NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept and ustekinumab for treating severe, chronic plaque psoriasis in children and young people [ID854]

Committee papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Adalimumab, etanercept and ustekinumab for treating severe, chronic plaque psoriasis in children and young people [ID854]

Contents:

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

Pre-meeting briefing
Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people [ID854]

Redacted

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

COMMON ABBREVIATIONS	
ADA	adalimumab
AG	assessment group
BSC	best supportive care
CDLQI	Children Dermatology Life Quality Index
CG	clinical guideline
EQ-5D	EuroQol Group measure of health states
ETA	etanercept
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
MTA	multiple technology assessment
MTX	methotrexate
NMA	network meta-analysis
PASI	Psoriasis Area and Severity Index
PedsQL	Paediatrics Quality of Life
PGA	Physician Global Assessment
PLB	placebo
QALY	Quality adjusted life year
RCT	randomized controlled trial
UST	ustekinumab

Key issues

Clinical effectiveness (I)

- Where will the technologies be used in the treatment pathway?
  - ADA has a marketing authorisation for people who had an inadequate response to or are inappropriate candidate for *topical therapy* & phototherapies
  - ETA and UST have a marketing authorisation for people who are inadequately controlled by, or are intolerant to, other *systemic therapies* or phototherapies
- What are the most appropriate comparators for each age group?
  - Systemic therapies, each other or best supportive care?
- How should severity be defined?
  - CG153 defined severe psoriasis as a total PASI ≥10, DLQI > 10
  - UST marketing authorisation includes "moderate" plaque psoriasis, others only for "severe"
  - Different trial inclusion criteria for ADA

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Key issues

Clinical effectiveness (II)

- Are all the treatments clinically effective (vs comparators & each other?)
  - Is the treatment effect maintained in the long-run?
  - What, if any, stopping/continuation rules should apply?
- Evidence synthesis:
  - Is it appropriate to incorporate adult evidence to compare the technologies?
  - Should the minimum amount of adult evidence be used (NMA scenario 1), or all relevant adult evidence (NMA scenario 2)?
  - Should the evidence synthesis be adjusted for placebo and age

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Key issues
Cost effectiveness

- Has best supportive care been properly defined for this population?
- Is it plausible that children and young people have a significantly lower HRQoL gain compared to adults?
  - Should the model use mapped children's QoL or adults QoL?
- Is it plausible that children have no hospitalisations during BSC?
  - Should the model use hospitalisation assumptions from previous appraisals?
- Should any of the scenario analyses be incorporated? (e.g. longer time horizon)
- Are there any factors which have not been sufficiently explored in the Assessment group's analysis?
- Innovation – carer disutility?
- Equalities – PASI for people with darker skin?

HRQoL; Health related quality of life; QoL: Quality of life; PASI: BSC: Best supportive care

