) (red line) showed the highest probability of ranking fifth, whilst Fumaderm and apremilast showed the highest probability of ranking fourth and third, respectively. In addition, median rank and SUCRA values were calculated for all treatments (

Table 21). DMF (LAS41008), Fumaderm and apremilast showed SUCRA values equal to [redacted] and [redacted] respectively.

Figure 5. Rankogram for PASI response at 16 weeks – scenario analysis

Table 21. Ranking outcomes for PASI response at 16 weeks – scenario analysis

Intervention	Median rank (95% CrI)	SUCRA
Adalimumab	[redacted]	[redacted]
Etanercept low-dose	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Fumaderm	[redacted]	[redacted]
DMF (LAS41008)	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

CrI: Credible interval; SUCRA: Surface under the cumulative ranking

PASI response at induction time - Scenario excluding Ohtsuki 2016

Regarding the ranking output, a rankogram of all competing treatments is presented in Figure 6. DMF (LAS41008) (red line) showed the highest probability of ranking eleventh, whilst Fumaderm and apremilast showed the highest probability of ranking tenth and ninth, respectively. In addition, median rank and SUCRA values were calculated for all treatments Table 22) DMF (LAS41008), Fumaderm and apremilast showed SUCRA values equal to [redacted] and [redacted] respectively.

Figure 6. Rankogram for PASI response at induction time – scenario analysis

Table 22. Ranking outcomes for PASI response at induction time – scenario analysis

Intervention	Median rank (95% CrI)	SUCRA
Ixekizumab	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]
Ustekinumab high-dose	[redacted]	[redacted]
Ustekinumab low-dose	[redacted]	[redacted]
Ustekinumab mixed	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]
Etanercept low-dose	[redacted]	[redacted]
Etanercept high-dose	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Fumaderm	[redacted]	[redacted]
DMF (LAS41008)	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

CrI: Credible interval; SUCRA: Surface under the cumulative ranking

PASI response at 16 weeks - Prior systemic therapies or phototherapy

Regarding the ranking output, a rankogram of all competing treatments is presented in Figure 7. DMF (LAS41008) (red line) showed the highest probability of ranking fifth, whilst Fumaderm and apremilast showed the highest probability of ranking fourth and third, respectively. In addition, median rank and SUCRA values were calculated for all treatments (

Table 23). DMF (LAS41008), Fumaderm and apremilast showed SUCRA values equal to [redacted] and [redacted] respectively.

Figure 7. Rankogram for PASI response at 16 weeks – subgroup analysis

Table 23. Ranking outcomes for PASI response at 16 weeks – subgroup analysis

Intervention	Median rank (95% CrI)	SUCRA
Adalimumab	[redacted]	[redacted]
Etanercept low-dose	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Fumaderm	[redacted]	[redacted]
DMF (LAS41008)	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

CrI: Credible interval; SUCRA: Surface under the cumulative ranking

PASI response at induction time - Prior systemic therapies or phototherapy

Regarding the ranking output, a rankogram of all competing treatments is presented in Figure 8. DMF (LAS41008) (red line) showed the highest probability of ranking eleventh, whilst Fumaderm and apremilast showed the highest probability of ranking tenth and ninth, respectively. In addition, median rank and SUCRA values were calculated for all treatments (Table 24). DMF (LAS41008), Fumaderm and apremilast showed SUCRA values equal to [redacted] and [redacted] respectively.

Figure 8. Rankogram for PASI response at induction time – subgroup analysis

Table 24. Ranking outcomes for PASI response at induction time – subgroup analysis

Intervention	Median rank (95% CrI)	SUCRA
Ixekizumab	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]
Ustekinumab high-dose	[redacted]	[redacted]
Ustekinumab low-dose	[redacted]	[redacted]
Ustekinumab mixed	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]
Etanercept high-dose	[redacted]	[redacted]
Etanercept low-dose	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Fumaderm	[redacted]	[redacted]
DMF (LAS41008)	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

CrI: Credible interval; SUCRA: Surface under the cumulative ranking

Section B: Clarification on cost-effectiveness data

Best supportive care

B1. PRIORITY QUESTION. CS, section 5.2, *De novo* analysis (page 161). Please explain what is included as part of best supportive care (BSC) used in the model.

Response: As has been accepted by NICE in previous appraisals, the cost of BSC was assumed to be similar to the pre-biologic patients in Fonia et al. 2010. This included systemic treatments, inpatient admission days, A&E visits, outpatient visits, day ward admissions and phototherapy sessions. The effectiveness of BSC was assumed to be the same as the placebo arm of the trials included in the NMA.

Drug doses and costs

B2. CS, section 5.2.3, Intervention technology and comparators (page 166). The stated mean dose of DMF in the BRIDGE trial at 9 weeks was 624 mg. However, the suggested maintenance dose for DMF is 360 mg based on the retrospective FUTURE study on Fumaderm.

- Please clarify whether there are any data from longer-term follow up of the participants in BRIDGE.

No long-term BRIDGE data is available. Long-term follow-up in the BRIDGE trial was off treatment. The short duration of the BRIDGE trial and the lack of down-titration instructions to investigators did not allow the trial to demonstrate the maintenance dose that is usually required in clinical practice. In the BRIDGE trial, the up-titration scheme was identical to that approved for Fumaderm's SmPC.

- Please clarify whether there are any data suggesting what the maintenance dose is likely to be in the UK.

Response: Clinical opinion gathered from UK dermatologists supports that in clinical practice the general range of Fumaderm dosing in stable patients is between 2 to 4 of 120 mg tablets per day, with 2 to 3 being the most common dose.

B3. PRIORITY QUESTION. CS, section 4.3, figure 5 (page 41).
FUTURE reported a mean Fumaderm dosing regimen ranging from 2.58 to 3.72 tablets/day depending on weight (Reich et al. 2009).

- Please explain why the same dosing regimen was applied to Fumaderm as for DMF in the BRIDGE trial.

Response: While specific data on the long-term dosing regimen, efficacy and safety of DMF (LAS41008) are not currently available, bridging to the data available for the anti-psoriatic medicine Fumaderm provides this information. As stated previously in the Almirall submission (page125), '*Fumaderm contains a combination of both DMF and the zinc calcium and magnesium salts of MEF, of which DMF is considered to be the active ingredient.[44] No clinically significant effect of MEF was demonstrated in a controlled clinical study comparing MEF at doses of up to 720mg per day to placebo in patients with psoriasis[183]'*

Dose equivalence between DMF and Fumaderm is therefore expected and agreed by CHMP.

Average dosing as reported in the FUTURE study[2] shows that, in clinical practice in Germany, the mean daily dose used for maintenance therapy is closer to 360 mg per day. As stated above, clinical opinion gathered from a range of UK dermatologists supports that this is also the mean dose in clinical practice.

However, the maximum licensed dose for Fumaderm in Germany is 720 mg per day. As a requirement of the licence application process, Almirall were directed to demonstrate non-inferiority to Fumaderm at an equivalent up-titration and dose regimen. To achieve this demonstration of non-inferiority at this dose, equivalent dosing of Fumaderm and DMF per day was required for the BRIDGE study, with a maximum daily dose up to 720 mg.

- Please provide the duration of the treatment period prior to maintenance therapy in FUTURE.

Response: This information is not provided in the publication of the FUTURE study and we do not have access to any data beyond this publication.

- Please clarify the effect of applying the dosing regimen reported in FUTURE on the weekly dose and cost of Fumaderm during the BRIDGE trial period.
    - Please explore the associated effect on the cost-effectiveness estimates for DMF followed by BSC compared to Fumaderm compared to BSC.

Response: As long-term data on DMF is not available, daily doses (tablets per day) from the FUTURE study are used when modelling the long-term effect of DMF in the cost-effectiveness analysis. Assuming most of the patients have a body weight between 80-100 kg, a mean daily dose of 3 tablets is considered appropriate (Table 7, from the FUTURE study publication). In the economic model, the mean maintenance dose is reached after a slow increase to the maximum dose during the up-titration period in the trial period of the model. This is in line with the regimen enforced in the BRIDGE trial and within the approved Fumaderm SmPC. Using the cost-effectiveness model, sensitivity analysis around the dosing was undertaken and showed that the results were not sensitive to how quickly patients reduced their dose from the maximum to three tablets.

B4. CS, section 5.5, Drug acquisition costs (page 179).

- Please explain why there is [redacted] in the model.

Response: Fumaderm is not licensed in the UK and not imported or distributed by the manufacturer. UK centres wanting to use Fumaderm have to source it from a limited number of importers who purchase the product in Germany and make it available in the UK. In investigating the cost of imported Fumaderm to UK centres it became apparent that the cost of imported Fumaderm [redacted]

- Please clarify the dose and pack sizes of Fumaderm initial and Fumaderm.

Response:

Fumaderm initial	30mg	Pack size 40 tablets
Fumaderm	120mg	Pack sizes 70, 100, 200 tablets

- Please clarify whether Fumaderm initial and Fumaderm are licensed in other EU countries for use in plaque psoriasis

Response: Fumaderm initial and Fumaderm are licensed only in Germany for use in plaque psoriasis.

- If Fumaderm initial and Fumaderm are licensed elsewhere, please state the prices in each country.

Response: Not applicable see above response.

- Please clarify the unit cost and dosing assumed for ixekizumab for the trial period and the maintenance period.

Response: The unit cost of ixekizumab is £1,125 for a 80 mg dose (http://www.mims.co.uk/drugs/skin/psoriasis-seborrhoea-ichthyosis/taltz)

In the trial period dosing is 160 mg at week 0, 80 mg at weeks 2, 4, 6, 8, 10 and 12.

In the maintenance period dosing is 80 mg every 4 weeks.

Health-related quality of life data

B5. PRIORITY QUESTION. CS, section 5.4, table 58 (page 170).

- Please provide the source data for Table 58.

Response: The source data for Table 58 in the Almirall submission document is provided below in Table 25. Additional analysis were run to explore the DLQI changes and correlation with PASI 50, PASI 75 and PASI 90 improvements achieved by patients on each arm of the BRIDGE trial.

Table 25: DLQI changes from BRIDGE trial at week 16

PASI	DMF (LAS41008)	Fumaderm	Placebo
<50	[redacted]	[redacted]	[redacted]
50 – 75	[redacted]	[redacted]	[redacted]
75- 90	[redacted]	[redacted]	[redacted]
>90	[redacted]	[redacted]	[redacted]

Source: Almirall Data on File. 2016

- Please clarify the computation undertaken to derive the values in Table 58. Are calculations for each PASI/treatment category based on estimating each patient's baseline DLQI and change in DLQI to derive each patient's quality of life increment and then averaging the resulting mapped individual patient's quality of life increments?

Response: The average change in DLQI for patients by PASI score was multiplied by -0.0162 from the ustekinumab re-estimation utilised in the NICE appraisal of ustekinumab. (TA180).[12]

- What are the baseline quality of life values implied in each of the 3 treatments when the mapping function is applied?

Response: Baseline DLQI was not used for this calculation.

Resource use and costs

B6. CS, section 5.5, Health-state unit costs and resource use (pages 180-181).

- For the pre-biologics, biologics and BSC, please tabulate each element of resource use derived from Fonia et al. (2010) separately and include
    - the unit cost applied to these elements
    - any inflation indexing
    - the implied annual cost for each of the pre-biologics, the biologics and BSC. Please provide an account of any discrepancies between the three annual totals.

Response: Details on the unit costs applied to each element are provided in Table 26 and details of inflation indexing in Table 27

Table 26: Estimating Unit Costs Inflated to 2014/15 GBP from Fonia et al.2010

Resource	Published Cost	Year	Inflation	Inflated Cost
Outpatient Visit	£ 101.58	2015	NA	£ 101.58
Inpatient Admission	£ 291.00	2009	293.1/267	£ 319.45
A&E Visit	£ 86.00	2009	293.1/267	£ 94.41
Day and ward admissions	£ 441	2009	293.1/267	£ 484.11
Phototherapy	£ 283	2009	293.1/267	£ 310.66
Drugs pre-biologic	£ 1,250.50	2009	293.1/267	£ 1,372.74
Drugs post-biologic	£ 10,707	2009	293.1/267	£ 11,753.64

Table 27. Estimating inflated Pre/Post biologic costs

Resource	Inflated Cost	Resource Use	
		Pre-biologic from Fonia et al 2010	**Post-biologic from Fonia et al 2010**
Outpatient Visit	£ 101.58	3.22	3.25
Inpatient Admission	£ 319.45	6.49	1.55
A&E Visit	£ 94.41	0.03	0.04
Day and ward admissions	£ 484.11	0.14	0.16
Phototherapy	£ 310.66	2.76	0.26
Drugs pre-biologic	£ 1,372.74	1	0
Drugs post-biologic	£ 11,753.64	0	1
Total		£ 4,628.51	£ 12,667.67

Using the inflated costs and the resource use from Fonia et al. (2010) the inflated pre-biologic annual costs are £4,628.51 and the inflated post-biologic annual costs are estimated to be £12,667.67. These are slightly different from updating the Fonia et al.(2010) total annual costs directly since outpatient costs in the model came from the National Schedule of Reference Costs: 2014-2015 Outpatient visit: Dermatology. BSC costs were calculated directly from the total Fonia et al. (2010) costs and do not use the outpatient visit unit costs from the National Schedule of Reference Costs.

- Please clarify what index and which two index values have been used to inflate the costs reported in Fonia et al. (2010).

Response: Hospital and Community Health Services Index was used from PSSRU Unit Costs of Health and Social Care 2015. The values 267 (2008/09) and 293.1 (2014/15) were used to inflate the unit costs from Fonia et al. 2010.

Excel model

B7. PRIORITY QUESTION. Please confirm whether Cells F8:J26 of the *Effectiveness* worksheet of the economic model are drawn from Table 38 (CS, page 120) of the clinical effectiveness section.

- If this is the case, please outline why the PASI response at induction is to be preferred to the PASI response at 16 weeks and why these estimates differ.

Response: We can confirm that the effectiveness data came from Table 38 in the Almirall submission. The model used the effectiveness at induction time given that each treatment is assessed at induction time to determine whether the treatment should be continued / stopped. Since induction time for some treatments is 12 weeks and others is 16 weeks this difference in the stopping rules is captured by using the effectiveness at induction.

- If this is not the case, please outline how cells F8:J26 of the *Effectiveness* worksheet of the economic model have been derived. Please clarify the impact of using the 16-week PASI response estimates.

Response: This question is not applicable since the effectiveness data has been derived from Table 38 in the Almirall submission document as per the above response.

B8. PRIORITY QUESTION. CS, section 5.9, Subgroup analysis (page 194). The ERG cannot identify how to implement the subgroup analysis in the submitted model. Please outline how to arrive at the cost-effectiveness estimates outlined in section 5.9 in the submitted Excel model.

Response: To implement the subgroup analysis the data from Table 44 in the Almirall submission were inputted into the effectiveness worksheet of the model.

References

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10. Angsten MS, R. E. Anti-TNF-alpha-therapy of psoriasis with Infliximab or Etanercept. Clinical, histological and immunohistochemical course. Aktuelle Dermatologie. 2007;33(8/9):310-6.
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12. National Institute for Health and Clinical Excellence (NICE). Ustekinumab for the treatment of adults with moderate to severe psoriasis. NICE technology appraisal guidance [TA180], 23 September 2009. Available at: https://www.nice.org.uk/guidance/ta180 Accessed January 2017.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

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

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question ð the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: David Chandler

Name of your organisation: Psoriasis and Psoriatic Arthritis Alliance (PAPAA)

Your position in the organisation: Chief Executive

Brief description of the organisation:

PAPAA is a principal source of advice, support and information on psoriasis and psoriatic arthritis in the United Kingdom. PAPAA provides support to people with psoriasis and psoriatic arthritis, their families and carers. PAPAA also supports healthcare professionals and assists the wider community to understand the needs of people affected by both conditions.

The organisation maintains a register of people with/or interested in both conditions. The register currently has >13,000 people, and is free to join.

Funding of the organisation is mainly via donations, legacies, and subscriptions. The organisation has a strict funding and external involvement policy and does not accept funding from commercial companies either directly, in kind or via third party agencies. This includes but not limited to, pharmaceutical companies, the tobacco industry, public relations agencies, lobbying firms and other organisations including charities whose activities could cause conflict, due to their own funding sources and policies.

Primary activity is to provide information, education and support, via a website (>850,000 page views during the past 12-months), information line (both electronic and voice), along with the provision of printed information, produced under The NHS England Information Standard scheme. Other activities include a biannual journal called Skin ǿnôBones Connection. Disease management and training programmes are also an important role the charity wishes to take forward.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

In order to inform this submission, we conducted an online survey via a random selection of individuals from our register. Those who responded reflect the views of most of the people we talk to via our information line.

Living with psoriasis regardless of the severity can be very distressing and have a profound effect on all aspects of an individualôs life. The day-to-day effects can be difficult and challenging.

In a range of free text answers from women and men aged between 41-87 years of age living in England, the following are representative quotes:

ñHorrendous. People treat you as if you are a leper. There is great ignorance about this conditionò

ñHorrible to start with because you don't know what on earth is wrongò

ñDebilitating, painful, depressing and time consumingò

ñMy psoriasis was confined to my scalp, knees and elbows but has now spread to my legs and other areas, although not severe. I find the worst thing is the itching, especially when I am in bed as it keeps me awake.ò

ñVery debilitating, embarrassing and saps what bit of energy you may have.ò

ñMy scalp itches all the time and I never know when it will be all over my body.ò

ñPainful, irritating, depressing.ò

ñAs a child I used to get bullied by other children, teachers would look at me oddly and that's carried on throughout life. I think it has made me more anxious.ò

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The following are typical responses and reflect the need to not only treat the symptoms, but also reduce anxiety and improve remission. Many people fear a return and a treatment, which can provide convincing efficacy, would be welcomed.

ñA treatment that doesn't just mask the symptoms but treats the underlying cause.ò

ñOne that will address the root of the problem without negative side effects.ò

ñI appreciate psoriasis cannot be cured but I would be happy if the itching and redness could be controlledò

ñFor years I have been offered creams and gels these have had very little impact.ò

ñTo be able to lead a more positive life. Less pain and discomfort.ò

ñTo calm the area of the psoriasis.ò

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

ñThat depends if one has a GP who is aware and a consultant who listens! Care and help is there but one has to fight for the more expensive treatments.ò

ñDon't know because I am on BUPA but although when I was diagnosed treatment was pretty meagre but then I'm not bad and I managed to treat myself and get advice from a Pharmacist who was much more help than the specialist.ò

ñNot good enough. Not enough options, long waiting times to see a consultant.ò

ñI have been prescribed 6 different treatments by Dermatology NHS Hospital, none worked.ò

ñThey seem to be getting better all the time. Pity about the cost complications.ò

ñA specialist at NHS hospital was cross that I asked her opinion of an "alternative" I had had recommended.ò work for the NHS and am not allowed to discuss other remedies!" For her it was EXOREX or nothing. She complained to my GP that I was a time waster and she had been unable to prescribe a hydrating remedy and asked him to do so!ò

ñFor years I have been offered creams and gels these have had very little impact.ò

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

We did not have anyone who responded to our survey currently being prescribed the treatment being appraised, but in general people want to see any new or change in their therapy to provide an immediate improvement of symptoms, such as reduction in itching, scaling and redness, with clearance

being a goal. Residue visible signs kept to a minimum. Treatments with little inconvenience and limited or no adverse reaction would be welcomed. Within the current treatment pathway, older topical medications are messy and time consuming to apply. The use of phototherapy although beneficial for many does require regular appointments, usually 3-times a week over a 6-week period, which can often be difficult for those in employment to complete.

In previous surveys, people have often mentioned that sometimes the affect of the treatment and the adverse events are worse than the psoriasis symptoms. Methotrexate often is described as being õpoisoned on a weekly basisö. And for some the increased infections, loss of hair and not being able to drink alcohol makes methotrexate particularly loathed.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

As this treatment is not routine within the NHS, it is difficult to assess any advantages that patients and carers might see. It is an oral medication, so that may be seen as an advantage for those who are progressing from more traditional topical treatments, although other oral therapies are available now. The BRIDGE trial did show efficacy versus placebo, but clearance was not an end-point, which most patientsø would like to achieve. Adverse events were reported in 84%, but appear to be related to gastrointestinal events, which are often reported in other oral medications for psoriasis.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

No information on this point.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)

- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

People have often expressed concerns to us about the effectiveness of current therapies and on occasions, the limited availability of the newer therapies, which they perceive to be more effective. The perception is that the high cost of more effective treatments is denying access and people feel they are being disadvantaged. The lack of availability of phototherapy is also of concern and some people feel that they are moved to more toxic therapies such as methotrexate instead of being offered PUVA or UVB therapy. There is also a lack of knowledge of psoriasis at primary care level and people are often not referred and continue on topical applications beyond the time when they no longer provide benefit. The NICE psoriasis guideline CG153, also appears to have had little affect in remedying the situation, when questioned people who contact us are often unaware of its existence or have seen little or any of the recommendations being applied.

Please list any concerns patients or carers have about the treatment being appraised.

We do not have any information on this.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

No comments on this.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Perhaps those who need to progress beyond topical therapy and are unsuitable for methotrexate due to liver toxicity issues, if the safety data shows no hepatic impact.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not that we are aware

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☑ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Assuming the administration is the same as the trial then it would appear plausible that this could be reflected in what patients experience with other therapies, that is an oral therapy taken twice daily. Although, the titration over 9 weeks may be disconcerting if no benefit is seen from therapy. Patients may become disillusioned, particularly given it was reported that the discontinuation rate was high due to the known adverse events. It would also be interesting to know who the intended prescriber will be. If prescribed at primary care that will be different as usually GPs are confined to topical prescribing.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Not particularly, it is disappointing that it was a placebo trial and PASI50 and PASI75 are seen as major achievements. Patients want to see at least PASI90 (90% improvement) or clearance with minimal adverse events, few achieved this within the study.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

No comment.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☑ No

If yes, please provide references to the relevant studies.

N/a

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None that we are aware of.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

There may be people who have difficultly swallowing oral medication, but there must be established ways these individuals can overcome that issue.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☑ No

If yes, please explain what makes it significantly different from other treatments for the condition.

N/a

Are there any other issues that you would like the Appraisal Committee to consider?

None

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Psoriasis is a life-long disease, that has major impact on an individual's life
- A variety of therapies offers choice, given the reoccurring nature and tachyphylaxis that people often experience on long-term therapies.
- Access to therapies is often restricted or difficult to access, particularly given limited choice at primary care.
- High cost of therapies limits choice for some who need to progress beyond topical applications.
- Any severity of psoriasis can have a profound psychological impact

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

[redacted], **on behalf of the British Association of Dermatologists' Therapy & Guidelines and Biologic Interventions Register sub-committees**

Name of your organisation: British Association of Dermatologists
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Moderate-to-severe psoriasis is currently treated with either phototherapy, progressing if necessary to conventional systemic therapies such as methotrexate and ciclosporin. As recognised and indicated in NICE guidance, ciclosporin and phototherapy cannot be used 'long-term' and so for those patients whose disease relapses rapidly following induction of clearance, methotrexate is the only approved intervention for long-term use. In those individuals unable to be controlled adequately by these means, biological therapies are prescribed if stipulated disease severity criteria are met (PASI 10, DLQI 10).

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

A further subgroup might be in people in whom biologic therapy is contraindicated and where dimetyl fumarate may have efficacy (notably, multiple sclerosis).

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Secondary care and specialist clinics.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Fumaric acid esters is a mixture of fumarates of which dimethyl fumarate is considered the active agent and is used in a number of dermatology centres for psoriasis with benefit (see www.cochrane.org/CD010497/SKIN_oral-fumaric-acid-esters-treatment-psoriasis). However, it is unlicensed and having access to a licensed version would be an important advantage. Loss of response to biologic therapy is a significant problem in anecdotal evidence, indicating that in those who respond, response can be sustained and complete.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

www.cochrane.org/CD010497/SKIN_oral-fumaric-acid-esters-treatment-psoriasis

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: ***United Kingdom Clinical Pharmacy Association***
Are you (tick all that apply):

- ✓ a specialist in the treatment of people with the condition for which NICE is considering this technology?

  a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

  an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- ✓ other? (please specify) ***I am a pharmacist with expertise in the treatment of dermatological diseases and a spokesperson for UKCPA in this area***

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Fumaric acid esters (FAE) have been used for many years in the treatment of psoriasis in Germany but have been little used in the UK. This was partly due to the lack of availability, absence of a licensed product and limited experience with the treatment. As noted in the scope, Fumaderm, the product licensed in German, has been used off-label.

There is now one licensed form of dimethyl fumarate (Tecdifera (Biogen)) – but it is licensed for treatment of MS.

FAEs have been recommended for treatment of moderate-sever e chronic plaque psoriasis that does not respond to topical therapy and this would be the logical place for DMF. As such, it would be compared with ciclosporin, methotrexate, PUVA, acitretin and apremilast (and possibly tofacitinib). The first three are probably the most commonly-used in the UK. All are limited by toxicities of various types and clinicians are sometimes faced with patients who have exhausted all the options but still would like an oral (vs injected) treatment. For such patients the question will be whether to use DMF or apremilast next.

DMF would need to be prescribed by a clinician experienced in the management of mod-severe psoriasis. The need for up-titration of the initial dose and ongoing monitoring of lymphocyte and leucocyte counts and renal function could also require input from specialist nurses and pharmacists.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The advantages of DMF are:

- *Oral administration*
- *Different side-effect profile from existing oral treatments (although some overlap)*
- *Delayed release, gastro-resistant formulation should reduce frequency of GI side effects (compared with older products e.g. Fumaderm)*
- *Substantial body of clinical experience with FAE in Germany*

The disadvantages are:

- *A high level of side effects leading to discontinuation of treatment in clinical trials*
- *The need for rigorous monitoring of lymphocytes and leucocytes during treatment to minimise risk of serious adverse events including PML*
- *The drug cost could be high*

In view of the risk of PML rigorous monitoring of patients would be essential. This is something to which patients would have to make a commitment. Similar considerations apply to methotrexate (because of drug-induced bone marrow suppression) and some patients have been considered unsuitable for methotrexate treatment because they have not been capable of complying with the requirement for regular blood tests (e.g. persistently missing monitoring appointments). It is quite possible that some patients whose disease might be suitable for DMF treatment would be excluded from it because lack of compliance with monitoring requirements would pose unacceptable risks.

NB: Sensitisation to DMF has been reported as a cause of irritant contact dermatitis arising from leather furniture and shoes. There could be a risk with capsules, especially if broken or opened by user.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No comment

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NHS staff would need education about the side effects of DMF and training in the implementation of an appropriate monitoring (i.e. testing at appropriate frequency with timely interpretation and follow up) scheme.

It may not be an issue that NICE can address but if LAS 41008 (DMF, Almirall) is marketed at a price that is very different from that of Tecdifera (DMF, Biogen) then some organisations could seek to use the cheaper of the two for both indications – thus one would be used off-label.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

No comment

NICE National Institute for Health and Care Excellence

Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Helen McAteer**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Psoriasis Association
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☒ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: The Psoriasis Association is a membership organisation (2300) and so draws on the information voluntarily provided by its members. In addition to being a membership organisation, the Psoriasis Association has a website (550,000 visitors in 2016), runs a helpline (1,000 enquiries in 2016), runs online forums (6,000 registered users in 2016) and communicates with 12,000 people via social media. This submission has been informed by informal, anecdotal information that we hear from patients and carers themselves, through the channels mentioned above.
Living with the condition	
8. What is it like to live with the condition? What do carers	Psoriasis is a lifelong condition with varying degrees of severity. The patients for whom this treatment is intended, those with moderate to severe disease, will have a degree of psoriasis that will not only be

experience when caring for someone with the condition?	visible to others, but also be itchy, painful and produce excess scales. The scales are unsightly, and can cause problems with employment and work colleagues in many industries. Owing to the highly visible nature of psoriasis, and its unsightliness, patients can often adopt negative coping mechanisms such as avoiding social situations (in the hope of avoiding negative reactions from members of the general public). This can mean that the condition itself is isolating and lonely. This can in turn lead to adopting unhealthy lifestyle choices, such as alcohol and drug use, lack of exercise and smoking. Patients with moderate to severe psoriasis have usually been through a long journey of treatment trial and error and expense. When psoriasis is first diagnosed, patients will usually be prescribed topical treatments (creams and ointments). Our latest membership survey found that people were spending on average two hours every day treating their (mild) psoriasis. This involves regularly moisturising the skin (essential in order to keep the skin comfortable, to help with itch and to reduce flakes from falling – having to share a desk at work can be very difficult for people with psoriasis), and applying creams and ointments with more active ingredients. The majority of respondents in our membership survey reported psoriasis impacting on their choice of clothing, from regularly "covering up" in the summer months in long sleeves and long trousers, to the colour of clothing on the top half of the body (men report frequently having light suits for work to help conceal the shedding of scales, whilst women consciously sought certain fabrics so as not to have clothing ruined by treatments). It is often unsustainable to treat psoriasis with topical treatments alone, and patients will need more help to cope with a flare, or to maintain the condition at a manageable level. The traditional next stage has been Ultraviolet Light Therapy, but for some patients

	this form of treatment is not considered owing to the time commitment required (attending the Dermatology Department three times per week for 10 weeks). Traditional systemic treatments for psoriasis would then be considered if the psoriasis was deemed to be moderate to severe in nature. It is vitally important however to measure, record and treat not only the physical symptoms of psoriasis, but the psychological impact the condition can have. Being a lifelong condition, the psychological impact may not initially be realised, which is why it is important for this assessment to be made over the course of the disease. Psoriasis in high impact areas such as the hands, feet, face or genitals is not only a problem for people owing to the visibility of the condition. Deep cracks to the fingertips (not to mention nail psoriasis) can be disabling for those whose trade requires use of the hands and fingers (e.g. musicians, artists, mechanics, not to forget general office-based administration roles). Psoriasis on the feet can make walking difficult, even wearing shoes. Psoriasis on the face can be especially distressing, and we know people avoid intimate relationships so as not to have to expose genital psoriasis. For those in steady relationships, sexual relationships can be difficult owing to the pain experienced by genital psoriasis. People report deliberately not having children in case they too develop psoriasis. For those with moderate – severe psoriasis who do want children, their choice of treatment is limited owing to the teratogenicity of traditional systemic medications. Psoriasis therefore can affect every stage of life to varying degrees – from bullying in school, through to difficulty writing in exams, choice of career, having children, holidays and long-term relationships. Access to treatments that are appropriate, suitable and reliable is vital.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There has long been a frustration amongst those with clinically moderate psoriasis that their psoriasis is not “bad enough” to warrant systemic, or newer biological therapies, yet it is too severe to manage with topical treatments alone. This patient population are stuck in limbo. Sadly there is a postcode lottery in terms of care available on the NHS, for some, usually those who have been in the system for a while, it is good. For many there is little access to secondary care (where drugs for moderate to severe psoriasis are prescribed) as lists are closed or extremely lengthy or GPs are unwilling / unable to refer.
10. Is there an unmet need for patients with this condition?	Yes.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The treatment is taken orally (rather than via injection, or time consuming topical treatments). There are fewer side effects than existing systemic medications. The treatment is established, with long-term safety and efficacy data. It is not immunosuppressive. It can be used for long-term management.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The gastro-intestinal side effects

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients for whom immunosuppression is not viable. Those with moderate disease but a PASI / DLQI <10 (so not eligible for biologics) and for whom other systemics have failed. Patients unable to inject. People who travel for work or domestic purposes.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	

Topic-specific questions	
16. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	

Key messages
17. In up to 5 bullet points, please summarise the key messages of your statement: • Psoriasis is a lifelong condition in which individuals respond differently to different treatments. For this reason a range of treatment options for all degrees of severity is required. • There is currently unmet need in the treatment of people with moderate psoriasis (for whom topical treatments nor biologics are suitable). • High impact sites such as the face, hands, feet and genitals should not be overlooked when defining treatment criteria (these sites will not produce a high PASI score). • Itch should be considered as a treatment outcome.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Dimethyl fumarate for treating moderate to severe chronic plaque psoriasis
Single Technology Appraisal Report.

Produced by ERG: Warwick Evidence

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Date completed: 22nd May 2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 14/189/02

Declared competing interests of the authors: None

Acknowledgements

The ERG team are grateful to Christopher Griffiths (Professor of Dermatology, University of Manchester) for helpful clinical input.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Mason JM, Loveman E, Cummins E, Nkuda C, Colquitt J, Royle P. Dimethyl fumarate for treating moderate to severe chronic plaque psoriasis. Single Technology Appraisal Report. Warwick Evidence, May 2017.

Contributions of authors:

James Mason co-ordinated the project. Emma Loveman (Senior Researcher) co-ordinated and conducted the critique of clinical effectiveness evidence. Ewen Cummins (Health Economist) conducted, reviewed and critiqued the cost-effectiveness evidence. Chidozie Nkuda (Research Fellow) conducted the critique of clinical effectiveness. Jill Colquitt (Senior Researcher) conducted the critique of clinical effectiveness evidence. Pamela Royle (Information Specialist) conducted the critique of the company searches and conducted ERG searches.

Word count: 57,232

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Adal	Adalimumab
AE	Adverse event
ANOVA	Analysis of Variance
Apre	Apremilast
BID	Twice daily
BSA	Body surface area
BSC	Best supportive care
CG	Clinical guideline
CI	Confidence interval
Ciclo	Ciclosporin
CrI	Credible interval
CSR	Clinical study report
DIC	Deviance Information Criterion
DLQI	Dermatology Life Quality Index
DMF	Dimethyl fumarate
EMA	European Medicines Agency
EQ-5D	EuroQol five dimensions questionnaire
Etan	Etanercept
FAE	Fumaric acid esters
FAS	Full analysis set
HCSC	Hospital and Community Health Services
HD	High Dose
HES	Hospital Episode Statistics
HRG	Healthcare Resource Group
HRQoL	Health-Related Quality of Life
Infl	Infliximab
ITC	Indirect Treatment Comparison
Ixek	Ixekizumab
LD	Low Dose
LOCF	Last observation carried forward
MIMS	Monthly Index of Medical Specialities
MRU	Medical Resource Unit
NHB	National Health Benefit

NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PASI	Psoriasis Area and Severity Index
PBI	Patient Benefit Index
PBQ	Patient Benefit Questionnaire
PGA	Physician's Global Assessment
PML	Progressive Multifocal Leukoencephalopathy
PNQ	Patient Need Questionnaire
PPS	Per protocol set
PUVA	Psoralen and Ultraviolet A (phototherapy)
QD	Once daily
RCT	Randomised controlled trial
SAS	Safety analysis set
SD	Standard deviation
Secu	Secukinumab
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TID	Three times daily
Tx	Treatment
Uste/Ustekin	Ustekinumab
WTP	Willingness To Pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The CS decision problem broadly meets the NICE scope (Box 1, overleaf) for the intervention and outcomes, although for the latter the ERG notes the exclusion of psoriasis symptoms in 'hard-to-treat' areas from the list of outcomes. While addressing the NICE scope for the population, the submitted evidence does not fully address the decision problem: the company anticipate that dimethyl fumarate (DMF) will be used in patients whose symptoms are refractory to other systemic non-biologic treatments, however the majority of the BRIDGE study population were treatment-naïve. The company excluded systemic non-biologic treatments from the list of comparators in the decision problem; hence, the decision problem does not meet the NICE scope for the comparators. The company's decision problem includes two of the three subgroups (previous use of systemic therapy and severity of psoriasis) stated in the NICE scope.

Box 1: NICE final scope for dimethyl fumarate for moderate to severe chronic plaque psoriasis

Intervention	Dimethyl fumarate (LAS41008)
Population	Adults with moderate to severe chronic plaque psoriasis
Comparators	Fumaric acid esters (does not currently have a marketing authorisation in the UK for this indication) Systemic non-biological therapies (including acitretin, ciclosporin, methotrexate, phototherapy with or without psoralen, apremilast) Systemic biological therapies (including etanercept, adalimumab, secukinumab and ustekinumab, ixekizumab [subject to NICE guidance]) Best supportive care
Outcomes	The outcome measures to be considered include: • Severity of psoriasis (including psoriasis area severity index) • Psoriasis symptoms on the face, scalp, nails and joints • Response rate • Remission rate • Relapse rate • Mortality • Adverse effects of treatment • Health-related quality of life (including dermatology quality of life index).
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. For the comparators, the availability and cost of biosimilars should be taken into account.
Other considerations	If the evidence allows, the following subgroups will be considered: • previous use of systemic non-biological therapy • previous use of biological therapy • severity of psoriasis (moderate, severe) Where the evidence allows, sequencing of different drugs and the place of dimethyl fumarate in such a sequence will be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted a systematic review that yielded a single phase III RCT (BRIDGE): the key clinical effectiveness evidence for DMF. The BRIDGE trial evaluated the efficacy and safety of DMF in adults with moderate-to-severe chronic plaque psoriasis. In total, 704 patients were randomised to receive DMF, Fumaderm, or Placebo (2:2:1) for 16 weeks. The primary efficacy endpoints, including PASI 75 and PGA 0 or 1 response rates, were reported for 671 patients who had received at least one dose of the study treatment (full analysis set, FAS).

The results of the BRIDGE study revealed that 37.5% of patients treated with DMF achieved PASI 75, compared to 15.3% treated with placebo ($P < 0.001$ for superiority efficacy) and 40.3% treated with Fumaderm ($P < 0.001$ for non-inferior efficacy). Similarly, 33.0% of patients treated with DMF achieved PGA scores of 0 or 1, compared to 13.0% treated with placebo ($P < 0.0001$) and 37.4% treated with Fumaderm.

Relapse rates, measured as PASI reduction ≥50% at 12 months were significantly lower for DMF (10.1%) compared to placebo (27.5%), but not different between DMF and Fumaderm (12.5%).

[redacted]

Health-related quality of life (measured by the PBI and DLQI) was better for patients who received DMF compared to patients who received placebo, but was not different for patients who received Fumaderm.

In pre-planned subgroup analysis the CS reported that [redacted]: the ERG were unable to verify this finding. In post-hoc subgroup analyses the CS reported that [redacted]

Treatment-emergent adverse events (TEAEs) leading to study drug withdrawal were experienced by 24.0%, 24.4% and 5.8% of the DMF, Fumaderm and placebo groups, respectively. The most common events leading to withdrawal were gastrointestinal disorders (17.9%, 14.8% and 2.2%, respectively).

The CS also submitted evidence from a Bayesian network meta-analysis (NMA) conducted to ascertain the relative efficacy of DMF over placebo and other systemic medicinal treatments for moderate and severe psoriasis. This NMA comprised 37 trials of each of the comparators in the CS decision problem.

The NMA considered PASI response outcomes of probability of achieving at least 50%, 75% and 90% relief in symptoms. A ranking of the treatments evaluated in the NMA revealed that DMF was more effective than placebo, but the least effective among the comparator treatments of adalimumab, etanercept, secukinumab, ixekizumab, apremilast and Fumaderm.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The BRIDGE trial was of reasonable quality, including a large patient sample and assessing key outcomes of relevance to clinical practice at 16 weeks. The primary efficacy analysis was not an intention-to-treat analysis, as 33 patients originally randomised were not included. The study population was broadly similar to those seen in UK clinical practice and participants were generally balanced on key characteristics. There was limited long-term follow-up, the numbers continuing in the 12-month off treatment follow-up were unclear and reasons for discontinuation during this period were likely to be unbalanced.

Overall, the systematic review and NMA were of reasonable quality. Although the CS excluded scalp and nail outcomes and one study of adalimumab appeared to have been excluded incorrectly, the ERG do not consider these likely to influence the overall results. Statistical

homogeneity in the NMA was not formally considered in the CS, however, the ERG considered that the similarity and consistency assumptions were met.

The main query from the ERG is the absence of systemic non-biological comparators. The company justifies this deviation from the scope, stating that DMF is likely to be positioned in clinical practice where other systemic non-biological treatments lack clinical efficacy, are contraindicated or toxic. Hence, treatments such as acitretin, methotrexate, and ciclosporin were considered irrelevant. The ERG believe that DMF use will often follow topical therapies and therefore that 15 trials of non-biological systemic treatments should have been included in a wider NMA.

In addition, the company's opinion about the anticipated position of DMF in the treatment pathway for moderate to severe psoriasis suggests that patients who will be treated with DMF would have received previous systemic non-biologic treatments. However, the study population in the BRIDGE trial were mostly treatment-naïve and, therefore, fundamentally different from the prospective target population. Although the company used a small post-hoc subgroup of patients who had previous experience of other systemic agents to meet their decision problem, the ERG agrees [redacted] and therefore not robust enough to infer clinical effectiveness.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submission uses a Markov state transition cohort model to compare two treatment sequences. This reflects the original model of the NICE assessment of etanercept and efalizumab [TA103], the York model, and its evolution over a number of NICE STAs. As with company assessment of clinical effectiveness, the company model and cost-effectiveness comparisons exclude systemic non-biologics (with the exception of apremilast).

The York model compared two treatments over a 10 year time horizon. These treatments are trialled by patients for a period, typically 16 weeks. At the end of the trial period patients are assessed for response. Those who achieve a PASI75 response receive ongoing maintenance treatment. Those who do not achieve a PASI75 response discontinue treatment and receive best

supportive care (BSC). Among the PASI75 responders it is assumed that 20% discontinue each year and go on to receive BSC. Adverse events are not considered.

The York model has been extended to permit two sequences of treatments to be compared. The current model permits up to four active treatments within a sequence. Patients trial the 1st line treatment in the sequence. Those who achieve a PASI75 response receive ongoing maintenance treatment with the 1st line treatment. Those discontinuing from the 1st line treatment, whether due to not achieving a PASI75 response or due to being among the 20% of PASI75 responders who discontinue each year, go on to trial the 2nd line treatment. This recurs until patients have worked through all active treatments in the sequence, after which they receive BSC.

The model applies a 2-week cycle and a 10 year time horizon. The perspective and discounting is aligned to the NICE reference case.

The company base case compares the two sequences:

Table 1: Company base case sequence

	1st line	2nd line	3rd line	4th line
Sequence 1	Dimethyl Fumarate	Adalimumab	Ustekinumab	BSC
Sequence 2	Adalimumab	Ustekinumab	BSC	BSC

A large number of treatments are considered in scenario analyses, including:

- Dimethyl fumarate (DMF)
- Apremilast (Apre)
- Adalimumab (Adal)
- Etanercept (Etan)
- Fumaderm (Fuma)
- Infliximab (Infl)
- Secukinumab (Secu)
- Ustekinumab (Uste)
- Ixekizumab (Ixek)

Apremilast, secukinumab and ixekizumab have confidential patient access schemes. These are not taken into account in the CS or this report. The ERG has prepared a separate confidential appendix that applies them.

Clinical effectiveness estimates are taken from the company NMA. The base case applies the estimates for PASI responses in CS Table 38: PASI response at induction including all studies. Scenario analyses apply values in CS Table 40 that exclude the Ohtsuki et al[1] study and Table 44 presents the subgroup of treatment-experienced patients.

Extensive scenario analyses are presented that compare:

- A comparator sequence with DMF followed by the comparator sequence, as in the base case.
- A comparator sequence with DMF displacing the 1st line treatment of the comparator sequence.
- A single treatment with DMF.
- A single treatment with BSC.
- The base case sequence 1 with the base case sequence 2 modified to have an additional 3rd line of DMF.

A baseline quality of life value of 0.70 is taken from the literature. The key quality of life values are the increments associated with the four response categories of less than PASI50, PASI50 to PASI75, PASI75 to PASI90 and PASI90. The quality of life increments for these are 0.05, 0.17, 0.19 and 0.21 respectively. In common with many previous NICE assessments in the area, these increments are the values for moderate to severe patients from the EQ-5D analysis of TA103. TA103 also supplies estimates of 0.12, 0.29, 0.38 and 0.41 for more severe patients.

DMF and Fumaderm are associated with higher monitoring frequencies than apremilast and the biologics, the latter requiring quarterly outpatient visits for monitoring during the maintenance treatment.

Other ongoing costs associated with plaque psoriasis, such as inpatient costs, are largely estimated from Fonia et al [2] which has become the main source for the more recent NICE

assessments. During the trial periods a cost per 2 week cycle of £225 is taken from the apremilast FAD [TA419], which is in turn based upon Fonia et al. Those receiving maintenance DMF and Fumaderm have other ongoing costs of £116 per 2 week cycle, based upon the Fonia et al pre-biologic costs, excluding outpatient and drug costs. Those receiving maintenance with apremilast or the biologics have other ongoing costs of £46 per 2 week cycle, based upon the Fonia et al post-biologic costs excluding the outpatient and drug costs. BSC is estimated to cost £185 per 2 week cycle, based upon the Fonia et al pre-biologic costs including the outpatient and drug costs.

The company base case (as shown in Table 1) estimates that the DMF sequence generates an additional 0.030 QALYs while saving £384, so dominating the comparator sequence. The probabilistic modelling results are similar.

Results are highly sensitive to the time horizon. A lifetime horizon increases the gain to 0.063 QALYs but DMF now generates additional costs of £973 resulting in a cost effectiveness estimate of £15,476 per QALY.

Company sensitivity analyses suggest that findings are sensitive to discontinuation rates, the cost of DMF, the monitoring costs associated with DMF, the non-responder costs and whether the NMA includes the Ohtsuki et al [1] study or not.

Company scenario analyses suggest that using DMF before a sequence of etanercept, adalimumab and ustekinumab dominates not using it before this sequence. Similarly, using DMF before a sequence of adalimumab and secukinumab dominates not using it before this sequence. But a direct comparison of DMF with BSC results in a cost effectiveness estimate of £35,256 per QALY.

Company scenario analyses that compares DMF followed by other treatments with apremilast followed by the same treatments yield losses of around 0.025 QALYs but also savings of between £2k and £3k and so cost effectiveness estimates in the South West quadrant of the cost effectiveness plane of between £98k and £125k per QALY.

Head to head comparisons with single treatments also yield cost effectiveness estimates in the South West quadrant of the cost effectiveness plane of between around £60k and £130k per

QALY. The exception to this is the analysis that applies the company NMA estimates for Fumaderm. This still results in a cost effectiveness estimate in the South West quadrant of the cost effectiveness plane but of only £31,887 per QALY.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

Validation work using the company assumptions provides lifetime cost effectiveness estimates compared to BSC of £32,805 per QALY for DMF, £39,653 per QALY for Fumaderm and typically around £50k to £60k per QALY for the apremilast and the biologics. The exceptions to this are secukinumab with a cost effectiveness estimate of £113k per QALY and ixekizumab with a cost effectiveness estimate of £114k per QALY. These estimates do not include the apremilast, secukinumab or ustekinumab PASs.