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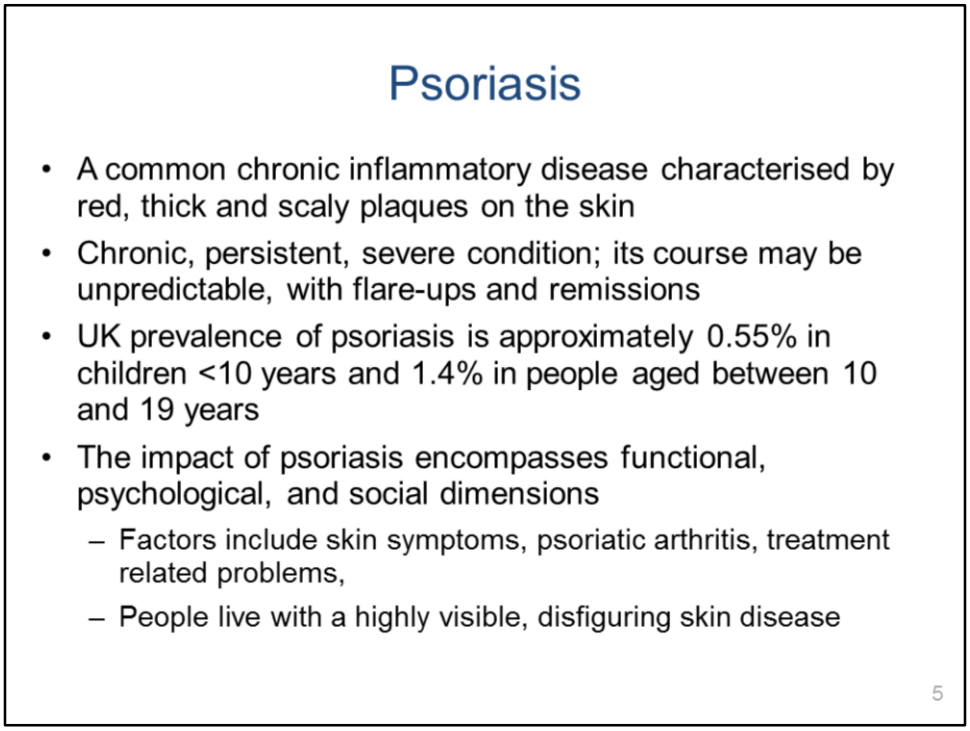
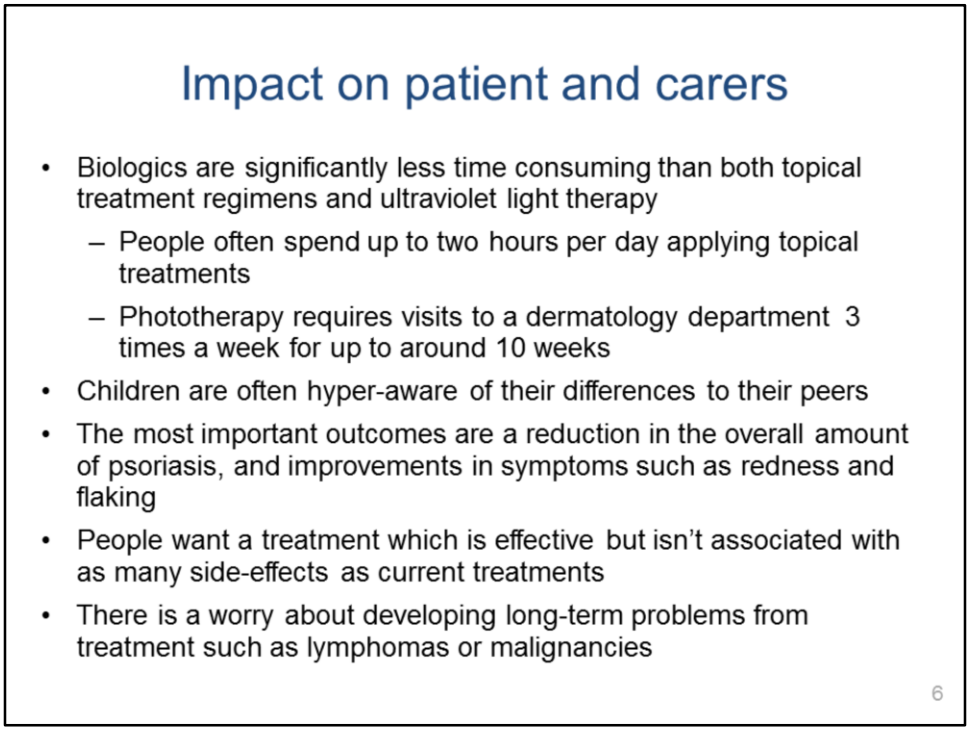
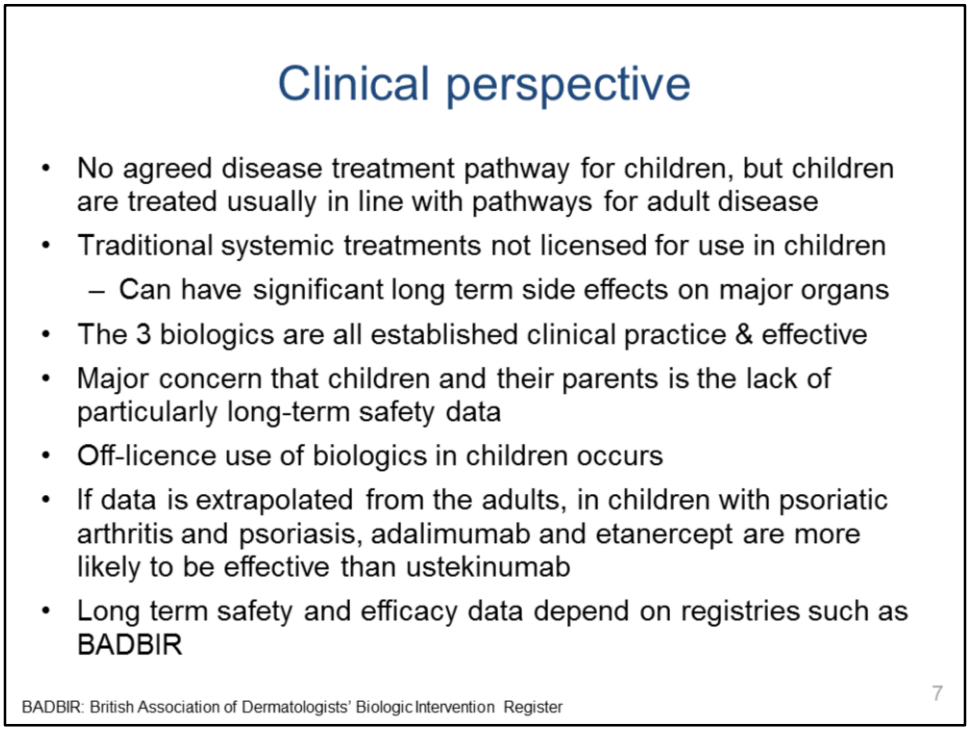


Source: Final NICE scope



Source: Patient and professional submissions (Psoriasis Association, Psoriasis and Psoriatic Arthritis Alliance, British Association of Dermatologists)



Source: Patient and professional submissions (Psoriasis Association, Psoriasis and Psoriatic Arthritis Alliance, British Association of Dermatologists)

Relevant NICE guidance (I)

- No NICE technology appraisal guidance for treating psoriasis in children and young people
- The following NICE technology appraisal (TA) guidance applies to adults:
  - TA 146, 103, 180 and 350 recommend adalimumab, etanercept, ustekinumab and secukinumab respectively as treatment options for adults with severe psoriasis who have not responded to, are intolerant to or contraindicated to standard systemic therapies such as ciclosporin, methotrexate or PUVA
  - TA 134 recommends infliximab as a treatment option for adults with very severe psoriasis who have not responded to, are intolerant to or are contraindicated to standard systemic therapies
  - TA 368 did not recommend apremilast for treating moderate to severe chronic plaque psoriasis
  - Other TA's still in progress (ixekizumab)

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Relevant NICE guidance (II)

Related Guidelines:

'Psoriasis: The assessment and management of psoriasis' (2012) NICE guideline 153
Review decision expected December 2016

Related Quality Standards:

'Psoriasis' (2013) NICE quality standard 40

Related NICE Pathways:

'Psoriasis' (2015) NICE pathway

CG153 covers assessing and managing psoriasis in adults, young people and children

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Overview of the technologies

Marketing authorisation

Technology	Marketing authorisation
Adalimumab (ADA)	Treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies
Etanercept (ETA)	Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies
Ustekinumab (UST)	Treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies

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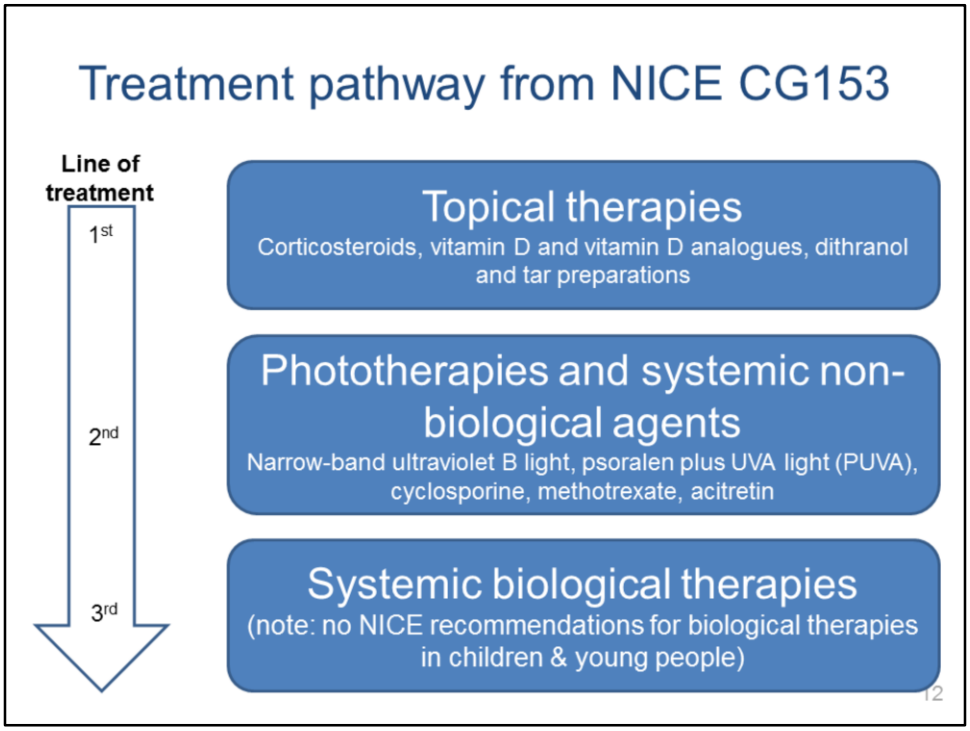
Source: Electronic Medicines compendium (eMC)