Further validation work by the ERG has attempted to move the model closer to the original York model by assuming 21 inpatient days with a unit cost per day of £248 for those on BSC. For etanercept against BSC this results in a cost effectiveness estimate of £17,906 per QALY, with this worsening to £21,712 per QALY if non-responders are also associated with an annual 21 inpatient days. These estimates are somewhat less than the TA103 estimates of £45,975 per QALY for continuous use etanercept and £29,420 per QALY for intermittent use etanercept. The company model is also less sensitive to using the quality of life increments for severe disease than TA103. This is due to the all-patient baseline quality of life value being retained for severe patients, and the associated ceiling effects reducing the quality of life increments for PASI75-90 and PASI90 to somewhat below the TA103 values.

The company has assumed that the Fumaderm maintenance dose of 360mg among good responders of the FUTURE study will also apply to DMF maintenance. The FUTURE trial dose titration appears to have been the same as the BRIDGE trial. But by the end of the trial period the average Fumaderm dose was around 517mg compared to 624mg average during weeks 10 to 16 of the BRIDGE study.

The ERG critique of the apremilast STA (as summarised in the FAD [TA419]) questioned the likelihood of the same discontinuation rate for all treatments due to different effectiveness,

modes of administration and adverse event profiles. The company has identified what appears to be a reasonable paper, Arnold et al [3] in the literature that enables discontinuation rates between year 1 and year 5 to be calculated. These estimates might be more appropriate for the base case. The company scenario analysis that applies these estimate that the DMF sequence ceases to dominate and results in small -0.006 QALY losses but larger net savings of -£2,828 and so a cost effectiveness in the South West quadrant of the cost effectiveness plane of £439k per QALY.

The company appears to have drawn the 2-weekly cost of £225 for non-responders trialling treatments from the apremilast [TA419] FAD. But the apremilast model uses a 4 weekly cycle rather than the 2 weekly cycle of the company model. ERG calculations from Fonia et al [2] suggest a £121 2 weekly estimate. This is a key model input.

Inpatient hospitalisation rates reported by Fonia et al have been previously questioned as being too high due to their tertiary setting, although the unit costs applied to these rates have not received similar scrutiny. NHS reference costs suggest a higher cost per day, with cost increasing as the length of stay falls. The ERG provides a scenario analysis that applies a £477 unit cost to inpatient days, rather than the £336 implied within Fonia et al when inflated to 2015-16 prices. The ERG further differentiate the unit cost to £408 for the pre-biologic period and £477 for the post biologic period.

Infliximab maintenance administration costs do not appear to have been estimated.

The company model applies the high dose estimates for etanercept and ustekinumab. In the opinion of the ERG the low dose values are more appropriate.

The company has assumed that Fumaderm is equivalent to DMF despite having its own NMA findings. It seems more reasonable for the base case to apply the NMA estimates.
Many plaque psoriasis patients will also have psoriatic arthritis. DMF is only indicated for plaque psoriasis while other treatments such as apremilast are indicated for both with a common dose for each condition. Patients with both plaque psoriasis and psoriatic arthritis might have their plaque psoriasis treated with DMF, but incur other costs treating their psoriatic arthritis. These patients if treated with apremilast would only incur the costs of apremilast for both their

plaque psoriasis and their psoriatic arthritis. It is unclear to the ERG how psoriasis should be viewed in the context of the NICE methods guide which states "*Costs that are considered to be unrelated to the condition or technology of interest should be excluded*".

The 10-year time horizon is broadly sufficient when comparing single treatments but is insufficient for treatment sequences to fully play out. It overestimates the net health benefits for the company base case. It is more appropriate to use a 25-year or lifetime horizon.

The company model does not apply the baseline quality of life value to those failing one treatment and trialling another. Instead it assumes that patients retain some of the quality of life increments that arose from the treatment they have failed on. While the ERG understands the company argument around this, it seems questionable (as the model predicts) to assume that those trialling adalimumab as 1st line have a worse experience than those trialling adalimumab as 2nd line. It also runs counter to some previous FADs which suggest that, due to responses occurring before the end of the trial period, patient gains from the drug they are trialling should be more front-loaded. This argues for applying either the baseline quality of life to the trial periods or applying the treatment quality of life gains of the treatment being trialled during the trial period.

The quality of life increments associated with a given PASI response may differ between treatments. To illustrate this it can be assumed that the actual PASI responses from 1% to 100% improvements follow a smooth distribution. The poor PASI50 response rate for DMF compared to, say, adalimumab would then suggest that DMF patients with a sub PASI50 response would have a somewhat worse distribution than those of adalimumab. The true quality of life increment for a sub PASI50 response among DMF patients would be less than that for adalimumab patients. Similarly, given the relatively low PASI90 response rate for DMF the distribution and true quality of life increment for these patients will be worse than those of adalimumab PASI90 responders. This latter element could have been in part explored through an examination of PASI100 response rates.

There is no explicit allowance for down titration costs for DMF or Fumaderm. These are assumed to be absorbed in routine monitoring.

The company base case test frequencies for DMF are somewhat higher than those of the draft SmPC.

The probabilistic modelling samples a number of common elements separately for each treatment. This will tend to overstate the degree of uncertainty. It also arbitrarily samples elements which can be argued to be assumptions or fixed within the SmPC, such as monitoring frequencies.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The CS undertook a rigorous search and applied two sets of inclusion criteria to identify clinical effectiveness studies of relevance to the decision problem. The company performed an NMA using the Bayesian approach, which allowed rank probabilities of the clinical efficacies of DMF and other systemic medicinal treatments to be calculated at 16 weeks or induction time.

The company has largely replicated the York cost-effectiveness model structure, with amendments to permit treatment sequences to be modelled in a manner similar to other NICE assessments of psoriasis.

For its base case the company has largely used standard sources for quality of life estimates and resource use that have been used in other NICE assessments of psoriasis. The usual assumption of a common 20% discontinuation rate has also been retained, though whether this is a strength can be questionned. The ERG's clinical expert was of the opinion discontinuation would be higher for DMF.

1.6.2 Weaknesses and areas of uncertainty

The ERG disagree with the decision problem positioning of DMF, to be used when non-biological systemic agents are not appropriate or have failed. We consider that DMF will be a valid treatment option after topical therapies have been used, in line with the majority of the

evidence in the BRIDGE trial, and (according to ERG's clinical expert) current use of Fumaderm in the UK. The key issue therefore remains that the clinical effectiveness of DMF is only measured against placebo, systemic biological treatments, apremilast and Fumaderm. The NMA does not include other systemic non-biological therapies. Hence, the ERG is uncertain about the relative efficacy of DMF compared to other systemic non-biological treatments in the treatment pathway for moderate-to-severe chronic plaque psoriasis.

To meet the decision problem positioning of DMF, the CS uses evidence from a small subgroup of the BRIDGE trial. The CS reports [redacted]

There is a lack of long-term follow-up data with DMF. While the ERG agrees that the link between fumaric acid esters and DMF is reasonable, there is limited evidence of the long term adverse events of fumaric acid esters or DMF presented in the CS.

The ERG do not know if the NMA meets the homogeneity assumption as no pairwise comparisons were presented. Scenario analyses of the NMA excluded one study judged by the CS to be of poor quality; in the opinion of the ERG other studies could have been excluded on the basis of quality and it is unclear what impact this would have had on the results.

The main weaknesses in the economics of the CS are summarised in section 1.5 above. A further weakness is a lack of clarity about which comparison or comparisons should be used to inform decision making. It should be borne in mind that company base case compares the DMF sequence of three treatments with the comparator sequence of two treatments. Adding another medicine to a treatment sequence will inevitably result in patient gains[1] almost regardless of how effective or ineffective that treatment is. In this context, the apremilast FAD [TA419] provides a useful commentary on the varying credibility of extensive scenario analyses. It is not clear to the ERG that the company has sufficiently considered under what circumstances DMF is likely to be

[1] This is barring any peculiar discounting or all-cause mortality effects which in the opinion of the ERG are unlikely.

cost-effective relative to apremilast. It is also not clear to the ERG that the company has taken sufficient note of apremilast and the biologics being approved by NICE only for severe patients.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has made a number of revisions to the base case. For the revised base case the ERG adopts a lifetime horizon, applies the low dose estimates for etanercept and ustekinumab, equalises patients quality of life when trialling treatments and removes the ceiling effect to quality of life, applies 14 days wastage to be in line with the apremilast FAD, revises the costs derived from Fonia et al and in particular the non-responder fortnightly cost, revises infliximab dosing and administration costs and applies the cost of a short GP appointment for blood tests not undertaken during a hospital outpatient monitoring visit. The more important of these changes are explored through univariable sensitivity analyses.

The ERG presents additional univariable sensitivity analyses concerning the time horizon, clinical effectiveness estimates, quality of life during the trial period, quality of life increments by response status, discontinuation rates, dosing, monitoring and the costs associated with psoriasis.

Given the nature of the assessment, the number of comparators and the FADs of previous NICE assessments the ERG presents an extensive set of pairwise comparisons of treatment sequences, but focusses particularly upon five:

Analysis 1:

Dimethyl fumarate to adalimumab to ustekinumab to BSC

Adalimumab to ustekinumab to BSC

Analysis 2:

Dimethyl fumarate to adalimumab to ustekinumab to BSC

Apremilast to adalimumab to ustekinumab to BSC

Analysis 3:

Dimethyl fumarate to BSC

BSC

Analysis 4:

Dimethyl fumarate to BSC

Apremilast to BSC

Analysis 5:

Dimethyl fumarate to BSC

Adalimumab to BSC

These comparisons have the full range of deterministic sensitivity analyses applied to them and are also modelled probabilistically in line with the NICE methods guide. The central estimates of costs effectiveness of the probabilistic modelling are broadly in line with the corresponding deterministic estimates. The impact of applying the TA103 quality of life values for severe patients is also fully explored for these comparisons.

Analysis 1:

Dimethyl fumarate to adalimumab to ustekinumab to BSC

Adalimumab to ustekinumab to BSC

For analysis 1, the company base case estimated the DMF sequence to dominate the comparator sequence when using a 10 year time horizon and to have a cost effectiveness of £15,467 per QALY when using a lifetime horizon. The ERG analysis improves the base case cost effectiveness estimate over the patient lifetime to £12,299 per QALY, in large part due to the revised cost of non-responders. The cost effectiveness estimate improves still further to £10,017 per QALY if patients are early responders and realise gains from treatment before the end of the trial periods, to £6,911 per QALY if the severe patient quality of life increments are applied, and to £8,396 per QALY if the DMF monitoring frequency is in line with the draft SmPC; applying the discontinuation rates of Arnold et al results in dominance. A higher maintenance dose for DMF of 480mg worsens the cost effectiveness estimate to £25,380 per QALY while applying

2015-16 NHS reference costs to inpatient admissions also slightly worsens the cost effectiveness estimates to £13,180 to £14,851 per QALY.

The cost effectiveness estimate if the severe patient quality of life values are appropriate of £6,911 per QALY improves further if patients are early responders, to £5,512 per QALY and with the draft SmPC monitoring to £4,718 per QALY. Higher DMF dosing of 480mg worsens it to £14,262 per QALY while current reference costs for inpatients worsens it to £7,366 to £8,345 per QALY.

Analysis 2:

Dimethyl fumarate to adalimumab to ustekinumab to BSC

Apremilast to adalimumab to ustekinumab to BSC

For analysis 2, DMF is associated with reasonable patient quality-of-life losses but also cost savings at the apremilast list price. These result in a cost effectiveness estimate in the South West quadrant, the company modelling assumptions estimating a cost effectiveness of £123k per QALY over a 10 year time horizon and £98,894 per QALY over a lifetime horizon. The ERG revised base case with a lifetime horizon estimates a cost effectiveness in the South West of £103k per QALY. All sensitivity analyses estimate DMF to be associated with patient losses in quality-of-life but cost savings, so pointing in the South West quadrant. If patients are early responders the cost effectiveness of DMF worsens to £92,139 per QALY, while the severe patient quality of life values worsen it to £54,383 per QALY. The SmPC dimethyl monitoring frequency improves it to £107k per QALY. A dimethyl maintenance dose of 480mg worsens cost-effectiveness to £86,850 per QALY while current IP reference costs worsen it to between £83,766 and £95,889 per QALY.

The cost effectiveness estimate if severe patient quality of life values are appropriate of £54,383 per QALY further worsens if patients are early responders, to £48,629 per QALY. It improves quite noticeably to £96,661 per QALY if the discontinuation rates of Arnold et al are applied, and improves slightly to £56,863 per QALY if the monitoring frequency of the draft SmPC is applied. A DMF maintenance dose of 480mg worsens it, to £46,070 per QALY and current IP costs also chabge it to between £44,435 and £50,866 per QALY.

Analysis 3:

Dimethyl fumarate to BSC

BSC

For analysis 3, comparing DMF with BSC, the cost effectiveness of DMF using the company assumptions is £35,256 per QALY over a 10 year time horizon and £32,805 per QALY over a lifetime. The ERG estimate is £25,567 per QALY. The worsening of cost-effectiveness compared to analysis 1 is largely due to postponing adalimumab and ustekinumab which are both estimated to have rather poor cost effectiveness estimates. Applying severe quality of life estimates improves the finding to £14,123 per QALY while applying the discontinuation rates of Arnold et al improves the finding to £20,850 per QALY. DMF maintenance dosing of 480mg worsens cost-effectiveness to £33,783 per QALY but current IP unit costs have little impact.

The cost effectiveness estimate of £14,123 per QALY if the severe patient quality of life values are appropriate, improves to £12,186 per QALY if patients are early responders, to £11,365 per QALY if the discontinuation rates of Arnold et al are applied and to £12,769 if draft SmPC monitoring levels are applied. DMF maintenance dosing of 480mg worsens cost-effectiveness to £18,662 per QALY but again current IP unit costs have little impact.

Analysis 4:

Dimethyl fumarate to BSC

Apremilast to BSC

For analysis 4, comparing DMF with apremilast, the CS cost effectiveness estimate in the South West quadrant of £96,093 per QALY over a 10 year time horizon is somewhat worse than for analysis 2, while the lifetime estimate of £94,400 per QALY is broadly in line with that of analysis 2. The ERG revised base cases apply a lifetime horizon and the cost effectiveness estimate of £93,837 per QALY is reasonably aligned with that of analysis 2. This underlines the differences that arise between analysis 1 and analysis 3, where an intervening cost ineffective sequence has a marked impact on the cost effectiveness estimate due to discounting and all-cause mortality effects. The other element to note is the artefact introduced by the 10 year horizon. Selecting 10-year horizon markedly improves the cost effectiveness of extended sequences

inanalyses 1 and 2 but has little impact upon short sequences in analyses 3 and 4, underlining the need for a lifetime horizon when the longer treatment sequences are being compared.

Analysis 5:

Dimethyl fumarate to BSC

Adalimumab to BSC

For analysis 5, comparing DMF with adalimumab, DMF is always estimated to result in patient losses in quality-of-life but also to yield cost savings and so cost effectiveness estimates lie in the South West quadrant of the cost effectiveness plane. The company base case assumptions result in estimates in the South West quadrant of £68,054 per QALY for a 10 year time horizon and £67,381 per QALY for a lifetime horizon. The ERG revised base case, when all-patient quality of life values are applied, results in an estimate of £65,934 per QALY in the South West quadrant suggesting that DMF is cost effective. Assuming early responders to treatment worsens this to £59,209 per QALY while the severe patient quality of live values worsen it to £35,337 per QALY. The Arnold et al discontinuation rates worsen it to £56,694 per QALY, but a DMF maintenance dose of 480mg only worsens it to £63,548 per QALY. Current IP unit costs worsen it to between £58,658 and £63,358 per QALY.

The cost effectiveness estimate of £35,337 per QALY in the South West quadrant if severe patient quality of life values are appropriate, worsens to £31,559 per QALY if patients are early responders and to £30,353 per QALY if the Arnold et al discontinuation rates are applied. A DMF maintenance dose of 480mg only worsens it to £34,058 per QALY, and current IP unit costs worsen it to between £31,437 and £33,956 per QALY.

Further analyses

A number of other comparisons are also made by the ERG with the default being to use the all-patient quality of life values. These comparisons can be broadly grouped into those where DMF 1st line is compared to DMF last in line, those where DMF followed by BSC is compared with the other treatments followed by BSC and those where the other active treatments are compared

with BSC. The latter are for model validation in the light of the FADs of previous NICE assessments.

In brief, 1st line DMF compared to last in line DMF causes small patient losses in quality-of-life , but also cost savings, resulting in cost effectiveness estimates in the South West quadrant and suggest 1st line use is cost effective. These results show some sensitivity to whether the all-patient or the severe patient quality of life values are used, and the DMF maintenance dose that is assumed.

DMF compared to all the other comparators results patient losses in quality-of-life, but also cost savings sufficient to offset these losses. The possible exception to this within the univariable sensitivity analyses that are presented is for the comparison with Fumaderm. These results show some sensitivity to whether patients are early responders, whether the severe patient quality of life values are applied and the DMF dosing that is assumed.

Other treatments compared to BSC result in more sizeable patient gains, but at considerable additional net costs. The base case for Fumaderm (based on NMA findings) is estimated to be within the upper NICE threshold of £30k per QALY, but none of the other treatments are estimated to be cost effective. The cost effectiveness for apremilast of £52,475 per QALY compared to BSC is in line with the most of the biologics but it should be borne in mind that this does not include the apremilast PAS. The estimate for infliximab is higher still. Those for secukinumab and ixekizumab are above £100k per QALY, but again these estimates to not include the PASs.

Conclusion

In summary, the CS base case inserts 1st line DMF in a sequence before 2nd line adalimumab and 3rd line ustekinumab and compares it with 1st line adalimumab and 2nd line ustekinumab. Thus DMF postpones treatment with the biologics. The CS base case applies a 10-year horizon and estimates that the DMF sequence dominates the comparator sequence. A company scenario analysis revising the CS base case to apply a lifetime horizon worsens the cost effectiveness of the DMF sequence to £15,467 per QALY.

ERG revisions to the company base case suggest that the cost effectiveness of the CS DMF sequence is £12,299 per QALY over a lifetime horizon. This compares to an ERG estimate for DMF compared to BSC of £25,567 per QALY over a lifetime horizon. The difference between these estimates is largely by construction. The main effect in the CS base case model is that it delays the adoption of the biologics which are estimated to have a very poor cost effectiveness. Delay reduces the impact of the biologics through discounting and all-cause mortality. If discounting and all-cause mortality are set to zero, within the lifetime model, the ERG £12,299 per QALY estimate for the DMF sequence is revised to £24,883 per QALY which is similar to the £25,567 per QALY estimate when DMF is directly compared with BSC. Delaying the cost-ineffective biologics will improve the overall cost effectiveness of the treatment sequence.

The focus of the CS is also upon its comparison with the expensive biologics. Less emphasis is placed upon comparison with apremilast. At list prices apremilast is somewhat cheaper than the biologics, before patient access schemes (PASs) are taken into account. The CS also applies quality of life values for moderate to severe patients when all the comparators it considers, including apremilast, have only been approved by NICE for severe patients. Head-to-head comparisons with apremilast at the discounted apremilast price are reported in the commercial-in-confidence appendix: these suggest, under a number of scenarios, that DMF may not be cost effective when compared to apremilast.

In the opinion of the ERG, DMF is most likely to be used in practice as an alternative to other systemic non-biologic therapies, consistent with its licensed indication and trial data. The head-to-head performance of DMF and other systemic non-biologic therapies has not been assessed.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

The CS provides an overview of psoriasis and the effect on patients carers and society in section 3.1 and 3.2 (pp29-31). Psoriasis is described as a chronic inflammatory skin condition which follows a relapsing and remitting course, is painful, disfiguring and disabling. The most common form of psoriasis is plaque psoriasis, in around 90% of cases, characterised by red, scaly plaques that can cause itching, stinging and pain. These descriptions are consistent with the final scope issued by NICE and by the NICE clinical guideline on psoriasis.[4]

There is a limited discussion of the epidemiology of psoriasis. The UK prevalence of psoriasis is given in the CS (p31) as an estimated 2%, with 1% having severe disease. In addition, the CS states (p29) that the majority of psoriasis cases occur before the age of 35 years and that men and women are equally likely to be affected. These rates concur with those reported in the NICE clinical guideline, where a prevalence range of 1.3% to 2.2% was reported.[5] The NICE clinical guideline states that psoriasis is most common in white people.

The CS briefly outlines the likely aetiology of psoriasis and key comorbidities such as psoriatic arthritis, cardiovascular disease, major adverse cardiac events, the potential increased risk from lymphoma and non-melanoma skin cancers and the profound effect psoriasis can have on the mental health of an individual. These descriptions all appear appropriate and in line with the NICE clinical guideline.

There is limited description of the grading of psoriasis; the CS states (p29) that psoriasis is generally graded as mild, moderate or severe based on assessment that takes in to account the extent of the area affected and the severity of lesions. The ERG agrees that psoriasis is generally graded in this way, most often using tools such as the Psoriasis Area and Severity Index (PASI) which is described in more detail in the CS Appendix. The NICE clinical guideline states that the approach to psoriasis therapy is largely governed by the extent and severity of disease.[5]

The CS adequately describes the impact psoriasis has on individuals, summarising evidence demonstrating that psoriasis has a significant effect on health related quality of life, physical

discomfort and disability, self-esteem, depression and anxiety.[4, 6] The CS also presents data from a recent UK report which estimated that four million working days are lost in the UK each year, at a cost of £0.5 billion.[7] Sources detailing the potential impact on the NHS are also provided. The CS cites a 2013 report by the King's fund [8] stating that psoriasis causes between 1.7-5% of 13 million GP consultations for skin diseases each year, although the ERG were unable to locate these proportions in the report. However, ERG's clinical expert agrees this proportion is reasonable.

2.2 Critique of company's overview of current service provision

The CS provides an overview of the NICE psoriasis pathway in figure 1 (p32) and the SIGN guideline in figure 2 (p34). The CS also summarises NICE technology appraisals for other treatments in Table 5. The current treatment pathway is summarised in the CS (p35). The CS outline of the treatment strategies appear to reflect the current NHS position that choice of therapy is guided by the extent and severity of disease, and the patient's needs and preferences. Treatment options include topical therapy, phototherapy and systemic therapy (which includes non-biological agents and biologic agents, in line with the NICE scope). For milder forms of psoriasis topical therapies are generally used as first-line treatments, with phototherapy being used as a second-line therapy, or for more extensive disease. Where psoriasis is not controlled then systemic non-biological agents are recommended. Systemic biologic therapies are recommended for severe disease in those who have failed or are contraindicated or intolerant to non-biological therapies. Currently in the NHS, fumaric acid esters (FAEs) are used on an unlicensed basis and, the CS states (p36), are used for people who are not suitable for non-biological agents.[9] The CS also states (p37) that existing non-biological therapies are not effective in all patients and that adverse effects can limit their use. The CS states that DMF will provide clinicians and patients with a licensed FAE for use in these instances. Advice to the ERG is that FAEs can be used at any point in the pathway after topical therapies have been used.

The CS states (p36) that it is anticipated that DMF will offer an additional treatment option in those in whom non-biological therapies are inappropriate through lack of efficacy, contraindications, tolerability and/or toxicity or when a patient states a preference. This is in line with the CS decision problem but not with the NICE scope (see CS Table 1, p12) or the majority

of the clinical evidence for DMF (see CS: Additional post-hoc subgroup analyses, p72-74). There is some possible contradiction in the first paragraph on CS page 37 which states that the anticipated position for DMF will be as an alternative to non-biological treatments, prior to biologics. However, CS figure 4 (p37) suggests that DMF will be used only when other non-biologics are unsuitable or contraindicated. The ERG clinical advisor reports that DMF is currently used as an alternative to non-biological systematic therapies when psoriatic arthritis is not an issue.

The CS cite recent publication of data from the British Association of Dermatologists Biologic Interventions Register which indicates that 7.6% of people with psoriasis receiving systematic non-biological therapies are receiving unlicensed FAEs.[10] The ERG note that the publication does not provide details of the point in the line of treatment where these FAEs were used.

2.3 Marketing authorisation

Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on 21st April 2017 (full indication: "for the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy") and marketing authorisation is expected in June 2017. No regulatory approvals outside of the UK are planned. CS p. 25 lists the main issues raised during the regulatory process:

1. Bridging the efficacy and safety data from Fumaderm® (licensed for use in Germany and which contains monoethyl fumarate as well as DMF) to DMF monotherapy. The regulator requiring justification of the extent to which efficacy and safety data can be extrapolated to the proposed DMF formulation.

2. The request for pharmacokinetic data to characterise the pharmacokinetic profile of DMF and to support bridging to Fumaderm.

3. The proposed indication of first-line systemic therapy.

4. The frequency of full blood count tests with DMF (LAS41008) is still being discussed with the regulatory authorities.[2]

Dimethyl fumarate (Tecfidera, Biogen Idec) is also indicated for the treatment of adult patients with relapsing remitting multiple sclerosis, at a starting dose of 120 mg twice a day for 7 days followed by 240 mg twice a day. The European Medicines Agency (EMA) issued advice in October 2015[11] in order to minimise the risk of progressive multifocal leukoencephalopathy (PML) in multiple sclerosis patients treated with Tecfidera. PML is a rare brain infection caused by the John Cunningham virus and can be fatal. At that time, 3 cases of PML had occurred in patients treated with Tecfidera; these cases occurred after long-term treatment in patients who had very low levels of lymphocytes over an extended period of time. Recommendations include a complete blood count including a lymphocyte count prior to starting treatment and every 3 months during treatment. The EMA also reviewed cases of PML which occurred with Fumaderm (contains DMF) and Psorinovo (contains slow release DMF) for psoriasis and made the following recommendations for Fumaderm:

- Before starting treatment, a complete blood count should be performed; in the presence of values outside the normal range, treatment should not be started.

- During treatment, blood cell counts should be monitored every 4 weeks; if the lymphocyte count drops below 0.7x109/L, the dose should be halved. If during a follow-up check after 4 weeks the lymphocyte count remains below this value, then treatment

[2] A final SmPC is available. The frequency of blood tests is: a) Before treatment; a current complete blood count (including differential blood count and platelet count) should be available. Treatment should not be initiated if leukopenia below 3.0x109/L, lymphopenia below 1.0x109/L or other pathological results are identified: b) During treatment; a complete blood count with differential should be performed every 3 months. Action is needed for: leukopenia (If a marked decrease in the total number of white blood cells is found, the situation should be monitored carefully and treatment with DMF should be discontinued at levels below 3.0x109/L); lymphopenia (If the lymphocyte count falls below 1.0x109/L but is ≥0.7 x109/L, blood monitoring should be performed monthly until levels return to 1.0x109/L or higher for two consecutive blood tests at which point monitoring can again be performed every 3 months). If the lymphocyte count falls below 0.7x109/L, the blood test must be repeated and if the levels are confirmed to be below 0.7x109/L, then treatment must be stopped immediately. Patients developing lymphopenia should be monitored after stopping treatment until their lymphocyte count has returned to the normal range

must be discontinued. If therapy is continued in presence of a lymphocyte count below 0.7x109/L, the risk of PML cannot be ruled out.

- If the lymphocyte count drops below 0.5x109/L, treatment should be discontinued.

A safety alert regarding PML in in multiple sclerosis patients treated Tecfidera has also been issued by the FDA (November 2014).

The proposed Summary of Product Characteristics (SmPC) for dimethyl fumarate (Skilarence) for psoriasis was provided to the ERG in the CS reference pack.[12] The final SmPC notes that cases of opportunistic infections, particularly of PML, have been reported with other dimethyl fumarate-containing products. It states that PML is an opportunistic infection caused by the John Cunningham virus (JCV) that can be fatal or cause severe disabilities. Persistent moderate or severe lymphopenia under treatment with DMF is considered a risk factor for PML. It also notes that early diagnosis of Fanconi syndrome (a disorder of the kidney tubes) and discontinuation of Skilarence treatment are important to prevent the onset of renal impairment and osteomalacia, as the syndrome is usually reversible.

Special warnings and precautions are listed. DMF may decrease leukocyte and lymphocyte counts, so prior to initiating treatment with DMF, a current complete blood count (including differential blood count and platelet count) should be available. During treatment a complete blood count with differential should be performed every 3 months. Action is needed in the following circumstances:

Leukopenia: If a marked decrease in the total number of white blood cells is found, the situation should be monitored carefully and treatment with DMF should be discontinued at levels below 3.0x109/L.

Lymphopenia: If the lymphocyte count falls below 1.0x109/L but is ≥0.7 x109/L, blood monitoring should be performed monthly until levels return to 1.0x109/L or higher for two consecutive blood tests at which point monitoring can again be performed every 3 months.

If the lymphocyte count falls below 0.7x109/L, the blood test must be repeated and if the levels are confirmed to be below 0.7x109/L, then treatment must be stopped immediately. Patients developing lymphopenia should be monitored after stopping treatment until their lymphocyte count has returned to the normal range Renal function (e.g. creatinine, blood urea nitrogen and urinalysis) should be checked prior to initiation of treatment and every 3 months thereafter. In the event of a clinically relevant change in renal function, particularly in the absence of alternative explanations, consideration should be given to dosage reduction or treatment discontinuation.

The SmPC states that patients should be made aware that they are likely to experience flushing in the first few weeks of taking DMF.

The United Kingdom Clinical Pharmacy Association (UKPCA) submission comments on the issue of PML. They state:

"In view of the risk of PML rigorous monitoring of patients would be essential. This is something to which patients would have to make a commitment. Similar considerations apply to methotrexate (because of drug-induced bone marrow suppression) and some patients have been considered unsuitable for methotrexate treatment because they have not been capable of complying with the requirement for regular blood tests (e.g. persistently missing monitoring appointments). It is quite possible that some patients whose disease might be suitable for DMF treatment would be excluded from it because lack of compliance with monitoring requirements would pose unacceptable risks."

DMF is a fumaric acid ester (FAE). The ERG identified a recent systematic review conducted to find reports of PML in psoriasis patients treated with FAEs (searches undertaken in February 2016)[13]. Eight single case reports were identified. Patients received FAE treatment for a minimum period of 1.5 years, median duration 3 years (IQR 2.4-3.5 years). Four cases were not linked to established risk factors for PML. All cases were linked to moderate-to-severe reductions in absolute lymphocyte-counts, with nadirs ranging from 200 to 792 cells per mm^3. Median exposure to lymphocytopenia was 2 years (range 1-5 years). FAE discontinuation and treatment with mefloquine and mirtazapine led to improvement of symptoms in 3 cases and a

stable condition in 2 cases. There were 2 patients with residual symptoms of PML. An immune reconstitution inflammatory syndrome (IRIS) following FAEs treatment discontinuation was reported in 5 cases. One patient died due to complications following IRIS. The review concluded that PML is infrequently linked to FAE treatment but that physicians and patients should be alert for new neurological symptoms and that periodic monitoring of lymphocyte counts and discontinuation of FAEs with moderate-to-severe lymphocytopenia are recommended.

3 Critique of company's definition of decision problem

3.1 Population

In CS Table 1 p.12, the company notes that the population included in their decision problem is more specific than both the NICE scope (adults with moderate to severe chronic plaque psoriasis) and the anticipated indication (adults with moderate to severe chronic plaque psoriasis in need of systemic medicinal therapy). The rationale provided for this is that the company anticipates DMF will be used in patients for whom other non-biologic systemic treatments are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference. This was re-iterated in clarification response A1, where the company further stated that in general and based on feedback from UK dermatologists using FAEs in clinical practice, the profile of the typical patient treated with FAEs, is:

- pre-biologic (i.e. has not reached the NICE recommended criteria for treatment with a biologic agent)
- with relatively stable disease, not acute or severe disease
- in need of longer term maintenance
- and who failed on other systemic non-biologic treatments or are contraindicated or intolerant to methotrexate, and ciclosporin

Evidence from one randomised controlled trial (RCT), the BRIDGE study, was included in the CS to support the decision problem. However, the ERG notes that the majority of the population [redacted] in the BRIDGE study were systemic-treatment naïve and do not meet the decision problem proposed in the CS. In addition, the assessment of the efficacy of DMF to meet the decision problem was made using a post-hoc analysis of the sub-group of systemically-treated patients (see CS Section 4.8). In response to a request for further justification, the company stated that results of the post hoc analyses demonstrated that the efficacy in the population who had previous systemic therapy in the BRIDGE trial was not significantly different from that seen in systemic-naïve patients, and that the baseline characteristics of the two groups were

comparable (clarification response A2). [redacted] The systemically-treated subgroup was not included in the original statistical analysis plan of the BRIDGE trial and was undertaken to respond to questions received during the regulatory process (clarification reposne A2).

3.2 Intervention

The intervention specified by the NICE scope and the company's decision problem is dimethyl fumarate (DMF, Skilarence), a fumaric acid ester. To improve tolerability, treatment begins with a low initial dose (30 mg orally once daily in the first week) with subsequent gradual increases up to a maximum daily dose of 720 mg (3 x 2 tablets of DMF 120 mg) at week 9. If a particular dose increase is not tolerated, it may be temporarily reduced to the last tolerated dose, and if treatment success is observed before the maximum dose is reached, no further increase of dose is necessary. After clinically relevant improvement of the skin lesions has been achieved, consideration should be given to careful reduction of the daily dose of DMF to the maintenance dose required by the individual. The same dosing schedule was used in the BRIDGE study, although a reduction to the last tolerated dose in case of intolerability was only permitted after week 4. The ERG considers that the intervention in the decision problem reflects its anticipated use in the UK and is appropriate for the NHS.

3.3 Comparators

The comparators listed in the NICE final scope are as follows:

- Fumaric acid esters (no current marketing authorisation in the UK for this indication)
- Systemic non-biological therapies (including acitretin, ciclosporin, methotrexate, phototherapy with or without psoralen, apremilast)
- Systemic biological therapies (including etanercept, adalimumab, secukinumab, ustekinumab, and ixekizumab [subject to NICE guidance])
- Best supportive care

However, the company considers the appropriate comparators to be:

- Fumaric acid esters
- Apremilast
- Systemic biological therapies (including etanercept, adalimumab, secukinumab and ustekinumab)
- Best supportive care (for people in whom biologic therapies are not tolerated or contraindicated).

The company therefore excludes systemic non-biological therapies (other than apremilast) from their decision problem and best supportive care is limited to people in whom biologic therapies are not tolerated or contraindicated. The company states that DMF is likely to be positioned where non-biological systemic therapies are clinically inappropriate through lack of efficacy, contraindications, tolerability and/or toxicity issues, or patient preference; therefore acitretin, methotrexate and ciclosporin are not relevant comparators. They also state that phototherapy is not a relevant comparator as its use is usually before systemic therapies, which are recommended when phototherapy has been ineffective, cannot be used or has resulted in rapid relapse. The ERG agrees with this exclusion. Apremilast is the only systemic non-biological therapy included in the company's decision problem; the CS states that DMF will occupy a similar position to apremilast but with DMF being suitable for patients with moderate to severe psoriasis (apremilast is recommended by NICE only in severe psoriasis). Ixekizumab is not mentioned in the company's decision problem, but is included in their NMA (see Section 3.1.2). The ERG considers that non-biological systemic therapies should have been included in the company's decision problem and requested that these be included in the NMA or full justification for their omission be provided. In clarification response 2, the company reiterated that in clinical practice DMF is likely to be positioned where other oral systemic therapies are clinically inappropriate, therefore they are not relevant comparators. The company state that this was agreed with NICE at the Decision Problem meeting, however, the ERG believe that the list of comparators used in the CS decision problem was discussed but not agreed at the decision problem meeting.

3.4 Outcomes

The outcomes considered in the company's decision problem (severity of psoriasis, response rate, remission rate, relapse rate, mortality, adverse effects of treatment, health-related quality of life) reflect most of those specified on the NICE scope. However, the company has omitted psoriasis symptoms affecting the face, scalp, nails and joints, as data on these are not available for DMF. The ERG considers that all other important outcomes have been included in the decision problem and that they are appropriate and clinically meaningful to patients.

3.5 Other relevant factors

The NICE scope specifies the following subgroups should be considered where evidence allows:

- previous use of systemic non-biological therapy
- previous use of biological therapy
- severity of psoriasis (moderate, severe)

The company's decision problem includes two of these subgroups, previous use of systemic non-biological therapy and severity of psoriasis. However, the subgroup analyses presented for the BRDGE study and the NMA are for previous systemic therapy or PUVA (versus systemic naïve), and do not distinguish between previous non-biological therapy and biological therapy. The ERG notes that only 3% of the BRIDGE study had prior biological therapy, and therefore considers the company's approach to be appropriate. The company also included age subgroup analyses in their decision problem.

The NICE scope also states, where the evidence allows, sequencing of different drugs and the place of DMF in such a sequence will be considered. The company does not address this.

No equity or equality issues relating to DMF have been identified by the NICE scope, the company decision problem or the ERG.

3.6 Other submissions - key issues

The UKCPA supports the ERG's view regarding appropriate comparators:

"FAEs have been recommended for treatment of moderate-severe chronic plaque psoriasis that does not respond to topical therapy and this would be the logical place for DMF. As such, it would be compared with ciclosporin, methotrexate, PUVA, acitretin and apremilast (and possibly tofacitinib). The first three are probably the most commonly-used in the UK. All are limited by toxicities of various types and clinicians are sometimes faced with patients who have exhausted all the options but still would like an oral (vs injected) treatment. For such patients the question will be whether to use DMF or apremilast next."

4 CLINICAL EFFECTIVENESS

4.1 Critique of the company's approach to systematic review

The ERG's assessment of the systematic review in the CS is summarised in Table 2. Overall, the quality of the company's systematic review was reasonable. Eligibility criteria were reported, however the exclusion of non-biological therapies (other than Fumaderm and apremilast) meant the systematic review did not fully address the NICE scope. The search strategy was rigorous to account for all relevant research and the included studies were in sufficient detail. The company appropriately conducted an NMA to compare DMF with the comparators in the absence of head-to-head trials, however statistical heterogeneity was not discussed and the ERG disagrees with the company's interpretation of the results.

Table 2: Overall quality of the systematic review

CRD Quality Item
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question? Yes, although the ERG disagrees with the exclusion of non-biological therapies and the limitation of eligible outcomes to specific endpoints (16 weeks or induction time).
2. Is there evidence of a substantial effort to search for all relevant research? Yes
3. Is the validity of included studies adequately assessed? Yes (but see Section 4.1.5 for differences between CS and ERG judgements)
4. Is sufficient detail of the individual studies presented? Yes
5. Are the primary studies summarised appropriately? Yes

The study selection was performed independently by two researchers, and a third researcher resolved any discrepancies. The processes for data extraction and quality assessment were not reported.

The submitted evidence broadly reflects the decision problem defined in the CS in terms of the study population, intervention, and outcome. However, the comparators do not fully address the NICE scope.

There is low chance of systematic error in the CS systematic review.

4.1.1 Description of company's search strategy

A systematic literature review was conducted to: 1) identify RCTs of DMF (LAS41008) and systemic treatment options, including phototherapy, in patients with moderate to severe psoriasis, and 2) to identify all potential studies that may have been relevant for indirect comparison of DMF (LAS41008) with the comparators relevant to the decision problem.

Databases searched were MEDLINE, MEDLINE In-Process, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register for Controlled Trials and trial registries. The database searches were not limited by a cut-off date, and were last updated in October 2016. The web sites of three relevant conferences from 2014 to 2016 were also searched. The reason given for excluding conference abstracts published before 2013 was based on the assumption that studies presented before this date as an abstract would be available as a full text publication by October 2016.

The search strategy combined disease terms for psoriasis with terms for specific interventions and used a validated search filter in MEDLINE or EMBASE to limit the search to randomised and other controlled trials. Only studies published in English were considered for inclusion. The searches resulted in identifying for inclusion one RCT of DMF and 37 studies for inclusion in the NMA.

The searches appeared systematic and appropriate to the research question, and were clearly reported. However, the ERG feels that the exclusion of conference abstracts published before 2013 is not justified by the published evidence on the fate of meeting abstracts presented at conferences. Our independent searches did not identify any additional relevant RCTs. However, we identified a before-and-after study by Lijnen et al 2016[14] which provide data on long term safety and effectiveness of DMF.

4.1.2 Statement of the inclusion / exclusion criteria used in the study selection

The CS reports a systematic review undertaken to identify trials on DMF and systemic treatment options for inclusion in an NMA. Two sets of eligibility criteria are presented; criteria for the

systematic literature review are listed in CS Table 24 (CS p. 79-80) and those for the NMA are listed in CS Table 26 (CS p. 84-85).

The eligible population (for both systematic reviews) reflect the decision problem, however excludes people with scalp or nail psoriasis despite these being outcomes relevant to the NICE scope. The ERG cannot see any rationale for the exclusion of these populations from the systematic reviews, however, it doesn't appear that any studies were excluded for this reason (CS Table 27).

The eligible interventions for the systematic review listed in CS Table 24 are mostly the same as those listed by the NICE scope and company decision problem, although best supportive care has been omitted. Infliximab, which is not a NICE scoped comparator, is also listed as an eligible intervention. However, the NMA criteria in CS Table 26 limit the interventions to Fumaderm, apremilast and the systemic biological therapies compared with each other or with placebo, which is in line with company decision problem (other than the absence of best supportive care) but deviates from the NICE scope. The company justifies this deviation, stating that in clinical practice DMF is likely to be positioned where other oral systemic therapies are clinically inappropriate for patients through lack of efficacy, contraindications, tolerability and/or toxicity issues, or patient preference. They state that acitretin, methotrexate, and ciclosporin are therefore not relevant comparators. The company also states that phototherapy is also not a relevant comparator as its use is usually before systemic therapies which are recommended when phototherapy has been ineffective, cannot be used or has resulted in rapid relapse. However, the ERG notes that the majority [redacted] of the patients in the BRIDGE study were treatment naïve, and that the company therefore used a small post-hoc subgroup of patients who had previous experience of other systemic agents to meet their decision problem. The company acknowledges [redacted] (CS p.74). In view of the post hoc nature of this subgroup and the small sample size, the ERG has concerns regarding the robustness of this analysis.

The outcomes listed for the wider systematic review include most of those required by the NICE scope, however, psoriasis symptoms on the face, scalp, nails and joints was omitted. Response rate was not explicitly stated, but is covered by the PASI and PGA. The outcomes for the NMA

were limited to PASI 50, 75 and 90 at 16 weeks or induction time (primary endpoint of pivotal studies: 12 weeks for secukinumab, etanercept, ustekinumab, ixekizumab; and or 16 weeks for adalimumab, apremilast, Fumaderm, DMF). This led to the exclusion of four studies of adalimumab that reported outcomes at 12 weeks[15-18] that could otherwise have been included.

A post hoc decision was made to exclude German language articles, leading to the exclusion of one study. The company does not discuss the implications of this exclusion. The ERG requested that the company explore the impact of excluding this study on the NMA (clarification question A19). The company stated that the study compared infliximab (n=6) to etanercept low-dose (n=6) in male psoriasis vulgaris patients. Only overall PASI score was reported at induction time for both arms, whereas the NMA focussed on PASI response (PASI50/75/90) at 16 weeks and induction time. The pdf was not provided and the ERG are unable to access the article to confirm this.

Phase II, III and IV RCTs were eligible for inclusion, with no limits relating to quality. A sensitivity analysis was undertaken based on study quality (see Section 4.3)

PRISMA flow diagrams are presented in CS Figure 15 (p.81) and CS Figure 16 (p. 87) with numbers included and excluded at each stage, and reasons for exclusion. Of 76 studies identified by the wider SLR, 37 were included in the NMA. The 39 excluded studies are provided in CS Table 27 with reasons for exclusion.

The ERG has checked these 39 studies against the company's criteria for the NMA (but note caveats above regarding these criteria). The ERG agrees most of these studies do not meet the company's criteria, but notes some differences in reasons for exclusion. However, the ERG considers that Menter et al. 2008 on adalimumab should have been included. At the factual accuracy check, the company notified the ERG that the CS contained an error and the NMA did indeed incorporate PASI 75 and PASI 90 data at 16 weeks from this study.

15 studies of non-biologics and 5 studies of non-biologics vs a biologic or second line therapy were excluded from the NMA. The ERG considers that these should have been included in the NMA to meet the NICE scope.

4.1.3 Identified Studies

One RCT of DMF was included. The BRIDGE study[20, 21] was a three arm comparison of DMF, Fumaderm® and placebo. Fumaderm is unlicensed in the UK but is included in the NICE scope, see above, and includes DMF, zinc, calcium and magnesium salts of monoethylfumarate. The BRIDGE study was sponsored by Almirall S.A. The pdf of the publication and the clinical study report (CSR) were provided to the ERG and have been used by the ERG to cross-check the data presented.

The RCT methodology was summarised in the CS section 4.3 and 4.4 (the latter detailed the analysis, and is considered in Section 4.1.7). The trial was undertaken in adults with moderate to severe chronic plaque psoriasis. The CS states the study had a 4-week run in period, (the ERG are unable to find details of this in the publication or CSR), a 16-week treatment period and up to one year off-treatment follow-up. In the schematic of the study, CS Figure 5, there was a screening period. It is unclear what the duration of this screening period was or if this was the 4-week run in period. The study was designed to assess the superiority of DMF to placebo and non-inferiority of DMF to Fumaderm (discussed in more detail in Section 4.1.7). CS Figure 6 describes the participant flow: 704 participants were randomised; 5 were not treated (DMF n=1; Fumaderm n=3; placebo n=1) and were excluded but no further details or reasons for non-treatment were reported; 699 participants received at least one dose of their allocated interventions, these make up the safety analysis set. Of these, 28 did not complete at least one assessment of the primary outcomes (PASI or PGA) and were excluded from the full analysis set (reasons provided in response to clarification request A7) which included 671 participants. 450 participants completed the 16-week treatment phase of the study and 369 entered the follow-up (clarification response A7 confirms that there were incorrect data for the placebo group in CS Table 10). The reasons for not entering follow-up were not formally recorded as study consent had ended, however, from comments recorded, the company have confirmed that many participants started an alternative treatment (clarification A7). 110 participants completed follow-up; reasons for not completing follow-up were provided in CS Table 10 and for those categorised as ‘other’ in clarification request A8. The proportion of ‘other’ was highest in the DMF arm. In response A8 the company state that ‘other’ reasons for study termination are comparable across groups and mainly relate to a worsening of the underlying disease and / or a

need for a new treatment. However, the ERG notes that the rates of study termination for these reasons is higher in the DMF arm and it is not clear why these have not been counted under 'lack of efficacy' in CS Table 10. Table 10 currently suggests that fewer participants withdrew from the follow-up phase of the study for lack of efficacy with DMF than the comparators (there may be some overlap, however, as the numbers provided in clarification A8 for 'other' reason were higher than indicated in CS Table 10).