Overview of the technologies
Administration

	Adalimumab (ADA)	Etanercept (ETA)	Ustekinumab (UST)
Dose	0.8 mg/kg (up to 40 mg/dose)	0.8 mg/kg (up to 50 mg/dose)	< 60kg: 0.75 mg/kg ≥ 60-≤ 100kg: 45 mg > 100kg: 90 mg
Admin.	subcutaneous injection	subcutaneous injection	subcutaneous injection
Freq.	Every 2 weeks^	Weekly	Week 0, 4 and every 12 weeks thereafter
Stop.	At 16 weeks if no response	At 12 weeks if no response	-
Cost*	Prefilled syringe or pen 40 mg: £352.14 Injectable solution, 40 mg vial: £352.14	Pre filled syringe 25 mg: £89.38 50 mg: £178.75	Prefilled syringe 45 or 90 mg: £2,147.00 Injectable solution, 40 mg vial: £2,147.00
Year 1 cost**	£9507.78	£9,474	£12,882

^Weekly for the first 2 weeks; * Unit costs from MIMS online; accessed January 2017; ** year 2 cost: ADA: £9,156; ETA: 9,295; UST: £8,588 11

Source: Electronic Medicines compendium (eMC)



CG153 - 1.3.1 General recommendations

Offer second- or third-line treatment options (phototherapy or systemic therapy) at the same time when topical therapy alone is unlikely to adequately control psoriasis, such as:

extensive disease (for example more than 10% of body surface area affected) **or**

at least 'moderate' on the static Physician's Global Assessment **or**

where topical therapy is ineffective, such as nail disease.

CG153 - 1.5.2 Systemic non-biological therapy

Offer systemic non-biological therapy to people with any type of psoriasis if:

•it cannot be controlled with topical therapy **and**

•it has a significant impact on physical, psychological or social wellbeing **and**

•one or more of the following apply:

•psoriasis is extensive (for example, more than 10% of body surface area affected or a PASI score of more than 10) **or**

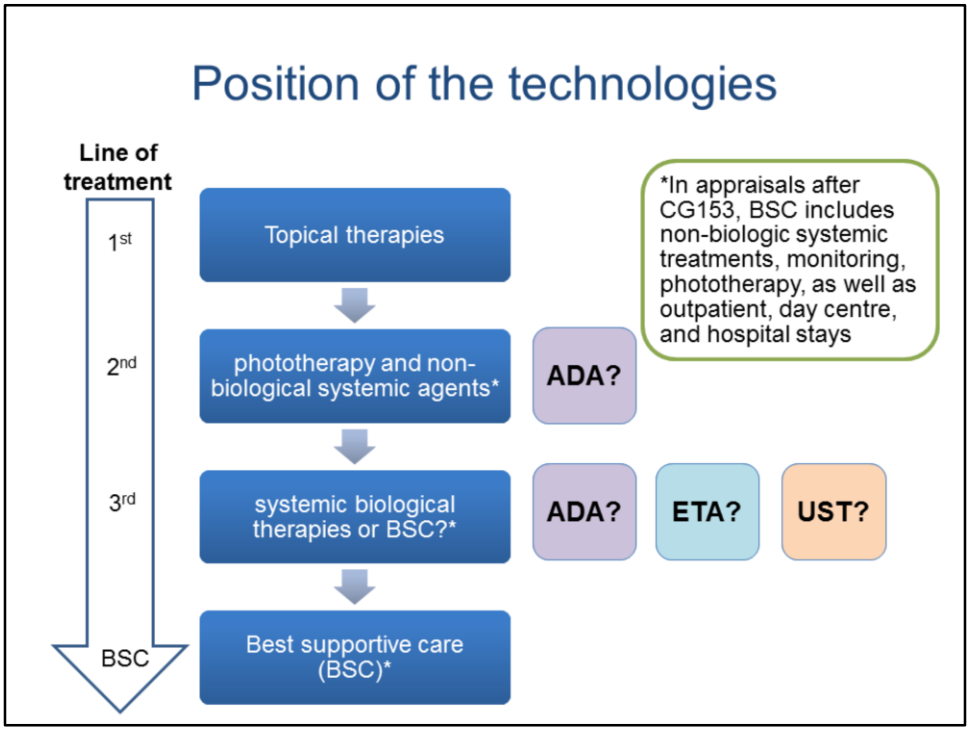
•psoriasis is localised and associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites) **or**

•phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months).

CG153 - 1.5.3 Systemic biological therapy

•The disease is severe as defined by a total PASI of 10 or more and a DLQI of more than 10.

•The psoriasis has failed to respond to standard systemic therapies


Position of the technologies
Line of treatment
1st
2nd
3rd
BSC
Topical therapies
phototherapy and non-biological systemic agents*
systemic biological therapies or BSC?*
Best supportive care (BSC)*
ADA?
ADA?
ETA?
UST?
*In appraisals after CG153, BSC includes non-biologic systemic treatments, monitoring, phototherapy, as well as outpatient, day centre, and hospital stays

Overview of the submissions

Company submissions:

- AbbVie (adalimumab)
- Janssen (ustekinumab)

Company non-submissions:

- Pfizer (etanercept)

Patient and professional submissions:

- Psoriasis Association; Psoriasis and Psoriatic Arthritis Alliance; British Association of Dermatologists

Assessment group's report:

- Centre for Reviews and Dissemination/Centre for Health Economics, York

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Clinical evidence

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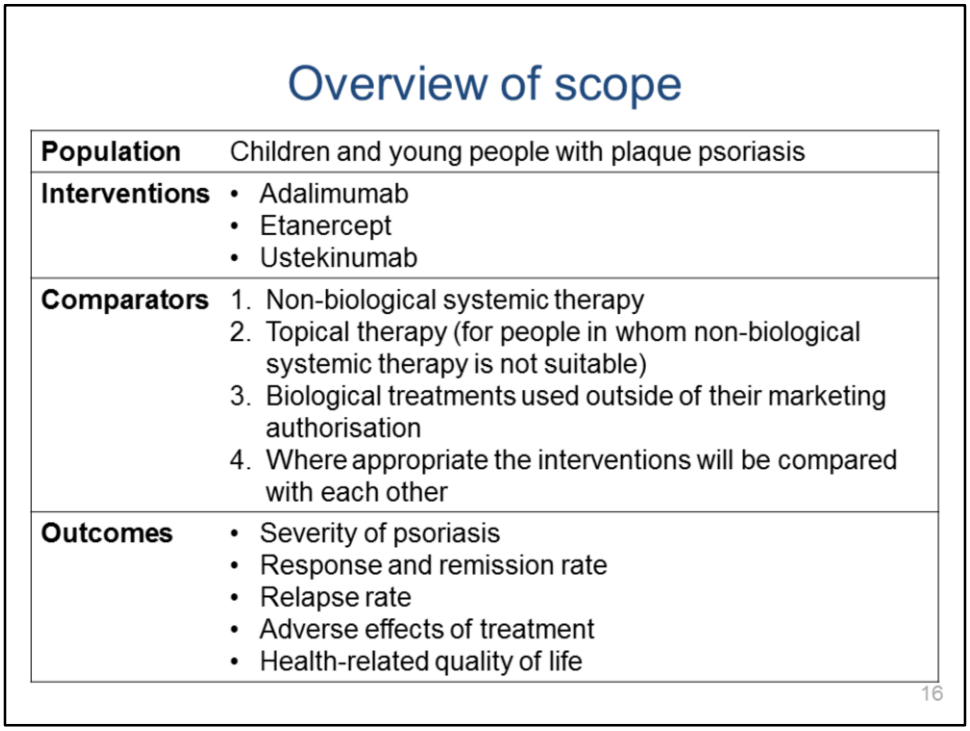
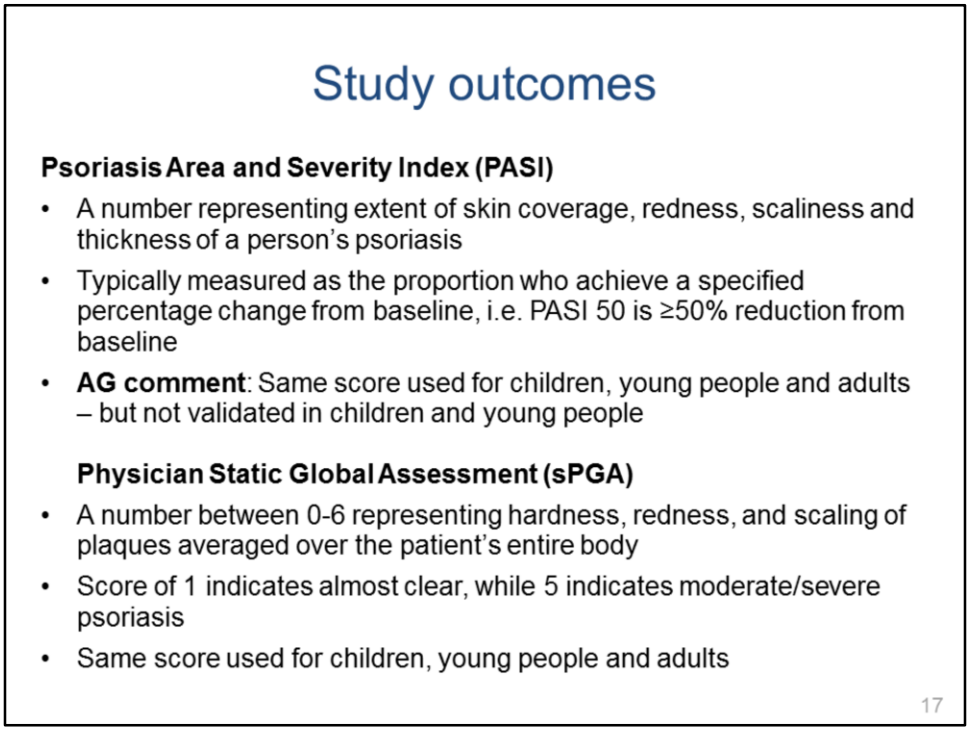
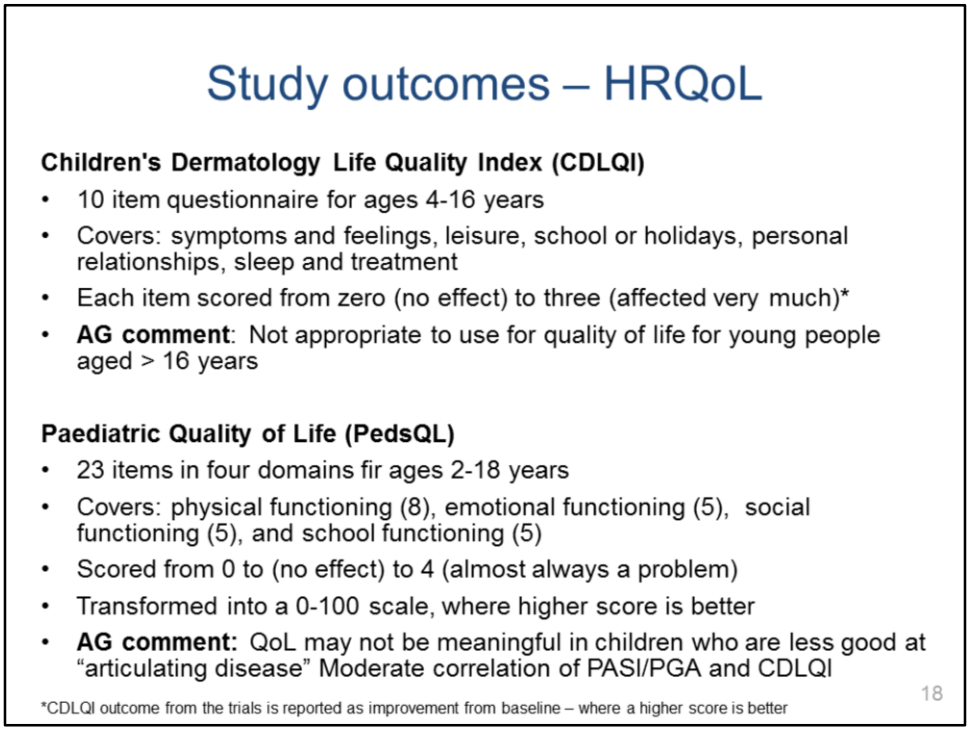


Source: NICE final scope



Assessment group:

- Although it is widely used, the PASI measure also has a number of deficiencies: its constituent parameters have never been properly defined; it is insensitive to change in mild-to-moderate psoriasis; estimation of disease extent is notoriously inaccurate; and the complexity of the formula required to calculate the final score further increases the risk of errors. It combines an extent and a severity score for each of the four body areas (head, trunk, upper extremities and lower extremities)
- PASI-based measures have discriminatory capability and are generally accepted for the assessment of treatment effects. However, clinical expert opinion is that PASI is not widely used in clinical practice.
- Despite the fact that it has not been validated in children, PASI has been chosen as the primary outcome variable of psoriasis in the economic evaluation because it is used in the majority of randomised controlled trials (RCTs)



- CDLQI scores can be divided into scoring bands: band 0 (score = 0-1), band 1 (score = 2-6), band 2 (score= 7-12), band 3 (score=13-18) and band 4 (score=19=30) that respectively correspond to no, small, moderate, very large or extremely large effects on the child's quality of life.