The dose of DMF was titrated over a 9 week period from 30mg daily up to 720mg daily, depending on an individuals response. The slow dose titration was designed to improve tolerability of DMF which can cause gastrointestinal adverse events. After week 4 (dose of 120mg once daily) reductions were permitted if there was any intolerance to DMF. CS Figure 5 shows a schematic of the trial and CS Table 8 shows the dose escalation of DMF. Participants attended the study centre at baseline, weeks 1, 3, 5, 8, 12 and 16. During the 12 month follow-up period participants attended the study centre at 2, 6 and 12 months. If a participant relapsed and needed a new systematic therapy during the follow-up period a final visit was conducted prior to initiation of the therapy (CS p41).

The eligibility criteria for the BRIDGE study are reported in CS Table 7 and Appendix 2. Participants were required either to have had prior therapy with systemic drugs for psoriasis that wastherapy that was discontinued (e.g. due to an adverse event or insufficient treatment effect), or to be naïve to systemic treatment but identified as a candidatesuitable for systemic treatment. There was a washout period for those on treatment (2 weeks for topical treatments, 1 month for conventional systemic drugs and phototherapy, 3 months for biologics). Those who had previously failed therapy with fumaric acid esters due to inadequate efficacy or lack of tolerability were not included in the study.

Outcomes assessed are discussed in more detail in Section 4.1.6.

The participant characteristics are summarised in CS page 54-55. The CS presents demographic and baseline characteristics in Table 11 for the safety analysis set (SAS) (data concur with the publication) and academic in confidence data for the full analysis set (FAS). The CS states that these were well balanced between treatment groups which the ERG generally agrees with,

although, notes that there were some small differences in the proportions receiving prior therapies in the DMF group (e.g % receiving prior methotrexate, prior acitretin and prior non-drug treatments slightly lower). The ERG agrees with the statement on CS p54 that the characteristics of those in the FAS appear to be comparable to the SAS and as such has presented the SAS data only, see Table 3.

To meet their decision problem the CS included a subgroup from the BRIDGE trial who were pre-treated with systemic therapies (as described above). Baseline characteristics for this subgroup were presented in CS Tables 21, 28 and 29, however the data in the latter two tables were incorrect. The company provided amended data for the pre-treated subgroup in clarifications A9 and A10 (clarification Tables 2 and 4), but the amended data do not align with those presented in CS Table 21. Moreover, the pre-treated subgroup sample sizes presented in CS Tables 21-23 and confirmed in clarification A9 [redacted] Tables 21-23 report on the subgroup of 'prior systemic therapies only', whilst the table in clarification A9 reports on the subgroup of 'prior systemic therapies or phototherapy' which the ERG notes is a different subgroup.

The CS states that the baseline demographics were comparable between the subgroups systemic naïve and pre-treated with systemics (CSp72 and Table 21). The ERG note that [redacted] Due to the differences in data presented between clarification Tables 2-3 and CS Table 21 it is unclear which patients were included in the NMA and how comparable the subgroups actually were.

The CS includes 37 studies of relevance to the decision problem as comparators (CS Figure 16). The patient characteristics and demographics are reported in CS Table 28, the disease characteristics in CS Table 29 (data repeated for 3 apremilast studies) and study characteristics (design, endpoints, eligibility criteria) in CS Table 31. The participant numbers (ITT) included in each arm are provided in the CS summary tables. The ERG has been unable to check all methodological details of these studies with their sources. As seen in CS Table 31 the populations all appear to be of relevance to the decision problem.

The CS (p 89) reports that the mean age of participants ranged from 39 to 50 years across study arms and that between 53% and 89% were male (where reported). The ERG agrees, noting that the mean age in most studies was around 45 years and most studies had 60-70% male participants. This is displayed graphically in CS Figures 17 and 18. The majority of the participants were Caucasian with the exception of four studies where the population was entirely Asian (PEARL, Japanese Ustekinumab Study Group, LOTUS, Ohtsuki 2016) (CS Table 28, CS Figure 21). No discussion of the generalisability of these latter populations to the decision problem is given. There was a range in the duration of psoriasis, from 13 to 22 years (CS Figure 19). The CS states that prior therapies were not reported clearly in the majority of the trials and where reported 'there was some diversity'. The ERG notes that one study (Papp 2005, Etanercept) reported that 11-12% of participants were treatment naïve; 23 studies reported the proportion of participants who had previously been given biologics and 18 studies reported the proportion of participants who had previously received conventional treatments. The proportions receiving these varied between the studies. As discussed in the CS, at baseline the mean PASI score ranged from 15 to 30, (although in most studies this was around 16-22, CS Figure 22) and BSA from 15% to 50% (although most were 20-30%). The DLQI ranged from 8 to 16 (CS reports 10-16). To assess similarity, the CS (pp 99-104) presents key characteristics from each study graphically, see Section 4.3 for further details.

Key baseline characteristics are summarised in Table 4 below. There do not appear to be any significant differences between participants within individual RCTs.

The CS does not include any non-randomised studies. The ERG has identified one additional relevant study, see Section 4.4.

Table 3: Key baseline characteristics from the BRIDGE Study

BRIDGE trial	Safety analysis set (SAS)		
	DMF (n = 279)	**Fumaderm (n = 283)**	**Placebo (n = 137)**
Male, %	62.4	65.4	67.9
Age (years), Mean (SD)	44.0 (15.2)	45.0 (13.8)	44.0 (14.3)
Race, % White	98.6	98.9	100.0
PASI total score, mean (SD)	16.3 (5.7)	16.4 (6.79)	16.2 (4.9)
PGA group, %[a]			
Moderate	60.7	60.1	60.3
Moderate to severe	34.8	34.4	37.4
Severe	4.5	5.5	2.3
Body surface area (%), mean (SD)	21.9 (11.6)	21.3 (12.5)	21.9 (12.3)
Prior conventional systemic therapy, %			
Methotrexate	7.2	13.8	10.2
Ciclosporin	4.3	2.8	5.8
Fumaderm®	3.2	3.9	2.9
Acitretin	2.9	5.3	6.6
Apremilast	0.4	0.4	0
Prior biological therapy, %			
Interleukin inhibitors[b]	2.5	1.4	2.2
TNF-a inhibitors[c]	0.4	2.1	0
Prior nondrug therapy including phototherapy, %	26.9	30.4	31.4

[a]The PGA scale was defined as: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, moderate to severe; 5, severe.
[b]Including secukinumab, ustekinumab and brodalumab. [c]Including adalimumab and etanercept.
PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; TNF, tumour necrosis factor

Table 4: Key baseline characteristics from the comparator studies

Trial name	Intervention and participant numbers	Age mean (SD)	Male (%)	PASI mean (SD)	BSA mean (SD)
CHAMPION[22, 23]	Adalimumab 40mg SC eow - 80mg at week 0 n=108	43 (12.6)	65	20 (7.5)	34 (19.9)
	Placebo n=53	41 (11.4)	66	19 (6.9)	28 (16.1)
JUNCTURE[24, 25]	Secukinumab 300mg SC ow (week 1-4) followed by every 4 weeks n=60	47 (14.2)	77	19 (6.4)	26 (12.8)
	Placebo n=61	44 (12.7)	62	19 (6.7)	26 (14.7)
ERASURE[26, 27]	Secukinumab 300mg SC ow (week 1-4) followed by every 4 weeks n=245	45 (13.5)	69	23 (9.2)	33 (19.3)
	Placebo n=248	45 (12.6)	69	21 (9.1)	30 (15.9)
FEATURE[24, 28]	Secukinumab 300mg SC ow (week 1-4) followed by every 4 weeks n=59	45 (12.6)	64	21 (8.0)	33 (18.0)
	Placebo n=59	47 (14.1)	66	21 (8.5)	32 (17.4)
FIXTURE[26]	Secukinumab 300mg SC ow (week 1-4) followed by every 4 weeks n=327	45 (13.2)	69	24 (9.9)	34 (19.2)
	Etanercept 50mg SC bid n=326	44 (13.0)	71	23 (9.8)	34 (18.0)
	Placebo n=326	44 (12.6)	73	24 (10.5)	35 (19.1)
Gottlieb 2003[29, 30]	Etanercept 25mg SC bid n=57	48 (NR)	58	18 (1.1)	30 (2.3)
	Placebo n=55	47 (NR)	67	20 (1.3)	34 (3.0)
Papp 2005[30-32]	Etanercept 25mg SC bid n=196	45 (12.0)	65	19 (8.2)	29 (18.0)
	Etanercept 50mg SC bid n=194	45 (12.4)	67	20 (8.8)	29 (17.2)
	Placebo n=193	45 (11.3)	64	19 (8.6)	27 (17.0)
CRYSTEL[33, 34]	Etanercept 25mg SC bid n=352	45 (11.8)	72	22 (10.3)	37 (21.9)
	Etanercept 50mg SC bid n=359	45 (11.9)	72	23 (10.3)	40 (23.7)
Leonardi 2003[30, 35]	Etanercept 25mg SC bid n=160	44 (0.9)	74	18 (0.7)	28 (1.5)
	Etanercept 25mg SC bid n=162	45 (1.0)	67	19 (0.7)	29 (1.6)
	Etanercept 50mg SC bid n=164	45 (0.8)	65	18 (0.7)	30 (1.6)

Trial name	Intervention and participant numbers	Age mean (SD)	Male (%)	PASI mean (SD)	BSA mean (SD)
	Placebo n=166	46 (1.0)	63	18 (0.6)	29 (1.4)
Tyring 2006[36, 37]	Etanercept 50mg SC bid n=311	46 (12.8)	65	18 (7.6)	27 (18.2)
	Placebo n=307	46 (12.1)	70	18 (7.4)	27 (17.2)
Strober 2011[38]	Etanercept 50mg SC bid n=139	45 (14.8)	61	19 (6.0)	25 (13.9)
	Placebo n=72	45 (13.9)	64	18 (6.4)	22 (13.4)
Bagel 2012[39]	Etanercept 50mg SC bid n=62	39[a] (NR)	53	16§ (NR)	16[a] (NR)
	Placebo n=62	42[a] (NR)	58	15§ (NR)	15[a] (NR)
Gottlieb 2011[40]	Etanercept 50mg SC bid n=141	43 (12.5)	70	19 (8.0)	24 (15.0)
	Placebo n=68	44 (13.6)	69	19 (6.9)	24 (15.5)
PRESTA[41, 42]	Etanercept 50mg BIW n=314	45 (13.0)	65	20 (11.0)	31 (22.0)
	Etanercept 50mg QW n=207	44 (12.5)	69	19 (10.0)	30 (22.0)
Bachelez 2015[43, 44]	Etanercept 50mg SC bid n=335	42[a] (NR)	70	19§ (NR)	25[a] (NR)
	Placebo n=107	4[a] (NR)	66	20§ (NR)	26[a] (NR)
UNCOVER - 2[45-47]	Etanercept 50mg SC bid n=358	45 (13.0)	66	19 (7.0)	25 (16.0)
	Ixekizumab biw n=351	45 (13.0)	63	19 (7.0)	25 (16.0)
	Ixekizumab every four weeks n=347	45 (14.0)	70	20 (7.0)	27 (17.0)
	Placebo n=168	45 (12.0)	71	21 (8.0)	27 (18.0)
UNCOVER - 3[45-47]	Etanercept 50mg SC bid n=382	46 (14.0)	70	21 (8.0)	28 (17.0)
	Ixekizumab biw n=385	46 (13.0)	66	21 (8.0)	28 (17.0)
	Ixekizumab every four weeks n=386	46 (13.0)	67	21 (8.0)	28 (16.0)
	Placebo n=193	46 (12.0)	71	21 (8.0)	29 (17.0)
PRISTINE[48, 49]	Etanercept 50mg SC bid n=137	44 (12.7)	74	21 (9.4)	33 (21.1)
	Etanercept 50mg SC bid n=136	44 (12.7)	65	21 (9.4)	33 (19.4)
Van de Kerkhof 2008[50, 51]	Etanercept 50mg SC bid n=96	46 (12.8)	62	21 (9.3)	27 (15.0)
	Placebo n=46	44 (12.6)	54	21 (8.7)	30 (17.8)
Asahina 2010[52]	Adalimumab 4 0mg SC eow n=38	48 (12.8)	84	25 (9.0)	43 (19.4)
	Adalimumab + loading dose 40mg SC eow - 80mg at week 0 n=43	44 (14.3)	81	30 (10.9)	48 (19.6)

Trial name	Intervention and participant numbers	Age mean (SD)	Male (%)	PASI mean (SD)	BSA mean (SD)
	Placebo n=46	44 (10.8)	89	29 (11.8)	47 (20.0)
X-PLORE[53]	Adalimumab 40mg SC eow - 80mg at week 0 n=43	50 (NR)	70	20 (7.6)	27 (16.8)
	Placebo n=42	46.5[a] (NR)	67	22 (10.0)	28 (19.3)
PHOENIX 2[54-56]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks n=409	45 (12.1)	69	19 (6.8)	26 (15.5)
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks n=411	47 (12.1)	67	20 (7.5)	27 (17.4)
	Placebo n=410	47 (12.5)	69	19 (7.5)	26 (17.4)
PHOENIX 1[57, 58]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks n=255	45 (12.5)	69	21 (8.6)	27 (17.5)
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks n=256	46 (11.3)	68	20 (7.6)	25 (15.0)
	Placebo n=255	45 (11.3)	72	20 (8.6)	28 (17.4)
ACCEPT[59]	Etanercept n=347	46 (13.4)	71	19 (6.2)	24 (13.9)
	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks n=209	45 (12.6)	64	21 (9.2)	27 (17.8)
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks n=347	45 (12.3)	67	20 (8.4)	26 (17.6)
LOTUS[60]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks n=162	40 (12.4)	78	23 (9.5)	35 (18.5)
	Placebo n=160	39 (12.2)	76	23 (9.5)	35 (19.6)
The Japanese Ustekinumab Study Group[61, 62]	Ustekinumab 45mg SC weeks 0, 4 and every 12 weeks n=64	47 (12.5)	83	30 (12.9)	47 (23.7)
	Ustekinumab 90mg SC weeks 0, 4 and every 12 weeks n=62	47 (12.8)	76	29 (11.2)	47 (19.7)
	Placebo n=32	49 (12.7)	84	30 (11.8)	50 (22.5)
PEARL[63, 64]	Ustekinumab 45mg SC weeks 0, 4, 16 n=61	41 (12.7)	82	25 (11.9)	42 (24.4)
	Placebo n=60	40 (10.1)	88	23 (8.6)	36 (21.4)
CLEAR[65-68]	Secukinumab 300mg SC ow (weeks 1-4) followed by 4-weekly n=337	45 (14.0)	68	22 (8.5)	33 (17.8)
	Ustekinumab 45mg (<100kg) - 90mg	45 (13.7)	74	22 (8.1)	32 (16.8)

Trial name	Intervention and participant numbers	Age mean (SD)	Male (%)	PASI mean (SD)	BSA mean (SD)
	(>100kg) SC weeks 0,4, every 12 weeks n=339				
AMAGINE-2[69, 70]	Ustekinumab 45mg (<100kg) - 90mg (>100kg) SC n=300	45 (13.0)	68	20 (8.2)	27 (19.0)
	Placebo n=309	44 (13.0)	71	20 (8.4)	28 (17.0)
AMAGINE-3[70, 71]	Ustekinumab 45mg (<100kg) - 90mg (>100kg) SC n=313	45 (13.0)	68	20 (8.4	28 (18.0)
	Placebo n=315	44 (13.0)	66	20 (8.7)	28 (17.0)
UNCOVER-1[72, 73]	Ixekizumab 80mg SC every 2 weeks n=433	45 (12)	67	20 (8.0)	28 (18.0)
	Ixekizumab 80 mg SC every 4 weeks n=432	46 (13)	67	20 (7.0)	27 (16.0)
	Placebo n=431	46 (13)	70	20 (9.0)	27 (18.0)
Ohtsuki 2016[1]	Apremilast 20 mg twice a day n=85	NR	NR	NR	NR
	Apremilast 30 mg twice a day n=85	NR	NR	NR	NR
	Placebo n=84	NR	NR	NR	NR
LIBERATE[74-77]	Apremilast 30mg oral n=83	46 (13.6)	59	19 (7.0)	27 (15.6)
	Etanercept 50 mg SC n=83	47 (14.1)	59	20 (7.9)	28 (15.7)
	Placebo n=84	43 (14.9)	70	19 (6.8)	27 (16.1)
Papp 2012[78, 79]	Apremilast 30mg oral bid n=88	44 (14.7)	57	19 (7.1)	31 (7.7)
	Placebo n=88	44 (13.7)	60	18 (5.7)	31 (6.7)
ESTEEM 1[80-84]	Apremilast 30mg oral bid n=562	46 (13.1)	67	19 (7.2)	24 (14.7)
	Placebo n=282	47 (12.7)	69	19 (7.4)	25 (14.6)
ESTEEM 2 [78-83, 85]	Apremilast 30mg oral bid n=272	45 (13.1)	64[b]	19 (7.1)	26 (15.4)
	Placebo n=136	46 (13.4)	73[b]	20 (8.0)	28 (15.8)

[a] median; [b] calculated by CS

bid: twice a day; biw: biweekly; BSA: body surface area; eow: every other week; ITT: intention to treat; IV: intravenous; NR: not reported; PASI: psoriasis area and severity index; od: once daily; ow: once weekly; SC: subcutaneous; SD: Standard deviation.

4.1.4 Relevant studies not included in the submission

As discussed in Section 4.1.2, the ERG considers that Menter et al. 2008 on adalimumab [18] was excluded incorrectly. However, the results from Menter et al. 2008 (adalimumab vs placebo: PASI 75: 71% vs 7%; PASI 90: 45% vs 2%) were within the range of the other three included studies of adalimumab (PASI 75: 63%-80% vs 4%-19; PASI 90: 40%-51% vs 0%-11%) and its omission is unlikely to have much of an impact on the NMA results. (The company notified the ERG that the CS contained an error and the NMA did indeed include Menter et al. (2008)).

4.1.5 Description and critique of the approach to validity assessment

The CS assessed methodological quality of the BRIDGE study (CS Section 4.6). This has been assessed by the ERG, see Table 5). The methodological quality assessments of the BRIDGE study conducted by the company and the ERG differed in their interpretations of ITT analysis. For instance, the efficacy analyses in this study were carried out using the full analysis set, which did not account for 33 patients who were randomised at baseline but were not assessed for the primary endpoints (PASI 75 and PGA 'clear/almost clear' at 16 weeks). Hence, contrary to the company's position, it is the opinion of the ERG that the efficacy analyses were not intention-to-treat (see Section 4.1.7). The BRIDGE study reported comparable dropout rates between DMF and Fumaderm, which were slightly higher than placebo. The company (in Appendix 4) and ERG assess this study as having a high risk of bias given the considerably high dropout rates (36% of the study participants had discontinued treatment protocol prior to week 16, and 85% had not completed the follow-up phase (CS Table 10)) together with the difference in reasons for withdrawal.

Table 5: ERG Quality Assessment of the BRIDGE study

	BRIDGE	
	COMPANY	**ERG**
Was randomisation carried out appropriately	Yes. Patients were randomised 2:2:1 ratio to receive DMF (LAS41008), Fumaderm or placebo	Yes. Randomization was carried out 2:2:1 (DMF: Fumaderm: placebo) using an interactive web-based response system (IWRS).
Was concealment of treatment allocation adequate?	Yes. Treatment allocation was concealed using a double dummy design and IWRS	Yes. IWRS accounts for allocation concealment.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes. The ERG agrees the groups were similar statistically
Were care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes. However, it is unclear whether blinding could be maintained given the difference in adverse events.
Were there any unexpected imbalances in drop-outs between groups?	No imbalances between the treatment groups. The drop-out rate in the study was higher than expected. This is likely to be due to the rigid titration period which did not allow clinicians and/or patients to individualise dosing. However the drop-out and discontinuation rates were comparable between the DMF (LAS41008) and Fumaderm treatment groups. In Appendix 4, the CS states: Yes. High amount of dropouts in LAS41008 and Fumaderm arm compared to placebo	Yes. Withdrawals were similar between DMF and Fumaderm, but slightly higher than placebo. However, the ERG considers the dropout rates very high, and ultimately, a potential source of bias especially as the reasons for withdrawal differed between DMF and placebo (adverse events 23%, 25%, 4% for DMF, Fumaderm and placebo, respectively).
Is there evidence the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so was this appropriate and were appropriate methods used to account for missing data?	Yes	No. The primary efficacy analysis was not intention-to-treat. Efficacy analyses were carried out using the full analysis set, which did not account for 33 patients originally randomized.
How closely do the RCT(s) reflect routine clinical practice?	The baseline characteristics of patients in the trial reflect those patients likely to receive DMF (LAS41008) in clinical practice. The outcomes measured are relevant to clinical practice.	The study outcomes are relevant to clinical practice in the UK. The ERG clinical advisor agrees that characteristics of participants in the BRIDGE trial are similar to those seen in UK clinical practice.
Source: Mrowietz et al 2016[20]		

The CS also undertook assessment of the risk of bias of the studies included in the NMA (CS Appendix 7).

In the ERG's quality assessment of the 36 comparator studies, risk of selection bias as measured by the appropriateness of randomisation and allocation concealment was deemed low in 25 studies (69%). In comparison, randomisation and allocation concealment were judged to be satisfactory in 22 (61%) studies respectively in the CS (CS Appendix 4, Tables 2 and 3). The ERG identified considerable disparities in dropout rates between treatment arms in 5 studies (14%), whereas the CS considered dropout rates to be imbalanced in only 2 studies (6%) (CS Appendix 4 Tables 2 and 3).

The primary efficacy analysis was considered to be intention-to-treat in 29 studies (81%) by the ERG, as opposed to 21 studies (58%) by the CS.

Reasons for the discrepancies in quality assessment between the ERG and the company have been summarised in Table 6.

With the exception of Ohtsuki et al.[1], the quality of the comparator studies was not described in the main text of the CS (page 104). The company excluded Ohtsuki et al. from the scenario analysis, stating it was the only trial with an unclear or high risk of bias for all 7 questions. In fact, this study (which was published as an abstract only) was unclear on 6 of 7 questions and low on one question (blinding) according to both company and ERG judgements (Appendix x). The ERG does not consider this to be a reasonable approach for selecting studies for sensitivity analysis. The ERG considers that a more reasonable approach would have been to identify key threats to validity *a priori,* and conduct sensitivity analyses where risk of bias was judged to be high, such as selection bias (as there is strong empirical evidence that this affects outcomes) and performance bias and detection bias (as there is some subjectivity in assessing these outcomes). As noted above, many of the studies had an unclear risk of selection bias, therefore Ohtsuki et al. is not unique in that aspect. Three studies (X-PLORE, ACCEPT, CRYSTEL) were not double-bind and therefore had a high risk of performance bias and detection bias. The ERG considers that these studies should have been excluded in a sensitivity analysis.

Table 6: Risk of bias for comparators as assessed by the company with ERG judgements where different.

Trial name	Random-isation	Concealment of allocation	Similar groups on prognostic factors	Blinding providers, participants & outcome assessors	Unexpected imbalances in drop-outs	More outcomes measured than reported	ITT analysis, appropriate, missing data accounted for	Rationale for deviations from the company's quality assessment
CLEAR[65-68, 86-88]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias	
Leonardi 2003[30, 35]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	
Gottlieb 2003[29, 30, 89, 90]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	
Tyring 2006[36, 37]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias	
Papp 2005[30-32]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	
Strober 2011[38]	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	
PRISTINE[48, 49]	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	
Bagel 2012[39]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: High risk of bias ERG: Low risk of bias	CS: High risk of bias ERG: Low risk of bias	CS: Letter #283 reports DLQI however letters have been excluded ERG: The same outcomes described in the methods were measured and reported in the results. CS: Efficacy analysis were based on randomised patients

								ERG: All patients randomized were included in the primary efficacy analysis.
Gottlieb 2011[40]	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	
Van de Kerkhof 2008[50, 51]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: Low risk of bias ERG: High risk of bias	Low risk of bias	Low risk of bias	CS: Patients in the placebo group had a significantly higher rate of discontinuation at 12 weeks than patients in the etanercept group ERG: dropout rates of 22% vs 6% (Placebo vs Etanercept), driven by higher rates of inefficacy in the placebo arm.
JUNCTURE[24, 25]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: High risk of bias ERG: Low risk of bias	CS: Evaluated by randomisation, nothing mentioned about ITT ERG: All patients randomized were included in the primary efficacy analysis according to treatment assignment at randomisation.
PHOENIX 2[54-56]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	
PHOENIX 1[57, 58]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	
ERASURE[26, 27]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: High risk of bias ERG: Low risk of bias	CS: The analyses of the efficacy end points included all the patients who underwent randomization according to the treatment assigned at randomization. ERG: All patients randomized were included in the primary efficacy analysis.
FIXTURE[26]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: High risk of bias ERG: Low risk of bias	CS: The analyses of the efficacy end points included all the patients who underwent randomization according to the treatment assigned at randomization. ERG: All patients randomized were included in the primary efficacy analysis.
Papp 2012[78, 79]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: Low risk of bias	Low risk of bias	Low risk of bias	CS: Approximately equal dropout at 16 weeks

					ERG: High risk of bias			ERG: Dropout rates at 16 weeks for Placebo vs Apremilast 10mg vs Apremilast 20mg vs Apremilast 30mg were 18% vs 11% vs 24% vs 20%. The ERG considers these rates imbalanced.
PRESTA[41, 42]	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	
FEATURE[24, 28]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: High risk of bias ERG: Low risk of bias	CS: Evaluated by randomisation ERG: All patients randomized were included in the primary efficacy analysis.
X-PLORE[53]	CS: Unclear risk of bias ERG: low risk of bias	CS: Unclear risk of bias ERG: low risk of bias	Low risk of bias	High risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	CS: Allocation concealment was not not explained ERG: randomization used a central, adaptive randomization procedure through an interactive voice response system
Bachelez 2015[43, 44]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	High risk of bias	
ESTEEM 2[78-83, 85]	CS: Unclear risk of bias ERG: low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias	CS: In period A (placebo-controlled phase; weeks 0–16), eligible patients were randomized (2 : 1) via an interactive voice response system to apremilast or placebo, respectively ERG: randomization likely to be appropriate
AMAGINE-2[69, 70]	Low risk of bias	CS: Unclear risk of bias ERG: low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: Nothing mentioned about allocation concealment ERG: interactive voice recognition system used
AMAGINE-3[70, 71]	Low risk of bias	CS: Unclear risk of bias ERG: low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: Nothing mentioned about allocation concealment ERG: interactive voice recognition system used
ESTEEM 1[80-84]	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias	
CHAMPION[2] [2, 23]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	

UNCOVER - 2[45-47]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	
UNCOVER-3[45-47]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	
ACCEPT[59]	CS: Low risk of bias ERG: Unclear risk of bias	Unclear risk of bias	Low risk of bias	CS: Unclear risk of bias ERG: High risk of bias	Low risk of bias	Low risk of bias	CS: High risk of bias ERG: Low risk of bias	CS: Adaptive randomization scheme that was stratified according to investigational site and baseline weight (<90 kg or ≥90 kg). ERG: The authors report the use of an adaptive randomization scheme without describing what this technique entails. CS: Patients were aware of their treatment assignment, although patients who were randomly assigned to ustekinumab received double injections (one injection of active treatment and one injection of placebo) to maintain blinding for the dose. All study personnel, except those who dispensed or administered a study agent, remained unaware of the treatment assignments throughout the study. ERG: patients not blinded to ustekinumab or entnercept treatment, unclear if outcome assessors were blinded or how this was maintained. CS: Analysis based on randomisation ERG: All patients randomized were included in the primary efficacy analysis according to assigned treatment.
LOTUS[60]	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias	CS: High risk of bias ERG: Low risk of bias	CS: Analysis based on randomisation ERG: All patients randomized were included in the primary efficacy analysis according to assigned treatment.
CRYSTEL[33, 34]	CS: Low risk of bias	CS: High risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: All enrolled patients were assigned randomly in a 1:1 ratio

	ERG: Unclear risk of bias	ERG: Unclear risk of bias						ERG: no details of randomisation CS: Open label study ERG: no details of allocation concealment
The Japanese Ustekinumab Study Group[61, 62]	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: Unclear risk of bias	
PEARL[63, 64]	Low risk of bias	CS: Unclear risk of bias ERG: Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: Unclear risk of bias ERG: Low risk of bias	CS: Not explained in text ERG: interactive voice response system CS: Analysis based on N randomised ERG: All patients randomized were included in the primary efficacy analysis according to assignment.
Asahina 2010[52]	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	CS: High risk of bias ERG: low risk of bias	CS: Primary and secondary efficacy analyses were conducted for the full analysis set population, defined as all patients who were randomized, received at least one dose of double-blind study drug, and had at least one assessment of efficacy under double-blind treatment. ERG: All randomised patients received at least one dose of study treatment and were included in the efficacy and safety analyses
LIBERATE[74-77, 91]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	
UNCOVER-1[72, 73]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	
Ohtsuki 2016[1]	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	

4.1.6 Description and critique of company's outcome selection

The CS decision problem included outcomes stated in the NICE scope with the exception of psoriasis symptoms on the face, scalp, nails and joints; the CS states that data on the complications of psoriasis are not available for DMF (CSp13). Included outcomes were severity of psoriasis; response rate; remission rate; relapse rate; mortality; adverse events; health-related quality of life. These were included in the BRIDGE trial.

Severity of psoriasis / response to treatment was assessed by the psoriasis area severity index (PASI), as the proportion achieving a reduction in score from baseline at week 16, at the 75% (primary outcome), 90% and 50% level and the mean percentage change from baseline. In addition, the proportion achieving a Physician's Global Assessment (PGA) of 'clear' or 'almost clear' at week 16 (score 0/1, also a primary outcome) and the change in body surface area (BSA) affected were reported. An outcome, treatment success, was also reported, this was a composite of the PGA 0/1 and/or PASI 90. Remission was defined as a score of 'clear' on the PGA. Relapse was defined as when the achieved maximal improvement from baseline was subsequently reduced by at least 50% based on the PASI score (CS p62). Two time to relapse analyses were presented: relapse during treatment and up to 12 months off treatment; and relapse occurring within 2 months after last study drug intake. In addition, an outcome of rebound (worsening of psoriasis from the baseline value, PASI ≥125%, CS p64) was reported.

Health-related quality of life was assessed using the Dermatology Quality of Life index (DLQI), a commonly used measure, and the Patient Benefit Index (PBI). The DLQI has 10 questions relating to symptoms and feelings, daily activities, leisure, work/school, personal relationships and treatment. Higher scores indicate greater effects on a patients' life. The CS Appendix 3 states that the PBI was calculated based on the Patient Need Questionnaire (PNQ) at the start of treatment and on the Patient Benefit Questionnaire (PNQ) at the end of treatment and during follow-up. PNQ asks participants to indicate how important they considered 25 different treatment goals on a 5-point scale from "not at all" to "very". In the PBQ participants were asked if the study treatment had helped them to achieve these goals.

CS Page 51 refers to the PASI total score as continuous data, for an alternative means to handle missing data. These data were not presented but were provided in response to clarification question A12, see Section 4.2.1.

The CS reports that outcome assessors in the BRIDGE study were blinded to treatment allocation (CS p.56), although as noted above, no details were provided of how blinding was carried out.

The CS does not describe what is considered to be the minimum important clinical difference for the outcomes. The ERG clinical expert confirmed that the PASI 75 and a 75% reduction in body surface area are important outcomes and that a change of at least 30% would be clinically meaningful. On the DLQI a 5-point improvement is an important difference.

Adverse events were reported for the BRIDGE study. These were not defined in the CS. [redacted]

4.1.7 Description and critique of the company's approach to trial statistics

With the exception of psoriasis symptoms on face, scalp, nails and joints, the CS reports trial results for all outcome measures relevant to the scope (CS p. 57-75).

The endpoints PASI 75 at week 16 and the proportion 'clear' or 'almost clear' in the PGA at week 16 were tested to show superiority of DMF over placebo, but only PASI 75 was tested to show non-inferiority of DMF versus Fumaderm. Sample size calculations for each of these

comparisons were reported in CS p. 46-47. For superiority of DMF over placebo, a difference of 40% in PASI between DMF and placebo was assumed (based on response rates of 50% and 10%, respectively), and a difference in PGA of 30% between DMF and placebo was assumed (based on response rates of 40% and 10%, respectively). For non-inferiority of DMF compared to Fumaderm, a non-inferiority margin of 15% was set. The CS states that this margin was well within the effect size compared to placebo but was also considered a reasonable maximal difference that was judged to be not clinically relevant.

The CS (p. 47) reports that the study was planned as an adaptive design. A planned interim analysis was performed when PASI and PGA data were available for one-third of the patients in order to address the implications of continuing with the original sample size and check for safety concerns. These data were not reported in the trial publication, CS or CSR. The data monitoring committee suggested an increase in sample size from 690 patients to 1070 patients, however the decision was taken not to make any adjustments to the sample size and the threshold for statistical significance was adjusted to be ≤0.0038.

The CS described three analysis sets (CS p. 48):

- Safety analysis set (SAS) n=699: all patients who were randomised and received at least one dose of study medication, DMF n= 279, Fumaderm n=283, placebo n=137;

- Full analysis set (FAS) n=671: all patients of the safety analysis set with at least one measurement of the primary variable PASI and PGA after Week 0, DMF n= 267, Fumaderm n=273, placebo n=131

- Per protocol set (PPS) n=626: all patients of the FAS for whom no relevant protocol deviations were documented, DMF n= 246, Fumaderm n=253, placebo n=127.

The CS states that all statistical analyses were based on the FAS and PPS, and that as results of both were consistent, only data for the FAS set were presented in the CS. The ERG has checked the PPS results for the primary outcomes in the CSR and agrees they are consistent with the FAS results.

The company argues that the FAS meets internationally accepted definitions of an ITT population because the FAS (defined as all randomised patients who received no less than one dose of treatment with at least one measurement of the primary efficacy endpoint) is the closest possible approximation of the ITT (clarification response A3). While the FAS was somewhat necessary, because only patients with measurement of the primary outcome could contribute to the analysis unless there was imputation of missing values, this is not an ITT analysis, e.g as defined by NICE[92]:

"An assessment of the people taking part in a trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully adhered to the treatment or switched to an alternative treatment. ITT analyses are often used to assess clinical effectiveness because they mirror actual practice, when not everyone adheres to the treatment, and the treatment people have may be changed according to how their condition responds to it."

The ERG considers that the primary efficacy analyses in the key RCT evidence should be based on the safety analysis set (which would be a modified intention-to-treat analysis) and has requested these results in clarification question A 12 (see Section 4.2.1).

The company used a hierarchical approach to deal with multiple comparisons. Non-inferiority testing was done at a 5% significance level only if both superiority comparisons led to a rejection of the null hypothesis in the FAS and PPS population. One-sided p-values were used for the superiority and non-inferiority testing.

The asymptotic Wald test for risk differences with two-sided 95% confidence intervals were used to analyse PASI 50, PASI 75, PASI 90 and the proportion of with 'clear' or 'almost clear' in the PGA. ANCOVA with factors treatment and centre and the corresponding baseline values as covariable were used to analyses percentage change from baseline in PASI, BSA and change from baseline in BSA. Kaplan-Meier estimates were provided for time to relapse and time to rebound. The DLQI was compared using Cochran-Mantel-Haenszel test for categorical data. The DLQI score and PBI score were analysed using ANOVA models with treatment and centre as factors. Success rate and remission rate according to the PGA were analysed using the Cochran-

Mantel-Haenszel test to obtain descriptive two-sided p-values. Treatment success and remission rate were stratified by centre.

Subgroup analysis

Pre-planned subgroup analyses (based on the FAS) were conducted for gender, age, (≤35, > 35 to ≤ 55 years and > 55 years old), race (Caucasian, Black or African American, Asian and Other), PASI severity (moderate: PASI >10 to ≤20%; severe: PASI >20%) and PGA severity (moderate = 3; severe = grouping of the categories moderate to severe [PGA score 4] with severe [PGA score 5]). Details of the analysis are presented on CS p.51. The co-primary efficacy endpoints were analysed using a linear binomial regression including treatment, subgroup variable and treatment-by-subgroup interaction. DLQI was analysed using an ANCOVA model with baseline DLQI score, treatment group, subgroup variable, centre and treatment-by-subgroup category. The CS states that the p-value of the treatment-by-subgroup interaction for active vs. placebo comparison was used to evaluate the homogeneity of the treatment effect between DMF and placebo across subgroup categories and that the statistical significance was set to 10%. However, this p-value was reported for the severity subgroup only and not for the other pre-planned or post-hoc analyses.

Post-hoc analyses were conducted for subgroups of patients who were receiving systemic therapy or PUVA for the first time [redacted] compared to those who had previous experience of other systemic agents such as methotrexate or ciclosporin [redacted]

4.1.8 Description and critique of the company's approach to the evidence synthesis

See Section 4.3 for synthesis of the BRIDGE study with the studies included in the network meta-analysis.

4.2 Summary of submitted evidence

The outcomes in the scope included: severity of psoriasis (measured using the PASI); psoriasis symptoms on 'difficult-to-treat sites' such as the face, scalp, nails and joints; response rate;

remission rate; relapse rate; mortality; adverse effects of treatment; and health-related quality of life (including DLQI).

Except for psoriasis at 'difficult-to-treat sites'; the outcomes in the CS decision problem were somewhat similar to the scope outcomes, see Section 3. In addition the CS presents outcomes including treatment success rate and time to rebound (see Section 4.2 for more details).

The efficacy analyses were based on the full analysis set (FAS) (CS Figures 7-10; CS Tables 13-17). The analyses of the primary efficacy endpoints entailed testing the hypotheses that DMF was superior to placebo and non-inferior to Fumaderm. However, the FAS does not account for 28 patients in the safety analysis set (SAS). The ERG considered the latter a better approximation of an intention-to-treat (ITT) analysis set. Hence, the ERG requested the results of the primary efficacy analyses for the SAS (clarification question A12).

Tables Table 7 and Table 8 summarise the efficacy results for the FAS and SAS respectively. Only the results for the primary outcomes are provided for the SAS. All results are for the assessment at the end of the treatment period, 16 weeks, unless stated.

4.2.1 PASI/PGA outcomes (severity)

The results show that the PASI 75 response rate was 37.5% with DMF compared to 15.3% with placebo, suggesting a statistically significant difference in the analysis for superiority. The PASI 75 response rate was 40.3% with Fumaderm, suggesting that DMF was non-inferior to Fumaderm. The ERG agrees that DMF was superior to placebo and non-inferior to Fumaderm (confidence intervals were less than the pre-specified 15% non-inferiority margin, see Section 4.1.7). PASI 90 response rates in the DMF were significantly higher than placebo, but not significantly different when compared to Fumaderm. [redacted]

Similarly, patients in the DMF arm were more likely than patients in the placebo arm to have a PGA score of 0 or 1, but were statistically comparable to patients in the Fumaderm arm.

The results of the primary efficacy analyses were broadly similar between the FAS and SAS. The ERG requested PASI continuous data (clarification request A12) and the findings were supportive of the primary efficacy endpoint as shown in Table 7.

4.2.2 Remission rates (clear PGA)

Remission rates were significantly higher in the DMF arm, compared to placebo. However, no statistically significant difference was observed between DMF and Fumaderm.

4.2.3 Relapse

Relapse rates were significantly lower for DMF compared to placebo, but not different between DMF and Fumaderm. Time to relapse appeared to be longer in the DMF arm, compared to the Fumaderm and placebo arms. [redacted]

The ERG notes some discrepancies in the sample sizes used to analyse time to relapse data at two months. In clarification response A4 the company explains that the numbers [redacted] represented respectively patients in the DMF, Fumaderm and placebo arms who completed the treatment at 16 weeks and entered into the follow-up phase and that these numbers are different from the FAS. However, CS Figure 6 reports that 176, 176, and 98 patients in the DMF, Fumaderm, and placebo arms respectively completed treatment at 16 weeks. CS Figure 6 also illustrates that 150, 153, and 66 participants in the DMF, Fumaderm and placebo arms respectively entered into the follow-up phase after completing the treatment phase.

4.2.4 Health-related quality of life

At 16 weeks, patients who received DMF had better HRQoL compared to patients who received placebo, but were no different from patients who received Fumaderm. CS table 17 presents DLQI data for other time points: at 2 months after completing treatment, DMF was associated with better HRQoL than placebo, but was no different when compared to Fumaderm. DMF showed [redacted]

Of note, the DLQI scores are based on observed cases not FAS (clarification request A6), which is data collected at Week 16 supplemented by the data collected at the end-of-treatment visit for those patients who withdrew from the study before Week 16. Upon further request to clarify the patient numbers, see Table 7; the company also acknowledged that baseline (and not screening) DLQI scores were reported in CS Table 17.

Table 7: Summary of the efficacy results in the BRIDGE trial for the FAS

Outcome	DMF N = 267	Fumaderm N = 273	Placebo N = 131	DMF *vs* Placebo Effect estimate with CI	DMF *vs* Fumaderm Effect estimate with CI
PASI 75	37.5%	40.3%	15.3%	22.2 (10.7 to 33.7)[a]	-2.8% (-14.0 to 8.4)[a]
PGA 0 or 1	33%	37.4%	13%	20.0 (8.0 to 30.0)[a]	-4% (-15.0 to 7.0)[a]
PASI 90	18.4%	22.3%	4.6%	13.8 (7.9 to 19.6)	-4% (-13.0 to 5.0)[c]
% change in mean PASI score (SD)	-50.8 (41.8)	-54.1 (39.9)	-27.0 (37.6)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% change in BSA	-13.2 (12.1)	-11.3 (10.3)	-4.9 (10.8)	-8.3 (-9.0 to -4.8)	-1.9 (-3.8 to -0.01)[c]
Remission rate	6.4%	7.7%	0.8%	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean DLQI (SD)[d]	n=253 5.4 (6.1)	n=259 6.1 (7.2)	n=118 8.5 (6.9)	-3.2 (-4.7 to -1.8)	-0.7 (-1.8 to 0.5)

Results for each treatment arm are as reported in the CS, and are no different from the BRIDGE publication. Only efficacy results relevant to the scope and decision problem are presented. FAS: full analysis set.

[a], effect estimates presented with 99.24% confidence intervals. Other estimates are presented with 95% confidence intervals.

[b], relapse rate PASI reduction ≥50% assessed 12 months after completing treatment. The CS also reports relapse rates assessed 2 months after completing treatment, which the ERG has not reproduced.

[c], The ERG calculated the treatment effect and 95% CI intervals

[d], Observed numbers provided in company clarification A6

Table 8: Summary of the efficacy results in the BRIDGE trial for the SAS

Outcome	DMF N = 279	Fumaderm N = 283	Placebo N = 137	DMF *vs* Placebo Effect estimate with CI	DMF *vs* Fumaderm Effect estimate with CI
PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA 0 or 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Effect estimates presented with 99.24% confidence intervals. SAS, safety analysis set

4.2.5 Subgroup analyses

The subgroups to be considered in the scope were: previous use of systemic non-biological therapy; previous use of biological therapy; and severity of psoriasis (moderate, severe). The subgroup analyses presented in the CS meet two of these, entailing pre-planned and post-hoc analyses of the efficacy endpoints based respectively on psoriasis severity and previous use of of systemic non-biological therapy.

[redacted]

Table 9 and Table 10 summarise the subgroup analyses results.

[redacted]

The results therefore suggest that severity is not an effect modifier. The ERG could not verify the subgroup analysis results of DMF vs Fumaderm because the relevant data were not given.

The CS (page 73) defines moderate psoriasis as a PASI score of greater than 10 but no greater than 20 or a PGA score of 3. For severe psoriasis, it was a PASI score of greater than 20 or a PGA score 4 or 5. [redacted] However, previous NICE Technology Appraisals for psoriasis drugs defined severe psoriasis as a PASI score no less than 10 and a DLQI score greater than 10 (see further discussion in Section 5.1.4). None

of the previous TAs considered a subgroup analysis based on moderate and severe psoriasis. Without raw DLQI data, it is impossible to ascertain any possible similarities or differences in disease status if psoriasis severity was also defined using DLQI in the present CS. However, the mean DLQI scores for DMF, Fumaderm and Placebo in the Bridge study were all above 10.

[redacted]

Table 9: Subgroup analyses (pre-planned) of the primary efficacy endpoints according to psoriasis severity

PASI 75		
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
PGA 0 or 1		
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

NR, not reported

Table 10: Subgroup analyses of the primary efficacy endpoints according to treatment status for previous systemic non-biological therapy (post-hoc)

PASI 75		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]		[redacted]	[redacted]
		[redacted]	
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

The CS also presented pre-planned subgroup results for gender and age, CS p68.

4.2.6 Adverse events

The CS reports adverse events from the BRIDGE study (pp128-130), for the definitions of adverse events used in the CS, see Section 4.1.6. The ERG requested longer-term data on adverse events, including in other indications. No additional data were provided by the company, which stated that safety data from other indications including MS cannot be extrapolated to psoriasis (clarification response A16).

The ERG has supplemented the re ported adverse events with data identified in the CSR. Data are presented for the safety analysis set (all patients who were randomised and received at least one dose of study medication. Table 11 provides an overview of adverse events. Treatment-emergent adverse events (TEAEs) leading to study drug withdrawal were experienced by 24.0%, 24.4% and 5.8% of the DMF, Fumaderm and placebo groups, respectively. [redacted] Serious adverse events were similar between groups, experienced by 3.2%, 2.8% and 3.6% of participants, respectively. The most common serious adverse events were cardiac disorders, occurring in [redacted] of the Fumaderm group (Table 13). Serious adverse events were judged to be related to the treatment in three patients from the Fumaderm group (erosive gastritis, gastroduodenitis and gastric ulcer) and in none of the other groups. One death was reported, this occurred in the Fumaderm group and was considered unrelated to the medication (subendocardial ischaemia).

TEAEs were experienced by 83.9%, 84.1% and 59.9% of patients in the DMF, Fumaderm and placebo groups, respectively (Table 11), and treatment-related adverse events were reported in 73.8%, and 73.9% and 40.1% of the patients, respectively. TEAEs occurring in >1% of all patients are summarized in Table 12. Most TEAEs were of mild to moderate intensity; severe intensity TEAEs occurred in 15.1%, 12.0% and 7.3% of the patients the DMF, Fumaderm and placebo groups, respectively. The most common TEAEs were

gastrointestinal disorders (DMF 62.7%, Fumaderm 63.3%, placebo 29.9%). As can be seen in Table 14, most of the events (gastrointestinal disorders, vascular disorders, blood and lymphatic disorders, skin and subcutaneous disorders) were similar between DMF and Fumaderm, while both groups had a higher occurrence of the events than the placebo group.

The CS specifies TEAEs of special interest relevant to DMF as decreases in lymphocyte and leukocyte counts, flushing, gastrointestinal events, serious and opportunistic infections, malignancies, renal injury and proteinuria, and hepatic injury. They state that this grouping of events was selected based on the risks known to be associated with Fumaderm treatment or potentially related to the immunological mode of action of DMF. The CS states that changes in haematology values were observed with DMF and Fumaderm that were comparable to those that have previously been observed with Fumaderm, i.e. increases in eosinophils and decreases in leukocytes and lymphocytes. The ERG has checked these data in the CSR but has not reproduced results. The CS also states that there was no clear relationship between blood disorders such as leukopenia and lymphocytopenia and the onset of infections, although notes than this should be interpreted with caution due to the low frequency of events. The CS does not make reference to PML, see Section 2.3 for details.

Adverse events were not explicitly considered in the company's economic model.

Table 11: Overview of adverse events

	DMF n=279	**Fumaderm n=283**	**Placebo n=137**
TEAEs leading to withdrawal	67 (24.0)	69 (24.4)	8 (5.8)
Serious TEAEs	9 (3.2)	8 (2.8)	5 (3.6)
Treatment-related serious TEAEs	0 (0.0)	3 (1.1)[a]	0 (0.0)
Serious AEs leading to death	0 (0.0)	1 (0.4)	0 (0.0)
TEAEs	234 (83.9)	238 (84.1)	82 (59.9)
Treatment related AEs	206 (73.8)	209 (73.9)	55 (40.1)

AIC marking removed where results are in the trial publication.

[a]CS Table 47 states [redacted], publication [redacted] states 3

Table 12: TEAEs leading to study drug withdrawal in more than 1 patient

	DMF n=279	Fumaderm n=283	Placebo n=137
Any event	**67 (24.0)**	**69 (24.4)**	**8 (5.8)**
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]

Table 13: Serious adverse events according to system organ class preferred term

	DMF n=279	Fumaderm n=283	Placebo n=137
Any event	**9 (3.2)**	**8 (2.8)**	**5 (3.6)**
Cardiac disorders	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Pregnancy, puerperium and perinatal conditions	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]

Table 14: TEAEs occurring in more than 1% of all patients (SAS)

System Organ Class Preferred Term	DMF n=279	Fumaderm n=283	Placebo n=137
Gastrointestinal disorders[a]	175 (62.7)	179 (63.3)	41 (29.9)
• Diarrhoea	108 (38.7)	113 (39.9)	22 (16.8)
• Abdominal pain upper	56 (20.1)[b]	64 (22.6)	11 (8.0)
• Abdominal pain	55 (19.7)	45 (15.9)	7 (5.1)
• Nausea	30 (10.8)	24 (8.5)	5 (3.6)
• Flatulence	15 (5.4)	16 (5.7)	7 (5.1)
• Vomiting	13 (4.7)	19 (6.7)	2 (1.5)
• Abdominal discomfort[c]	8 (2.9)	11 (3.9)	2 (1.5)
• Abdominal distension[c]	4 (1.4)	[redacted]	2 (1.5)
• Dyspepsia[c]	6 (2.2)	[redacted]	2 (1.5)
• Constipation[c]	6 (2.2)	[redacted]	0 (0.0)
• Gastrointestinal disorder[c]	[redacted]	8 (2.8)	0 (0.0)
Vascular disorders	[redacted]	[redacted]	[redacted]
• Flushing	51 (18.3)	46 (16.3)	2 (1.5)
• Hot flush	7 (2.5)	5 (1.8)	1 (0.7)
Blood and lymphatic disorders	[redacted]	[redacted]	[redacted]
• Lymphopenia	28 (10.0)	30 (10.6)	0 (0.0)
• Eosinophilia	25 (9.0)	17 (6.0)	0 (0.0)
• Leukocytosis	[redacted]	[redacted]	[redacted]
• Leukopenia	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
• Pruritus	24 (8.6)	28 (9.9)	15 (10.9)
• Erythema	27 (9.7)	23 (8.1)	3 (2.2)
• Burning skin sensation	22 (7.9)	20 (7.1)	3 (2.2)

AIC marking removed where results are in the trial publication.
[a]CS Table 48 has a footnote symbol without a footnote. [b] [redacted] [c] From CSR.

4.3 Indirect comparison

The CS reports an NMA (pp 75 – 127); the ERG have checked this for three key assumptions, including homogeneity, similarity and consistency (see Table 15).

Statistical homogeneity was not formally considered in the CS, no pairwise comparisons were presented within the NMA and it is therefore unclear whether there was statistical heterogeneity between studies. The CS present summary details from the included studies which could be used to assess clinical homogeneity (see below) although this is not explicitly

made clear in the CS. Therefore, it is unclear to the ERG whether the homogeneity assumption is satisfied.

The CS included 37 trials in the NMA. In testing the similarity assumption, all 37 trials were assessed for comparability in age, sex, duration of psoriasis, disease severity at baseline (PASI and BSA), comorbidity of psoriatic arthritis, and race (CS page 99). The assessment revealed no major differences in these characteristics across the included trials on inspection. The ERG agrees that age distribution was somewhat similar across the NMA trials. Similarly, there were more men than women, and all patients across the NMA trials had moderate or severe psoriasis (mean PASI score 15 to 30) at baseline. The mean duration of psoriasis in patients at baseline was prolonged across the NMA trials (14-23 years), except for the BRIDGE and Ohtsuki trials in which no such data was reported. Where reported, patients with psoriatic arthritis at baseline were a minority of all patients in 24 of the 25 NMA trials that reported it. The PRESTA trial was the outlier having included only patients with psoriatic arthritis. Thirty of the 34 trials that reported race at baseline included a substantial majority of Caucasian participants. The other four trials (Ohtsuki 2016, PEARL, The Japanese Ustekinumab Study, and LOTUS) included Asian participants only. CS page 99 also reports that the company compared prior use of systemic therapy and baseline DLQI score across the 37 trials. However, the CS does not present these results saying (CSp 104) that 'for all other possible effect modifiers not enough data were available to draw strong conclusions' which the ERG assumes is referring to these analyses. The similarity assumption should have also considered differences in analysis methods, given that ITT analyses were reported in 27 out of the 37 NMA trials. The mode of administration of the placebos was varied across the trials. However, the ERG is not certain that oral and intravenous placebos are similar. Nonetheless, the CS provides no evidence that the company performed network meta-regression analysis on risk of bias or any of the baseline characteristics of the studies. For instance, the company assessed all studies of secukinumab to be double-blind but not ITT; whereas studies of other comparators were assessed to have a combination and high and low risks of bias within both of these risk of bias domains. These differences between comparators may potentially explain any heterogeneity observed across the NMA studies. Additionally, in CS section 4.10.2 (page 82), the company refers to the usual recommended doses for etanercept and ustekinumab as low doses, but does not justify the rationale for including studies of higher doses of these drugs in the NMA / as separate nodes in the NMA. Despite these reservations, a considerable majority of the trials were

similar for each characteristic; hence, the ERG agree that the NMA has satisfied the similarity assumption.

An overall inconsistency model was fitted to test the consistency assumption. Although patient characteristics were not compared between direct and indirect evidence trials, inconsistency was assessed by comparing the Deviance Information Criterion (DIC), which is a Bayesian measure of model fit, with the inconsistency models. In order to satisfy the consistency assumption, the DIC statistic should be lower than that of the inconsistency model. In CS Table 46, the DIC statistic is lower or equal to that of the inconsistency model, satisfying the consistency assumption.

The company submitted one NMA with 37 trials in the network and using the Bayesian approach. Table 15 summarises the quality of reporting in the NMA. Overall, the quality of reporting in the NMA was fair. The ERG queries the absence of systemic non-biological therapies from the NMA inclusion criteria because drugs belonging to this class may serve as appropriate comparators for DMF, which is also an oral systemic treatment (see discussion in Section 3).

Table 15: NMA critique

Homogeneity 1. Is homogeneity considered by the study authors?	No
2. Are the studies homogenous in terms of patient characteristics and study design?	Yes
3. Is the method used to determine the presence of statistical heterogeneity adequate?	Not reported
4. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. sub group analysis, sensitivity analysis, meta-regression)	No
Similarity 1. Is the assumption of similarity stated?	Yes
2. Has the assumption been justified?	Yes
Consistency 1. Does the analysis explicitly assess consistency?	Yes
2. Are patient or trial characteristics compared between direct and indirect evidence trials?	No
3. If inconsistency is reported, is this accounted for by not combining the direct and indirect evidence?	Not applicable

In the statistical model for the NMA, the company categorised the PASI score to obtain PASI 75 response rates. However, the ERG queries the relevance of categorisation, given that most of the NMA trials already report PASI 75 rate as an endpoint.

One study of adalimumab appeared to have been excluded from the NMA because the outcomes were stated to be reported for the treatment arm only (CS Table 27). The ERG has checked the publication of this study (Menter et al 2008[18] and the PASI 75 and 90 were reported for the placebo arm and therefore this is an error in the CS. As discussed in 4.1.2, this study meets the inclusion criteria for the NMA and should therefore have been included in the NMA. An error was made in the CS, whereby the Menter et al. (2008) study was excluded from the feasibility assessment (37 studies), but included in the NMA (38 studies). Therefore the NMA results include data for PASI75 and PASI90 at 16 weeks from the Menter et al. (2008) study. In addition, the ERG queries the exclusion of studies reporting outcomes at time points other than 16 weeks or induction time, CS p86, 105. The CS defines induction time as *"…the time point at which the primary endpoint was measured in the pivotal studies of the medicine…"* (CS Table 27). For secukinumab, etanercept, ustekinumab and ixekizumab this was 12 weeks; for adalimumab and apremilast this was at 16 weeks. The CS does not justify this definition and the ERG considers that all intervention studies evaluating PASI response as the primary outcome, irrespective of the assessment period, are potentially relevant to the NMA. Cai et al. (2016), Gordon et al. (2006), and Zhang et al. (2015) examined the efficacy of adalimumab compared to placebo on PASI response at 12 weeks[15, 16, 93]. Maari et al. (2014) examined the efficacy of adalimumab compared to placebo on PASI response at day 56.[94] These studies meet the CS decision problem and could have been included in the NMA.

The ERG identified three systematic reviews of relevance to the appraisal. These revealed five additional studies of potential relevance to the NICE scope and the decision problem. The company provided additional clarification (clarification response A18) on reasons for exclusion, and the ERG agree with with these for three of the five additional studies. However, Langner et al.[95] evaluated the efficacy of fumaric acid esters over placebo on PASI 50 and PASI 75 response rates and Mroweitz at al. compared the effects of DMF versus placebo on PASI 50 and 75 at 16 weeks. In clarification response A18, the company stated that these studies were excluded in line with the inclusion/exclusion criteria for the systematic review (conference abstract published before 2013). However, this was based on the company's assumption 'that studies presented before as an abstract were available as a full text publication within this time-frame'. It was clear from the Cochrane review that the Mrowietz study will not be published in full (study authors response to request for data), and there appears to be no full publication available for the Langer study. The ERG therefore

considers that these studies should have been considered for inclusion in the fumarates arm of the NMA to avoid publication bias.

Table 16: Appraisal of methodological reporting of the NMA (based on the CS)

Rationale and searches	
Is the rationale for the NMAs and the study objectives clearly stated?	Yes.
Are searches stated and do they appear appropriate?	Yes.
Are inclusion/exclusion criteria adequately reported?	Yes (CS Table 24). However, the ERG disagrees with the absence of systemic non-biological therapies from the inclusion criteria.
Is the quality of the included studies assessed?	Yes. However, there are some disparities between the CS and the ERG's assessment (Section 4.1.5)
Model methods	
Is the statistical model described?	Yes.
Is there a justification for the choice of outcome measure provided?	Yes. However, it is not clear how or why the company categorised continuous PASI scores to obtain PASI 75 response rates. Nonetheless, the ERG requested clarification. See narrative below.
Has a structure of the networks been provided?	Yes.
Has the choice of fixed or random effects model been justified?	Yes.
Is any of the programming code used in the statistical programme provided?	Yes
Is a sensitivity analysis presented, is this appropriate?	Yes. Sensitivity analysis was presented based on excluding poor quality studies. The ERG consider this approach to sensitivity analysis reasonable, but differ from the company in the quality assessment, as well as the studies to be excluded as part of the sensitivity analysis. (See discussion in Section 4.1.5).
Results	
Are the results of the NMA presented?	Yes
Does the study describe an assessment of the model fit?	Yes
Is the evidence combined and the results presented?	Yes
Has there been any discussion around the model uncertainty?	Yes
Are the point estimates of the relative treatment effects accompanied by some measure of variance?	Yes
Discussion	
Is heterogeneity discussed?	No
Does the discussion flow from the results seen?	No. The ERG disagrees with the interpretations of the results. See discussion below
Are the results compared (where relevant) to those just using direct comparative evidence?	No
Have the authors commented on how their results compare with other published studies?	No
Are the author's interpretations of the results in line with those seen?	No. See discussion below

4.3.1 Results

The company performed the NMA using the Bayesian approach, which allowed rank probabilities to be calculated at 16 weeks (CS Table 34) and induction time (CS Table 38). There were more comparators in the latter analysis because it also entailed analyses of comparators evaluated at 12-16 weeks. The median probabilities were reported with 95% credible intervals. The company also performed a scenario analysis, which entailed excluding poor quality studies from the NMA, and a subgroup analysis based on the use of previous systemic therapy and/or phototherapy. NMA modelling was tested using criteria such as the DIC statistic, convergence and autocorrelation graphs. The random effects model had the best fit for all analyses and therefore all results presented were for the random effects models.

Tables 17 and 18 summarise the results of the basecase NMA at 16 weeks and induction time respectively. Of note, the cost-effectiveness model uses the PASI responses from the basecase NMA at induction time (CS table 57). Of all the active interventions, DMF is the least effective treatment in the results shown. In the company's interpretations of these results, DMF demonstrated superior efficacy to placebo and inferior efficacy to the other comparators. In addition, the CS does not provide any analyses based on pre-specified superiority thresholds or non-inferiority margins to inform their decision. On request (clarification question A20), the company provided a ranked list comparing the effectiveness of the different interventions examined in the base case NMA. Tables 19 and 20 present the median rank of each intervention for PASI response at 16 weeks and induction time respectively. These results confirm that DMF is ranked the least effective intervention for improving PASI response at 16 weeks and induction time, compared to other active interventions in the NMA.

CS tables 36 and 40 present the results of the scenario analysis (excluding one poor quality study) at 16 weeks and induction time. Mean (SD) and median (95% credible intervals) absolute probabilities were reported. The scenario analyses offered no alternate interpretation to the base case NMA results and rankings at 16 weeks and induction time and have not been reproduced here. The ERG consider that other studies could have been excluded from the NMA in the scenario analysis of quality (Section 4.1.5) and it is unclear what impact this would have had on the results.

CS tables 42 and 44 present the results of the subgroup analysis according to prior use of systemic therapy and/or phototherapy. The ERG considered this subgroup not relevant

because phototherapy was neither a comparator nor a subgroup of interest within the scope or decision problem. However, the results also offered no alternate interpretations to the base case NMA and rankings in patients with previous exposure to systemic therapy and/or phototherapy at 16 weeks and induction time.

Table 17: Absolute probabilities of achieving PASI response at 16 weeks

Intervention	Probability (Median, 95% CrI)		
	PASI 50	PASI 75	PASI 90
Placebo	0.22 (0.19, 0.24)	0.08 (0.07, 0.10)	0.02 (0.01, 0.02)
Adalimumab	0.88 (0.83, 0.92)	0.72 (0.64, 0.78)	0.45 (0.37, 0.54)
Etanercept low-dose	0.67 (0.54, 0.77)	0.43 (0.31, 0.56)	0.19 (0.12, 0.29)
Apremilast	0.58 (0.50, 0.64)	0.34 (0.28, 0.41)	0.14 (0.10, 0.18)
Fumaderm	0.54 (0.39, 0.69)	0.31 (0.19, 0.45)	0.12 (0.06, 0.21)
DMF (LAS41008)	0.47 (0.33, 0.62)	0.25 (0.15, 0.39)	0.09 (0.04, 0.16)

CrI, Credible Intervals; DMF, Dimethyl Fumarate; PASI, Psoriasis Areas Severity Index; PASI 50, 50% or greater resolution of psoriasis symptoms; PASI 75, 75% or greater resolution of psoriasis symptoms; 90% or greater resolution of psoriasis symptoms

Table 18: Absolute probabilities of achieving PASI response at induction time

Intervention	Probability (Median, 95% CrI)		
	PASI 50	PASI 75	PASI 90
Placebo	0.16 (0.14, 0.17)	0.05 (0.05, 0.06)	0.01 (0.01, 0.01)
Ixekizumab	0.98 (0.97, 0.98)	0.91 (0.89, 0.93)	0.74 (0.71, 0.78)
Secukinumab	0.94 (0.93, 0.96)	0.83 (0.80, 0.86)	0.61 (0.56, 0.65)
Ustekinumab high-dose	0.91 (0.89, 0.93)	0.77 (0.74, 0.80)	0.52 (0.47, 0.56)
Ustekinumab low-dose	0.89 (0.87, 0.91)	0.73 (0.69, 0.76)	0.46 (0.42, 0.50)
Ustekinumab mixed	0.85 (0.82, 0.88)	0.67 (0.62, 0.71)	0.39 (0.34, 0.45)
Adalimumab	0.83 (0.79, 0.87)	0.64 (0.58, 0.70)	0.36 (0.31, 0.43)
Etanercept high-dose	0.76 (0.74, 0.78)	0.54 (0.51, 0.57)	0.28 (0.25, 0.30)
Etanercept low-dose	0.62 (0.57, 0.66)	0.38 (0.34, 0.42)	0.16 (0.13, 0.18)
Apremilast	0.50 (0.45, 0.56)	0.27 (0.23, 0.32)	0.10 (0.08, 0.12)
Fumaderm	0.45 (0.36, 0.55)	0.23 (0.16, 0.31)	0.08 (0.05, 0.12)
DMF (LAS41008)	0.38 (0.29, 0.48)	0.18 (0.12, 0.25)	0.05 (0.03, 0.09)

CrI, Credible Intervals; DMF, Dimethyl Fumarate; PASI, Psoriasis Areas Severity Index; PASI 50, 50% or greater resolution of psoriasis symptoms; PASI 75, 75% or greater resolution of psoriasis symptoms; 90% or greater resolution of psoriasis symptoms. Induction time is the time point at which the primary endpoint was measured in the pivotal studies of the medicine

Table 19: Ranking outcomes for PASI response at 16 weeks - base case

Intervention	Median rank (95% CrI)	SUCRA
Adalimumab	1 (1, 1)	100.0%
Etanercept low-dose	2 (2, 4)	76.1%
Apremilast	3 (2, 5)	53.6%
Fumarates	4 (2, 5)	45.5%
LAS41008	5 (3, 5)	24.7%
Placebo	6 (6, 6)	0.1%

CrI: Credible interval; SUCRA: Surface under the cumulative ranking

Table 20: Ranking outcomes for PASI response at induction time - base case

Intervention	Median rank (95% CrI)	SUCRA
Ixekizumab	1 (1, 1)	100.0%
Secukinumab	2 (2, 3)	90.7%
Ustekinumab high-dose	3 (2, 4)	81.5%
Ustekinumab low-dose	4 (3, 5)	72.4%
Ustekinumab mixed	5 (4, 6)	62.3%
Adalimumab	6 (5, 7)	56.6%
Etanercept high-dose	7 (6, 7)	45.8%
Etanercept low-dose	8 (8, 8)	36.2%
Apremilast	9 (9, 11)	24.0%
Fumaderm	10 (9, 11)	19.8%
DMF (LAS41008)	11 (9, 11)	11.0%
Placebo	12 (12, 12)	0.0%

CrI: Credible interval; SUCRA: Surface under the cumulative ranking

Cross-validation of NMA results.

In assessing the base case NMA for its external validity, the ERG found the results to be broadly consistent with previous NICE technological appraisals. For instance, the technology appraisal guidance [TA419] revealed that apremilast was more effective than placebo, but not as effective as biologic therapies in improving PASI 75 response rates at 16 weeks. Similarly, the technology appraisal guidance [TA350] found secukinumab to be more effective than etanercept and adalimumab, but of similar efficacy to ustekinumab in improving PASI 75 response rates. These results are somewhat similar to the present NMA which ranks the efficacy of secukinumab slightly higher but comparable to ustekinumab, but considerably higher than adalimumab, etanercept, and apremilast. The ERG could not ascertain the

external validity of the base case NMA in relation to DMF, given the lack of previous NMAs evaluating the relative efficacy of DMF over systemic biologic therapies.

4.4 Additional work on clinical effectiveness undertaken by the ERG

The ERG identified a non-RCT of DMF and summarises this below. The CS uses data from a retrospective study (FUTURE) study in the economic evaluation but few details of the study are presented in the CS. The ERG has summarised details of the FUTURE study below. Details of the reported adverse events in the FUTURE study were also provided by the company in clarification response A17.

Lijnen et al 2016[14]

The ERG identified a Dutch before-and-after study of DMF in people with moderate-to-severe psoriasis with an insufficient response to topical therapies, phototherapy and/or systemic agents. The aim of the study was to assess the long-term safety and effectiveness of high dose DMF because doses up to 1680mg daily were sometimes used in their centre. 176 people with a mean age of 47 years, 28% of whom had received prior systemic treatment for psoriasis, were included. The median DMF treatment duration was 28 months and the median maintenance dose was 480mg (IQR 270-960 mg), reached at 8 months. 24% of people discontinued DMF before reaching a maintenance phase, most commonly due to adverse events.

The study endpoint was the PGA where there was a mean improvement (assessed for 122 patients reaching the maintenance phase), of 1.7 points. 60 (49%) participants reached a PGA score of 'clear' or 'minimal' at maintenance, from 3 at the start of treatment.

One or more adverse events were experienced in 86% of people, most commonly skin flushing and gastrointestinal complaints but these were stated as not being correlated to treatment dose, i.e. were dose independent. There were 6 cases of cardiovascular events (myocardial infarction 2; angina 1; percutaneous coronary intervention 1; atrial fibrillation 1; heart valve replacement 1) and five new cases of malignancies. The study does not report whether any of these events were thought to be treatment-related.

FUTURE study[96]

The CS makes the case that the monoethylfumarate (MEF) component of Fumaderm does not contribute to efficacy or safety and that it is appropriate to assume that the long-term safety and efficacy evidence available for Fumaderm can be applied to DMF (CS p. 136). The company refers to the FUTURE study,[96] a multicentre retrospective study of 984 patients from 163 centres in Germany. Included patients were either those who were treated continually with FAE for 24 months (71%) or treated over at least 36 months with interruptions of not more than 6 months. Mean age was 50.5 years and 58.2% were male. Diagnoses included chronic stable (plaque-type) psoriasis (87.3%), scalp psoriasis (38.3%) and nail psoriasis (22.6%). Severity according to PGA was moderate, moderate-to-severe or severe in 93% of cases (PASI at baseline was only available for a small subgroup of patients, n=107). FAEs were the first systemic therapy in 80.6% of patients. For all patients, the mean therapy duration without interruption was 44.1 months (max. 216 months) and 46.6 months (max. 264 months) with interruptions. The study reports dosage according to number of tablets (containing 30mg and 120 mg DMF for Fumaderm Initial and Fumaderm). Patients with significant improvement or full clearance according to the last documentation had a mean dose of 3 and 2.8 tablets, respectively, in the maintenance phase. This is equivalent to 360 mg and 336 mg DMF, respectively (360mg maintenance dose used in the CS economic model, CSp166).

According to the PGA measure, 67% of patients were markedly improved or clear after six months of therapy and this increased to 80% at end of follow-up (24 months or > 36 months).

A therapy change occurred in 171 (17.4%) of patients during treatment and reasons for this were documented in 103 (10.5%). This was due to an inadequate response in 58 patients (5.9% of total) and to side effects in 18 patients (1.8 % of total), and the reason was unknown in 7% of total. During long-term therapy, 41% of patients had lymphopenia (after 24 months) and 12% had leukopenia (after 24 months). An elevation of liver enzymes occurred in 13% (after 3 months) and an elevation of the creatinine level in 6 % (after 24 months). For deviations in blood count measures, no therapeutic changes (e. g. dose adjustment or discontinuation of therapy) were required in 94.2% of patients; for alterations or hepatic or renal parameters no changes were required in 96.1% of patients. Other adverse events were not reported.

4.5 Conclusions of the clinical effectiveness section

DMF is clinically effective in people with moderate to severe plaque psoriasis when compared with placebo, and non-inferior to Fumaderm in the BRIDGE trial. Adverse event rates were similar between the two active treatments in this study, and higher than the placebo rate. Study outcomes were reported at 16 weeks. The population in the trial are considered by the ERG to be generalisable to the UK NHS population.

In a network meta-analysis results showed that DMF was the least effective treatment when compared to adalimumab, etanercept, secukinumab, ixekizumab, and apremilast. The network includes on other non-biological treatment, Fumaderm, but does not include other systemic non-biological therapies in line with the CS decision problem.

The relative efficacy of DMF over other systemic non-biological treatments is unclear as these were not included in the company decision problem. This is because the company anticipate that the position of DMF in clinical practice will be after systemic non-biological treatments have failed or are contraindicated.

The ERG believe the positioning of DMF will be after topical therapies have been used rather than after non-biologics as in the CS decision problem, and this is in line with the majority of the evidence in the BRIDGE trial.

To meet the decision problem evidence from a small, post-hoc subgroup analysis of the BRIDGE trial is required. [redacted]

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 Objective of the cost effectiveness review and search strategy

Two systematic literature reviews were conducted for published cost-effectiveness analysis.

Review 1 was undertaken to identify evidence on the cost-effectiveness of DMF (LAS41008) for the treatment of psoriasis. The databases searched were Medline, Medline In-Process, Embase EconLit, NHS EED, and Web of Science. A search filter was applied to limit the results to cost effectiveness and health economic studies and the searches were limited to English language only. The searches were updated to January 2017. Additional searches of abstracts from four key conferences from 2013 to January 2017 were also conducted.

Sixty unique references were screened, and 58 were excluded. The full text of the remaining two articles were assessed for eligibility but excluded. Therefore, no cost-utility studies for DMF (LAS41008) in the treatment of psoriasis were identified.

Review 2 aimed to identify published cost-effectiveness studies of regimens for the treatment of psoriasis in adults in order to inform the development of the economic model. The basis of the review was a systematic review of cost-effectiveness analyses of treatments for psoriasis reported by Zhang et al.[93]. This included 53 studies published up until the end of 2013. These were screened for eligibility for the updated review. The search strategy was based on that used in Zhang et al. The databases and dates searched (up until January 2017) were the same as those for Review 1 (above).

In addition, the NICE website was searched for previous technology appraisals for psoriasis, and the bibliographies relevant studies were checked. No date restrictions were applied in the searches.

5.1.2 Inclusion/exclusion criteria

The inclusion/exclusion criteria for Review 1 and Review 2 were reported in Table 49 and Table 50 of the CS respectively. They appeared appropriate to the search question.

5.1.3 Studies included

The searches resulted in the identification of nine UK cost-utility models assessing the cost-effectiveness of biologic therapies for moderate-to-severe psoriasis. These were reported in 16 publications (see Table 21 below).

The company literature review of the cost effectiveness of treatments for plaque psoriasis is extensive, appears reasonable and identifies a number of papers within the literature as well as the previous NICE assessments in the area. Most of the 9 identified UK cost effectiveness studies relate to NICE assessments, with only Sawyer et al[97] not being so but this being authored by the members of the CG153 review.

Lists of excluded studies, with reasons, for Review 1 and Review 2 are listed in Appendix 10 and 13 respectively of the CS. The reasons appear justified. Independent searches by the ERG did not identify any additional studies that we think should have been included.

Table 21: Studies in the cost effectiveness review of biologic therapies for moderate-to-severe psoriasis.

National Institute for Health and Care Excellence. Apremilast for treating moderate to severe plaque psoriasis: Technology appraisal guidance [TA419]. 2016. URL: https://www.nice.org.uk/guidance/ta419
National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance [TA350]. 2015. URL: https://www.nice.org.uk/guidance/ta350
National Institute for Health and Care Excellence. Ustekinumab for the treatment of adults with moderate to severe psoriasis: Technology appraisal guidance [TA180]. 2017. URL: https://www.nice.org.uk/guidance/ta180
National Institute for Health and Care Excellence. Adalimumab for the treatment of adults with psoriasis: Technology appraisal guidance [TA146]. 2008. URL: https://www.nice.org.uk/guidance/ta146
National Institute for Health and Care Excellence. Infliximab for the treatment of adults with psoriasis: Technology appraisal guidance [TA134]. 2008. URL: https://www.nice.org.uk/guidance/ta134
National Institute for Health and Care Excellence. Etanercept and efalizumab for the treatment of adults with psoriasis: Technology appraisal guidance [TA103]. 2006. URL: https://www.nice.org.uk/guidance/ta103
Loveman E, Turner D, Hartwell D, Cooper K, Clegg A. Infliximab for the treatment of adults with psoriasis. Health Technol Assess 2009;13 Suppl 1:55-60. http://dx.doi.org/10.3310/hta13suppl1/09
Mughal F, Barker J, Cawston H, Damera V, Bewley A, Morris J, et al. Cost-effectiveness of apremilast in moderate to severe psoriasis in the UK. Journal of the American Academy of Dermatology 2016;1):AB243 (abstract 3092).
Mughal F, Barker J, Cawston H, Damera V, Bewley A, Morris J, et al. Cost-effectiveness of apremilast in moderate-tosevere chronic plaque psoriasis: A model analysis in the U.K. British Journal of Dermatology 2016;175:74 (abstract P108).
Hinde S, Wade R, Palmer S, Woolacott N, Spackman E. Apremilast for the Treatment of Moderate to Severe Plaque Psoriasis: A Critique of the Evidence. Pharmacoeconomics 2016;34:587-96. http://dx.doi.org/10.1007/s40273-016-0382-3
National Institute for Health and Care Excellence. Apremilast for treating moderate to severe plaque psoriasis: Technology appraisal guidance [TA368]. 2015. URL: https://www.nice.org.uk/guidance/ta368
Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Vergel YB, et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health Technol Assess 2006;10:1-233, i-iv.
Sizto S, Bansback N, Feldman SR, Willian MK, Anis AH. Economic evaluation of systemic therapies for moderate to severe psoriasis. Br J Dermatol 2009;160:1264-72. http://dx.doi.org/10.1111/j.1365-2133.2008.08962.x
Sawyer LM, Wonderling D, Jackson K, Murphy R, Samarasekera EJ, Smith CH. Biological therapies for the treatment of severe psoriasis in patients with previous exposure to biological therapy: a cost-effectiveness analysis. Pharmacoeconomics 2015;33:163-77.
Mughal F, Cawston H, Kinahan D, Morris J, Tencer T, Zhang F. Cost-Effectiveness of Apremilast In Moderate to Severe Psoriasis In Scotland. Value in Health 2015;18:A420.
Lloyd A, Reeves P, Conway P, Reynolds A, Baxter G. Economic evaluation of etanercept in the management of chronic plaque psoriasis. Br J Dermatol 2009;160:380-6. http://dx.doi.org/10.1111/j.1365-2133.2008.08863.x

In the opinion of the ERG the most important cost effectiveness studies identified by the company are the previous NICE assessments in the area and the publications associated with them.

5.1.4 Review conclusions

The company literature review of the cost effectiveness of treatments for plaque psoriasis is extensive, appears reasonable and identifies a number of papers within the literature as well as the previous NICE assessments in the area. Most of the 9 identified UK cost effectiveness studies relate to NICE assessments, with only Sawyer et al[97] not being so but this being authored by the members of the CG153 review. In the opinion of the ERG the company literature review does not draw out some of the relevant details of the submissions of the previous NICE assessments or the FADs, and how these have tended to evolve over time. As a consequence, the ERG presents its own summary of the NICE assessments in this section This is likely to be sufficient for most readers who may then wish to move on to section 5.2. A more detailed ERG summary of the individual assessments is then presented.

The company identifies the original York model, from TA103[98], as the most commonly used model structure. Patients trial an active treatment for a given induction period. At the end of the trial period non-reponders discontinue active treatment and receive best supportive care (BSC). Responders continue with maintenance therapy, but have an annual discontinuation rate applied. Those that discontinue from maintenance therapy receive BSC.

The company notes that the model for the STA of secukinumab [TA350][99] slightly adapted the York model. An additional stage in year immediately after the trial period applies a discontinuation rate among those who respond, with those discontinuing here receiving BSC much as those discontinuing after the trial period due to non-response. Figure 28 of the company submission suggests that after the first year those on maintenance treatment after the post-trial year are assumed to remain on maintenance treatment indefinitely.

The company also summarises the models for the apremilast STA [TA368][100] and rapid review [TA419][101] as essentially using the York model but with those discontinuing moving onto another active treatment until the last-in-line treatment, and then BSC. The company notes that the apremilast model structure permits one more active treatment in the apremilast containing sequence than in the comparator sequence.

Summary of previous NICE assessments: Approvals

Previous NICE appraisals have limited drug use to those who have not responded to standard systemic therapies, or are contraindicated to or cannot tolerate standard systemic non-biological therapies.

Table 22: Previous NICE TAs' approvals

	Treatment	Group	PASI	DLQI	Trial	Continuation rule
TA103	Etanercept	Severe	≥ 10	> 10	12 wk	PASI75, or PASI50 and DLQI 5pt fall
TA146	Adalimumab				16 wk	
TA180	Ustekinumab				16 wk	
TA350	Secukinumab*				12 wk	
TA419	Apremilast*				16 wk	
TA442	Ixekizumab*				12 wk	
TA134	Infliximab	V.Severe	≥ 20	> 18	10 wk	
* And the company provides the treatment with the agreed patient access scheme (PAS)						

Summary of previous NICE assessments: Clinical effectiveness

The clinical effectiveness estimates of the previous NICE assessments are compared with those of the current company submission's base case below.

Table 23: Previous NICE TAs' clinical effectiveness: PASI50

	TA103	TA134	TA146	TA180	TA350	TA419	TA442	CG153	Current
BSC	14%	14%	15%	13%	12%	17%	14%	4%	16%
Ciclo. 3mg	81%		58%						
Ciclo. 5mg	81%		76%						
Methotrexate	82%		61%						
Fumaderm	53%								45%b
Dim. fumarate									38%
Apremilast						AIC			50%
Etan. 25mg	62%	63%	63%	65%	61%	68%	64%	79%a	62%
Etan. 50mg	73%	75%	75%	76%					76%
Efalizumab	55%	56%	54%	51%					
Adalimumab			86%	81%	77%	83%	78%		83%
Ustekin. 45mg				88%	87%	91%	87%		89%
Ustekin. 90mg				90%	90%	94%	90%		91%
Secukinumab					93%				94%
Ixekizumab							AIC		98%
Infliximab		94%	94%		92%	95%	93%		94%
a Estimate pooled across biologics b Company NMA result. Economic model equalises this with the estimate for dimethyl fumarate									

Table 24: Previous NICE TAs' clinical effectiveness: PASI75

	TA103	TA134	TA146	TA180	TA350	TA419	TA442	CG153	Current
BSC	3%	4%	5%	4%	4%	6%	5%	1%	5%
Ciclo. 3mg	55%		34%						
Ciclo. 5mg	55%		55%						
Methotrexate	59%		37%						
Fumaderm	27%								23%[b]
Dim. fumarate									18%
Apremilast						AIC			27%
Etan. 25mg	34%	36%	38%	39%	37%	43%	41%		38%
Etan. 50mg	46%	50%	52%	52%					54%
Efalizumab	27%	29%	29%	26%					
Adalimumab			67%	58%	55%	62%	58%		64%
Ustekin. 45mg				69%	70%	77%	71%	57%[a]	73%
Ustekin. 90mg				74%	75%	81%	75%		77%
Secukinumab					80%				83%
Ixekizumab							AIC		91%
Infliximab		81%	81%		80%	85%	81%		82%

[a] Estimate pooled across biologics
[b] Company NMA result. Economic model equalises this with the estimate for dimethyl fumarate

Table 25: Previous NICE TAs' clinical effectiveness: PASI90

	TA103	TA134	TA146	TA180	TA350	TA419	TA442	CG153	Current
BSC	0%	1%	1%	1%	1%	1%	1%	<1%	1%
Ciclo. 3mg	26%		12%						
Ciclo. 5mg	26%		27%						
Methotrexate	31%		14%						
Fumaderm	9%								8%[b]
Dim. fumarate									6%
Apremilast						AIC			10%
Etan. 25mg	12%	13%	14%	15%	15%	19%	19%		16%
Etan. 50mg	19%	22%	24%	24%					28%
Efalizumab	8%	9%	10%	8%					
Adalimumab			37%	30%	28%	35%	32%		37%
Ustekin. 45mg				40%	42%	51%	46%	32%[a]	46%
Ustekin. 90mg				46%	48%	57%	51%		52%
Secukinumab					55%				61%
Ixekizumab							AIC		74%
Infliximab		54%	55%		54%	64%	59%		59%

[a] Estimate pooled across biologics
[b] Company NMA result. Economic model equalises this with the estimate for dimethyl fumarate

Concentrating on the PASI75 response estimates the estimates of the current CS NMA appear to be broadly in line with those of previous assessments. The response rates for etanercept compared to the other biologics are also in line with expert opinion provided during the apremilast STA [TA419].

With the exception of initial MTA of etanercept and efalizumab [TA103][98] and the infliximab assessment [TA146][102], the assessments have typically only considered the biologics as comparators. This may be reasonable for comparisons between biologics but may be less reasonable for non-biologics such as DMF.

The company NMA suggests that Fumaderm is marginally more effective than DMF, and previous NICE TAs could not have included DMF. The effectiveness estimates for Fumaderm in TA103 are marginally better than those of the current NMA.

The previous assessments appear to have used the following quality of life estimates.

Table 26: Previous TAs' quality of life increments

TA	TA103 TA419	TA103 TA134	TA146			TA180	TA350	TA442	
Source	TA103	TA103	TA146			TA180	TA350	TA442	
Patients	All	Severe	Mod.	Severe	Severe	All	All	Severe	Severe*
PASI<50	0.05	0.12	0.045	0.063	0.055	0.04	0.11	0.012	0.021
PASI50-75	0.17	0.29	0.102	0.178	0.189	0.17	0.19	0.1	0.117
PASI75-90	0.19	0.38			0.167	0.22	0.23	0.131	0.141
PASI90+	0.21	0.41	0.130	0.308	0.307	0.25	0.26	0.144	0.148
PASI100								0.153	0.198
* EQ-5D-5L supplemented by additional psoriasis specific questions									

Note that the PMB for the apremilast assessment [TA419] suggests that the company estimated quality of life values from trial data for the DLQI<10 at baseline and the DLQI≥10 at baseline but only provdes the TA103 estimates.

There is some suggestion in the FADs of previous assessments that patients should either be assumed to have the same quality of life during their trial periods regardless of the treatment they are trialling, or to be assumed to instantly respond to the treatment and so immediately

get the treatment specific quality of life benefits as the nearest proxy available for the rapid response that some treatments cause.

Assessments using the York model have typically used the 10 year time horizon of TA103 and a 20% annual discontinuation rate among non-responders. When modelling one treatment against another a 10 year time horizon is likely to be sufficient since relatively few will remain on treatment at 10 years. But as models have moved to modelling sequences of treatments this is less likely to be the case. There has been some move to longer horizons as longer treatment sequences have been modelled.

Assessments have typically moved from assuming that non-responders are hospitalised each year for 21 days as drawn from TA103 to adopting the estimates of Fonia et al.[2] Furthermore, the Committees have increasingly seen Fonia et al as possibly being overestimates due to the setting being a tertiary hospital. But it should also be noted that the treatments under consideration have only been approved for severe patients for whom the estimates of Fonia et al may be more reasonable.

Generally, the cost effectiveness of the biologics has been estimated to be relatively poor unless there are large quality of life gains, typically in severe cases, and quite large cost offsets due to hospitalisations among non-responders. The cost effectiveness of many of the biologics rests upon comparison with other biologics rather than with BSC. Intermittent etanercept has been increasingly viewed as less attractive than continuous or near continuous etanercept among more severe cases of psoriasis.

The ERG summary of the individual assessments is provided below, with much being similar in content to the company submission section 5.1 and appendices 15-20.

TA103: Etanercept and efalizumab MTA

The FAD for TA103 recommends etanercept at a dose of up to 25mg twice weekly among those who have failed to respond to, cannot tolerate or are contraindicated to standard non-biologic systemic therapies provided that disease is severe, as defined by a PASI score of at least 10 and a DLQI score of more than 10. Treatment with etanercept should be discontinued at 12 weeks if patients do not have a PASI75 response, or a PASI50 response coupled with a 5 point DLQI reduction.

The FAD summarises the AG report as noting that in one trial patients continued taking etanercept for 24 weeks after the 12 week placebo controlled period and there was no lessening of response at 36 weeks. SAEs were low at around 1% in both arms and discontinuations due to adverse events were also low at around 2% in both arms.

Table 4.5.3 of the AG report presents the results of the AG evidence synthesis, the central estimates of which are reported below.

Table 27: TA103 clinical effectiveness estimates

	PASI50	PASI75	PASI90
BSC	14%	3%	0%
Etanercept 50mg	73%	46%	19%
Etanercept 25mg	62%	34%	12%
Efalizumab	55%	27%	8%
Ciclosporin	81%	55%	26%
Fumaderm	53%	27%	9%
Infliximab	93%	79%	52%
Methotrexate	82%	59%	31%

As far as the ERG can ascertain, these clinical effectiveness estimates are used for the all patient modelling and the modelling of the more severe 4th quartile DLQI patients. The modelling of the 4th quartile DLQI patients appears to only vary the inpatient days among non-responders and the quality of life values as reviewed below.

Table 6.2.12 of the AG report presents the mean gain in quality of life for a given PASI response, and the mean gain in quality of life fort a given response among the 4th quartile DLQI patients. Those of the latter are roughly double those of the former.

Table 28: TA103 quality of life increments: mean (s.e.)

Response	All patients	4th quartile DLQI
PASI<50	0.05 (0.01)	0.12 (0.03)
PASI50-75	0.17 (0.04)	0.29 (0.06)
PASI75-90	0.19 (0.04)	0.38 (0.08)
PASI90+	0.21 (0.05)	0.41 (0.09)

Both continuous use and intermittent use etanercept were modelled. For intermittent use 12 week treatment cycles were separated by 29 days, with 3.2 treatment cycles per year. Intermittent use etanercept appears to assume the same clinical effectiveness as continuous use etanercept.

The direct drug costs were taken from standard sources with the exception of Fumaderm, with costs of £2.39 per 30mg tablet and £2.03 per 120mg tablet being provided by the Greater Manchester Dermatology Service.

Resources use for laboratory tests and outpatient visits were differentiated by treatment. The main distinctions were the very much higher annual number of full blood counts, liver function tests and urea and electrolytes for Fumaderm with these being required up to 15 times annually when compared with 2 to 4 times for etanercept and 4 for infliximab. Annual outpatient visits were also differentiated by treatment with 4 for etanercept compared to 5 to 6 for Fumaderm and infliximab. This resulted in annual ongoing administration, monitoring and outpatient costs as below, with the infliximab administration costs substituting for some outpatient visits.

Table 29: TA103 administration, monitoring and outpatient costs (2004-05 costs)

	Admin.	Monit.	OP
BSC	..	£0	£113
Etanercept 50mg intermittent	..	£8	£226
Etanercept 25mg intermittent	..	£8	£226
Etanercept 25mg continuous	..	£8	£226
Efalizumab	..	£16	£226
Ciclosporin	..	£7	£368
Fumaderm	..	£50	£311
Infliximab	£508	£8	£57
Methotrexate	..	£154	£255

Fumaderm was associated with slightly higher monitoring and OP costs than etanercept: £361 compared to £235 or an increase of £126 in 2004/05 costs and £161 in 2016 costs when inflated by 28% using the HSCS index. Both are somewhat higher than the £113 for BSC.

For the scenario analysis of an annual 21 inpatient days for non-responders a cost per inpatient day of £248 in 2003/04 prices was applied, based upon the weighted average of

elective inpatient HRG data for major dermatological conditions codes J39 and J40. This presumably results in an annual inpatient cost per non-responder of £5,208, or £200 per fortnight. Uprating this for inflation using the HSCS by 32% to 2016 prices suggests an annual cost of £6,881, or £265 per fortnight.

The AG report cites HES data as providing a mean length of stay in 2002/03 for psoriasis of 19.6 days. Audits at Hope Hospital, Salford and St. John's Institute of Dermatology, London provided estimates of mean lengths of stay of 22.3 days and 22.7 days respectively. As far as the ERG can determine, these are the source of the 21 days estimate. The AG report states that "*No data were available to inform an estimate of the rate of hospitalisation, so estimates were based upon a range of scenarios, based upon expert opinion*". It appears that the scenario analysis assumes that all non-responders are admitted once per year.

Table 30: TA103 AG report cost effectiveness estimates for etanercept vs BSC

	25mg continuous	25mg intermittent	50mg
Base case: All patients QoL and no IP for non-responders			
Δ QALYs vs BSC	0.116	0.116	0.123
Δ Costs vs BSC	£9,665	£7,743	£14,860
ICER vs BSC	£83,258	£66,703	£121k
All patients QoL and 21 days IP for non-responders			
Δ QALYs vs BSC	0.116	0.116	0.123
Δ Costs vs BSC	£5,337	£3415	£10,258
ICER vs BSC	£45,975	£29,420	£83,378
4th quartile DLQI patients and no IP for non-responders			
Δ QALYs vs BSC	0.222	0.222	0.235
Δ Costs vs BSC	£9,665	£7,743	£14,860
ICER vs BSC	£43,479	£34,834	£63,103
4th quartile DLQI patients and annual 21 days IP for non-responders			
Δ QALYs vs BSC	0.222	0.222	0.236
Δ Costs vs BSC	£5,337	£3415	£10,258
ICER vs BSC	£23,905	£15,297	£43,395

The FAD states that results are sensitive to the baseline DLQI and to whether non-responders are hospitalised for 21 days each year, which additively result in a cost effectiveness estimate of £14,460 per QALY for intermittent etanercept. This is reasonably similar to the £15,297 per QALY of the above table.