Assessment group:

- The CDLQI is not considered appropriate for use as health-related quality of life assessment tool beyond the age of 16 years. Validated scores that would be appropriate for 16-18 year olds are the Pediatric Quality of Life (PedsQL) and Teenager's Quality of Life Index (T-QoL)
- Quality of life measurements may not be particularly meaningful in younger children who are less good at articulating how much the disease is bothering them. In the case of younger children, proxy measurements may more accurately reflect parental perception or concern. There is only moderate correlation between PASI/PGA response measures and CDLQI; some children with relatively mild disease can have very poor HRQoL scores, while others with more severe disease can have acceptable HRQoL.
- PedsQL is measured by self-report in children and adolescents ages 5-18 years, and parent proxy-report of child HRQOL is measured for children and adolescents

ages 2-18 years.

Trial M04-717 (adalimumab)

Study Type	Multicentre RCT (n=114)
Population	• Aged 4 to <18 years • Failed or can't have phototherapy • Failed topical therapy and require systemic therapy to control disease • Severe chronic plaque psoriasis*
Intervention	• Adalimumab 0.8mg/kg (standard dose) • (Adalimumab 0.4mg/kg (half dose) no marketing authorisation)
Comparators	• Methotrexate (MTX)
Outcomes	• **Proportion achieving a ≥75% improvement in PASI (PASI75) response at week 16** • PASI 50 and 90 response • Proportion achieving a PGA of 0/1 (clear or minimal) at week 16 • Improvement from baseline in CDLQI and PedsQL
Time-points	**Period A:** 16 week study – Double blind phase (ADA vs. MTX) **Period B (responders):** 16-36 weeks – Withdrawal/no medication **Period C (non-responders):** 16-36 weeks – re-treatment phase **Period D:** 36-52 weeks - Long term follow up**

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Source: Assessment group report, table 4 (page 55)

Primary outcome is marked in bold

*Severe chronic plaque psoriasis defined as having one of the following:

- Physician's Global Assessment (PGA) ≥ 4
- Body surface area (BSA) involved > 20%
- Very thick lesions with BSA > 10% - Psoriasis Area and Severity Index (PASI) > 20
- PASI > 10 and at least one of the following:
    - Active psoriatic arthritis unresponsive to non-steroid anti-inflammatory drugs (NSAIDs)
    - Clinically relevant facial involvement
    - Clinically relevant genital involvement
    - Clinically relevant hand and/or foot involvement
    - Children's Dermatology Life Quality Index (CDLQI) > 10
- [redacted]

Trial 20030211 (etanercept)

Study Type	Multicentre RCT (US and Canada)
Population	• Aged 4 to 17 years • Treatment with systemic therapy or phototherapy or poorly controlled with topical therapy • Stable, moderate-to-severe plaque psoriasis*
Intervention	• Etanercept (standard dose)
Comparators	• Placebo (PLB)
Outcomes	• **Proportion achieving a ≥75% improvement in PASI (PASI75) response at week 12** • PASI 50 and 90 response • Clear or almost clear status of sPGA • Improvement from baseline in CDLQI and PedsQL
Time-points	12 week study – Double blind phase (n=211) Up to week 36 – Open-label follow-up (n=208): Weeks 36-48 – Re-randomised 'withdrawal-retreatment' (n=138) Weeks 48-312 – Open-label follow-up (n=194)

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Source: Assessment group report, table 4 (page 55)

Primary outcome is marked in bold

*Stable, moderate-to-severe plaque psoriasis defined as:

- PASI score of at least 12;
- A sPGA of at least 3 (where 0 indicates clear and 5 severe psoriasis), and psoriasis involvement of at least 10% of the body-surface area;
- A history of psoriasis for at least 6 months; and,
- Previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids) or psoriasis considered by the investigator as poorly controlled with topical therapy.