The AC concluded that etanercept was unlikely to be cost effective except among those with a poor quality of life who would be likely to require hospital admissions for treatment. Expert opinion suggested that these corresponded with those who has failed previous systemic therapies, had a PASI at least 10 and a DLQI more than 10.

TA134 Infliximab

The FAD for TA134 recommends induction infusion and thereafter infusions every 8 weeks with infliximab at a dose of $5mgkg^{-1}$ among those who have failed to respond to, cannot tolerate or are contraindicated to standard systemic therapies provided that disease is very severe, as defined by a PASI score of at least 20 and a DLQI score of more than 18. Treatment with infliximab should be discontinued at 10 weeks is patients do not have a PASI75 response, or a PASI50 response coupled with a 5 point DLQI reduction.

The company submitted a model with a 10 year time horizon based upon the York model with both intermittent and continuous use etanercept 25mg, efalizumab and BSC as comparators.

Quality of life values, for both all patients and the worst affected, were drawn from TA103 with the values for the 4th quartile were used for the company base case. Costs were also drawn from the TA103 report, with on-responders being assumed to have an IP admission of 21 days each year.

For the comparison with BSC the company cost effectiveness estimate was £22,240 per QALY, with this increasing to £41,351 per QALY when the TA103 all patient quality of life values were applied. Results were sensitive to the quality of life values, the costs of inpatient stays and the discontinuation rates.

The Committee considered that "*the clinical benefit of infliximab in the 4th-quartile DLQI group could be assumed to be equivalent to its benefit, measured by improvement in PASI score, in the all-patient group defined on the basis of a PASI of 10 or more and a DLQI greater than 10*".

For the comparison with etanercept among the 4th quartile DLQI group the company cost effectiveness estimates ranged from £33,000 to £44,000 per QALY against intermittent use etanercept and £26,000 to £35,000 per QALY against continuous use etanercept. The Committee was persuaded that for this group continuous use etanercept was the appropriate comparator for those with very severe disease, despite it not being recommended in TA103.

Very severe disease was defined as a PASI of 20 or more combined with a DLQI of more than 18.

TA146 Adalimumab

The FAD for TA146 recommends adalimumab at an initial subcutaneous dose of 80mg, followed by a subcutaneous dose of 40mg after one week and fortnightly in severe patients, as defined the FAD of TA103. The stopping rule is as per TA103, albeit at 16 weeks rather than 12 weeks. The company performed an ITC of adalimumab with etanercept, efalizumab, infliximab, ciclosporin and methotrexate with BSC as the link.

The FAD notes that the company based its model on the York model, but included new quality of life data derived from PASI response rates and changes in the EQ-5D from the CHAMPION study and the M02-528 study. The ERG commented that little information was provided about the new data. The company submission is complicated by sometimes grouping PASI50-75 with PASI75-90 and sometimes not.

Table 31: Quality of life increments: TA146

	DLQI<=10	DLQI>10	
<PASI50	0.045	0.063	0.055
PASI50-75	0.102	0.178	0.189
PASI75-90			0.167
PASI90	0.130	0.308	0.307

As with TA103 it appears that the clinical effectiveness estimates are retained for whichever subgroup is being modelled with only the quality of life increments changing.

Trial periods varied by treatment: 12 weeks for etanercept and efalizumab, 14 weeks for infliximab and 16 weeks for adalimumab. An annual drop-out rate of 20% among responders was taken from the York model. Etanercept given intermittently was assumed to cost 88% of continuous use etanercept, compared to the 74% applied in TA103. The Committee preferred the 74% of TA103.

The FAD suggests that BSC was assumed to be associated with 21 inpatient days compared to none for the biologics, with this assumption being a key driver of results. Partly based upon expert opinion the Committee accepted 21 days as the most appropriate estimate.

The company base case only included patients with a DLQI score of more than 10. Among these patients the company cost effectiveness estimate for adalimumab compared to BSC was £30,500 per QALY, while among those with a DLQI of less than 10 it was £80,100 per QALY.

The cost effectiveness of adalimumab compared to etanercept varied between £36,700 per QALY for intermittent use etanercept and adalimumab dominating etanercept for continuous use etanercept. Due to expert opinion indicating that patients with severe disease were either not treated intermittently or had very small gaps between treatments due to flares the Committee accepted that the time between etanercept treatments could be very short. As a consequence, the true cost effectiveness would be somewhere between the £36,700 per QALY for intermittent use etanercept and adalimumab dominance for continuous use etanercept.

TA180 Ustekinumab

The FAD for TA180[103] recommends ustekinumab at a subcutaneous dose of 45mg[3], followed by another at week 4 and then every 12 weeks in severe patients, as defined the FAD of TA103. The stopping rule is also as per TA103.

Comparisons with adalimumab, intermittent and continuous use etanercept 25mg, etanercept 50mg, efalizumab, infliximab and BSC were made using a mixed treatment comparison.

The company based its model on the York model, with trial periods of 10 weeks for infliximab, 12 weeks for etanercept and 16 weeks of adalimumab and ustekinumab. A 20% discontinuation rate was assumed for non-responders.

Quality of life values were based upon a mapping between the DLQI and the EQ-5D, with PASI response groups mean changes in DLQI then being used to infer their quality of life using a similar procedure to TA103.

3 The FAD also specifies that the higher 90mg dose for those over 100kg be supplied at the same price as the 45mg dose. There is now price equivalence due to a 90mg vial being available at the same price as the 45mg vial.

Non-responders were assumed to require an annual inpatient stay of 21 days, as per TA103. The Committee expressed some concerns about this estimate but noted that it was similar to that used in previous appraisals.

The company estimated ustekinumab had a cost effectiveness of £29,600/QALY when compared to BSC, £27,100/QALY when compared to intermittent use etanercept 25mg, and to dominate adalimumab due to slightly greater patient gains and small cost savings. The Committee was concerned about the cost assumed for intermittent etanercept noting that at a cost of 74% of continuous use etanercept the cost effectiveness estimate of ustekinumab compared to intermittent use etanercept increased to £68,300 per QALY. But as in TA146, the Committee was also aware of the arguments about retreatment intervals and that ustekinumab was estimated by the company to dominate continuous use etanercept.

TA350 Secukinumab

The FAD for TA350[99] recommends secukinumab with a patient access scheme, using a subcutaneous dose of 300mg on weeks 0, 1, 2, 3 and 4, then every 4 weeks in severe patients, as defined by the FAD of TA103.[98] The stopping rule is also as per TA103.

Three meta-analyses were presented by the company. The base case assessed response after the induction periods of 10 weeks for infliximab, 12 weeks for secukinumab, etanercept and ustekinumab and 16 weeks for adalimumab. A second analysis assessed response at 12 weeks for all treatments, while the third followed the base case but assessing secukinumab at 16 weeks. The company was also able to assess results by a baseline DLQI of more than 10, except for adalimumab, and stated that similar results were shown in terms of PASI responses.

The TA103 model was adapted to allow for the year immediately after the trial period. In essence it appears that a first year discontinuation rate among responders of 12% was estimated from trial data with subsequent years applying the 20% of TA103. Those discontinuing treatment were assumed to receive BSC and be in the less than PASI50 response health state. A 10 year time horizon was adopted.

Trial EQ-5D data was pooled across all time points and trials with the company settling upon a model that estimated changes in quality of life as a function of the PASI response relative to

baseline at that timepoint, how much the patients' baseline DLQI differed from the mean DLQI and the product of these terms. The mean baseline quality of life was 0.642.

Data from Health Episode Statistics provided an estimate of a mean length of stay of 10.7 days for psoriasis which was costed at £499 per day. Those on BSC were assumed to require one inpatient stay each year. The ERG noted that the HES data suggested a very much lower total number of psoriasis admissions than would be implied by the company budget impact analysis, which raised questions about the assumption that on average BSC patients are hospitalised once per year.

The company estimated the cost effectiveness for secukinumab compared to etanercept to be £2,515 per QALY, with it dominating all other biologics. The company cost effectiveness estimate for secukinumab compared to BSC was £7,231 per QALY.

The ERG made various changes to the company model and presented two scenarios around inpatient and other resource use: one based upon Fonia et al [2] where the number of inpatient days for non-responders increased by only 5 days, and one applying the company assumptions. The Fonia et al estimates resulted in a cost effectiveness estimate of £52,760 per QALY for secukinumab compared to BSC with secukinumab extendedly dominating the other biologics and dominating infliximab. Using the company resource use estimates reduced the cost effectiveness relative to BSC to £14,902 per QALY, £8,899 per QALY compared to etanercept and £6,979 per QALY compared to adalimumab. The other treatments were either dominated or extendedly dominated.

The Committee expressed some concerns about the 10 year time horizon due to psoriasis being a lifelong condition. The Committee also viewed both the resource use estimates of the company and of Fonia et al as probable overestimates. Fonia et al examined a tertiary centre which would treat the most severe patients. Expert opinion also suggested that hospitalisations for psoriasis had fallen in recent years in part due to the availability of biologics. The Committee concluded that the resource use of Fonia et al was more representative of current practice than the estimates of the company. Expert opinion suggested that the 20% discontinuation rate was probably an overestimate.

The Committee was concerned about the utility values provided by the company, and concluded that the patient gains were probably underestimated.

The Committee considered the cost effectiveness estimates compared to the other biologics to be the most appropriate with these ranging between £17,700 per QALY against ustekinumab 90mg to £42,400 per QALY against etanercept. Given the uncertainty around the quality of life increments applied within the modelling, the relative effectiveness compared to etanercept and the PAS inclusive price of secukinumab the Committee concluded that the cost effectiveness of secukinumab was likely to be in line with those of the other biologics.

TA368 and TA419 Apremilast

The original STA of apremilast [TA368] has been superseded by a rapid review [TA419]

The base case involved a 10 year horizon and 20% discontinuation rate. The ERG suggested a common 20% discontinuation was unlikely to be realistic due to differential effectiveness, mode of administration and AEs.

The Committee viewed the 6.49 inpatient days estimate of the ERG, based on Fonia et al [2], and the 26.6 days per year of the company to both be too high. Clinical experts noted that in current practice the proportion of patients admitted would be somewhat less than the 30% assumed by Fonia et al. The ERG estimated a cost of £225 per 28 day model cycle, this being based upon Fonia et al but excluding outpatient and systemic therapy costs. This was applied during the induction periods when patients were trialling treatments.

The company estimated that apremilast would only involve one outpatient visit per year compared to four for the biologics. Expert opinion suggested that while fewer monitoring visits for apremilast might occur in the longer term, in the short term applying four monitoring visits for apremilast would be reasonable. The Committee concluded that equal monitoring visits were appropriate and that 14 days wastage of apremilast treatment should be applied.

The FAD for the original TA368 considered apremilast at a number of positions.

- Its license permits it to be used after one but not all systemic therapies have failed and before the biologics. The company did not provide any analyses for this position and the clinical experts did not say they would offer the drug at this point. Consequently, the Committee did not consider this position further.

- Despite poorer clinical efficacy, the Committee considered apremilast might still displace biologics given patient preference for oral administration or for other reasons.
    - For apremilast before biologics among patients with severe disease the cost effectiveness estimate was around £30,300 per QALY. But the uncertainty around this estimate, the likelihood of the Fonia et al costs being underestimates and the lower effectiveness of apremilast let the Committee to note recommend apremilast at this point.
    - For apremilast before biologics among patients with moderate disease, BSC was the only comparator due to biologics not being offered to those with moderate disease. The Committee concluded that the cost effectiveness estimate might be around £60,000 per QALY and so did not recommend apremilast at this point.
    - For apremilast displacing a biologic the experts noted that apremilast was unlikely to be used this way. The apremilast sequence was also estimated to be cost saving but inferior with costs per QALY lost ranging from £21,100 to £39,100, although these estimates were not based upon the Committee preferred assumptions. In the light of this the Committee did not recommend apremilast at this point.
- The Committee concluded that the most likely position for apremilast was after biologics had failed or were not tolerated. Since a sequence with apremilast prior to the biologics dominated a sequence with apremilast after the biologics the Committee did not recommend apremilast at this point.

The FAD for the rapid review [TA419] noted that the company included the Committee's preferred assumptions, including a cost per 28 day cycle of £348 for BSC and £225 for non-responders trialling other treatments, no reduction in monitoring visits for apremilast compared to biologics and 14 days wastage of apremilast.

Validation work by the ERG showed that the cost effectiveness estimates for the biologics exceeded £30k per QALY, but it was outside the Committee's remit to explore this any further. Apremilast prior to biologics delayed use of the "cost ineffective" biologics, thus improving the cost effectiveness estimate of apremilast. The Committee agreed it could not make a decision from the cost effectiveness analyses provided.

The company presented a cost effectiveness of apremilast compared to BSC of less than £30k per QALY. The Committee agreed that apremilast is cost effective for those who cannot take biologics or after biologics have failed.

The Committee noted that apremilast was not as effective but was cheaper than the biologics. It would have valued a direct comparison with biologics to estimate the savings per QALY lost. The results were apparently similar to the cost effectiveness estimates of other biologic therapies compared with BSC and so apremilast could be recommended among severe patients where all non-biologic systemic treatments had failed, were not tolerated or were contraindicated.

TA442 Ixekizumab

The FAD for TA442 recommends ixekizumab with a patient access scheme at a subcutaneous dose of 160mg on week 0, 80mg fortnightly until week 12 and 80mg every 4 weeks thereafter. The stopping rule is also as per TA103.

The company base case compared ixekizumab with etanercept, adalimumab, ustekinumab, secukinumab and infliximab using an NMA. The response rates for secukinumab were lower than those of TA350 due to the company including more trials of secukinumab than TA350. The clinical effectiveness estimates for ixekizumab are redacted.

The model structure was essentially that of TA103 but with those discontinuing one therapy moving onto other therapies before BSC. The 20% annual discontinuation rate of TA103 was applied. A lifetime horizon was adopted for the base case. Each treatment sequence involved a first line followed by three subsequent treatments, after which patients moved on to BSC. The committee understood from the clinical experts that some of the biological treatments are known to work less well if they are used after another biological treatment. The company noted that it was infeasible to analyse the data by number of previous treatments.

The company used the trial subgroup with a baseline DLQI of more than 10 to estimate the quality of life values. The Committee viewed analysing this subgroup quality of life data as appropriate.

The Committee also concluded that it would be appropriate to include the utility gains of treatment during each treatment's induction period due to the speed of response with ixekizumab.

The costs of BSC were estimated from Fonia et al.[2] As with TA350 the Committee viewed these as probable overestimates, but the best source available.

The cost effectiveness estimates of all sequences compared to BSC were above £30k per QALY.

The Committee discounted sequences with etanercept or infliximab as 1st line treatments, based on expert advice that these did not represent current treatment. Pairwise comparisons of sequences showed those with 1st line ixekizumab either dominated or had cost effectiveness estimates of less than £30k per QALY.

Sequences with ixekizumab as 2nd line were also considered. The only pairwise comparison where the ixekizumab sequence was not dominant was secukinumab followed by ustekinumab followed by infliximab against adalimumab followed by ixekizumab followed by infliximab. The ixekizumab sequence was less costly and less effective, with a cost effectiveness of more than £50k per QALY lost.

The ERG estimated the cost effectiveness of all active treatments against BSC, without any sequencing. The cost effectiveness estimates were between £46k and £74k per QALY gained for the comparator treatments, compared to £41k per QALY for ixekizumab. The Committee concluded that the cost effectiveness of ixekizumab was similar to the other treatments.

CG153

Sawyer et al [97] was authored by members of the NICE Psoriasis Guideline Development Group and appears to summarise the modelling that underlies the guideline. A common effect for biologics was assumed, and applied to both first use of biologics and second use of biologics for those who failed on their first biologic.

The base case assumed a common 20% annual discontinuation rate for the biologics and a time horizon of 10 years. It also assumed the patient benefits were only experienced while on treatment.

Quality of life estimates were taken from Woolacott et al [104] with the base case using the estimates for the all patient group, and a sensitivity analysis using those of the worst 4th DLQI quartile.

BSC was associated with an annual cost of £11,436, mainly due to all patients requiring 5 day care visits, 82% of patients requiring an IP stay of 21 days and 18% of patients requiring 2.55 IP stays of 21 days. Those responding to biologics had a 76% reduction in their hospitalisation rate, based upon Fonia et al. [2] But the drug costs of the biologics resulted in a total ongoing annual cost of £12,456.

The base case analysis suggests that a second biologic after failure of the first results in a net cost of £5,747 and a gain of 0.325 QALYs, leading to a cost effectiveness estimate of £17,861 per QALY when compared with BSC. But results were sensitive to assumptions around efficacy and hospitalisation rates, with inpatient costs being the majority of costs in both arms. Cost effectiveness estimates ranged between £10k per QALY and £50k per QALY.

The paper concludes by noting that more research on healthcare resource use among patients with severe and very severe psoriasis is required, as is better evidence for long term response to and discontinuation from biologics, for both first treatments with biologics and e particularly for sequential use of biologics.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	The scope specifies: • Other fumaric acid esters • Systemic non-biological therapies: - Apremilast - Acitretin - Ciclosporin - Methotrexate - Phototherapy ±psoralen • Systemic biologic therapies: - Etanercept	The treatments in the CS include: • Other fumaric acid esters • Systemic non-biological therapies: - Apremilast • Systemic biologic therapies: - Etanercept - Adalimumab - Secukinumab - Ustekinumab - Ixekizumab

	- Adalimumab - Secukinumab - Ustekinumab - Ixekizumab • Best supportive care	• Best supportive care The company base case compares a treatment sequence of adalimumab followed by ustekinumab and then best supportive care with the same treatment sequence preceded by dimethyl fumarate. Other pairs of treatment sequences are compared in scenario analyses.
Patient group	As per NICE scope. "*Adults with moderate to severe chronic plaque psoriasis*"	Yes.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost utility.
Time horizon	Sufficient to capture differences in costs and outcomes	10 years. Results are sensitive to this being extended. The 10 year time horizon is insufficient to reflect the differences in costs and outcomes between the sequences of technologies being compared.
Synthesis of evidence on outcomes	Systematic review	Yes. The economics rests upon the clinical effectiveness estimates of the NMA.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	For the base case the all patient estimates of TA103 are applied. These are estimate using EQ-5D data mapped onto PASI changes via the DLQI.
Benefit valuation	Time-trade off or standard gamble	The valuation of the EQ-5D uses the standarrd UK tariff estimated by time trade off.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.

Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		A wide range of sensitivity and scenario analyses are presented.

5.2.2 Model structure

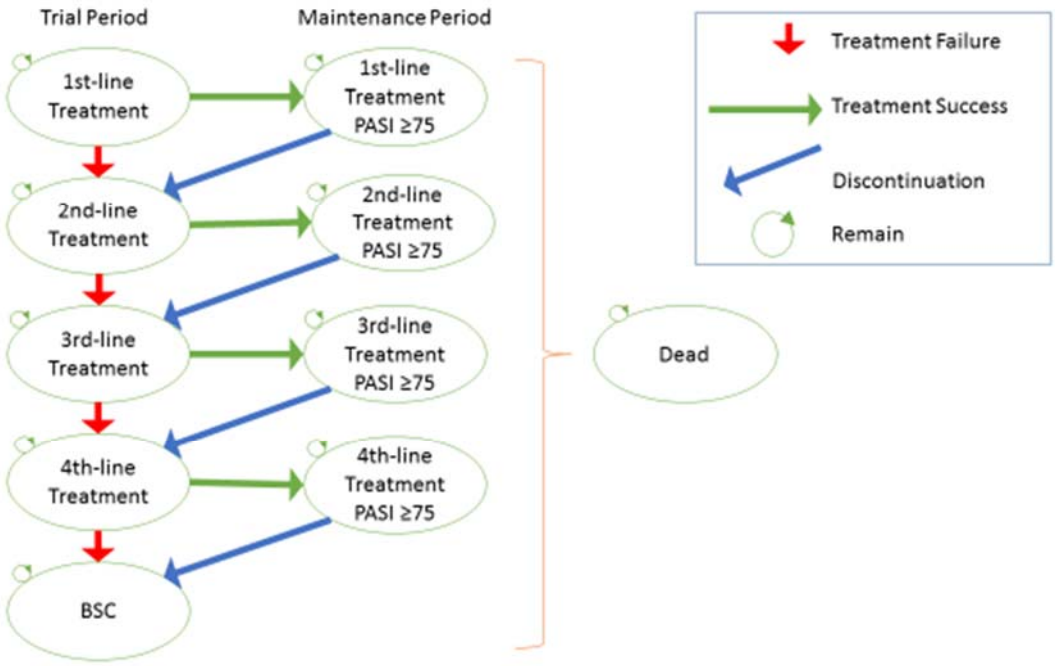
The company submission uses a Markov state transition cohort model, comparing two treatment sequences. Each treatment sequence can have up to 4 active treatments. The model structure is derived from the original York model [TA103] and broadly the same as that of the apremilast STA [TA368] and rapid review [TA419], although it may permit more active treatments.

Patients receive each active treatment for a treatment specific trial duration, typically 16 weeks. At the end of this trial period patients are assessed for response.

- Those achieving a PASI75 response remain on their current active treatment for maintenance therapy. An annual 20% are assumed to lose response and to move onto the next line of treatment.
- Those not achieving a PASI75 response are treatment failures and move onto the next line of treatment.
- Those discontinuing from the last in line active treatment receive best supportive care (BSC).

Age specific annual mortality rates drawn from UK life tables are applied to all health states. Treatment and response status have no effect upon mortality.

Figure 1: ***Model structure***



Note that within the model implementation all patients pass through 4 lines of treatment before the final move to BSC, even if some of the interim treatments are themselves BSC. For instance, for a comparison of DMF with BSC the treatment sequences that are compared are actually:

- DMF -> BSC -> BSC -> BSC -> BSC
- BSC -> BSC -> BSC -> BSC ->

The interim BSC "treatments" model patients as trialling BSC for a single 2 week model cycle. Non-responders move onto the next line of therapy, while the small proportion of BSC PASI75 responders remains in this state for another single 2 week model cycle before all discontinue and move on to the next line of therapy.

A baseline quality of life value is taken from the literature. Quality of life increments for not achieving a PASI50 response, achieving between a PASI50 and a PASI75 response, achieving between a PASI75 and a PASI90 response and achieving a PASI90 response are taken from another source in the literature.

- The baseline quality of life value is applied to those on 1st line treatment during the 1st line treatment trial period.

- Those achieving a PASI75 response and remaining on maintenance therapy have the average of the PASI75 to PASI90 response and the PASI90 response quality of life increments applied, weighted by the treatment specific PASI75 to PASI90 response and PASI90 response rates of their current treatment.
- Those not achieving a PASI75 response by the end of the trial period and progressing onto the next in line treatment have the no PASI50 response and the PASI50 to PASI75 response quality of life increments applied, weighted by the treatment specific no PASI50 response and PASI50 to PASI75 response rates of their *previous* treatment.
- Those achieving a PASI75 response by the end of the trial period but subsequently discontinuing and progressing onto the next in line treatment also have the no PASI50 response and the PASI50 to PASI75 response quality of life increments applied, weighted by the treatment specific no PASI50 response and PASI50 to PASI75 response rates of their *previous* treatment.
- Those discontinuing from the last in line active treatment move onto BSC and have the 4 quality of life increments applied, weighted by the BSC estimated patient distribution between the 4 response states.

Direct drug costs are applied. These are differentiated by whether the treatment is being received during the trial period or during the maintenance period.

In a similar manner, treatment specific medical resource use is applied differentiated by whether the drug is being received during the trial period or during the maintenance period.

Adverse events are not considered. The company justifies this due to them not having been included in pervious NICE technology assessments or in the original York Assessment Group model.

5.2.3 Population

The patient age at baseline is 50 years and an average weight of 77.8kg is drawn from the FUTURE trial of Fumaderm as reported in Reich et al.[96] An equal 50:50 balance between male and female is assumed

These compare with around 2/3rd being male and an average age of 44 years in the BRIDGE trial. The proportion of male patients and baseline age only affect the all-cause mortality within the model.

5.2.4 Interventions and comparators

The company base case compares two treatment sequences.

Table 32: ***Company base case sequences***

	1st line	2nd line	3rd line	4th line
Sequence 1	Dimethyl Fumarate	Adalimumab	Ustekinumab	BSC
Sequence 2	Adalimumab	Ustekinumab	BSC	BSC

The company also includes extensive scenario analyses comparing a range of other treatment sequences, the full list of possible treatments within these sequences being:

- Dimethyl fumarate (DMF)
- Apremilast (Apre)
- Adalimumab (Adal)
- Etanercept (Etan)
- Fumaderm (Fuma)
- Infliximab (Infl)
- Secukinumab (Secu)
- Ustekinumab (Uste)
- Ixekizumab (Ixek)

5.2.5 Perspective, time horizon and discounting

The perspective follows the NICE reference case: the patient perspective for health effects, the NHS/PSS perspective for costs. Costs and benefits are discounted at 3.5%.

The base case applies a 10 year time horizon. The company argues that this is sufficient to capture the full costs and benefits of treatment with DMF. Results are sensitive to a longer time horizon.

5.2.6 Treatment effectiveness and extrapolation

The treatment effectiveness is based upon the company NMA estimartes for responses at the end of induction as below, with the exception of the estimates for Fumaderm and infliximab. These treatment effects are assumed to apply regardless among those starting a treatment regardless of whether it is being used 1st line, 2nd line, 3rd line or 4th line.

Table 33: Central treatment effectiveness estimates

		PASI 50	PASI 75	PASI 90	Trial (wks)
Dimethyl fumarate	DMF	38%	18%	6%	16
Apremilast	Apre	50%	27%	10%	16
Adalimumab	Adal	83%	64%	37%	16
Etanercept	Etan	76%	54%	28%	12
Fumaderm	Fuma	38%	18%	6%	16
Infliximab	Infl	94%	82%	59%	10
Secukinumab	Secu	94%	83%	61%	12
Ustekinumab	Uste	91%	77%	52%	16
Ixekizumab	Ixek	98%	91%	74%	16
BSC	BSC	16%	5%	1%	..

DMF is estimated to have a relatively poor clinical effectiveness compared to the other active treatments, but is estimated to be superior to BSC. Fumaderm is assumed to have the same clinical effectiveness as DMF. The clinical effectiveness of infliximab was not considered in the company NMA. The clinical effectiveness estimates for infliximab are an average of those reported in TA350, Secukinumab for moderate to severe plaque psoriasis and TA419, Apremilast for treating moderate to severe psoriasis.

Extrapolation is based upon patients who attain a PASI75 response remaining on treatment and retaining their best response; either a PASI75 response or a PASI90 response. This is coupled with a common 20% annual discontinuation rate among these patients with PASI75 response patients discontinuing at the same rate as PASI90 patients. Those who discontinue lose their response and move onto the next in line treatment.

5.2.7 Health related quality of life

A baseline quality of life of 0.70 is drawn from Revicki et al [22] though this has no impact upon the deterministic cost effectiveness results. Quality of life increments for the four possible responses are taken from Woolacott et al.[104]

- Less than PASI50: 0.05 QoL increment
- PASI50 to PASI75: 0.17 QoL increment
- PASI75 to PASI90: 0.19 QoL increment
- PASI90: 0.21 QoL increment

Woolacott et al use a two stage process to estimate quality of life, though the write up of this is not entirely clear to the ERG. The ERG reading of the AG report is that the first stage groups the patient data by baseline DLQI quartiles and subsequent PASI response status and calculates the mean change in DLQI for each of these groups, as well as doing so for the all patients' data grouped by PASI response. The EQ-5D data of the trial is then used to map the change in DLQI onto the change in the EQ-5D using an OLS regression. This mapping is used to estimate the change in EQ-5D that would be associated with the mean change in DLQI that is associated with a given baseline DLQI and PASI response category.

The company also supplies estimates of the quality of life increments based upon the DLQI values of the BRIDGE study using Woolacott et al mapping function for use in a sensitivity analysis.

Table 34: BRIDGE DLQI quality of life values using Woolacott et al mapping function

	DMF	Fuma	Placebo
Less than PASI 50	0.03	0.02	0.01
PASI50 to PASI 75	0.11	0.10	0.08
PASI75 to PASI 90	0.14	0.14	0.09
PASI90	0.19	0.16	0.18

These DLQI mapping suggests slightly greater gains for a given PASI response for DMF compared to Fumaderm, and some increased gains compared to placebo or BSC. But the increments are smaller than those used in the base case as drawn from Woolacott et al.

5.2.8 Resources and costs

Direct drug costs

The direct drug costs for DMF are marked as CIC by the company. Packs of 42 30mg dose tablets are available for the 1st 3 weeks titration, with packs of 90 and 180 120mg dose tablets available thereafter. The 30mg and 120mg tablets are the same cost with the 42, 90 and 180 pack sizes costing £89.04, £190.80 and £381.60 respectively, or £2.12 per tablet.

During the DMF16 week trial period the daily dose by week is specified as 1, 2 and 3 30mg tablets for the first three weeks followed by 1, 2, 3, 4, 5 and 6 120mg tablets for the next six weeks. The dosing for weeks ten to sixteen during BRIDGE is apparently less than the daily 720mg of week nine, with an average daily dose of 624mg. This results in an average daily

dose of 3.96 tablets during the trial period, an average total dose of 444 tablets, and a cost over the 16 week trial period of £939. This is then divided by 8 to yield a cost per 2 week model cycle of £117.

During the maintenance phase the average daily dose among those with a good response and remaining on treatment is assumed to be the same 3 tablets or 360mg, matching Fumaderm maintenance therapy reported in Reich et al.[96]This results in an annual maintenance cost of £2,321, or £89 per 2 week model cycle.

The direct drug costs for Fumaderm are also marked as CIC by the company. These are based upon the German cost per tablet of €2.43 being divided by the January 2017 exchange rate of £1=€1.18 to arrive at a price in sterling of £2.07. This cost is then inflated by an undocumented import charge of 22% to arrive at a cost per tablet of £2.52 which is 19% more expensive than DMF. The company states at clarification that:

"In investigating the cost of imported Fumaderm to UK centres it became apparent that the cost of imported Fumaderm varies considerably with many centres paying significantly more than the price we have used for our analysis. However in order to arrive at a reasonable and conservative price, and on the advice of UK experts, we have taken the German list price, converted this to sterling using the current exchange rate and applied a 22% import charge to account for the additional cost charged by the importers. We have been advised that this price is close to the (confidential) price actually charged to centres buying larger volumes but much less than the price charged to some other centres."

The dosing for Fumaderm is assumed to be the same for DMF. The 19% higher cost for Fumaderm implies on trial drug costs per 2 week model cycle of £140 and maintenance drug costs per 2 week model cycle of £106. The higher drug cost of Fumaderm and company default assumption of equivalence means the Fumaderm is dominated by DMF.

The BNF cost for apremilast of £550 for 56x30mg tablets is applied, with a daily dose of 60mg during both the 16 week trial period and maintenance resulting in a cost per model cycle of £275. A confidential PAS is available for apremilast, which the company cannot factor into its analyses.

The BNF cost for adalimumab of £704 for 2x40mg tablets is applied, with a loading dose of 80mg and 40mg fortnightly thereafter. This results in an average cost per 2 week mode cycle during the trial period of £440 and a cost during the maintenance period of £352.

The MIMS biosimilar cost for etanercept of £656 for 4x50mg rather than the BNF brand price of £715 is applied. A weekly dose of 50mg is applied during both the 12 week trial period and maintenance, resulting in a cost per 2 week model cycle of £328.

The MIMS biosimilar cost for infliximab of £378 for 100mg rather than the BNF brand price of £420 is applied. A dose of 5mg/kg or 389mg per administration is assumed. Vial sharing is assumed which results in a cost per administration of £1,469. Without vial sharing this would increase by a relatively modest 3% or £42 to £1,510.Administrations occur at week 0, 2, 6 during the 10 week trial period resulting in trial cost of £4,407 and an average cost per 2 week model cycle of £881. Maintenance dosing is every 8 weeks so an average cost per 2 week model cycle of £367.

The MIMS cost for secukinumab of £1,219 for 2x150mg is applied. Dosing is 300mg per week for the first 4 weeks and then monthly after week 4. This results in six administrations over the 12 week trial period at a cost of £7,313, or £1,219 per 2 week model cycle. The cost per 2 week model cycle during the maintenance phase falls to £609. A confidential PAS is available for secukinumab, which the company cannot factor into its analyses.

The BNF cost for ustekinumab of £2,147 per 45mg is applied. Dosing is an initial dose of 45mg, followed by another at 4 weeks and then 45mg every 12 weeks. The two administrations during the 16 weeks trial period result in a cost of £4,292, or £537 per 2 week model cycle. The maintenance cost is one sixth of £2,147 or £358 per 2 week model cycle.

The MIMS cost for ixekizumab of £1,125 per 80mg is applied. The submission does not state the dosing that is assumed but given the trial period of 16 weeks it appears to average out to 106mg per fortnight which results in a total trial cost of £12,000 or £1,500 per 2 week model cycle. Maintenance dosing is 80mg per month at a cost of £563 per 2 week model cycle.

This results in the following 2 weekly drug costs.

Table 35: *Trial and maintenance drug costs*

	Trial costs			Maintenance costs	
	Weeks	Total	2 week	Annual	2 week
Dimethyl fumarate	16	£939	£117	£2,319	£89
Apremilast*	16	£2,200	£275	£7,175	£275
Adalimumab	16	£3,521	£440	£9,187	£352
Etanercept	12	£1,968	£328	£8,557	£328
Fumaderm	16	£1,118	£140	£2,761	£106
Infliximab	10	£4,407	£881	£9,582	£367
Secukinumab*	12	£7,313	£1,219	£15,899	£609
Ustekinumab	16	£4,294	£537	£9,336	£358
Ixekizumab	16	£12,000	£1,500	£14,675	£563
* A confidential PAS is available which has not been factored into the company analyses.					

Pack size and drug wastage is not considered.

Administration and monitoring

Administration and monitoring costs are applied within the model, differentiated by trial and maintenance periods. The total trial resource use is averaged over the duration of the trial period to give the cost per fortnightly cycle. Infliximab is associated with an additional day case attendance for each administration. These are reportedly drawn from the relevant appendix of the NICE CG153. The total trial cost for apremilast and the biologics excluding infliximab is the same at £214, but due to their differing trial durations the costs per fortnightly cycle differ slightly as outlined below.

Table 36: Admin. and monitoring resource use and costs during trial periods

	Unit Cost	DMF/Fuma	Apre	Infl	Secu/Etan	Others
OP visits	£102	4	2	1	2	2
Liver Function Test	£1	4	2	3	2	2
Full blood count	£3	4	2	3	2	2
Urea and electrolytes	£1	4	2	3	2	2
IP day cases	£319	..	..	3	..	..
Trial cost		£427	£214	£1,076	£214	£214
Trial duration (wks)		16	16	10	12	16
Cost per 2 wk cycle		£53	£27	£215	£36	£27

The annual administration and resource use during maintenance is outlined below. Ixek is associated with one glomerular filtration rate measurement and so has slightly higher

fortnightly costs than the other biologics. It appears that there is no explicit allowance for IP day case administration for infliximab. The frequency of full blood counts for dimethyl fumarate is apparently still under discussion. The company adopts what it describes as the conservative estimate of assuming the 12 per year recommended by the EMA, though does not associate these with an outpatient visit.

Table 37: Admin. and monitoring resource use and costs during maintenance

	Cost	DMF/Fuma	Apre	Infl	Ixek	Others
OP visits	£102	6	4	4	4	4
Liver Function Test	£1	5	4	4	4	4
Full blood count	£3	12	4	4	4	4
Urea and electrolytes	£1	5	4	4	4	4
Glom. Filtration rate	£294	0	0	0	1	0
Day cases	£319	..	..	..	..	..
Annual cost		£657	£427	£427	£721	£427
Cost per 2 wk cycle		£25	£16	£16	£28	£16

Other resource use

Other resource use estimates in the model are largely drawn from Fonia et al.[2] Fonia et al is a study among 76 UK based patients, estimating resource use in the 12 months preceding and first 12 months during biologic use. The company notes that in the pre-biologic period only 25% of patients were using fumarates.

During the trial periods of each treatment the model assumes that patients are non-responders. The company notes that the TA419 ERG noted that the use of Fonia et al for this was "*uncertain*". In the light of this the company uses the TA419 ERG estimate of a £5,850 annual cost for non-responders, or £225 fortnightly cost. The TA419 ERG estimates for this are reported by the company as ranging between £45 and £348.

During the maintenance periods of each treatment the model applies the pre-biologic estimates of Fonia et al to DMF and Fumaderm and the post-biologic estimates of Fonia et al to apremilast and the biologics.

Table 38: Maintenance period other resource use and costs

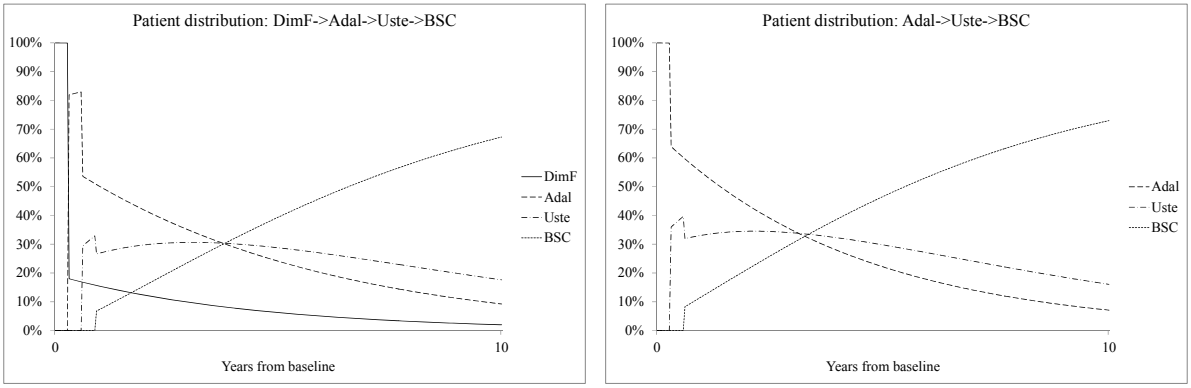
	Cost	DMF/Fuma	Apre	Biologics
Inpatient Days	£319	6.49	1.55	1.55
A&E visits	£94	0.03	0.04	0.04
Day cases	£484	0.14	1.16	1.16
Phototherapy	£311	2.76	0.26	0.26
Annual cost		£3,003	£1,142	£1,142
Cost per 2 wk cycle		£116	£44	£44

Those receiving BSC have an annual cost of £4,798, or a £185 fortnightly cost applied. This is apparently based upon the costs reported for pre-biologics in Fonia et al of £1,249 for pre-biologic systemic treatments plus £1 for other supportive drugs and £2,957 for IP admissions, OP visits, A&E visits, day case admissions and phototherapy. These costs are then inflated by 14% to arrive at an annual cost for BSC of £4,798 in 2014/15 prices.

5.2.9 Cost effectiveness results

The company base case evolution of the patient distribution between the various treatments over the 10 year time horizon is shown below. Estimates includes mortality, but after 10 years this is low at only 4%.

Figure 2: Patients on treatment between baseline and 10 years



The above illustrates how the modelling of treatment sequences occurs. In the DMF arm all patients trial DMF for 16 weeks. But at 16 weeks only 18% achieve a PASI75 response and receive maintenance treatment with DMF, this proportion being reduced by 20% each year due to discontinuations. At 16 weeks the 82% who did not achieve a PASI75 response with DMF go on to trial adalimumab, the slight uptick in the proportion trialling adalimumab over the next 16 weeks being the mirror image of those discontinuing from maintenance DMF.

After another 16 weeks 64% of those trialling adalimumab achieve a PASI75 response and receive maintenance treatment with adalimumab. The remainder then trial ustekinumab.

The base case cost effectiveness estimates that arise from this are as below.

Table 39: Company base case deterministic cost effectiveness estimates

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->Adal->Uste->BSC	7.100	£74,600	0.030	-£384	Dominant
Adal->Uste->BSC	7.070	£74,984			

Due to the first sequence in effect placing DMF before the second sequence and this having no effect upon the clinical effectiveness of the subsequent treatments it is almost necessarily the case that the first sequence yields more QALYs[4]. This is mainly a function of the first sequence containing an additional treatment, rather than a function of the clinical effectiveness of DMF which is relatively poor compared to the other active treatments.

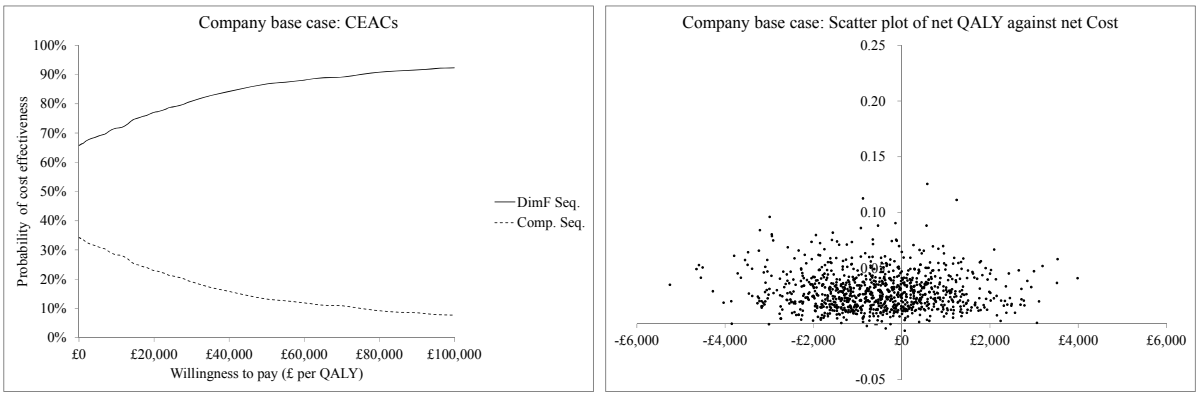
The sequence with DMF is also estimated to save money. As a consequence, using DMF prior to adalimumab followed by ustekinumab is estimated to dominate not using DMF.

In essence, the company base case argues that DMF extends the treatment sequence without affecting the treatment effectiveness of subsequent treatments. Since DMF is cheap it can be tried first and some patients will benefit sufficiently from it. Those that do not can then progress onto the more expensive treatments. Eventually all patients will progress onto the more expensive treatments.

The probabilistic modelling over 1,000 iterations suggests reasonably similar central cost effectiveness estimates of net gains of 0.029 QALYs, net savings of £545 and as a consequence dominance for the DMF sequence over the comparator sequence.

[4] This is admittedly subject to the time horizon being sufficient for the treatment sequences to largely play out.

Figure 3: Company base case CEACs and scatter plot



The scatter plot shows net gains ranging between -0.006 QALYs and 0.126 QALYs, but the vast majority of simulations estimating a net gain from the DMF sequence over the comparator sequence. Net costs are more mixed, ranging between savings of £5,250 to additional costs of £3,986. The CEAC suggests that the DMF sequence is the most likely to be cost effective at all willingness to pay values.

Note that it appears the results have not converged over 1,000 iterations. The ERG will consequently run the model over 10,000 iterations in its exploratory analyses of section 5.4.

5.2.10 Sensitivity analyses

The company presents a number of sensitivity analyses, the full list of which can be found in section 5.8 of the company submission. The ERG does not present those around discount rates for reasons of space, of those around the percentage of male patients or the baseline age as the model is insensitive to these. The deterministic sensitivity analyses are presented below, followed by scenario analyses around the time horizon and the sequences compared.

Table 40: Deterministic sensitivity analyses

	Δ QALYs	Δ Costs	ICER
DMF 10% annual withdrawal	0.046	-£1,414	Dominant
DMF 30% annual withdrawal*	0.020	£160	£7,967
Other Tx 10% annual withdrawal	0.004	-£1,508	Dominant
Other Tx 30% annual withdrawal	0.048	£412	£8,499
Arnold et al [3] withdrawal rates	-0.006	-£2,828	£439k SW
Baseline QoL = 0.6	0.030	-£384	Dominant
Baseline QoL = 0.8	0.031	-£384	Dominant
PASI QoL increments = 0.03, 0.15, 0.17, 0.19**	0.030	-£384	Dominant
PASI QoL increments = 0.07, 0.19, 0.21, 0.23**	0.030	-£384	Dominant
DMF 12 annual GP visits ongoing	0.030	£16	£547
Non-responder cost per cycle £0.00	0.030	-£1,849	Dominant
Non-responder cost per cycle £45.04	0.030	-£1,556	Dominant
Non-responder cost per cycle £348.22	0.030	£418	£13,804
DMF tablet cost +£0.88	0.030	£601	£19,853
DMF Week 10 to Week 16 120mg weekly dose reduction	0.030	-£557	Dominant
NMA patients systemic or PUVA experienced	0.030	-£368	Dominant
NMA excluding low quality studies	0.032	-£479	Dominant

* These values are taken from the ERG amended electronic model. The total costs and total QALYs in both arms cross checks with those given in table 74 of the CS but imply net costs and QALYs that differ from those given in table 74 of the CS.

** These values are taken from the ERG amended electronic model. The total QALYs in both arms do not cross checks with those given in table 74 but dimethyl fumarate is still estimated to dominate. Table 74 cannot be correct for the lower QoL increments as the total QALYs exceed those of the base case.

Results show a reasonable sensitivity to withdrawal rates, and applying the treatment specific estimates of Arnold et al [3] suggests that the DMF sequence no longer dominates the comparator sequence due to the 14% annual discontinuation rate for DMF being somewhat higher than the 9% rate of adalimumab and 4% rate of ustekinumab.

Results show virtually no sensitivity to the baseline quality of life values due to there being no survival effects. Results are also insensitive to the quality of life increments that are applied in the company sensitivity analyses in part because these values maintain the absolute difference between the PASI response health states but more due to ceiling effects as reviewed later

Applying 12 annual GP visits for DMF, so aligning this with the base case number of full blood counts, causes the DMF sequence to be of very slightly higher cost than the comparator sequence, without affecting the net QALY gain.

Non-responders costs have some impact, as does increasing the DMF cost by £0.88 per tablet or 42%.

Neither the company NMA restricted to those with prior experience of systemic or PUVA treatment nor the company NMA excluding low quality studies has much of an impact upon results.

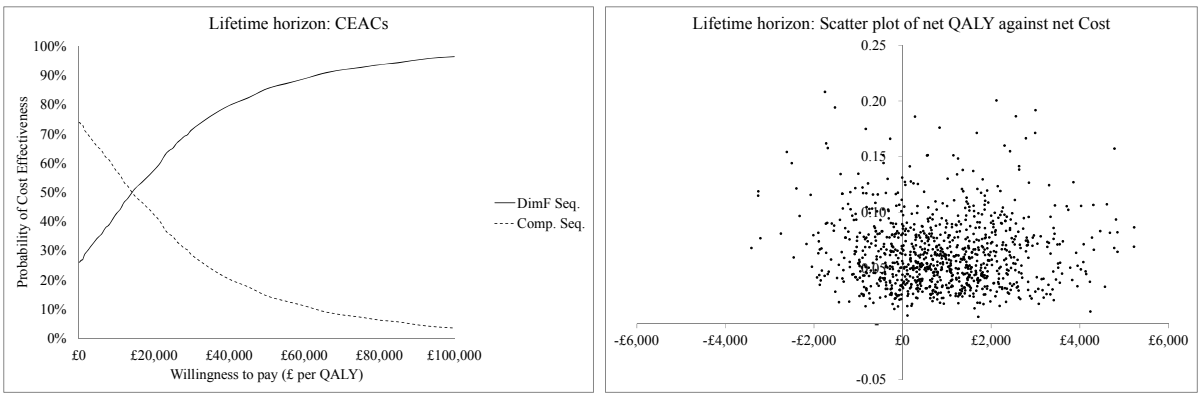
Extending the time horizon is explored with a 20 year analysis and a lifetime analysis.

Table 41: 10 year, 20 year and lifetime horizons

10 year horizon: Base case	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->Adal->Uste->BSC	7.100	£74,600	0.030	-£384	Dominant
Adal->Uste->BSC	7.070	£74,984			
20 year horizon	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->Adal->Uste->BSC	11.562	£107,112	0.058	£745	£12,898
Adal->Uste->BSC	11.504	£106,367			
Lifetime horizon	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->Adal->Uste->BSC	15.562	£132,611	0.063	£973	£15,476
Adal->Uste->BSC	15.499	£131,638			

The central probabilistic modelling estimates over 1,000 iterations are broadly in line with the above and suggest net gains of 0.064 QALYs, net costs of £853 and a lifetime cost effectiveness of £13,426 per QALY for the DMF sequence versus the comparator sequence.

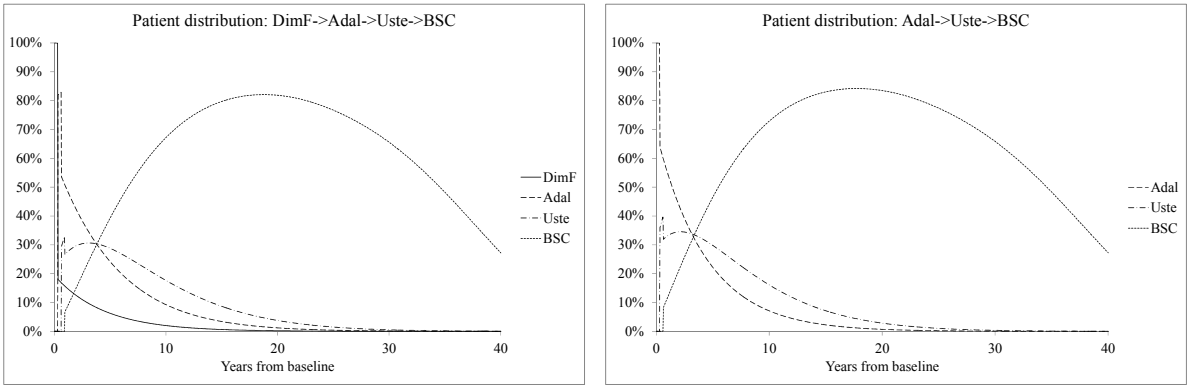
Figure 4: Lifetime horizon CEACs and scatter plot



The scatter plot is more dispersed in terms of net QALYs than that of the 10 year base case modelling of the company, though all simulations suggest a net gain from using DMF. Net gains range from 0.006 QALYs to 0.208 QALYs while net costs shift rightwards to range from a saving of £3,412 to a net cost of £5,227. The CEAC suggests that up to a willingness to pay of around £14,000 the comparator sequence has the highest likelihood of being the most cost effective, while above this the DMF sequence has the highest likelihood of being the most cost effective.

The longer time horizons cause the dimethyl treatment sequence to result in larger net QALYs but to no longer be cost saving. This is because the longer time horizons permit the treatment sequences to more fully play out with virtually all patients eventually reverting to BSC rather than curtailing them at 10 years with the final balance of treatments between the arms still differing. The following patient distributions include mortality, with the decline in those receiving BSC from around year 20 being due to more dying than are moving onto BSC from the last in line treatments.

Figure 5: Patients on treatment between baseline and 40 years



The values for baseline, 10 years, 20years, 30 years and 40 years are tabulated below.

Table 42: Patients on treatment at baseline, 10 years, 20 years, 30 years and 40 years

	DMF->Adal->Uste->BSC				Adal->Uste->BSC		
	DMF	Adal	Uste	BSC	Adal	Uste	BSC
Baseline	100%	0%	0%	0%	100%	0%	0%
10 years	2%	9%	18%	67%	7%	16%	73%
20 years	0%	1%	4%	82%	1%	3%	83%
30 years	0%	0%	1%	66%	0%	0%	66%
40 years	0%	0%	0%	27%	0%	0%	27%

With a ten year time horizon only 67% have progressed through to BSC in the DMF arm compared to 73% in the comparator arm. The higher costs of adalimumab and ustekinumab have not been as fully realised in the DMF arm as in the comparator arm.

A range of scenario analyses covering different sequences are also presented. These can be divided into those where DMF is an addition to and 1st line to the treatments of the comparator sequence and those where DMF displaces the 1st line treatment of the comparator sequence. For the comparison with Fumaderm two analyses are presented: one assuming equivalence and the other using the estimates of the NMA for Fumaderm of 45% PASI50, 23% PASI75 and 8% PASI90. A final scenario where the placement of DMF is changed from being 1st line in the base case sequence to being last in line is also explored and is grouped with the second set of analyses.

Table 43: Alternative sequences: dimethyl fumarate additional 1st line treatment

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->Etan->Adal->Uste->BSC	7.214	£79,405	0.006	-£1,206	Dominant
Etan->Adal->Uste->BSC	7.208	£80,611			
DMF->Adal->Secu->BSC	7.121	£91,337	0.028	-£2,156	Dominant
Adal->Secu->BSC	7.093	£93,493			
DMF->BSC	6.560	£43,460	0.062	£2,198	£35,256
BSC	6.498	£41,262			

As in the company base case, using DMF as the new 1st line treatment with the comparator sequence thereafter is estimated to dominate simply retaining the comparator sequence.

This is with the exception of simply comparing DMF with BSC the cost effectiveness of which is poor at £35,256 per QALY.

These estimates arise because the company model estimates all the other active treatments to have a cost effectiveness compared to BSC that is somewhat worse than the £35,256 per QALY cost effectiveness estimate for DMF compared to BSC.

Table 44: Alternative sequences: dimethyl fumarate alternative 1st line treatment

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->Adal->Uste->BSC	7.100	£74,600	-0.024	-£2,924	£123k SW
Apre->Adal->Uste->BSC	7.124	£77,524			
DMF->Adal->Secu->BSC	7.121	£91,337	-0.023	-£2,277	£98,829 SW
Apre->Adal->Secu->BSC	7.145	£93,614			
DMF->BSC	6.560	£43,460	-0.041	-£3,987	£96,093 SW
Apre->BSC	6.602	£47,447			
DMF->BSC	6.560	£43,460	-0.219	-£14,914	£68,054 SW
Adal->BSC	6.779	£58,374			
DMF->BSC	6.560	£43,460	-0.177	-£10,075	£57,079 SW
Etan->BSC	6.737	£53,535			
DMF->BSC	6.560	£43,460	-0.323	-£21,277	£65,951 SW
Infl->BSC	6.883	£64,737			
DMF->BSC	6.560	£43,460	-0.325	-£42,160	£130k SW
Secu->BSC	6.885	£85,620			
DMF->BSC	6.560	£43,460	-0.285	-£18,770	£65,748 SW
Uste->BSC	6.846	£62,231			
DMF->BSC	6.560	£43,460	-0.361	-£47,205	£131k SW
Ixal->BSC	6.922	£90,666			
DMF->BSC	6.560	£43,460	0.000	-£450	Dominant
Fuma->BSC	6.560	£43,910			
DMF->BSC	6.560	£43,460	-0.023	-£730	£31,887 SW
Fuma (NMA) ->BSC	6.583	£44,190			
DMF->Adal->Uste->BSC	7.100	£74,600	-0.020	-£1,705	£86,234 SW
Adal->Uste->DMF->BSC	7.120	£76,305			

SW: South west quadrant of the cost effectiveness plane: reduced costs and quality of life

If DMF displaces the 1st line treatment from existing treatment sequences it results in worse patient outcomes. These patient losses are quite significant when DMF is being compared directly with only one other active treatment as there are no subsequent treatments in the sequence to recover from DMF's relatively poor 18% PASI75 response rate. But it also results in reasonably large cost savings and so to a cost effectiveness estimate in the South West quadrant of the cost effectiveness plane. These cost effectiveness estimates are most

easily interpreted as the cost effectiveness of the comparator sequence relative to the sequence containing DMF so indicate that DMF remains cost effective.

These results are a consequence of the company model estimating all the other active treatments to have a cost effectiveness compared to BSC that is somewhat worse than the £35,256 per QALY cost effectiveness estimate for DMF compared to BSC, as reviewed in greater detail in section 5.2.11 below. Displacing these treatments with the DMF improves the overall cost effectiveness of the treatment sequence at conventional willingness to pay thresholds. While the DMF sequence results in patient QALY losses, the associated savings will when spent elsewhere in the NHS result in QALY gains for other patients that more than outweigh the QALY losses among the patients being treated with DMF. This also rolls through to the comparison of using DMF as 1st line compared to using it as 3rd line.

It should be borne in mind that the above scenario analyses exploring treatment sequences all report results for a 10 year time horizon. Compared to longer time horizons this tends to favour DMF containing sequences, the degree of this increasing with the number of treatments within the sequence. This particularly affects the sequences with a number of active treatments, and so the comparison of 1st line DMF with 3rd line DMF, a lifetime horizon reducing the South West quadrant ICER from £86,234 to £49,551.

5.2.11 Model validation and face validity check

The company submitted model can be used to provide estimates of each active treatment against BSC as below. Given the concerns around the time horizon outlined in section 5.2.10 above these estimates adopt a lifetime horizon, though since only one active treatment is under consideration this is not as important as when sequences with several active treatments are being compared.

Table 45: Active treatments cost effectiveness vs BSC: Lifetime horizon

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->BSC	14.896	£95,406	0.069	£2,270	£32,805
Apre->BSC	14.941	£99,653	0.114	£6,517	£57,071
Adal->BSC	15.134	£111k	0.307	£18,284	£59,584
Etan->BSC	15.087	£106k	0.260	£13,144	£50,616
Fuma->BSC	14.896	£95,880	0.069	£2,744	£39,653
Infl->BSC	15.244	£118k	0.417	£25,032	£59,982
Secu->BSC	15.247	£141k	0.420	£47,494	£113k
Uste->BSC	15.206	£116k	0.379	£22,412	£59,165
Ixek->BSC	15.288	£146k	0.461	£52,648	£114k
BSC	14.827	£93,136			

The cost effectiveness of DMF is estimated to be poor compared to BSC, but it is better than that of all the other active treatments. The net gains are somewhat less than the other active treatments but it is also cheaper than the other active treatments. This is the reason why company sensitivity analyses with DMF displacing another active treatment results in a cost effectiveness estimate in the South West quadrant of the cost effectiveness plane.

As reviewed in section 5.1.4 above in TA103 the cost effectiveness estimates for etanercept against BSC were sensitive to whether it was assumed that BSC was associated with an annual 21 day inpatient stay and whether the quality of life increments for the 4th quartile DLQI were used. The current model can be revised to apply an annual 21 day inpatient visit to BSC with this being costed at the £248 per day of TA103, and to also apply the quality of life increments of the 4th quartile DLQI. It is unclear to the ERG whether non-responders during the etanercept trial period were assumed to also incur a pro rata 21 day inpatient visit. The ERG assumption is that they were not, but scenarios of non-responders also incurring the higher annualised 21 day inpatient visit during the drug treatment periods can also be performed[5].

The cost effectiveness estimates that follow are presented for a lifetime horizon. Due to only single treatments being compared with either BSC this is broadly sufficient. The differences

[5] Note that this also revises the fortnightly cost of non-responders to be £121 due to the value of the apremilast FAD relating to a 28 day cycle and also due to the ERG review in section 5.3.2 below. It also reduces the baseline quality of life to 0,5 to avoid ceiling effects as reviewed in section 5.3.3 below.

in the cost effectiveness estimates between the 10 year time horizon and the lifetime horizon are relatively small. For instance, the cost effectiveness estimate for etanercept compared to BSC when the 21 day IP for BSC is applied is £16,159 per QALY for a 10 year time horizon compared to £15,892 per QALY for a lifetime horizon.

In what follows two sets of values are given for etanercept and ustekinumab as it appears that the company base case has applied the NMA estimates for high dose (HD) etanercept and ustekinumab when the low dose (LD) estimates may be more relevant.

Table 46: Scenario analyses ICERs: 21 day IP and 4th quartile DLQI QoL

IP days	BSC 21 day IP		BSC & NR 21 day IP	
QoL	Base	4th quart	Base	4th quart
DMF	Dom'ing	Dom'ing	Dom'ing	Dom'ing
Apre	£7,831	£7,447	£16,170	£15,376
Adal	£24,035	£21,757	£27,066	£24,501
Etan LD	£17,906	£15,970	£21,712	£19,364
Etan HD	£15,892	£14,127	£18,433	£16,386
Fuma	Dom'ing	Dom'ing	Dom'ing	Dom'ing
Infl	£28,841	£25,911	£30,053	£26,999
Secu	£81,671	£73,951	£83,201	£75,336
Uste LD	£26,103	£23,665	£28,703	£26,022
Uste HD	£25,466	£23,195	£27,901	£25,413
Ixek	£82,150	£75,891	£84,133	£77,722
Dom'ing: The treatment is dominating BSC				

In the opinion of the ERG the key values in the above are the estimates for etanercept low dose compared to BSC: £17,906 per QALY when BSC is associated with an annual 21 day inpatient stay with this falling to £15,970 per QALY is the 4th DLQI quartile quality of life increments are applied.

It may be argued that non-responders during the trial period of TA103 were also associated with an annual 21 day inpatient stay in which case the relevant values are £21,712 per QALY and £19,364 per QALY. The company NMA clinical effectiveness estimates for etanercept are also slightly better than those of TA103, as are though those for BSC. Applying the estimates of TA103 has little impact on results. The £21,712 per QALY estimate worsens to £22,488 per QALY while the £19,364 per QALY estimate worsens slightly to £19,937 per QALY.

This compares to the TA103 estimates of £45,975 per QALY for the 21 day IP scenario and £23,905 per QALY when the severe quality of life increments are applied for continuous use etanercept and £29,420 per QALY and £15,297 per QALY for intermittent use etanercept. The TA103 estimates for continuous use etanercept are somewhat higher than those of the current model, and also show more sensitivity to the use of the 4th quartile DLQI increments compared to the current model.

The lack of sensitivity of the current model to the 4th quartile DLQI increments is due to the all patient baseline quality of life value of 0.70 being retained. As quality of life cannot exceed 1.00 this results in ceiling effects. The TA103 quality of life increments for severe patients of 0.38 for a PASI75-90 response and 0.41 for a PASI90 response are reduced to only 0.30, which is little different from the 0.29 increment for a PASI50-75 response.

One of the main curiosities of the model is that over a lifetime horizon the company model yields a cost effectiveness estimate of £32,805 per QALY for DMF->BSC compared to BSC but this improves considerably to £15,476 per QALY for the comparison of DMF->Adal->Uste->BSC with Adal->Uste->BSC. As outlined above the bilogics are estimated to have a very poor cost effectiveness compared to BSC. Delaying the use of the biologics reduces their impact due to discounting and all cause mortality. If discounting and all cause mortality is set to zero the cost effectiveness estimate for DMF->BSC compared to BSC improves rom £32,805 per QALY to £28,954 per QALY but the cost effectiveness of DMF->Adal->Uste->BSC with Adal->Uste->BSC worsens from £15,476 to £24,398 per QALY. A substantial aspect of the relatively good cost effectiveness performance of the DMF sequence of the company base case arises by construction. It seems that anything cheap that delays the use of the biologics (including no treatment at all) will improve the cost effectiveness of the sequence.

5.3 ERG cross check and critique

5.3.1 Base case results

The ERG has rebuilt the company model and given the company inputs and assumptions agrees with the company model results.

5.3.2 Data Inputs: Correspondence between written submission and sources cited

Population characteristics

The baseline age of 50 years and 77.8kg corresponds with that reported for the FUTURE trial of Fumaderm by Reich et al.[96] Reich et al also report 58.2% being male which is roughly midway between the 50% assumed in the company base case and the 65% of the BRIDGE trial.

Fumaderm dosing and dimethyl fumarate dosing

Reich et al [96] report the results of the FUTURE retrospective study of 984 Fumaderm patients, 71% of whom were treated continuously for at least 2 years. 87% of patients has plaque psoriasis but there was also a reasonable prevalence of scalp psoriasis, 38%, and nail involvement, 23%. Most, 97%, were classified as moderate to severe by PGA though 18% had a PASI score of less than 10, while 37% had a PASI score of more than 20. For the vast majority of patients, 81%, Fumaderm was the 1st systemic treatment and was the 2nd systemic treatment for a further 14%. Dose up titration appears to follow that of the BRIDGE study up to nine weeks.

They report that at the end of the FUTURE induction trial period the balance between the daily numbers of tablets was 12.6% using less than 3, 25.2% using 3, 16.6% using 4, 10.3% using 5, 34.9% using 6 and 0.4% using more than 6. Assuming that the first category were using 2 and the last 7 this averages to 4.3 tablets per day at the end of the trial period and a daily dose of 517mg. Among those with a good response the average daily maintenance dose was 3 tablets or 360mg, or 70% of the end of trial period daily dose.

The 517mg end of the FUTURE trial induction mean dose for Fumaderm is somewhat less than the company reported 624mg average during weeks 10 to 16 in the DMF arm of the BRIDGE study. The company has assumed that the higher BRIDGE induction trial dosing applies to Fumaderm rather than the FUTURE induction trial dosing.

The company has also assumed that the 360mg average maintenance dose among Fumaderm good responders will apply to DMF during its maintenance period. Whether the DMF dose would drop to 360mg and only 58% of the mean week 10 to week 16 dose, among those with a good response who receive ongoing therapy, is unknown due to the BRIDGE trial follow-up being off treatment. The ERG will conduct a scenario analysis that assume the trial prior

dosing for Fumaderm is 70% that of DMF and that the maintenance dose for DMF is 70% of the BRIDGE trial week 10 to 16 average dose.

Lijnen et al[14] examined the long term safety of high dose DMF in moderate to severe psoriasis. 176 Dutch patients were treated with DMF for a median duration of 28 months. 78% of the included patients had psoriasis vulgaris and 63% had psoriasis for over 10 years. 82% of the patients had received prior phototherapy and 28% received prior systemic treatment. Only 18% had received neither. This may be more in line with the modelled population when DMF is being considered as an alternative to the biologics than the BRIDGE study.

The Lijnen et al study protocol in terms of dosing was reasonably similar to the BRIDGE study. Patients started on a daily dose of 30mg, with this being increased on a weekly basis by 30mg up to a daily dose of 240mg. The dose was then increased by 120mg every third week until a satisfactory effect was achieved. The main difference with the BRIDGE study in terms of dosing was instead of an upper limit of 720mg at week 9 the upper limit was 1680mg at week 28. Patients were then down titrated to a minimum maintenance dose depending upon psoriatic skin symptoms.

24% of patients discontinued treatment before reaching the maintenance phase. Of the 76% who reached the maintenance phase the median time to this was 8 months, with an interquartile range of 5 to 12 months. During the trial the median maximum dose was 740mg which is not dissimilar to the BRIDGE study, but the interquartile range of 600mg to 1,160mg suggests a reasonable proportion of patients continued to increase their dose beyond the maximum of the BRIDGE study and the draft DMF SmPC. The median maintenance dose was 480mg, but the interquartile range of 270mg to 960mg again suggests a reasonable proportion of patients remained on a maintenance dose above the maximum of the BRIDGE study and the draft DMF SmPC.

In the light of this the ERG will conduct a scenario analysis of a maintenance dose for DMF and Fumaderm of 480mg.

Apremilast induction cost

The company costing of apremilast does not take into account the availability of an induction pack for the first fortnight which is £10 cheaper than the cost of ongoing apremilast of the 56 tablet 30mg pack. This has little effect upon results.

Etanercept and infliximab cost

The company has costed both etanercept and infliximab using the cost of the generic. This may be conservative if there continues to be some use of Enbrel and Remicade in the NHS. Also note that generic etanercept is only available in 50mg pre-filled pens which means that twice weekly dosing with 25mg is not possible.

Ixekizumab induction cost

The FAD of TA442 recommends a trial period of 12 weeks for ixekizumab. The company model suggests it applies a trial period of 16 weeks but due to a coding error it applies the secukinumab trial period duration of 12 weeks.

Ixekizumab requires a starting dose of 160mg, followed by 80mg every fortnight for 12 weeks from week 2 followed by a maintenance dose of 80mg every 4 weeks. To the ERG this suggests a total of 9 doses during the 16 week trial period at a total cost of £10,125. This in turn suggests an average cost per 2 week cycle of £1,266 rather than the £1,500 of the company if the induction period is the 16 weeks the company intended to apply.

But given the 12 week induction period of the TA442 FAD this suggests a total of 7 doses during induction at a 2 weekly cost of £1,313 rather than the 8 doses assumed by the company at a 2 weekly cost of £1,500. Note that the 8th dose falls at week 12 and the ERG assumption is that this does would not be taken if the patient was being taken off the drug due to lack of response.

Discontinuation rates

Assuming a common 20% annual discontinuation rate among PASI75 responders has been criticised during previous NICE appraisals due to the different administration routes and side effect profiles of treatments. The company identifies Arnold et al[3] as providing estimates of treatment specific discontinuation rates.

Arnold et al report the results of a retrospective analysis of 373 moderate to severe psoriasis patients who received a total of 696 treatment courses at a German teaching hospital between 20013 and 2014. Mean age was 52 years and mean duration of disease was 20 years and 39% also had psoriatic arthritis. Drug survival time was estimated as the time between the first dose and last dose, with cessation being assumed if the patient stopped treatment for more than three months. Arnold et al report cumulative 1 year, 2 year, 3 year, and 5 year survival

rates for acitretin, ciclosporin A, fumaric acid esters, methotrexate, adalimumab, etanercept, infliximab and ustekinumab as below. The company annual discontinuation rates derived from Arnold et al are also reported below.

Table 47: Arnold et al treatment survival and discontinuation rates

	Arnold et al treatment survival rates				Company
	1 year	2 year	3 year	5 year	Annual disc.
ACI	37%	23%	23%	16%	..
Cicl	16%	0%	0%	0%	..
FAEs	46%	41%	35%	25%	14%
MTX	43%	27%	20%	10%	..
Adal	70%	53%	49%	49%	9%
Etan	60%	48%	38%	29%	16%
Infl	53%	37%	37%	11%	33%
Uste	90%	83%	83%	75%	4%

The values the company derives from Arnold et al cross check with the implied constant annual discontinuation rates between year 1 and year 5.

In its sensitivity analysis, the company assumes that the discontinuation rate for fumaric acid esters applies to both DMF and Fumaderm, and the discontinuation rate for etanercept applies to apremilast. Given the PASI75 response rates of 54% for etanercept and only 27% for apremilast the latter assumption is questionable. That said, the 16% discontinuation rate for etanercept is not that much different from the 14% for FAEs which might have been the more natural choice for apremilast.

DLQI quality of life coefficients

The coefficient report by the company for Currie et al[105] is an order of magnitude greater than most of the others, but this is a typo by the company and the coefficient of Currie et al is -0.025.

Fonia et al costs of BSC, biologics and non-responders

The company applies a cost of BSC of £185 per fortnight, or £4,798 per annum. This is slightly higher than the £4,629 inflated cost reported by the company in its clarification response as drawn from Fonia et al [2], the derivation of which is also provided within the

clarification response. Applying the 2015 dermatology outpatient cost rather than inflating that in Fonia et al would increase this slightly to £4,701 per annum.

The company applies a higher cost per non-responder during the trial periods of £225 per fortnight, or £5,850 per annum. This appears to have been drawn from the ERG report and FAD of the apremilast STA [TA368]. But as the apremilast FAD makes clear this is cost is per 28 day cycle of the apremilast model and so only £112 per fortnight or £2,925 per annum. ERG calculations based on the company clarification response suggest an annual cost of £3,001 or £128 per fortnight.

The doubling of the non-responder costs disadvantages the treatment sequence with the larger number of treatments and so the longer period spent on trial and as a non-responder. As a consequence, this error disadvantages the DMF sequences in which DMF is modelled as preceding the comparator sequence of biologics.

Back calculation from table 6 of Fonia et al suggests a phototherapy rate of 2.72 rather than 2.76 for the 12 months prior to starting a biologic. Company indexation for inflation is based upon the Hospital and Community Health Services index values for 2008/09 and 2014/15: 267.0 and 293.1 resulting in a price inflation of 9.8%. But the costs in Fonia et al are stated as being in June 2008 prices. To the ERG this suggests using the index values for 2007/08 and 2015/16: 257.0 and 297.0 resulting in price inflation of 15.6%. Applying these changes results in the following.

Table 48: ERG Cross Check of Fonia et al costings

	Unit costs		Resource use per annum	
	07/08	15/16	Pre biologic	Post biologic
OP	£72	£102*	3.22	3.25
IP days	£291	£336	6.49	1.55
A&E	£86	£99	0.03	0.04
Day case	£441	£510	0.14	1.16
Phototherapy	£283	£327	2.72	0.26
Drugs pre biologic	£1,251	£1,445	1.00	0.00
Drugs post biologic	£10,707	£12,373	0.00	1.00
Inc Drug Costs			£4,922	£13,906
Exc Drug and OP Costs			£3,149	£1,202
* Based upon the 2014/15 reference cost rather than Fonia et al indexed				

To the ERG this suggests a fortnightly cost for BSC of £189 and a fortnightly cost for non-responders of £121, and that the model should also update the indexing of the Fonia et al unit costs. The £121 may appear low but it should be borne in mind that the model separately accounts for OP visits among the non-responders when trialling new drugs. It is also broadly in line with the £225 per 28 days estimated by the ERG of the apremilast STA [TA419].

Inpatient rates and unit costs

Previous assessments have questioned whether the inpatient resource use estimates of Fonia et al [2] might be overestimates due to the data relating to a tertiary centre. But the comparator treatments under consideration have only been approved for severe patients, among whom the estimates of Fonia et al may be more reasonable. Fonia et al report using NHS reference costs as the source of unit costs. Some questions have also been raised as to whether the cost per day might tend to be higher for shorter stays than for longer stays. The 2015-16 NHS reference costs give the following for codes ND07E-K: Skin disorders without interventions.

Table 49: 2015-16 NHS reference costs for IP skin disorders without interventions

CC Score	Elective				Non Elective				All
	FCEs	Cost	LoS	£/day	FCEs	Cost	LoS	£/day	£/day
19+	7	£4,340	11.3	£385	824	£5,401	15.0	£359	£360
14-18	126	£5,216	9.9	£526	6,106	£3,881	10.5	£370	£373
10-13	241	£2,872	6.9	£416	12,856	£3,064	7.9	£386	£386
6-9	644	£2,553	5.1	£503	20,444	£2,463	6.1	£405	£408
2-5	1,604	£1,691	3.1	£538	23,776	£1,886	4.3	£437	£442
0-1	1,536	£1,078	1.8	£603	10,629	£1,485	3.2	£467	£477

Another set of reference costs are available for skin disorders with interventions, and these are typically that bit higher than those reported in the above table. All these costs are somewhat higher than the £336 unit cost of Fonia et al, inflated to 2015-16 prices.

There is also a general pattern of the cost per day falling as the number of complications and comorbidities increases and the length of stay increases. In the light of the above the ERG will conduct a scenario analysis that applies a £477 unit cost to inpatient days, and also a scenario analysis that differentiates the unit cost as £408 for the pre-biologic period and £477 for the post biologic period. These may be underestimates if plaque psoriasis admissions tend to be elective rather than non-elective. It should also be borne in mind thst Fonia et al only provide estimates that permit the mean number of inpatient days per year to be inferred. The average length of stay may be the same pre-biologic and post biologic, with the rate of admission being the main determinant of the mean number of inpatient days.

Infliximab drug and administration costs

The infliximab SmPC suggests assessment at 14 weeks but the TA134 recommends assessment at 10 weeks. The company model trial period is 10 weeks.

The company model applies the £377 cost of generic infliximab rather than the £420 cost of Remicade.

The company model assumes divisible vials for infliximab which seems incorrect. The ERG will assume indivisible vials of 100mg.

The company assumes that during the 10 week trial period infliximab is administered three times as an inpatient admission, applying the inflated Fonia et al [2] cost of £319. The 8 weekly

administrations thereafter, an annual 6-7 administrations, do not appear to be costed though infliximab is associated with the same quarterly monitoring costs of the other biologics. While specific to chemotherapy, the 2015-16 NHS reference costs given costs of delivering the first simple parenteral administration as £199 and subsequent elements as £212. In the light of this the ERG will apply an administration cost of £212 per infliximab administration.

If infliximab is central to the assessment these costs may require further thought and development.

OP reference costs

The ERG has not been able to source the £101 cost per outpatient visit from the 2014-15 NHS reference costs. They do provide a consultant led follow up cost of £97, with the 2015-16 NHS reference costs suggesting £99. These cost differences have minimal impact upon results. Given the ERG indexing of Fonia et al [2] the ERG will apply the 2015-16 cost.

5.3.3 Data Inputs: Correspondence between written submission and electronic model

Clinical effectiveness estimates

The clinical effectiveness estimates of the company base case mostly correspond with the clinical effectiveness estimates of table 38 of the company submission: the NMA PASI response estimates at induction time.

The values applied for etanercept and ustekinumab in the model are the high dose values of the company NMA. In the opinion of the ERG the low dose values should be applied. The ERG will apply the low dose values of the company NMA.

The company NMA estimates for Fumaderm are not applied in the economic model. The company NMA estimates favour Fumaderm over DMF. The company base case assumes Fumaderm is equivalent to DMF. This is not obviously reasonable and for the ERG revised base case the ERG will apply the company NMA results.

5.3.4 ERG commentary on model structure, assumptions and data inputs

Base case comparator

The executive summary of the company submission suggests that DMF will:

"…be used in a specific group of patients: those for whom other non-biologic systemic treatments (methotrexate, ciclosporin and acitretin) are not appropriate or have failed and who are considered unsuitable for biologic therapy given their current disease state or personal preference".

The company consequently appears to argue for either BSC or apremilast being the main comparator for DMF. As a consequence, the ERG present a full set of analyses comparing the cost effectiveness of DMF with both BSC and apremilast.

Model structure: patients with both psoriatic arthritis and plaque psoriasis
The prevalence of psoriatic arthritis among moderate to severe plaque psoriasis patients may be quite high; e.g. Arnold et al [3] suggest around 40% though Lijnen et al [14] suggest only 14%. The prevalence of psoriatic arthritis may also increase with the severity of the plaque psoriasis which may be relevant in the light of previous plaque psoriasis appraisals approving treatment for the more severe. This may raise the possibility of one drug being used to treat both plaque psoriasis and psoriatic arthritis.

For instance, apremilast has been approved by NICE both for plaque psoriasis [TA419] and for psoriatic arthritis [TA433]. The apremilast dose for plaque psoriasis and psoriatic arthritis is the same. The approval for psoriatic arthritis is subject to patient having peripheral arthritis with at least 3 tender joints and at least 3 swollen joints and not having responded to at least 2 standard DMARDs. Treatment should be stopped at 16 weeks is a PsARC response has not occurred.

Apremilast may be used to kill two birds with one stone. In contrast, DMF is only licensed for plaque psoriasis. It may be that patients with both plaque psoriasis and psoriatic arthritis who have their plaque psoriasis treated with DMF will still incur the costs of another drug such as apremilast for treatment of their psoriatic arthritis.

In this regard it should be noted that the NICE methods guide states that: '*Costs that are considered to be unrelated to the condition or technology of interest should be excluded.'*
This raises the question of whether the condition is the underlying immune disorder or is limited to plaque psoriasis. The ERG assumption is that the underlying condition is limited to plaque psoriasis. But the situation is not entirely clear cut and it can be argued that there is an underlying condition which gives rise to the plaque psoriasis and the psoriatic arthritis.

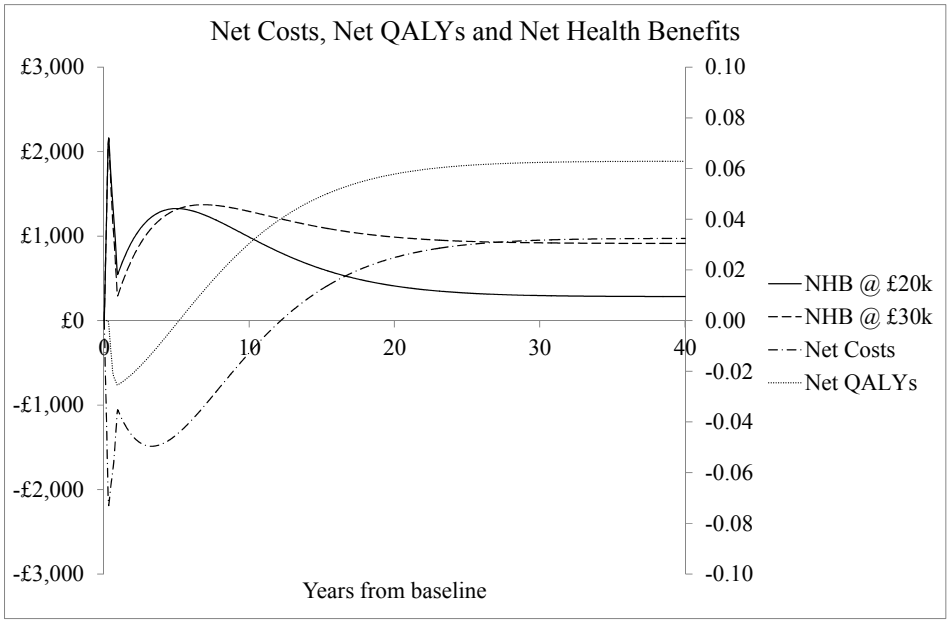
Tecfidera

Dimethyl fumarate is available for relapse remitting multiple sclerosis as Tecfidera, marketed by Biogen in 120mg gastro resistant capsules at a cost of £343 for 14, or £24.50 per capsule. The dimethyl fumarate of the current submission is available as 120mg gastro resistant tablets at a cost that is roughly an order of magnitude less than Tefidera. The ERG is not aware of any commercial links between the company and Biogen or another third party in the development of dimethyl fumarate. There is the possibility of market segmentation with it seeming likely from relatively early in product development that treating multiple sclerosis will bear a higher drug cost than treating plaque psoriasis. The ERG is aware that there has been some consideration of disease specific PASs being considered by NICE to permit market segmentation but does not know the outcome of this or indeed if it would have any bearing on this point.

Time horizon: Company base case

The 10 year time horizon of the company base case can be explored in more detail by graphing the net costs, net QALYs and net health benefits (NHB) at willingness to pay (WTP) values of £20k per QALY and £30k per QALY.

Figure 6: Net costs, net QALYs and NHBs over time: Company base case



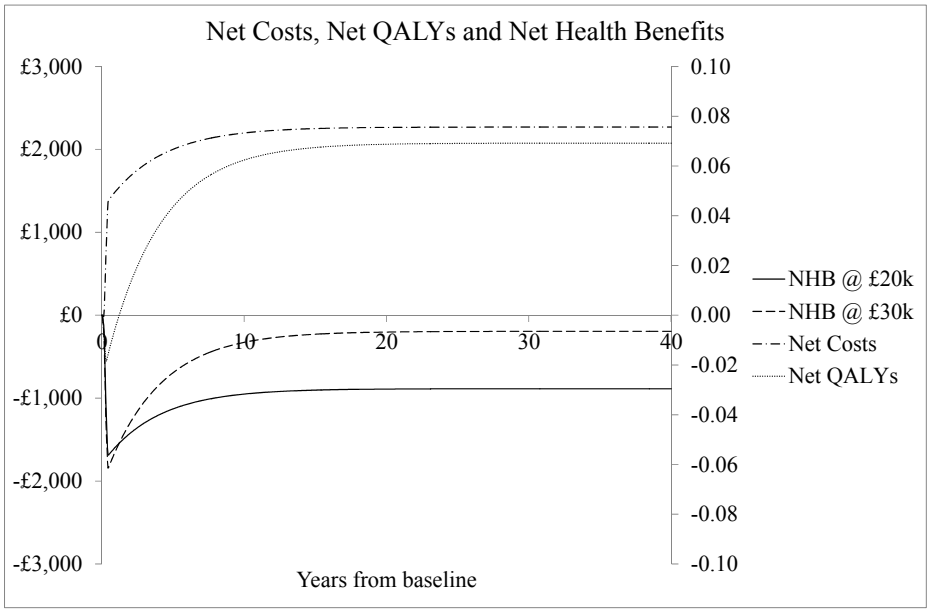
The above shows that there is a sweet spot for the time horizon for the company base case of between 4.5 years and 12.2 years. Below this range the DMF sequence results in QALY

losses compared to the comparator sequence, while above this range it results in net costs rather than net savings. The company base case time horizon of 10 years falls within this range where the DMF sequence is estimated to dominate the comparator sequence. But the company base case results in positive net health benefits at all time horizons at WTP values of £20k per QALY and £30k per QALY.

Time horizon: compared to BSC

With a 10 year time horizon the company estimates that the cost effectiveness of DMF compared to BSC is £35,256 per QALY. This results in negative net health benefits at WTP values of both £20k per QALY and £30k per QALY.

Figure 7: Net costs, net QALYs and NHBs over time: versus BSC



The 10 year time horizon is broadly sufficient for the DMF treatment to play out and net health benefits have broadly stabilised by 10 years. Net health benefits are negative at all time horizons.

Extending the time horizon beyond 10 years has little effect for the comparison of DMF with BSC. It also has relatively little effect for the other comparisons with single treatments, but given their superior effectiveness results still show some sensitivity to the time horizon. For instance, the net health benefits for the comparison with adalimumab at 10 years are £8,345 at a WTP of £20k per QALY and £10,538 at a WTP of £30k per QALY, but it takes until 20 years for these to stabilise at £8,861 at a WTP of £20k per QALY and £11,200 at a WTP of £30k per QALY

Thus when comparing single treatments a 10 year horizon is broadly adequate, but when comparing treatment sequences a 25 year time horizon is required.

Quality of life ceiling effects

The company results show little effect when changing the quality of life increments from the all-patient to severe patient increments reported by Woolacott et al.[104] This is partly due to the quality of life increments being added to a base case quality of life of 0.70, with a ceiling of 1.00 being placed on quality of life values. This limits the maximum gain to 0.30, which is sufficient for the deterministic all-patient quality of life increments, but insufficient for the deterministic severe patient quality of life increments for PASI75-90 of 0.38 and PASI90 of 0.41. In the light of this the ERG have arbitrarily reduced the baseline quality of life for severe patients to 0.5 in order to avoid the undesirable ceiling effects, though any value less than 0.59 would suffice.

Adverse events, Discontinuations and Serious Adverse Events

Treatment related adverse events were considerably higher for DMF at 74%, almost double the 40% rate of the placebo arm. Treatment discontinuations due to adverse events during the 16 week trial period were higher in the DMF arm at 23% compared to only 4% in the placebo arm. Treatment discontinuations due to a lack of efficacy were lower in the DMF arm at 4% compared to 15% in the placebo arm. Overall the treatment discontinuations during the trial period were higher in the DMF arm at 37% compared to 29% in the placebo arm. The large difference in treatment discontinuations due to adverse events between the arms may argue for adverse events to have been considered if these lead to additional GP appointments or an increase in prescriptions.

Commonly, only serious adverse events may be considered within economic analyses. The CSR shows SAEs to have been reasonably balanced between the arms at 3.2% for DMF and 3.6% for placebo, with none of these being assessed as treatment related.

Some concerns have been expressed around the possibility of PML being associated with DMF, but as far as the ERG is aware there is no evidence of this.

Age related quality of life

If the time horizon is extended to a 40 years or more the baseline age of 50 suggests that patient quality of life for a given model health state will decline over the period of the model

due to increasing comorbidities. There is an argument that quality of life values should be age weighted. This will have no impact if only the base quality of life value of 0.700 is weighted as there are no survival effects from treatment. The quality of life increments associated with PASI responses would have to be weighted as well for this to have any impact upon results.

Treatments' costs and quality of life during the trial periods and post-trial periods

The cost effectiveness estimate of £15,476 per QALY for the company base case treatment sequences with a lifetime horizon is quite different from the cost effectiveness estimate of £32,805 per QALY for DMF compared to BSC with a lifetime horizon. This might be due to the effects of discounting and mortality, but setting these to zero still results in differences between the cost effectiveness estimates for the two scenarios: £24,398 per QALY compared to £28,954 per QALY. This is curious since all that the comparison of DMF with BSC has done is to subtract the common elements of adalimumab and ustekinumab from the treatment sequences of the company base case. Intuition suggests that there should be little to no net effect and that the cost effectiveness estimates for the two scenarios should be broadly in line.

In order to explore this it needs to be recognised that the model always simulates treatment sequences of 4 treatments; i.e. the base case compares:

- DMF -> Adal -> Uste -> BSC
- Adal -> Uste -> BSC -> BSC

While the scenario analysis of DMF against BSC compares:

- DMF -> BSC -> BSC -> BSC
- BSC -> BSC -> BSC -> BSC

With those at the end of the treatment sequence incurring the costs of BSC and the quality of life value of BSC. With this in mind the costs and QALYs associated with the 1st, 2nd, 3rd and 4th lines of treatments in each arm for the base case and the scenario analysis of DMF against BSC can be compared. In order to remove any timing artefacts the following sets discount rates and mortality to zero and adopts a lifetime horizon.

The costs associated with the different lines of treatment can be divided into:

- the drug costs
- the other medical resource use (MRU) during the trial period when patients are assumed to be non-responders
- the MRU subsequent to the trial period among responders
- the MRU among those who have cycled through the 4 treatments and are now off treatment

Table 50: Company base case sequences: no discounting or mortality: Costss

Drug costs	1st	2nd	3rd	4th	Off Tx
DMF->Adal->Uste->BSC	£2,812	£29,892	£36,527	£0	..
Adal->Uste->BSC->BSC	£29,893	£36,532	£0	£0	..
On trial Non-Responder costs	1st	2nd	3rd	4th	Off Tx
DMF->Adal->Uste->BSC	£1,800	£1,800	£1,800	£225	..
Adal->Uste->BSC->BSC	£1,800	£1,800	£225	£225	..
Other MRU post trial	1st	2nd	3rd	4th	Off Tx
DMF->Adal->Uste->BSC	£3,392	£4,734	£5,650	£194	£201,130
Adal->Uste->BSC->BSC	£4,734	£5,651	£194	£194	£206,296

There is agreement between the costs on the diagonals where like is being compared with like; e.g. the direct drug costs of 2nd line adalimumab in the DMF->Adal->Uste->BSC sequence are essentially the same as the direct drug costs of 1st line adalimumab in the Adal->Uste->BSC->BSC sequence.

In the above the on trial non-responder costs are less for BSC than for the active treatments. This only arises due to BSC having a trial period of 2 weeks within the model structure so the on trial non-responder costs are one eighth those of the active treatments with 16 week trial periods: 8 * £225 = £1,800.

For the post-trial MRU associated with the active treatments the common diagonal elements for adalimumab and ustekinumab and one BSC can be removed to leave the £3,392 for 1st line DMF and the £194 for 4th line BSC in the comparator sequence: a net cost of £3,199. This compares with the off treatment MRU of £201,130 in the DMF sequence and £206,296 in the comparator sequence: a net cost of £5,167. The ratio between these is 62% which is

similar to the ratio between the per cycle post trial MRU of £141 for DMF PASI75 responders and £185 for BSC of 76%. But the modelled ratio is still that bit less than that of the per cycle costs and the ERG is at a loss to explain the intuition behind this.

The pattern of costs, excluding the common diagonal elements is essentially the same for the comparison of DMF followed by BSC with BSC and is consequently not reported here for reasons of space. The post-trial MRU use when the common diagonal elements are netted out is identical and the 62% ratio also applies.

The QALYs associated with each treatment line can also be subdivided into those accrued during the trial period and those among patients who achieved a PASI75 response and receive ongoing maintenance treatment.

Table 51: Company base case sequences: no discounting or mortality: QALYs

On trial QALYs	1st	2nd	3rd	4th	Off Tx
DMF->Adal->Uste->BSC	0.215	0.240	0.250	0.032	..
Adal->Uste->BSC->BSC	0.215	0.250	0.032	0.029	..
Post-trial QALYs	1st	2nd	3rd	4th	Off Tx
DMF->Adal->Uste->BSC	0.726	2.597	3.130	0.002	32.295
Adal->Uste->BSC->BSC	2.597	3.131	0.002	0.002	33.125

The on trial QALYs are equal for 1st line DMF and 1st line adalimumab. But looking at the quantities on the diagonal the on trial QALYs for 1st line adalimumab are less than those for 2nd line adalimumab by 0.024 QALYs. This is because for 1st line adalimumab the on trial period has the baseline 0.700 quality of life value applied and no increment. 2nd line adalimumab has the baseline 0.700 quality of life value applied plus an increment for these patients being DMF non-responders. This quality of life increment arises from having previously received DMF but having failed on it so no longer having a PASI75 response. The proportion of DMF patients who do not achieve a PASI50 response is 1-38%=62%. The proportion who only achieve a PASI50-75 response with DMF is 38%-18%=20%. This yields an assumed balance of 62:20 or 76:24 among those who have not responded to or have responded to but subsequently failed on DMF. This is used to weight the quality of life increments for a less than PASI50 response of 0.05 and of a PASI50-75 response of 0.17 to arrive at a quality of life increment for 2nd line treatments subsequent to 1st line DMF of [redacted]

The company argument appears to be that those trialling a treatment 1st line have no quality of life increment compared to baseline, but they do have a quality of life increment when trialling it after having failed on another treatment. This increases the total QALYs in the sequence with more treatments, typically the DMF sequence in the company modelling.

Table 52: Company scenario sequences: no discounting or mortality: QALYs

On trial QALYs	1st	2nd	3rd	4th	Off Tx
DMF->BSC ->BSC->BSC	0.215	0.030	0.029	0.029	..
BSC ->BSC->BSC ->BSC	0.027	0.029	0.029	0.029	..
Post-trial QALYs	1st	2nd	3rd	4th	Off Tx
DMF->BSC ->BSC->BSC	0.726	0.002	0.002	0.002	37.595
BSC ->BSC->BSC ->BSC	0.002	0.002	0.002	0.002	38.425

The same QALY pattern occurs among those "trialling" BSC 1st line and 2nd line. But the discrepancy is less at only 0.003 QALYs. This is due to the 2 week trial period for BSC being one eighth that of adalimumab: 8 * 0.003 = 0.024 QALYs.

There may be an argument for those who achieved a PASI75 response from their previous treatment line having a quality of life increment applied as they will have just lost PASI75 response status when considering a new treatment rather than starting from baseline. But it seems harder to justify an increment among those who never achieved a PASI50 response from their previous treatment. In the opinion of the ERG, given the low PASI50 response rate for DMF applying this quality of life increment is questionable.

To the ERG it seems most reasonable and most transparent for the model to assume either that:

- Patients trialling a treatment are modelled as starting from a common baseline quality of life value and the proportion with a PASI75 response gradually increases over the trial period based upon the response rate of the treatment they are trialling.
- Patients trialling a treatment are modelled as starting from a common baseline quality of life value and remain at this quality of life value during the trial period with the PASI75 response only being achieved at the end of the trial period.

The DMF clinical study report provides support for the first bullet point[6], which would tend to favour the more effective treatments and so worsen the cost effectiveness estimates of DMF. But it would be complicated to implement within the company model. As a consequence the ERG exploratory base case will apply the second bullet point which appears to be more in line with previous Committee preferences where a preference has been stated. It will also explore the impact of assuming that the PASI75 response occurs at the start of the trial period causing additional patient gains to be realised during the trial period, which might also argue for differentiating non-responder costs.

Within the current context equalising the trial periods' quality of life value at the baseline while setting discounting and mortality to zero causes the net gain from the DMF sequence of the company base case to fall from 0.105 QALYs to 0.083 QALYs. When coupled with the net cost of £2,561 these result in the cost effectiveness estimate increasing from £24,398 per QALY to £30,843 per QALY. Implementing the same changes for the scenario comparing DMF followed by BSC with BSC has little impact upon net gains, these falling from 0.084 QALYs to 0.083 QALYs. Coupled with the net costs of £2,423 this causes the cost effectiveness estimate to worsen from £28,954 per QALY to £29,160 per QALY. These ICERs are not "real" but are rather illustrative. But the equalisation of the net gain at 0.083 QALYs for the comparison of the company base case sequences and the comparison of the scenario analysis is in line with intuition. The cause of the slight differences in the net costs remains unclear.

Quality of life as a function of the DLQI

The company at clarification provided the mean changes in DLQI by response status separately for DMF, Fumaderm and placebo. For the company sensitivity analysis this data is then mapped onto quality of life using the mapping function reported in the ustekinumab STA [TA180] as drawn from a reanalysis of the Woolacott et al [104] data, with a DLQI coefficient of -0.016.

[6] CSR sections 11.4.1.4 and 11.4.1.5

Table 53: BRIDGE DLQI changes and inferred quality of life increments

	Δ DLQI			Δ EQ-5D QoL		
PASI	DimF	Fum	BSC	DimF	Fum	BSC
<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75-90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

This data is for all patients and is not presented for the subgroup of patients with severe disease. It can also be noted that the DLQI coefficient applied by the company is the lowest of those available, though for the most part the coefficients are of similar magnitude.

The coefficient report by the company for Currie et al [105] is an order of magnitude greater than most of the others, but this is a typo by the company and the coefficient of Currie et al is -0.025 which is not that dissimilar to the TA180 reanalysis.

Currie et al surveyed all patients with a primary diagnosis of psoriasis who were treated at Llandough hospital over a two year period. Patients were sent questionnaires with both the DLQI and the EQ-5D, 94 of patients replying. The estimated quality of life for a DLQI of zero was 0.956 with every DLQI point reducing quality of life by 0.02548, the regression explaining 27% of the variance.

The other outlier reported by the company is the Heredi et al [106] function which includes a variety of other items in addition to the DLQI. However, Heredi et al also report quality of life as a function of the DLQI alone with a coefficient of -0.02, which cross checks with the cited reference.

The above differentiation of the change in DLQI by PASI response and by treatment raises the possibility of it being sensible to differentiate quality of life values by treatment. Given the poor clinical effectiveness of DMF compared to the biologics in the company NMA it might be anticipated that those with a less than PASI50 response might tend to have a smaller DLQI improvement with DMF than with the biologics. Similarly, those with a PASI90 response may still be doing worse with DMF than with the biologics. In this regard it is disappointing that the company NMA has not considered PASI100 response rates.

Consequently, the ERG will conduct scenario analyses which apply the quality of life gains of DMF calculated using the DLQI based upon the -0.016 coefficient of TA180 and the -0.025 coefficient of Currie et al.

Subcutaneous injection training costs

The biologics are typically self injected which required one off training costs to be included. These have typically been estimated as requiring three hours of nurse time. The company model makes no allowance for this. In the opinion of the ERG this is correct since patients in both arms will at some point move onto subcutaneous administration. The scenario analyses that compare single treatments are in order to better understand the model and abstract from the complexities of sequencing. They should not be read as suggesting that patients will not move through treatment sequences. The possible exception to this is if patients are severe and move straight from an oral treatment to infliximab with no further treatments.

Titration costs

The draft SmPC states that:

"If treatment success is observed before the maximum dose is reached, no further increase of dose is necessary. After clinically relevant improvement of the skin lesions has been achieved, consideration should be given to gradual reduction of the daily dose of Skilarence to the maintenance dose required by the individual."

The up titration to the maximum allowable daily dose of 720mg appears to require ongoing assessment. This raises the possibility of more frequent monitoring for DMF during the trial period. The company allows for monthly monitoring during the trial period for DMF and Fumaderm, compared to only once every two months for apremilast and the biologics.

The model assumes that patients down titrate from an average of around 5 daily tablets at the end of the trial period to an average of 3 daily tablets based upon the Fumaderm trial reported by reported in Reich et al.[96] This suggests that on average patients have their dose reduced twice which implies a minimum of two assessments, though this appears to be the floor and the average number of assessments may well be higher than this. The company assumes that after the trial period those with a good response to DMF or Fumaderm require one outpatient visit every two months compared to one outpatient visit every three months for apremilast

and the biologics. This may underestimate the monitoring requirement during the down titration phase.

The ERG will undertake a sensitivity analysis that adds two outpatient visits to those with a good response to DMF or Fumaderm.

Monitoring costs

The draft SmPC states that:

"During treatment a complete blood count with differential should be performed every 3 months… Renal function (e.g. creatinine, blood urea nitrogen and urinalysis) should be checked prior to initiation of treatment and every 3 months thereafter… It is recommended to monitor hepatic function (SGOT, SGPT, gamma-GT, AP) prior to initiation of treatment, and every 3 months thereafter"

The model assumes that full blood counts are required every month but does not cost any visit for these.

For the base case the ERG will make the same assumptions as the company base case but cost those that are in addition to the routine outpatient monitoring schedule at the £36 cost of a 9.22 minute GP appointment from the PSSRU 2016 Unit Costs of Health and Social Care. The ERG will also perform a scenario analysis that reduces the frequency of these tests to those of the draft SmPC.

Probabilistic modelling

The probabilistic modelling samples the assumed common 20% annual discontinuation rate using an arbitrary distribution separately for each treatment. In the opinion of the ERG a sampled value should be applied equally across the treatments. The arbitrary distribution is also not obviously justified.

When Arnold et al [3] is chosen as the source the sampling distribution are arbitrary rather than being drawn from Arnold et al.

The probabilistic modelling samples the assumed administration and monitoring resource use, applying arbitrary distributions. The values are also sampled independently for each treatment which seems likely to overstate the degree of uncertainty around these variables. In

the opinion of the ERG it is better to treat these elements as assumptions and not sample them in the probabilistic modelling.

The probabilistic modelling samples the resource use derived from Fonia et al [2] separately for each treatment. In the opinion of the ERG the sampled values should be applied equally across the treatments.

The probabilistic modelling samples the £255 cost per cycle for non-responders using an arbitrary distribution separately for each treatment. In the opinion of the ERG a sampled value should be applied equally across the treatments. The arbitrary distribution is also not obviously justified.

The unit costs applied to resource use are not sampled. The ERG has not addressed this and as a consequence the degree of uncertainty stemming from this will be understated within the probabilistic modelling.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

In the light of the company submission and the apremilast FAD, the ERG presents a number of different analyses that model the cost effectiveness of:

- Dimethyl fumarate coming before the comparator sequence
- Dimethyl fumarate displacing the 1st line treatment of the comparator sequence
- Dimethyl fumarate as 1st line in a treatment sequence compared to last line in a treatment sequence
- The individual treatments compared to BSC

In the light of the company submission and the apremilast FAD the ERG presents a number of different analyses . For reasons of space the ERG will concentrate upon five comparisons:

- the sequences of the company base case: Analysis 1,
- the comparison of dimethyl fumarate followed by adalimumab and ustekinumab with apremilast followed by adalimumab and ustekinumab: Analysis 2
- dimethyl fumarate with BSC: Analysis 3

- dimethyl fumarate with apremilast: Analysis 4
- dimethyl fumarate with adalimumab: Analysis 5

Since the company is only considering comparators that NICE has approved for use among severe patients it can be argued that the base case should apply the TA103 quality of life increments for severe patients. In the opinion of the ERG this would be more in line with the FAD of TA103, but practice during the intervening STAs has been variable. For the five main comparisons outlined above the ERG will present a full set of sensitivity analyses when using the all patient quality of life estimates and when using the severe patient quality of life estimates.

The cost effectiveness of DMF against the other comparators then follows. There are some forther comparisons of sequences, but given the previous assessments, the five main ERG analyses and the apremilast FAD the ERG concentrates upon pairwise comparisons of DMF with the comparator treatments and the comparator treatments with BSC.

The ERG has revised the company model to:

- Apply a lifetime time horizon
- Take into account the apremilast induction pack cost
- Apply a 12 week trial period for ixekizumab and revise the induction costs accordingly
- Apply the low dose etanercept and ustekinumab NMA estimates
- Equalise the trial period quality of life values between treatments at the baseline value
- Apply 14 days wastage to apremilast, Fumaderm and DMF due to an assumed 28 day pack size for each[7]

[7] Due to the model structure this has been implemented within a placeholder without any discounting, so will be a slight over estimate.

- Revise the costs derived from Fonia et al [2] to reflect the ERG calculation for BSC and more importantly to roughly halve the cost per fortnightly cycle for non-responders during trial periods to only £121

- Apply the £36 cost of a 9.22 minute GP appointment for full blood counts that are not covered by the outpatient monitoring schedule

- Assume indivisible vials for infliximab, and an administration cost of £212 per dose

- Revise the PSA sampling to equalise various cost elements between treatments rather than sample them independently for each treatment

- Revise the PSA to not sample elements that can be argued to be by assumption, such as the number of outpatient monitoring visits

The ERG presents scenario analyses that:

- SA01: Apply a 10 year time horizon

- SA02: Apply the company NMA results for the systemic or PUVA experienced and the company NMA results excluding low quality studies

- SA03: Assume that the quality of life gains among those achieving a PASI75 occur from the start of the trial period rather than the start of the maintenance period

- SA04: Arbitrarily reducing the baseline quality of life to 0.6

- SA05: Apply the quality of life increments of Woolacott et al [104] for severe patients, this also arbitrarily reducing the baseline quality of life value to 0.5 to avoid quality of life ceiling effects

- SA06: Apply the quality of life estimates from applying the DLQI coefficients of the secukinumab STA [TA180] reestimation of Woolacott et al [104] and Currie et al [105] to the BRIDGE trial DMF DLQI changes

- SA07: Apply the discontinuation rates of Arnold et al [3]

- SA08: Assume a trial dose for Fumaderm of 70% that of the BRIDGE trial and a maintenance dose for DMF of 70% that of the BRIDGE trial average dose during weeks 10-16 based upon Reich et al [96]

- SA09: Apply a maintenance dose of 480mg for DMF and for Fumaderm as drawn from Linjen et al [14]

- SA10: Reduce the etanercept drug costs by 26% to reflect previous assessments' modelling of intermittent etanercept

- SA11: Apply two additional outpatient visits among good responders to DMF and Fumaderm for down titration[8]

- SA12: Reduce the frequency of full blood counts, renal monitoring and liver function tests for DMF and Fumaderm to that of the draft DMF SmPC

- SA13: Apply a £225 cost per fortnight per non-responder trialling a treatment as in the company base case

- SA14: Apply 2015-16 NHS reference costs per inpatient day of £477, and also a differentiate the unit cost as £408 for the pre-biologic period and £477 for the post biologic period.

[8] Due to the model structure this has been implemented within a placeholder without any discounting, so will be a slight over estimate.

5.4.1 Five main comparisons: All-patient quality of life

Analysis 1: DMF->Adal->Uste->BSC vs Adal->Uste->BSC: All patient QoL

For the treatment sequences of the company base case the ERG revisions suggest the following cost effectiveness estimates when using the all patient quality of life increments.

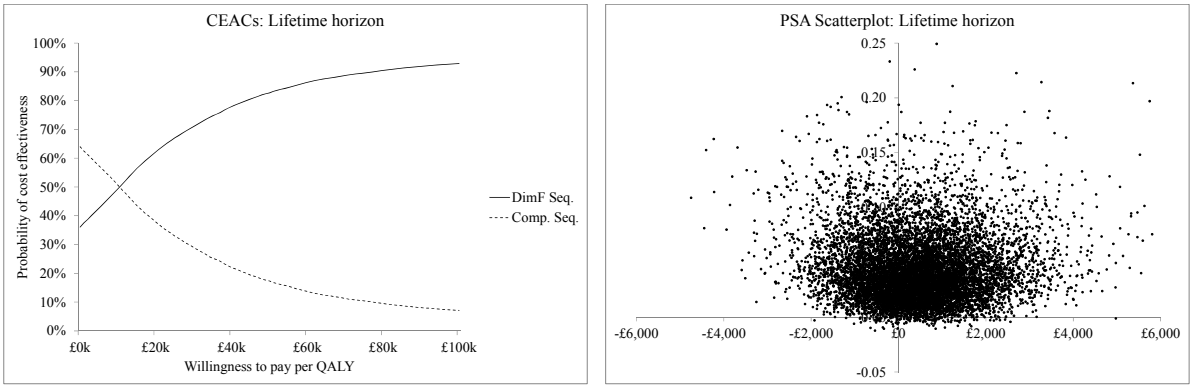
Table 54: Analysis 1: All patient QoL: Deterministic estimates

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->Adal->Uste->BSC	15.484	£131,491	0.043	£532	£12,299
Adal->Uste->BSC	15.441	£130,960			

The ERG revisions have improved the cost effectiveness estimate from £15,476 per QALY to £12,299 per QALY. This suggests that adding DMF to the treatment sequence benefits patients at sufficiently moderate additional cost for it to be cost effective.

The central probabilistic estimates are a net gain of 0.043 QALYs, a net cost of £442 and so a cost effectiveness estimate of £10,193 per QALY. The CEAC and scatterplot are presented below.

Figure 8: Analysis 1: All patient QoL: Probabilistic estimates



Analysis 2: DMF->Adal->Uste->BSC vs Apre->Adal->Uste->BSC: All patient QoL

For the treatment sequences where DMF replaces apremilast with both then being followed by adalimumab and ustekinumab the ERG revisions suggest the following cost effectiveness estimates when using the all patient quality of life increments.

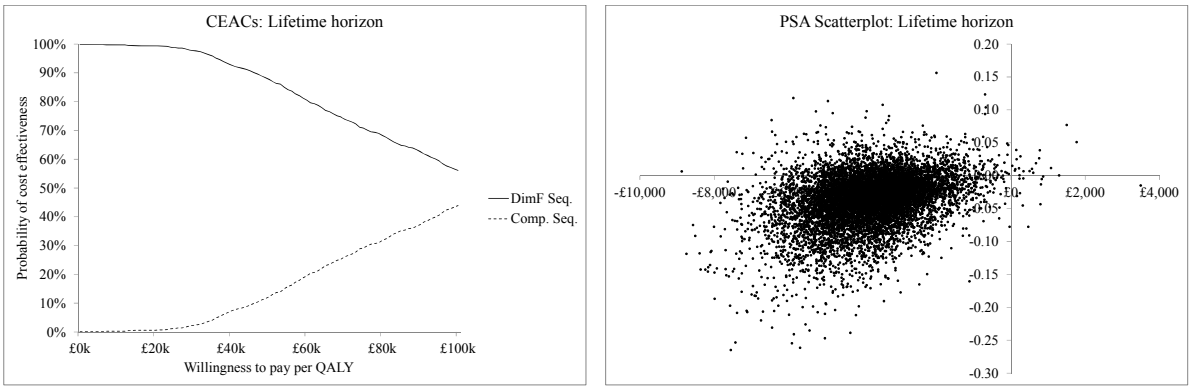
Table 55: Analysis 2: All patient QoL: Deterministic estimates

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->Adal->Uste->BSC	15.484	£131,491	-0.036	-£3,699	£103k SW
Apre->Adal->Uste->BSC	15.520	£135,191			

This suggests that while DMF is worse for patients than apremilast it results in sufficient savings for it to be cost effective. Note that this comparison does not include the apremilast PAS.

The central probabilistic estimates are a net loss of 0.036 QALYs, a net saving of £3,816 and so a cost effectiveness estimate of £105k per QALY in the South West quadrant of the cost effectiveness plane, the CEAC and scatterplot being presented below.

Figure 9: Analysis 2: All patient QoL: Probabilistic estimates



Analysis 3: DMF->BSC vs BSC: All patient QoL

For the direct comparison of DMF with BSC the ERG revisions suggest the following cost effectiveness estimates when using the all patient quality of life increments.

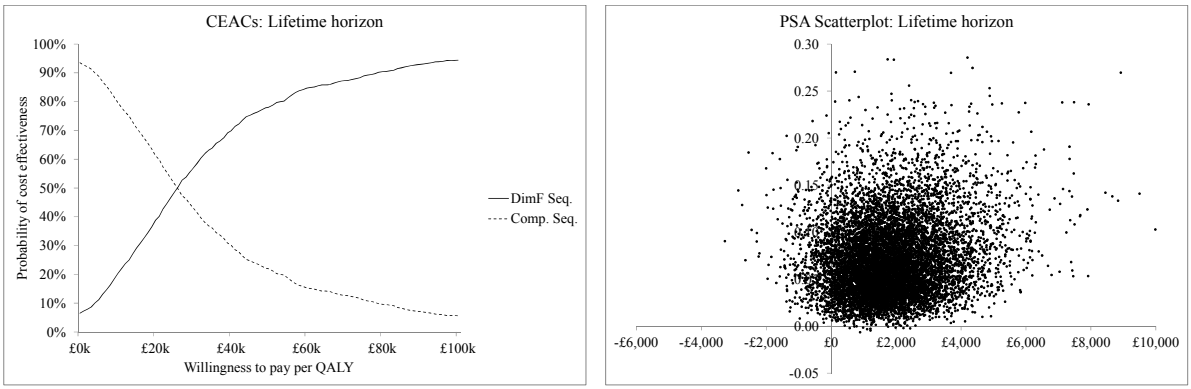
Table 56: Analysis 3: All patient QoL: Deterministic estimates

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF ->BSC	14.889	£96,787	0.069	£1,760	£25,567
BSC	14.820	£95,027			

The ERG revisions improve the estimated cost effectiveness of DMF compared to BSC from £32,805 per QALY of the CS to £25,567 per QALY. This suggests that it may be cost effective when compared to BSC, given the NICE willingness to pay thresholds of £20k per QALY and £30k per QALY.

The central probabilistic estimates are a net gain of 0.071 QALYs, a net cost of £1,817 and so a cost effectiveness estimate of £25,567 per QALY, the CEAC and scatterplot being presented below.

Figure 10: Analysis 3: All patient QoL: Probabilistic estimates



Analysis 4: DMF->BSC vs Apre->BSC: All patient QoL

For the direct comparison of DMF with apremilast the ERG revisions suggest the following cost effectiveness estimates when using the all patient quality of life increments.

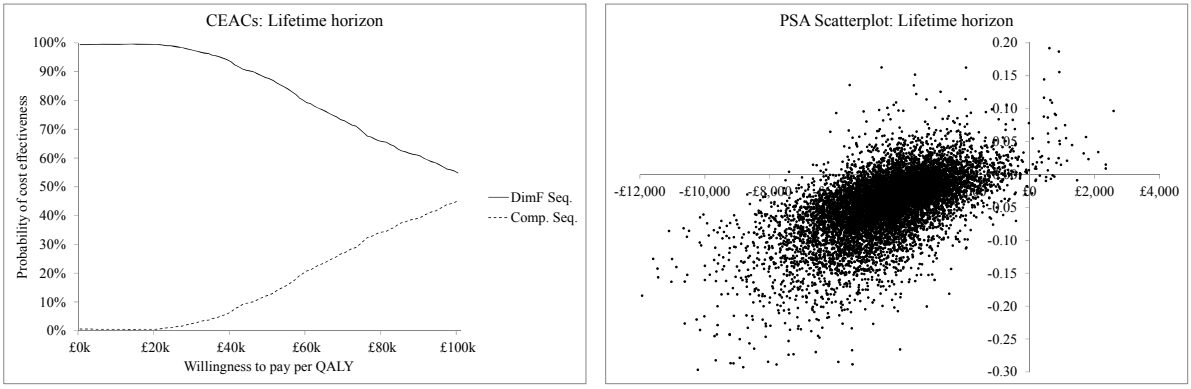
Table 57: Analysis 4: All patient QoL: Deterministic estimates

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->BSC	14.889	£96,787	-0.045	-£4,201	£93,837 SW
Apre->BSC	14.933	£100,988			

The direct comparison of DMF with apremilast results in a similar cost effectiveness estimate as analysis 2 above. DMF results in patient losses but the cost savings are sufficient for DMF to be cost effective. As for analysis 2 above, this does not incorporate the apremilast PAS.

The central probabilistic estimates are a net loss of 0.045 QALYs, a net saving of £4,376 and so a cost effectiveness estimate of £97,289 per QALY in the South West quadrant of the cost effectiveness plane, the CEAC and scatterplot being presented below.

Figure 11: Analysis 4: All patient QoL: Probabilistic estimates



Analysis 5: DMF->BSC vs Adal->BSC: All patient QoL

For the direct comparison of DMF with adalimumab the ERG revisions suggest the following cost effectiveness estimates when using the all patient quality of life increments.

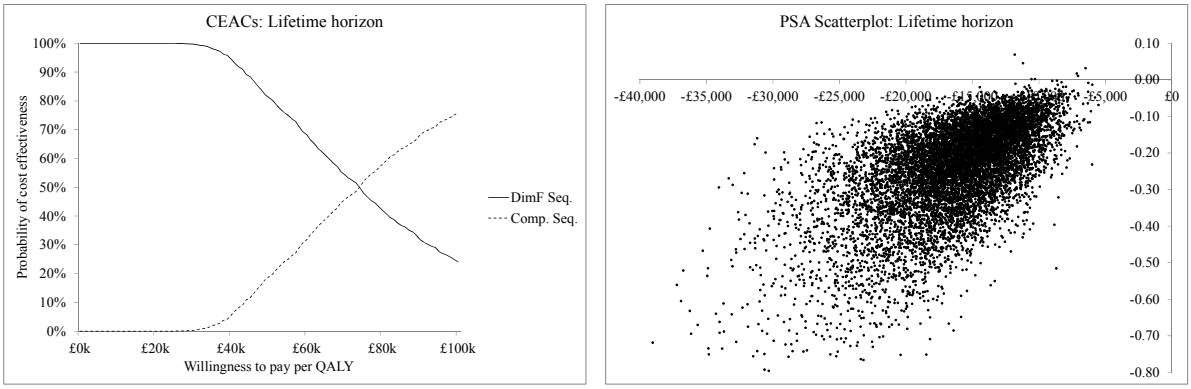
Table 58: Analysis 5: All patient QoL: Deterministic estimates

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF-> BSC	14.889	£96,787	-0.237	-£15,626	£65,934 SW
Adal-> BSC	15.126	£112,412			

For the comparison with adalimumab the patient losses are around five times those of the comparison with apremilast. The cost savings from only using DMF increase though by proportionately less than the patient losses. This results in a csot effectiveness estimate of £65,934 per QALY in the South West quadrant of the cost effectiveness plane, suggesting that DMF is cost effective compared to adalimimab.

The central probabilistic estimates are a net loss of 0.239 QALYs, a net saving of £16,324 and so a cost effectiveness estimate of £68,225 per QALY in the South West quadrant of the cost effectiveness plane, the CEAC and scatterplot being presented below.

Figure 12: Analysis 5: All patient QoL: Probabilistic estimates



5.4.2 Five main comparisons: Severe quality of life

Analysis 1: DMF->Adal->Uste->BSC vs Adal->Uste->BSC: Severe QoL

For the treatment sequences of the company base case the ERG revisions suggest the following cost effectiveness estimates when using the severe quality of life increments.

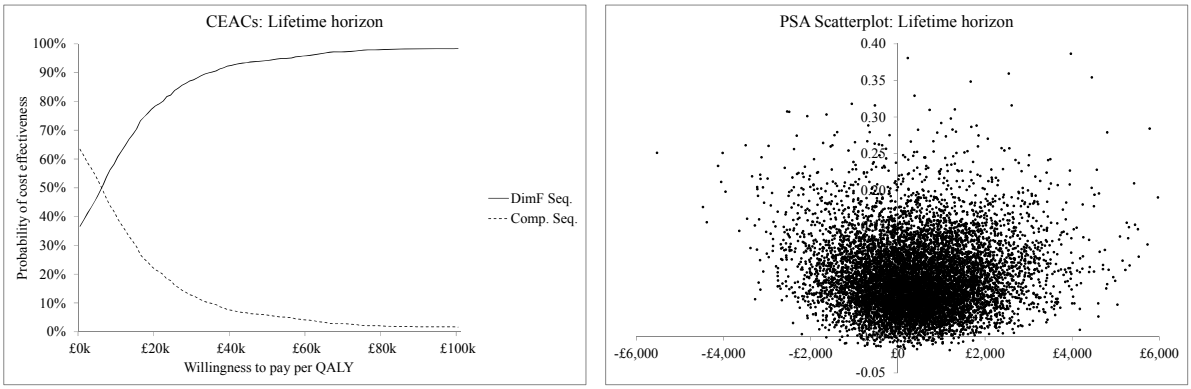
Table 59: Analysis 1: Severe QoL: Deterministic estimates

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->Adal->Uste->BSC	13.758	£131,491	0.077	£532	£6,911
Adal->Uste->BSC	13.682	£130,960			

If the severe patient quality of life increments are applied the patient gains roughly double and the cost effectiveness estimate falls to only £6,911 per QALY.

The central probabilistic estimates are a net gain of 0.080 QALYs, a net cost of £441 and so a cost effectiveness estimate of £5,550 per QALY, the CEAC and scatterplot being presented below.

Figure 13: Analysis 1: Severe QoL: Probabilistic estimates



Analysis 2: DMF->Adal->Uste->BSC vs Apre->Adal->Uste->BSC: Severe QoL

For the treatment sequences where DMF replaces apremilast with both then being followed by adalimumab and ustekinumab the ERG revisions suggest the following cost effectiveness estimates when using the severe quality of life increments.

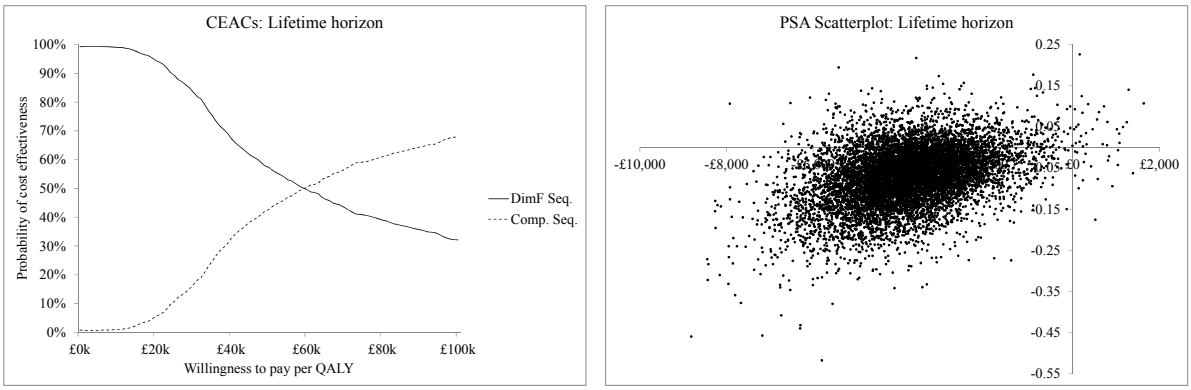
Table 60: Analysis 2: Severe QoL: Deterministic estimates

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->Adal->Uste->BSC	13.758	£131,491	-0.068	-£3,699	£54,383 SW
Apre->Adal->Uste->BSC	13.826	£135,191			

If the severe patient quality of life increments are applied the patient losses from DMF use inctead of apremilast roughly double and the cost effectiveness estimate falls to £54,383 per QALY in the South West quadrant of the cost effectiveness plane. This still suggests that the savings from using DMF instead of apremilast are still sufficient to offset the patient losses. This does not include the apremilast PAS.

The central probabilistic estimates are a net loss of 0.069 QALYs, a net saving of £3,801 and so a cost effectiveness estimate of £54,779 per QALY in the South West quadrant of the cost effectiveness plane, the CEAC and scatterplot being presented below.

Figure 14: Analysis 2: Severe QoL: Probabilistic estimates



Analysis 3: DMF->BSC vs BSC: Severe QoL

For the direct comparison of DMF with BSC the ERG revisions suggest the following cost effectiveness estimates when using the severe quality of life increments.

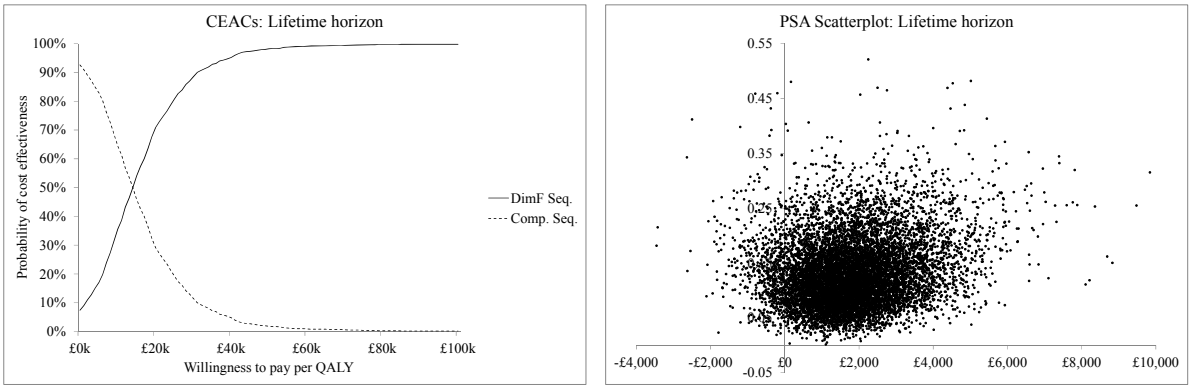
Table 61: Analysis 3: Severe QoL: Deterministic estimates

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF ->BSC	12.655	£96,787	0.125	£1,760	£14,123
BSC	12.531	£95,027			

Applying the severe patient quality of life increments increases the patient gains and the cost effectiveness estimate falls to £14,123 per QALY.

The central probabilistic estimates are a net gain of 0.132 QALYs, a net cost of £1,806 and so a cost effectiveness estimate of £13,700 per QALY, the CEAC and scatterplot being presented below.

Figure 15: Analysis 3: Severe QoL: Probabilistic estimates



Analysis 4: DMF->BSC vs Apre->BSC: Severe QoL

For the direct comparison of DMF with apremilast the ERG revisions suggest the following cost effectiveness estimates when using the severe quality of life increments.

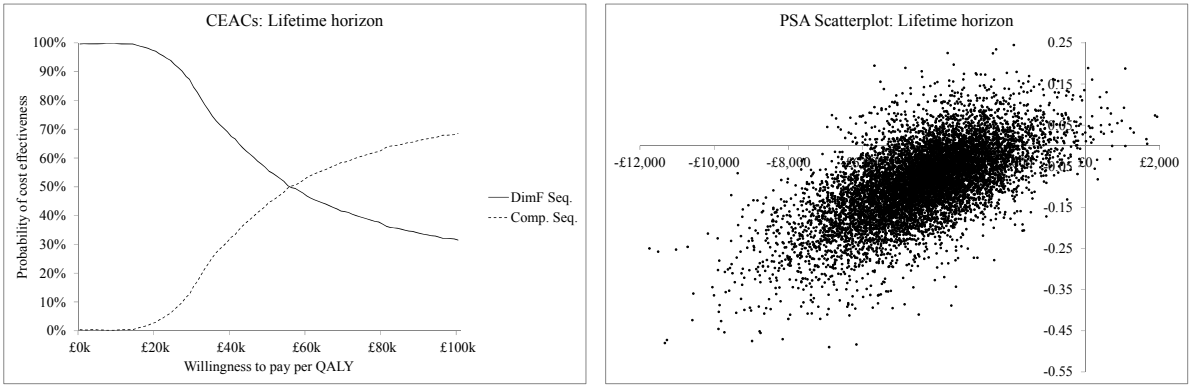
Table 62: Analysis 4: Severe QoL: Deterministic estimates

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF->BSC	12.655	£96,787	-0.084	-£4,201	£49,942 SW
Apre->BSC	12.739	£100,988			

Applying the severe patient quality of life increments roughly doubles the patient losses and the cost effectiveness estimate falls to £49,842 per QALY in the South West quadrant of the cost effectiveness plane. Again, this does not included the apremilast PAS.

The central probabilistic estimates are a net loss of 0.087 QALYs, a net saving of £4,358 and so a cost effectiveness estimate of £49,927 per QALY in the South West quadrant of the cost effectiveness plane, the CEAC and scatterplot being presented below.

Figure 16: Analysis 4: Severe QoL: Probabilistic estimates



Analysis 5: DMF->BSC vs Adal->BSC: Severe QoL

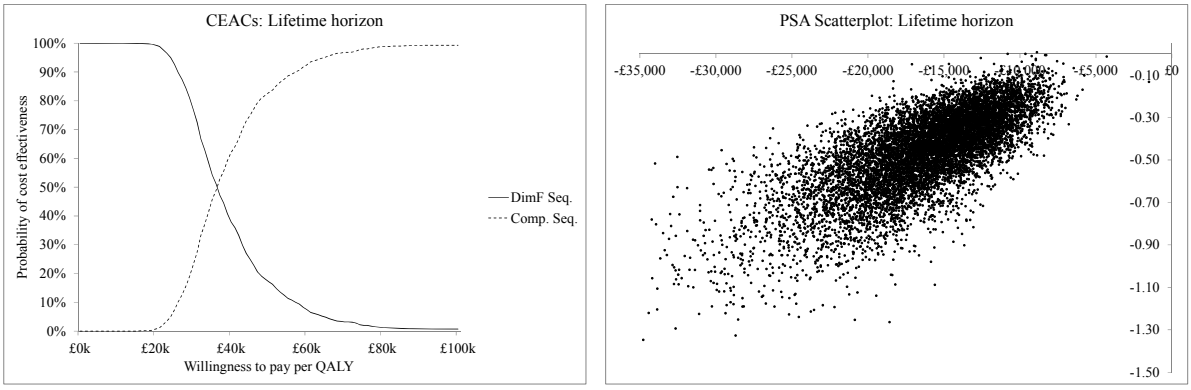
For the direct comparison of DMF with adalimumab the ERG revisions suggest the following cost effectiveness estimates when using the severe quality of life increments.

Table 63: Analysis 5: Severe QoL: Deterministic estimates

	QALYs	Costs	Δ QALYs	Δ Costs	ICER
DMF-> BSC	12.655	£96,787	-0.442	-£15,626	£35,337 SW
Adal-> BSC	13.098	£112,412			

The central probabilistic estimates are a net loss of 0.046 QALYs, a net saving of £16,254 and so a cost effectiveness estimate of £35,634 per QALY in the South West quadrant of the cost effectiveness plane, the CEAC and scatterplot being presented below.

Figure 17: Analysis 5: Severe QoL: Probabilistic estimates



5.4.3 Five main comparisons: Deterministic sensitivity analyses

The ERG deterministic sensitivity analyses result in the following estimates.

Table 64: Five analyses: All patient QoL: Sensitivity Analyses

		DMF->Adal->Uste->BSC Adal->Uste->BSC	DMF->Adal->Uste->BSC Apre->Adal->Uste->BSC	DMF->BSC BSC	DMF->BSC Apre->BSC	DMF->BSC Adal->BSC
		Analysis 1	Analysis 2	Analysis 3	Analysis 4	Analysis 5
	Base case	£12,299	£102k SW	£25,567	£93,837 SW	£65,934 SW
SA01	10 yr horizon	Dominant	£127k SW	£27,049	£95,845 SW	£66,552 SW
SA02a	NMA experienced	£12,654	£102k SW	£25,857	£93,837 SW	£66,497 SW
SA02b	NMA ex LQ	£11,216	£105k SW	£24,772	£96,103 SW	£67,119 SW
SA03	PASI75 QoL trial	£10,017	£92,139 SW	£22,326	£84,161 SW	£59,209 SW
SA04	Baseline QoL 0.6	£12,299	£103k SW	£25,567	£93,837 SW	£65,934 SW
SA05	Severe QoL	£6,911	£54,383 SW	£14,123	£49,942 SW	£35,337 SW
SA06a	QoL DLQI TA180	£13,723	£118k SW	£28,168	£106k SW	£70,462 SW
SA06b	QoL DLQI Currie	£8,725	£74,880 SW	£17,909	£67,568 SW	£44,799 SW
SA07	Discontinuation	Dominant	£183k SW	£20,850	£114k SW	£56,694 SW
SA08	70% DMF dosing	£20,692	£92,465 SW	£30,839	£85,733 SW	£64,403 SW
SA09	DMF 480mg	£25,380	£86,850 SW	£33,783	£81,207 SW	£63,548 SW
SA10	Intermit Etan.	..	..	..	..	..
SA11	DMF +2 OP	£13,127	£102k SW	£26,087	£93,037 SW	£65,783 SW
SA12	DMF monit. freq.	£8,396	£107k SW	£23,115	£97,605 SW	£66,646 SW
SA13	£225 non-resp.	£28,403	£102k SW	£36,021	£93,747 SW	£65,847 SW
SA14a	£477 IP	£14,851	£83,766 SW	£25,287	£77,620 SW	£58,658 SW
SA14b	£408/£477 IP	£13,108	£95,889 SW	£25,430	£88,100 SW	£63,358 SW

Table 65: Five analyses: Severe patient QoL: Sensitivity Analyses

		DMF->Adal->Uste->BSC Adal->Uste->BSC	DMF->Adal->Uste->BSC Apre->Adal->Uste->BSC	DMF->BSC BSC	DMF->BSC Apre->BSC	DMF->BSC Adal->BSC
		Analysis 1	Analysis 2	Analysis 3	Analysis 4	Analysis 5
	Base case	£6,911	£54,383 SW	£14,123	£49,942 SW	£35,337 SW
SA01	10 yr horizon	Dominant	£66,857 SW	£15,006	£51,001 SW	£35,661 SW
SA02a	NMA experienced	£7,090	£54,320 SW	£14,256	£49,942 SW	£35,631 SW
SA02b	NMA ex LQ	£6,296	£56,047 SW	£13,694	£51,259 SW	£36,064 SW
SA03	PASI75 QoL trial	£5,512	£48,629 SW	£12,186	£44,552 SW	£31,559 SW
SA04	Baseline QoL 0.6	£6,911	£54,383 SW	£14,123	£49,942 SW	£35,337 SW
SA05	Severe QoL	..	..	..	..	..
SA06a	QoL DLQI TA180	..	..	..	..	..
SA06b	QoL DLQI Currie	..	..	..	..	..
SA07	Discontinuation	Dominant	£96,661 SW	£11,365	£60,486 SW	£30,353 SW
SA08	70% DMF dosing	£11,628	£49,049 SW	£17,036	£45,629 SW	£34,516 SW
SA09	DMF 480mg	£14,262	£46,070 SW	£18,662	£43,220 SW	£34,058 SW
SA10	Intermit Etan.	..	..	..	..	..
SA11	DMF +2 OP	£7,377	£53,857 SW	£14,411	£49,517 SW	£35,256 SW
SA12	DMF monit. freq.	£4,718	£56,863 SW	£12,769	£51,948 SW	£35,719 SW
SA13	£225 non-resp.	£15,961	£54,052 SW	£19,899	£49,895 SW	£35,290 SW
SA14a	£477 IP	£8,345	£44,435 SW	£13,969	£41,311 SW	£31,437 SW
SA14b	£408/£477 IP	£7,366	£50,866 SW	£14,048	£46,889 SW	£33,956 SW

The cost effectiveness estimates for DMF shows some sensitivity to:

- The time horizon
- Whether PASI75 patients experience their response early in the trial period
- Applying the severe patient quality of life increments
- Applying the DLQI function of Currie et al
- Applying the discontinuation rates of Arnold et al

- DMF maintenance dosing
- The fortnightly cost of non-responders during trial periods
- The cost per inpatient day

Additional treatment sequences

Other treatment sequences can be considered that compare adding DMF to the start of a sequence with adding it to the end, and with sequences containing etanercept.

Table 66: *Additional sequences*

		DMF->Adal->Uste->BSC Adal->Uste->DMF->BSC	DMF->Apre->Adal->Uste Apre->Adal->Uste->DMF	DMF->Etan->Uste->BSC Etan->Uste->BSC	DMF->Etan->Uste->BSC Etan->Uste->-DMF->BSC
	Base case	£88,456 SW	£103k SW	£15,964	£90,581 SW
SA01	10 yr horizon	£107k SW	£112k SW	Dominant	£111k SW
SA02a	NMA experienced	£87,241 SW	£102k SW	£16,235	£88,598 SW
SA02b	NMA ex LQ	£93,017 SW	£108k SW	£14,835	£94,611 SW
SA03	PASI75 QoL trial	£104k SW	£100k SW	£13,332	£99,947 SW
SA04	Baseline QoL 0.6	£88,456 SW	£103k SW	£15,964	£90,581 SW
SA05	Severe QoL	£45,843 SW	£53,659 SW	£8,934	£46,764 SW
SA06a	QoL DLQI TA180	£91,240 SW	£108k SW	£17,659	£95,908 SW
SA06b	QoL DLQI Currie	£58,010 SW	£68,739 SW	£11,228	£60,977 SW
SA07	Discontinuation	£95,347 SW	£102k SW	Dominant	£96,703 SW
SA08	70% DMF dosing	£80,613 SW	£94,751 SW	£23,517	£82,313 SW
SA09	DMF 480mg	£76,232 SW	£89,751 SW	£27,735	£77,696 SW
SA10	Intermit Etan.	£88,456 SW	£103k SW	£18,002	£77,804 SW
SA11	DMF +2 OP	£88,456 SW	£103k SW	£16,709	£90,581 SW
SA12	DMF monit. freq.	£92,305 SW	£108k SW	£12,452	£94,638 SW
SA13	£225 non-resp.	£76,230 SW	£91,389 SW	£30,521	£78,143 SW
SA14a	£477 IP	£74,279 SW	£87,945 SW	£17,712	£75,753 SW
SA14b	£408/£477 IP	£83,437 SW	£98,125 SW	£16,494	£85,332 SW

While not shown in the above, the patient differences between sequences that add DMF to the start of a sequence with those that add it to the end are small, typically around or less than 0.01 QALYs. These lead to quite large estimates for the cost per QALY in the South West quadrant of the cost effectiveness plane.

Replacing adalimumab in the sequences of the company base case with etanercept results in a slightly worse cost effectiveness estimate for DMF than when compared to adalimumab.

5.4.4 Comparisons with other treatments

When DMF is compared with the individual treatments it is typically associated with patient losses, but the savings are sufficient to justify these. These results show some sensitivity to whether the severe quality of life increments or the Currie et al DLQI quality of life function is applied, with etanercept also being sensitive to whether the direct drug costs are reduced to those assumed for intermittent dosing. Note that the above does not include the secukinumab or ixekizumab PASs.

This is with the exception of Fumaderm. Given the company NMA DMF is estimated to be slightly inferior to Fumaderm but also to only result in relatively modest cost savings. Depending upon which sensitivity analyses are applied these can either singly or jointly result in DMF not being cost effective compared to apremilast. Obviously, if the company preferred assumption of equivalence is applied Fumaderm is formally dominated due to the higher company estimates for the Fumaderm drug cost.

Table 67: Dimethyl fumarate comparisons with individual treatments

		DMF->BSC Etan->BSC	DMF->BSC Fuma->BSC	DMF->BSC Infl->BSC	DMF->BSC Secu->BSC	DMF->BSC Uste->BSC	DMF->BSC Ixek->BSC
	Base case	£70,444 SW	£34,207 SW	£77,272 SW	£128k SW	£65,822 SW	£116k SW
SA01	10 yr horizon	£70,526 SW	£34,730 SW	£77,765 SW	£129k SW	£66,527 SW	£117k SW
SA02a	NMA experienced	£69,936 SW	£30,419 SW	£77,101 SW	£128k SW	£65,468 SW	£115k SW
SA02b	NMA ex LQ	£71,408 SW	£34,951 SW	£78,269 SW	£129k SW	£66,187 SW	£117k SW
SA03	PASI75 QoL trial	£66,854 SW	£30,672 SW	£73,324 SW	£119k SW	£59,126 SW	£108k SW
SA04	Baseline QoL 0.6	£70,444 SW	£34,207 SW	£77,272 SW	£128k SW	£65,822 SW	£116k SW
SA05	Severe QoL	£37,270 SW	£18,180 SW	£41,441 SW	£69,069 SW	£35,332 SW	£62,568 SW
SA06a	QoL DLQI TA180	£79,648 SW	£39,214 SW	£80,317 SW	£132k SW	£69,470 SW	£117k SW
SA06b	QoL DLQI Currie	£50,639 SW	£24,932 SW	£51,065 SW	£84,417 SW	£44,169 SW	£74,872 SW
SA07	Discontinuation	£76,390 SW	£32,166 SW	£117k SW	£140k SW	£52,145 SW	£125k SW
SA08	70% DMF dosing	£67,030 SW	£19,518 SW	£76,227 SW	£127k SW	£64,552 SW	£115k SW
SA09	DMF 480mg	£65,124 SW	£45,740 SW	£75,644 SW	£126k SW	£63,843 SW	£114k SW
SA10	Intermit Etan.	£35,318 SW	..	..	..	..	..
SA11	DMF +2 OP	£70,107 SW	£34,609 SW	£77,169 SW	£128k SW	£65,697 SW	£116k SW
SA12	DMF monit. freq.	£72,031 SW	£32,309 SW	£77,758 SW	£129k SW	£66,413 SW	£116k SW
SA13	£225 non-resp.	£68,407 SW	£34,116 SW	£76,295 SW	£127k SW	£65,736 SW	£115k SW
SA14a	£477 IP	£60,792 SW	£34,179 SW	£70,881 SW	£122k SW	£58,935 SW	£109k SW
SA14b	£408/£477 IP	£67,027 SW	£34,193 SW	£75,009 SW	£126k SW	£63,384 SW	£113k SW

5.4.5 Comparisons with BSC

When the individual treatments are compared with BSC with the exception of Fumaderm their cost effectiveness is relatively poor. The only sensitivity analyses that suggest this may not be the case are those that apply the severe quality of life increments and the Currie et al DLQI quality of life function. Note that the above does not include the apremilast, secukinumab or ixekizumab PASs.

Table 68: ***Treatment comparisons with BSC***

		Aper->BSC BSC	Adal->BSC BSC	Etan->BSC BSC	Fuma->BSC BSC	Infl->BSC BSC	Secu->BSC BSC	Uste->BSC BSC	Ixek->BSC BSC
	Base case	£52,475	£56,850	£52,806	£27,849	£68,719	£111k	£58,006	£102k
SA01	10 yr horizon	£54,550	£57,822	£53,754	£29,113	£69,572	£113k	£59,005	£104k
SA02a	NMA experienced	£52,835	£57,267	£52,806	£27,256	£68,719	£111k	£57,880	£102k
SA02b	NMA ex LQ	£51,816	£56,962	£52,455	£27,337	£68,839	£111k	£57,765	£102k
SA03	PASI75 QoL trial	£46,304	£50,727	£48,461	£24,487	£64,287	£102k	£51,816	£94,778
SA04	Baseline QoL 0.6	£52,475	£56,850	£52,806	£27,849	£68,719	£111k	£58,006	£102k
SA05	Severe QoL	£28,561	£30,674	£28,410	£15,226	£37,033	£60,251	£31,309	£55,569
SA06a	QoL DLQI TA180	£58,440	£61,167	£59,095	£31,001	£72,102	£116k	£61,725	£105k
SA06b	QoL DLQI Currie	£37,156	£38,889	£37,572	£19,710	£45,842	£74,069	£39,244	£67,041
SA07	Discontinuation	£47,823	£50,693	£50,431	£23,681	£77,032	£111k	£49,282	£102k
SA08	70% DMF dosing	£52,475	£56,850	£52,806	£27,849	£68,719	£111k	£58,006	£102k
SA09	DMF 480mg	£52,475	£56,850	£52,806	£36,942	£68,719	£111k	£58,006	£102k
SA10	Intermit Etan.	£52,475	£56,850	£31,486	£27,849	£68,719	£111k	£58,006	£102k
SA11	DMF +2 OP	£52,475	£56,850	£52,806	£28,338	£68,719	£111k	£58,006	£102k
SA12	DMF monit. freq.	£52,475	£56,850	£52,806	£25,544	£68,719	£111k	£58,006	£102k
SA13	£225 non-resp.	£58,774	£59,135	£55,679	£35,518	£69,633	£112k	£59,967	£103k
SA14a	£477 IP	£45,914	£51,148	£46,838	£27,636	£63,339	£106k	£52,402	£97,463
SA14b	£408/£477 IP	£50,131	£54,822	£50,678	£27,745	£66,808	£109k	£56,015	£100k

5.5 Conclusions of the cost effectiveness section

The economic review has presented the company case, reviewed it and presented alternative estimates using the clinical effectiveness estimates of the company NMA. A key concern is that DMF has not been assessed across its licensed indication. The CS does not address the cost effectiveness of DMF compared to a number of non-biological systemic therapies as required by the scope.

For the comparators that are considered in the opinion of the ERG the company base case analysis is biased on a number of counts.

It may be questionable to compare sequences with different numbers of treatments within them, as in the company base case. By design, a sequence with more treatments will almost always result in greater patient quality-of-life gains than one with fewer.

The main source of bias within the model is restricting the time horizon to 10 years, which is insufficient to permit the treatment sequences of the company base case to play out.

The other main source of bias within the model is the fortnightly cost that is assumed to apply to those trialling treatments. It appears that the company has inadvertently doubled this. This introduces a quite serious bias against treatment sequences with more treatments than the comparator sequence.

The company appears to have applied the clinical effectiveness of high dose etanercept and ustekinumab when the low dose estimates appear more appropriate.

DMF is only indicated for plaque psoriasis when others such as apremilast and etanercept are indicated for both plaque psoriasis and psoriatic arthritis. It may not be clinically appropriate to treat patients with both clinical conditions with DMF, but the cost effectiveness of of DMF is likely to be poor in patients requiring treatment for both psoriatic arthtitis and plaque psoriasis.

The submission may have introduced bias by assuming that the patient quality of life for those trialling a treatment is higher if trialled after having failed on a previous treatment than if trialled

1st line. It may be more reasonable to assume the same quality of life when trialling a treatment regardless of the point in the sequence it is being trialled at. It may also be more reasonable to assume that those attaining a response do so reasonably swiftly rather than this only occurring at the end of the trial period. This would imply that quality of life values when trialling treatments should be treatment specific, which might in turn argue for different psoriasis costs when trialling treatments.

In the opinion of the ERG the CS pays insufficient attention to the comparison with apremilast, to adequately explore circumstances in which DMF would be cost effective compared to apremilast.

The CS has chosen to compare DMF to treatments NICE has only approved for patients with severe disease. The company cost effectiveness estimates for DMF in part rests upon an assumption that those being treated do not have severe disease. This limits patient benefits and also reduces the cost offsets of the more effective treatments. This in part causes the company to estimate the biologics to have a very poor cost effectiveness compared to BSC. In the opinion of the ERG the CS does not sufficiently consider what the NICE restrictions imply for model inputs specific to the severe patient group. At a minimum it can be argued that the quality of life increments for the various PASI responses should be those of severe patients rather than of all patients.

It is also assumed that the quality of life increments for a sub PASI50 response and for a PASI90 response are the same regardless of treatment. This may be a reasonable assumption to make across treatments with similar response rates. The response rates for DMF are worse than those of apremilast and very much worse than those of the biologics. Consequently, the quality of life increments for a sub PASI50 response and for a PASI90 response of DMF might be worse than those of the comparators.

The dosing for DMF during maintenance is drawn from the FUTURE trial of Fumaderm. The BRIDGE trial average end of induction trial dose for DMF was similar to that of Fumaderm. These were both above the end of induction trial dose for Fumaderm during the FUTURE trial.

The FUTURE trial maintenance dose for Fumaderm may consequently be an underestimate of that for DMF.

It is unclear whether there would be additional down titration costs. The monitoring frequency for DMF is also unclear given the company submission and draft SmPC.

Adverse events have not been considered. The observed rate of serious adverse events may not be a particular concern between the arms of the BRIDGE trial. Of more concern is the high rate of more moderate adverse events and whether these would lead to additional GP visits or prescriptions.

As in all plaque psoriasis assessments there is uncertainty around the resource use for non-responders receiving treatments and for those on BSC. Fonia et al has been criticised as perhaps providing rates that are too high due, reflecting tertiary care, but it should be borne in mind that the company is assessing the cost effectiveness of DMF against treatments approved by NICE only for severe patients. The inpatient cost per day of Fonia et al may also now be too low given current reference costs and possibly shorter lengths of stay.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG has made a number of revisions to the base case. The more important of these are explored through univariable sensitivity analyses, with further univariable sensitivity analyses also being presented. Given the nature of the assessment, the number of comparators and the FADs of previous NICE assessments the ERG presents an extensive set of pairwise comparisons of treatment sequences. But it focusses upon five:

- Analysis 1:
  - Dimethyl fumarate to adalimumab to ustekinumab to BSC
  - Adalimumab to ustekinumab to BSC
- Analysis 2:
  - Dimethyl fumarate to adalimumab to ustekinumab to BSC
  - Apremilast to adalimumab to ustekinumab to BSC
- Analysis 3:
  - Dimethyl fumarate to BSC
  - BSC
- Analysis 4:
  - Dimethyl fumarate to BSC
  - Apremilast to BSC
- Analysis 5:
  - Dimethyl fumarate to BSC
  - Adalimumab to BSC

These comparisons have the full range of deterministic sensitivity analyses applied to them and are also modelled probabilistically in line with the NICE methods guide. The impact of applying the TA103 quality of life values for severe patients is also fully explored for these comparisons.

For analysis 1, comparing DMF prior to adalimumab and ustekinumab, the company base case estimated the DMF sequence to dominate the comparator sequence when using a 10 year time horizon and to have a cost effectiveness of £15,467 per QALY when using a lifetime horizon.

The ERG analysis improves the base case cost effectiveness estimate over the patient lifetime to £12,299 per QALY, in large part due to the revised cost of non-responders. The cost effectiveness estimate improves still further if patients are early responders and realise gains from treatment before the end of the trial periods, to £10,017 per QALY, if the severe patient quality of life increments are applied, to £6,911 per QALY, and if the DMF monitoring frequency is in line with the draft SmPC, to £8,396 per QALY, while applying the discontinuation rates of Arnold et al results in dominance. A higher maintenance dose for DMF of 480mg worsens the cost effectiveness estimate to £25,380 per QALY while applying 2015-16 NHS reference costs to inpatient admissions also slightly worsens the cost effectiveness estimates to £13,180 to £14,851 per QALY.

The cost effectiveness estimate if the severe patient quality of life values are appropriate of £6,911 per QALY improves further if patients are early responders, to £5,512 per QALY and with the draft SmPC monitoring to £4,718 per QALY. Higher DMF dosing of 480mg worsens it to £14,262 per QALY while current reference costs for inpatients worsens it to £7,366 to £8,345 per QALY.

For analysis 2, comparing DMF followed by adalimumab and ustekinumab with apremilast followed by adalimumab and ustekinumab, DMF is associated with reasonable patient losses but also cost savings at the apremilast list price. These result in a cost effectiveness estimate in the South West, the company modelling assumptions estimating a cost effectiveness of £123k per QALY over a 10 year time horizon and £98,894 per QALY over a lifetime horizon. The ERG revised base case with a lifetime horizon estimates a cost effectiveness in the South West quadrant of £103k per QALY. All sensitivity analyses estimate DMF to be associated with patient losses but cost savings, so points in the South West quadrant. If patients are early responders the cost effectiveness of DMF worsens to £92,139 per QALY, while the severe patient quality of life values worsen it to £54,383 per QALY. The SmPC dimethyl monitoring frequency improves it to £107k per QALY. A dimethyl maintenance dose of 480mg worsens it to £86,850 per QALY while current IP reference costs worsen it to between £83,766 and £95,889 per QALY.

The cost effectiveness estimate if the severe patient quality of life values are appropriate of £54,383 per QALY further worsens if patients are early responders, to £48,629 per QALY. It improves quite noticeably to £96,661 per QALY if the discontinuation rates of Arnold et al are applied, and improves slightly to £56,863 per QALY if the monitoring frequency of the draft SmPC is applied. A DMF maintenance dose of 480mg worsens it, to £46,070 per QALY and current IP costs also improve it to between £44,435 and £50,866 per QALY.

For analysis 3, comparing DMF with BSC, the cost effectiveness of DMF using the company assumptions is £35,256 per QALY over a 10 year time horizon and £32,805 per QALY over a lifetime. The ERG estimate is also very much worse than that of analysis 1 at £25,567 per QALY. This worsening compared to analysis 1 is largely due to postponing adalimumab and ustekinumab which are both estimated to have rather poor cost effectiveness estimates. The severe quality of life estimates improve it to £14,123 per QALY and applying the discontinuation rates of Arnold et al improves it to £20,850 per QALY. DMF maintenance dosing of 480mg worsens it to £33,783 per QALY but current IP unit costs have little impact.

The cost effectiveness estimate if the severe patient quality of life values are appropriate of £14,123 per QALY improves to £12,186 per QALY if patients are early responders, to £11,365 per QALY if the discontinuation rates of Arnold et al are applied and to £12,769 if the draft SmPC monitoring is applied. DMF maintenance dosing of 480mg worsens it to £18,662 per QALY but again current IP unit costs have little impact.

For analysis 4, comparing DMF with apremilast, the cost effectiveness estimates of the company in the South West quadrant of £96,093 per QALY over a 10 year time horizon is somewhat worse than that of analysis 2, while the lifetime estimate of £94,400 per QALY is broadly in line with that of analysis 2. The ERG revised base cases apply a lifetime horizon and the cost effectiveness estimate of £93,837 per QALY is reasonably aligned with that of analysis 2. This underlines the differences that arise between analysis 1 and analysis 3 where an intervening cost ineffective sequence had a marked impact on the cost effectiveness estimate due to discounting and all cause mortality effects. The other element to note is the artefact introduced by the 10 year horizon. Selecting 10-year horizon markedly improves the cost effectiveness of extended sequences inanalyses 1 and 2 but has little impact upon short sequences in analyses 3 and 4,

underlining the need for a lifetime horizon when the longer treatment sequences are being compared.

For analysis 5 which compares DMF with adalimumab, DMF is always estimated to result in patient losses in quality-of-life but also to yield cost savings and so cost effectiveness estimates in the South West quadrant of the cost effectiveness plane. The company base case assumptions result in estimates in the South West quadrant of £68,054 per QALY for a 10 year time horizon and £67,381 per QALY for a lifetime horizon. The ERG revised base case when the all patient quality of life values are applied this result in an estimate of £65,934 per QALY in the South West suggesting that DMF is cost effective. Early responders worsen this to £59,209 per QALY while the severe patient quality of live values worsen it to £35,337 per QALY. The Arnold et al discontinuation rates worsen it to £56,694 per QALY, but a DMF maintenance dose of 480mg only worsens it to £63,548 per QALY. Current IP unit costs worsen it to between £58,658 and £63,358 per QALY.

The cost effectiveness estimate if the severe patient quality of life values are appropriate of £35,337 per QALY in the South West worsens to £31,559 per QALY if patients are early responders and to £30,353 per QALY if the Arnold et al discontinuation rates are applied. A DMF maintenance dose of 480mg only worsens it to £34,058 per QALY, and current IP unit costs worsen it to between £31,437 and £33,956 per QALY.

The central estimates of costs effectiveness of the probabilistic modelling are broadly in line with the corresponding deterministic estimates.

A number of other comparisons are also made by the ERG with the default being to use the all patient quality of life values. These comparisons can be broadly grouped into those where DMF 1st line is compared to DMF last in line, those where DMF followed by BSC is compared with the other treatments followed by BSC and those where the other active treatments are compared with BSC. The latter are for model validation in the light of the FADs of previous NICE assessments.

In brief, 1st line DMF compared to last in line DMF causing only quite small patient losses. There are also cost savings which result in cost effectiveness estimates in the South West quadrant that suggest 1st line use is cost effective. These results show some sensitivity to whether the all patient or the severe patient quality of life values are used, and the DMF maintenance dose that is assumed.

DMF compared to all the other comparators results in patient losses. But there are also cost savings and these are sufficient to offset the patient losses. The possible exception to this within the univariable sensitivity analyses that are presented is for the comparison with Fumaderm. These results show some sensitivity to whether patients are early responders, whether the severe patient quality of life values are applied and the DMF dosing that is assumed.

The other treatments relative to BSC result in more sizeable patient gains. But there are considerable additional net costs. The base case for Fumaderm is estimated to be within the upper NICE threshold of £30k per QALY, but none of the other treatments are estimated to be cost effective. The cost effectiveness for apremilast of £52,475 per QALY compared to BSC is in line with the most of the biologics but it should be borne in mind that this does not include the apremilast PAS. The estimate for infliximab is higher still. Those for secukinumab and ixekizumab are above £100k per QALY, but again these estimates to not include the PASs.

7 END OF LIFE

In the opinion of the ERG the NICE end-of-life criteria are not met, i.e. the treatment is not indicated for patients with a short life expectancy (less than 24 months) and there is no evidence that treatment extends life by at least an additional 3 months, compared to current NHS care.

8 OVERALL CONCLUSION

The main differences of opinion between the company and the ERG and uncertainties in the economics are:

- Should systemic non-biologic treatments other than apremilast be modelled?
- Has the economic model paid sufficient attention to the comparison with apremilast?
- Has the economic model sufficiently reflected comparator treatments which are only approved by NICE for severe patients?
- Should the clinical estimates for low dose etanercept or high dose etanercept be applied?
- Should the clinical estimates for low dose ustekinumab or high dose usteminumab be applied?
- Is a 10 year time horizon sufficient or is a lifetime horizon more appropriate?
- What quality of life should be applied for those trialling treatments, and should it be differentiated between treatments due to early response?
- Are the quality of life increments for a sub PASI50 response and a PASI90 response for a treatment with poor response rates likely to be the same as those for a treatment with good response rates?
- Does the Fumaderm FUTURE trial give a reasonable estimate for the maintenance dose of DMF, in the light of its end of induction mean dose being somewhat less than that of the BRIDGE trial?
- What fortnightly cost should be applied for those trialling treatments?
- How should the costs of Fonia et al be viewed in the light of the patient group and the current NHS reference costs?
- Should non-serious adverse events be costed?

In summary the CS base case inserts 1st line DMF in a sequence before 2nd line adalimumab and 3rd line ustekinumab and compares it with 1st line adalimumab and 2nd line ustekinumab. DMF postpones treatment with the biologics. The CS base case applies a 10 year horizon and estimates that the DMF sequence dominates the comparator sequence. Revising the CS base case to apply a lifetime horizon worsens the cost effectiveness of the DMF sequence to £15,467 per QALY.

ERG revisions to the company base case suggest that the cost effectiveness of the CS DMF sequence is £12,299 per QALY over a lifetime horizon. This compares to an ERG estimate for DMF compared to BSC of £25,567 per QALY over a lifetime horizon. The difference between these estimates is largely by construction. The insertion of another treatment into a sequence results in patient QALY gains, almost regardless of how poorly it performs clinically. But the main effect in the model is that it delays the adoption of the biologics. The model estimates that the biologics have a very poor cost effectiveness. Delay reduces the impact of the cost-ineffective biologics through discounting and all-cause mortality. If discounting and all-cause mortality is set to zero the ERG £12,299 per QALY estimate for the DMF sequence is revised to be £24,883 per QALY which is quite similar to the £25,567 per QALY estimate when DMF is directly compared with BSC. By model construction it appears that anything that delays the cost-ineffective biologics, including no treatment at all, will improve the overall cost effectiveness of the treatment sequence.

The focus of the CS is also upon comparison with the expensive biologics. Less emphasis is placed upon comparison with apremilast. At list prices apremilast is somewhat cheaper than the biologics, and cheaper still when the patient access schemes are taken into account. The CS also applies quality of life values for moderate to severe patients when all the comparators it considers, including apremilast, have only been approved by NICE for severe patients. Head to head comparisons with apremilast at the discounted apremilast price are reported in the commercial-in-confidence appendix. They suggest that under a number of scenarios DMF may not be cost effective when compared to apremilast.

In the opinion of the ERG, DMF is most likely to be used in practice as an alternative to other systemic non-biologic therapies, consistent with its licensed indication and trial data. The head-to-head performance of DMF and other systemic non-biologic therapies has not been assessed.

8.1 Implications for research

If DMF is to be used in the indication proposed by the company in its submission, then adequately powered clinical trials should directly inform equivalence with Fumaderm in the relevant patient population i.e. patients who have completed or were ineligible for systemic non-biologic therapies. Trial design should better inform long term follow-up, discontinuation sequencing and resource use uncertainties. Inclusion of a genenic health-related quality of life measure would reduce modelling requirements.

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10 APPENDICES

A confidential PAS appendix is supplied separately.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE the end of **1 June 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Positioning of DMF (LAS41008)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the report the ERG disagree with the positioning of DMF based on clinical feedback. They also state that agreement on the exclusion of non-biologic therapies was not reached at the Decision Problem meeting. Key extracts from the report are below: Page 24-25, Section 1.6.2 The ERG report states: *The ERG disagree with the decision problem positioning of DMF, to be used when non-biological systemic agents are not appropriate or have failed. We consider that DMF will be a valid treatment option after topical therapies have been used, in line with the majority of the evidence in the BRIDGE trial, and (according to ERG's clinical expert) current use of fumaderm in the UK.* Page 42, Section 3.3 The ERG report states *'In clarification response 2, the company reiterated that in clinical practice DMF is likely to be positioned where other oral systemic therapies are clinically inappropriate, therefore they are not relevant comparators. The company state that this was agreed with NICE at the Decision Problem meeting, however,*	Not applicable.	The view of the ERG is misleading and whilst we appreciate and recognise the input from the ERG clinical expert this does not reflect the feedback received from the wider clinical community. As per the Almirall response to the ERG clarification questions based on feedback from UK dermatologists using FAEs in clinical practice, the profile of the typical patient treated with FAEs, is a patient who is: • pre-biologic (i.e. has not reached the NICE recommended criteria for treatment with a biologic agent) • with relatively stable disease, not acute or severe disease • in need of longer term maintenance • and who failed on other systemic treatments or are contraindicated or intolerant to methotrexate, and ciclosporin We would also challenge the ERG statements that the comparators were not agreed during the Decision Problem meeting. During this meeting the above position of DMF was discussed in detail and it was agreed that the appropriate comparators were: Fumaderm, apremilast, the biologics and best supportive care. We would also highlight that any comparison of DMF versus the non-biologic systemics is also unnecessary as in clinical practice (and based on clinical feedback) patients eligible for a non-biologic systemic medicine would not be	This is ERG opinion not a factual error, no change.

the ERG believe that the list of comparators used in the CS decision problem was discussed but not agreed at the decision problem meeting.'		prescribed DMF after topical therapies in preference to well-established and less expensive conventional systemic therapies.	

Issue 2 Updated SmPC details

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Following CHMP positive opinion on 21 April the following details have been agreed with the regulatory authorities. Page 36, Section2.3 *The frequency of full blood count tests with DMF (LAS41008) is still being discussed with the regulatory authorities*.	Addition of a footnote to highlight that a final SmPC is available and confirms the frequency of blood tests as follows: *Before treatment* *Prior to initiating treatment with Skilarence, a current complete blood count (including differential blood count and platelet count) should be available. Treatment should not be initiated if leukopenia below 3.0x10^9/L, lymphopenia below 1.0x10^9/L or other pathological results are identified.* *During treatment* *During treatment a complete blood count with differential should be performed every 3 months. Action is needed in the following circumstances:* *Leukopenia: If a marked decrease in the total number of white blood cells is found, the situation should be monitored carefully and treatment with DMF should be discontinued at levels below 3.0x10^9/L.* *Lymphopenia: If the lymphocyte count falls below 1.0x10^9/L but is ≥0.7 x10^9/L, blood monitoring should be performed monthly until levels return to 1.0x10^9/L or higher for two consecutive blood tests at which point monitoring can again be performed every 3 months.*	Following CHMP positive opinion on 21 April a final SmPC was provided to NICE (via email) on 26 April. This confirms the monitoring requirements as per the proposed amendment.	Agreed, footnote added (p34)

	If the lymphocyte count falls below 0.7x10^9/L, the blood test must be repeated and if the levels are confirmed to be below 0.7x10^9/L, then treatment must be stopped immediately. Patients developing lymphopenia should be monitored after stopping treatment until their lymphocyte count has returned to the normal range		

Issue 3 Updated SmPC details

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 37 to 38, Section 2.3 The SmPC details in the ERG report are now out of date following CHMP positive opinion. A final SmPC was provided to NICE (via email) on 26 April 2017. *'The proposed Summary of Product Characteristics (SmPC) for dimethyl fumarate (Skilarence) for psoriasis was provided to the ERG in the CS reference pack.[12] The draft SmPC notes that cases of opportunistic infections, particularly of PML, have been reported with other dimethyl fumarate-containing products. It states that PML is an opportunistic infection caused by the John Cunningham virus (JCV) that can be fatal or cause severe disabilities. Persistent moderate or severe lymphopenia under treatment with DMF is considered a risk factor for PML. It also notes that early diagnosis of Fanconi syndrome (a disorder of the kidney tubes) and discontinuation of Skilarence treatment are important to prevent the onset of renal impairment and osteomalacia, as the*	The following amendments are recommended – text to be removed is scored through and new text provided in red. *The proposed Summary of Product Characteristics (SmPC) for dimethyl fumarate (Skilarence) for psoriasis was provided to the ERG in the CS reference pack.[12] The ~~draft~~ final SmPC notes that cases of opportunistic infections, particularly of PML, have been reported with other dimethyl fumarate-containing products. It states that PML is an opportunistic infection caused by the John Cunningham virus (JCV) that can be fatal or cause severe disabilities. Persistent moderate or severe lymphopenia under treatment with DMF is considered a risk factor for PML. It also notes that early diagnosis of Fanconi syndrome (a disorder of the kidney tubes) and discontinuation of Skilarence treatment are important to prevent the onset of renal impairment and osteomalacia, as the syndrome is usually reversible.* *Special warnings and precautions are listed. DMF may decrease leukocyte and lymphocyte counts, so prior to initiating treatment with DMF, a current complete blood count (including differential blood count and platelet count) should be ~~available. Treatment should not be initiated if leukopenia below 3.0x10^9/L, lymphopenia below 1.0x10^9/L or other~~*	Although not available at the time of the submission a final SmPC is now available and was provided to NICE (via email) on 26 April 2017.	Agreed, updated (p35-36)

syndrome is usually reversible. *Special warnings and precautions are listed. DMF may decrease leukocyte and lymphocyte counts, so prior to initiating treatment with DMF, a current complete blood count (including differential blood count and platelet count) should be available. Treatment should not be initiated if leukopenia below 3.0x10^9/L, lymphopenia below 1.0x10^9/L or other pathological results are identified. During treatment a complete blood count should be performed every 3 months. Monitoring and discontinuation of treatment is needed in specified circumstances (discontinuation if white blood cells level below 3.0x10^9/L or lymphocyte count drops below 0.8x10^9/L). Some cases of renal toxicity have been reported during post-marketing surveillance with fumaric acid esters, therefore renal function (e.g. creatinine, blood urea nitrogen and urinalysis) should be checked prior to initiation of treatment and every 3 months and dose reduction or treatment discontinuation considered for clinically relevant change. The ERG notes that the draft SmPC recommendations for monitoring and discontinuation differ slightly to those made by the EMA, and that as noted above the frequency of full blood count tests with DMF is still being discussed with the regulatory authorities.'*	~~*pathological results are identified. During treatment a complete blood count should be performed every 3 months. Monitoring and discontinuation of treatment is needed in specified circumstances (discontinuation if white blood cells level below 3.0x10^9/L or lymphocyte count drops below 0.8x10^9/L). Some cases of renal toxicity have been reported during post-marketing surveillance with fumaric acid esters, therefore renal function (e.g. creatinine, blood urea nitrogen and urinalysis) should be checked prior to initiation of treatment and every 3 months and dose reduction or treatment discontinuation considered for clinically relevant change*~~*. During treatment a complete blood count with differential should be performed every 3 months. Action is needed in the following circumstances:* *Leukopenia: If a marked decrease in the total number of white blood cells is found, the situation should be monitored carefully and treatment with DMF should be discontinued at levels below 3.0x10^9/L.* *Lymphopenia: If the lymphocyte count falls below 1.0x10^9/L but is ≥0.7 x10^9/L, blood monitoring should be performed monthly until levels return to 1.0x10^9/L or higher for two consecutive blood tests at which point monitoring can again be performed every 3 months.* *If the lymphocyte count falls below 0.7x10^9/L, the blood test must be repeated and if the levels are confirmed to be below 0.7x10^9/L, then treatment must be stopped immediately. Patients developing lymphopenia should be monitored after stopping treatment until their lymphocyte count has returned to the normal range Renal function (e.g. creatinine, blood urea nitrogen and urinalysis) should be checked prior to initiation of treatment and every 3 months thereafter. In the event of a clinically relevant change in renal function, particularly in the absence of alternative explanations, consideration should be given to dosage reduction or treatment discontinuation.* ~~*The*~~		

	~~*ERG notes that the draft SmPC recommendations for monitoring and discontinuation differ slightly to those made by the EMA, and that as noted above the frequency of full blood count tests with DMF is still being discussed with the regulatory authorities.*~~*'*		

Issue 4 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15, Section 1.2 onwards Fumaderm is incorrect in places throughout the document with a lower case 'f'	'fumaderm' to be changed to 'Fumaderm' throughout	Typographical error	Changed throughout

Issue 5 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15, Section 1.2 The percentage of patients achieving a PGA score of 0 or 1 in the following sentence is incorrect. The correct figure is 33% (see page 17, CS) '*Similarly, 37.0% of patients treated with DMF achieved PGA scores of 0 or 1, compared to 13.0% treated with placebo (P < 0.0001) and 37.4% treated with Fumaderm'*	'*Similarly, ~~37.0%~~ 33% of patients treated with DMF achieved PGA scores of 0 or 1, compared to 13.0% treated with placebo (P < 0.0001) and 37.4% treated with Fumaderm'*	Factual inaccuracy	Agree, changed (p13)

Issue 6 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15, Section 1.2 The time to relapse for Fumaderm is incorrect in the following sentence. The correct figure is [redacted] days (see page 63, CS) [redacted]	[redacted]	Factual inaccuracy	Agree, changed (p13)

Issue 7 Appropriateness of time horizon

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following statements are misleading and fail to acknowledge different perspectives and/or previous NICE appraisals. Page 23, Section 1.5 *'It is more appropriate to use a 25-year or lifetime horizon'*	Page 23, Section 1.5 '*The ERGs preference was ~~It is more appropriate~~ to use a 25-year or lifetime horizon'* Page 177, Section 5.5 '*The ~~main source of bias~~ most influential assumption within the model is restricting the*	There are different perspectives for justifying time horizons. Methodological implications as well as precedent and fairness are important in determining the appropriate time horizon. Previous decisions have been based on 10-year time horizons. To maintain consistency and impartiality it is important that DMF	No factual error. No revision required. See section 5.1.15 of the NICE methods guide.

Page 177, Section 5.5 *'The main source of bias within the model is restricting the time horizon to 10 years, which is insufficient to permit the treatment sequences of the company base case to play out.'*	*time horizon to 10 years, which ~~is~~ the ERG considers insufficient to permit the treatment sequences of the company base case to play out'*.	be judged to the same standards as those treatments previously assessed, including apremilast which also used treatment sequences and a 10-year time horizon.	

Issue 8 Clarify the changes to etanercept and ustekinumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26, Section 1.7 The following sentence requires clarification to specify that costs and effectiveness estimates for low dose etanercept and ustekinumab were included. *'For the revised base case the ERG adopts a lifetime horizon, applies the low dose estimates for etanercept and ustekinumab....',*	The following amendment is proposed: *'For the revised base case the ERG adopts a lifetime horizon, applies the low dose cost and effectiveness estimates for etanercept and ustekinumab……..'*	To specify that costs and effectiveness for low dose etanercept and ustekinumab were included. .	No factual error. No revision required. The ERG only revises the clinical effectiveness estimates to be those of low dose etanercept and low dose ustekinumab within the company model. If this is incorrect and further revisions should be made to correctly model low dose etanercept and low dose ustekinumab, then the ERG would be grateful if the company could outline which other inputs should be revised.

Issue 9 Apremilast scenarios

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following statements are not transparent and further details are required on the specific scenarios. Page 32, Section 1.7 *… under a number of scenarios, that DMF may not be cost effective when compared to apremilast.* Page 187, Section 8 *… under a number of scenarios DMF may not be cost effective when compared to apremilast.*	Include details, which are not due to/related to the PAS for apremilast, on the scenarios for which DMF is and is not cost-effective and at what thresholds.	This would help the evaluation of the evidence by the company or the public.	No factual error. No revision required.

Issue 10 Study exclusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 46, Section 4.1.1. The following text fails to acknowledge that the observational, single arm study the Lijnen et al 2016 study was excluded from the SLR based on study design. '*However, we identified a before-and-after study by Lijnen et al 2016 which provide data on long term safety and effectiveness of DMF*'	In order to accurately reflect the company submission the following amendment is recommended. '*However, we identified a before-and-after study by Lijnen et al 2016 which provides data on long term safety and effectiveness of DMF*. This study was excluded by the manufacturer on the basis of study design'	To accurately reflect the company submission.	Helpful clarification, however, the CS does not provide the full list of excluded studies, therefore not a factual error.

Issue 11 Clarification on study inclusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 48, Section 4.1.2 The following statement is incorrect in that the Menter *et al*. 2008 study was included in the NMA. Due to an error in the Almirall submission the Menter *et al.* 2008 study was incorrectly listed in the list of excluded studies and incorrectly excluded from the feasibility assessment (37 studies) but was actually included in the NMA (38 studies) with PASI 75 and PASI 90 data at 16 weeks incorporated in the NMA. '*However, the ERG considers that Menter et al. 2008 on adalimumab should have been included (this was established after the clarification request was submitted to the company), see Section 4.3*."	In order to accurately reflect the NMA the following amendment is recommended. '*However, the ERG considers that Menter et al. 2008 on adalimumab should have been included (this was established after the clarification request was submitted to the company), see Section 4.3.* It should be noted that while within the CS the study appeared to have been excluded this was due to an error in the CS but PASI 75 and PASI 90 data at 16 weeks, from the study, were actually incorporated in the NMA	To highlight that there was an error in the CS submission and data from the Menter et al 2008 was included in the NMA.	The ERG acknowledge the CS reported an error and for accuracy have changed text to (p46): *However, the ERG considers that Menter et al. 2008 on adalimumab should have been included. At the factual accuracy check, the company notified the ERG that the CS contained an error and the NMA did indeed incorporate PASI 75 and PASI 90 data at 16 weeks from this study*

Issue 12 Incorrect statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 48, Section 4.1.2 The following statement is incorrect. '*15 studies (plus CS ref 133[19], reason for exclusion incorrect in CS) of non-biologics and 5 studies of non-biologics vs a biologic or second line therapy were excluded from the NMA'*	Delete the statement "(plus CS ref 133[19], reason for exclusion incorrect in CS)".	Reference133 (Sandhu 2003) in the CS submission has not been excluded incorrectly. This study was correctly excluded on the basis it compares methotrexate at an unlicensed dose (0.5mg/kg) to cyclosporin 4mg/kg.	The ERG considered this should have been excluded on the grounds of 'comparing conventional treatment arms to each other or placebo' but agree if the dose was unlicensed this could also be the reason and therefore the statement is deleted (p46)

Issue 13 Clarification on tables

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51, Section 4.1.3 We would like to clarify the ERG statement '*The ERG is unclear why this is'* in the below paragraph. '*The company provided amended data for the pre-treated subgroup in clarifications A9 and A10 (clarification Tables 2 and 4), but the amended data do not align with those presented in CS Table 21. Moreover, the pre-treated subgroup sample sizes presented in CS Tables 21-23 and confirmed in clarification A9 (DMF 44; Fumadern 59; placebo 30; total 133) do not align with those presented in clarification Tables 2 and 3 (DMF 93; Fumadern 112; placebo 58; total 263. The ERG is unclear why this is'*. The two sets of tables report different populations. Tables 21-23 report on the subgroup of 'prior systemic therapies only', whilst the table in clarification A9 reports on the subgroup of 'prior systemic therapies or phototherapy'.	The following amendment is proposed: *'The company provided amended data for the pre-treated subgroup in clarifications A9 and A10 (clarification Tables 2 and 4), but the amended data do not align with those presented in CS Table 21. Moreover, the pre-treated subgroup sample sizes presented in CS Tables 21-23 and confirmed in clarification A9 (DMF 44; ~~Fumadern~~Fumaderm 59; placebo 30; total 133) do not align with those presented in clarification Tables 2 and 3 (DMF 93; ~~Fumadern~~Fumaderm 112; placebo 58; total 263. ~~The ERG is unclear why this is~~ Tables 21-23 report on the subgroup of 'prior systemic therapies only', whilst the table in clarification A9 reports on the subgroup of 'prior systemic therapies or phototherapy'*	To provide additional clarification and also correct a typographical error.	Helpful clarification that the post hoc subgroup used in the BRIDGE trial analysis is different to the subgroup used for the NMA. Text changed as suggested with additional text as follows (p49): *Tables 21-23 report on the subgroup of prior systemic therapies only, whilst the table in clarification A9 reports on the subgroup of prior systemic therapies or phototherapy which the ERG notes is a different subgroup.*

Issue 14 Study exclusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 52, Section 4.1.3 The following text fails to acknowledge that the observational, single arm study Lijnen *et al*. 2016 was excluded from the SLR based on study design. '*The ERG has identified one additional relevant study, see Section 4.4'*	*'The ERG has identified one additional relevant study, see Section 4.4. This study was excluded by the manufacturer on the basis of study design'*	To accurately reflect the company submission.	As with Issue 10 not a factual error, no change made.

Issue 15 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 55, Section 4.1.3, Table 4 With the exception of the CHAMPION study the PASI mean (SD) data in Table 4 is incorrect. BSA mean (SD) data is replicated in the PASI mean (SD) columns	Correct PASI mean (SD) figures to be added to Table 4. See Table 29 in CS for correct figures.	Factual inaccuracy	Agreed, this is a transcription error, Table corrected (p52).

Issue 16 Study exclusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59, Section 4.1.4 We would like to clarify the point made in the below statement that omission of Menter et al. 2008 is unlikely to have an impact on the NMA results. This is incorrect as the study was included in the NMA. *'As discussed in Section 4.1.2, the ERG considers that Menter et al. 2008 on adalimumab 18 was excluded incorrectly. However, the results from Menter et al. 2008 (adalimumab vs placebo: PASI 75: 71% vs 7%; PASI 90: 45% vs 2%) were within the range of the other three included studies of adalimumab (PASI 75: 63%-80% vs 4%-19; PASI 90: 40%-51% vs 0%-11%) and its omission is unlikely to have much of an impact on the NMA results.'* Due to an error in the Almirall submission the Menter *et al.* 2008 study was incorrectly listed in the list of excluded studies and incorrectly excluded from the feasibility assessment (37 studies) but was actually included in the NMA (38 studies) with PASI 75 and PASI 90 data at 16 weeks incorporated in the NMA.	Not applicable.	To highlight the error in the Almirall submission	The paragraph has been appended (p56): *(The company notified the ERG that the CS contained an error and the NMA did indeed include Mentor et al, 2008)*

Issue 17 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75, Section 4.2.4, Table 7 The placebo figure of -4.9 (10.7) for % change in BSA is incorrect.	Correct figure to -4.9 (10.8)	Factual inaccuracy	Agreed, changed (p72)

Issue 18 Study exclusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 83, Section 4.3 The following statement is incorrect due to an error in the Almirall submission. '*One study of adalimumab was excluded from the NMA because the outcomes were stated to be reported for the treatment arm only (CS Table 27). The ERG has checked the publication of this study (Menter et al 2008) and the PASI 75 and 90 were reported for the placebo arm and therefore this is an error in the CS. As discussed in 4.1.2, this study meets the inclusion criteria for the NMA and should therefore have been included in the NMA*' As stated above due to an error in the Almirall submission the study was excluded from the feasibility assessment (37 studies) but included in the NMA (38 studies) with PASI 75 and PASI 90 data at 16 weeks incorporated in the NMA.	*One study of adalimumab ~~was~~ appeared to have been excluded from the NMA because the outcomes were stated to be reported for the treatment arm only (CS Table 27). The ERG has checked the publication of this study (Menter et al 2008) and the PASI 75 and 90 were reported for the placebo arm and therefore this is an error in the CS. As discussed in 4.1.2, this study meets the inclusion criteria for the NMA and should therefore have been included in the NMA. An error was made in the CS, whereby the Menter et al. 2008 study was excluded from the feasibility assessment (37 studies), but included in the NMA (38 studies). Therefore the NMA results include data for PASI75 and PASI90 at 16 weeks from the Menter et al. 2008 study.'*	To highlight the error in the Almirall submission.	Agreed, text amended (p80)

Issue 19 Programme Code

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 85, Section 4.3, Table 16 It is not correct to state that a copy of the programming code used in the statistical programme was not provided. A copy was provided in Appendix 8 of the Almirall submission.	Amend 'No' to 'Yes'	Factual inaccuracy	Agreed, changed to 'Yes'

Issue 20 Incorrect interpretation of comparative efficacy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 86, Section 4.3.1 The following statement is incorrect: '*In the company's interpretations of these results, DMF demonstrated superior efficacy to placebo and non-inferior efficacy to the other comparators. The ERG queries the company's assertions, given the absence of pairwise comparisons using DMF as the reference treatment. For instance, adalimumab appears to be clearly superior to DMF, hence it would be unreasonable to assume that DMF is non-inferior to adalimumab'* The CS does not state 'non-inferior' efficacy and concludes in the following CS, pages 19 and 117, '*DMF (LAS 41008) shows superior efficacy compared with placebo and inferior efficacy when compared with biologics, apremilast and Fumaderm'*.	The following amendment is proposed. *'In the company's interpretations of these results, DMF demonstrated superior efficacy to placebo and ~~non-~~ inferior efficacy to the other comparators. ~~The ERG queries the company's assertions, given the absence of pairwise comparisons using DMF as the reference treatment. For instance, adalimumab appears to be clearly superior to DMF, hence it would be unreasonable to assume that DMF is non-inferior to adalimumab'~~*	To accurately reflect the company submission.	Agreed, text amended

Issue 21 Clarification on study exclusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 89, Section 4.4 The following text fails to acknowledge that the observational, single arm study the Lijnen et al 2016 study was excluded from the SLR based on study design. '*The ERG identified a non-RCT of DMT and summarises this below*'	The following amendment is proposed: *'The ERG identified a non-RCT of ~~DMT~~* DMF *and summarises this below.* <u>This study was excluded by the manufacturer on the basis of study design</u>'	To accurately reflect the company submission and also correct a typographical error.	As with Issue 10 not a factual error, no change made. DMT typo corrected.

Issue 22 Confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 120, Section 5.28 The information below marked as CIC is no longer confidential *The direct drug costs for fumaderm are also marked as CIC by the company. These are based upon the German cost per tablet of €2.43 being divided by the January 2017 exchange rate of £1=€1.18 to arrive at a price in sterling of £2.07. This cost is then inflated by an undocumented import charge of 22% to arrive at a cost per tablet of £2.52 which is 19% more expensive than DMF. The company states at clarification that:* *"In investigating the cost of imported Fumaderm to UK centres it became apparent that the cost of imported Fumaderm varies considerably with many centres paying significantly more than the price we have used for our analysis. However in order to arrive at a reasonable and conservative price, and on the advice of UK experts, we have taken the German list price, converted this to sterling using the current exchange rate and applied a 22% import charge to account for the additional cost charged by the importers. We have been advised that this price is close to the (confidential) price actually charged to centres buying larger volumes but much less than the price charged to some other centres."*	Remove confidentiality mark up	The information is no longer confidential	CIC removed (p117)

Issue 23 Baseline Utility Value

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 147, Section 4.3.4 The following sentence does not highlight that the value of 0.5 is arbitrary and not supported by any evidence. It should also be noted that this should be tested in sensitivity analysis. *'In the light of this the ERG have reduced the baseline quality of life for severe patients to 0.5'*	*'In the light of this the ERG have reduced the baseline quality of life for severe patients to an arbitrary value of 0.5'*	To highlight that 0.5 is an arbitrary value.	Text amended (p144) *In the light of this the ERG have arbitrarily reduced the baseline quality of life for severe patients to 0.5 in order to avoid the undesirable ceiling effects, though any value less than 0.59 would suffice.*

Issue 24 Model Structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 187, Section 8 The following statement requires clarification: *'The difference between these estimates is largely by construction. The insertion of another treatment into a sequence results in patient QALY gains, almost regardless of how poorly it performs clinically'* *The phrase 'almost regardless'* is too vague and needs to be clarified.	To clarify the statement including what is meant by '*almost regardless'*	Clarification	No factual error. No revision required.

The difference between these estimates is the result of a previously reported, validated and accepted model structure. The insertion of another treatment into a sequence results in patient QALY gains if the additional treatment is sufficiently more effective than BSC to offset the differences due to discounting and mortality.			

Issue 25 Typographical Errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Typographical errors. Pages 16 and 91 'sekukinumab' Pages 63, 64, 88 and 89 'apremilsat' Pages 80 and 180 'apermilast' Page 86 'Tables X and X' Pages 93 and 95 'CG163'	Page 91 'sekukinumab' to'secukinumab' Pages 63,64,88 and 89 'apremilsat' to 'apremilast' Pages 80 and 180 'apermilast' to 'apremilast' Page 86 'Tables X and X' to 'Tables 17 and 18' Pages 93 and 95 'CG163' to 'CG153'	Typographical errors	Agreed, changed