CADMUS trial (ustekinumab)

Study Type	Multicentre RCT
Population	• Aged 12 to <18 years • Candidate for systemic therapy or phototherapy or poorly controlled with topical therapy • Moderate-to-severe plaque psoriasis* for at least 6 months
Intervention	• Ustekinumab 0.75 mg/kg (standard dose) • Ustekinumab 0.375 mg/kg (½ dose) (no marketing authorisation)
Comparators	• Placebo (PLB)
Outcomes	• **Proportion of participants who achieved sPGA score of 'cleared' or 'minimal'** • PASI 50, 75 and 90 response • Improvement from baseline in CDLQI and PedsQL
Time-points	12 week study – Double blind phase (n=100) Weeks12-52 – Placebo crossover period (n=100) Weeks 52-60 – follow-up (n=97)

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Source: Assessment group report, table 4 (page 55)

Primary outcome are marked in bold

*Stable, moderate-to-severe plaque psoriasis defined as ≥6 months with the following :

- Baseline PASI score ≥12;
- sPGA ≥3;
- ≥10% body surface area involved with psoriasis

Trial inclusion criteria – defining severity

Trial	Inclusion criteria – definition of severity of psoriasis

ADA M04-7117	Meet one of the following:
	• Physician's Global Assessment (PGA) ≥ 4
	• Body surface area (BSA) involved > 20%
	• Very thick lesions with BSA > 10% - PASI > 20
	• PASI > 10 and at least one of the following:
	  • Active psoriatic arthritis unresponsive to NSAIDs
	  • Clinically relevant facial, genital or hand/foot involvement
	  • Children's Dermatology Life Quality Index (CDLQI) > 10

ETA 20030211	Psoriasis Area and Severity Index (PASI) ≥ 12 Physician's Global Assessment (PGA) ≥ 3 Body surface area (BSA) involved ≥10%
UST CADMUS	Psoriasis Area and Severity Index (PASI) ≥ 12 Physician's Global Assessment (PGA) ≥ 3 Body surface area (BSA) involved ≥10%

- **CG153 and previous appraisals have defined severe psoriasis as PASI ≥ 10 and DLQI ≥ 10**

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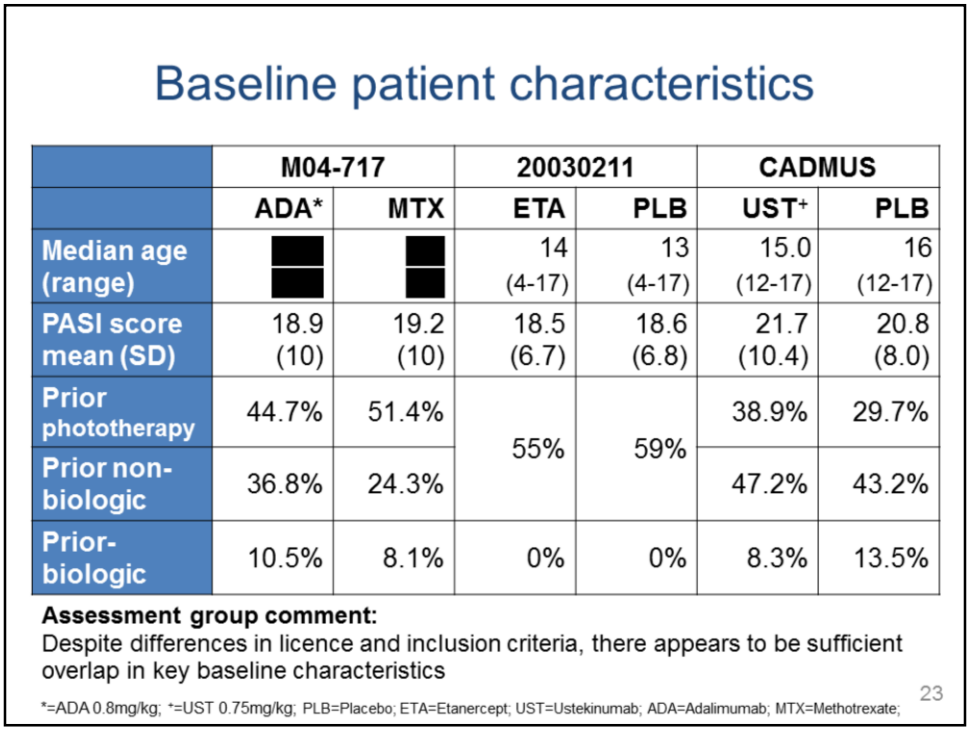

Baseline patient characteristics

	M04-717		20030211		CADMUS	
	ADA*	MTX	ETA	PLB	UST+	PLB
Median age (range)	[redacted]	[redacted]	14 (4-17)	13 (4-17)	15.0 (12-17)	16 (12-17)
PASI score mean (SD)	18.9 (10)	19.2 (10)	18.5 (6.7)	18.6 (6.8)	21.7 (10.4)	20.8 (8.0)
Prior phototherapy	44.7%	51.4%	55%	59%	38.9%	29.7%
Prior non-biologic	36.8%	24.3%			47.2%	43.2%
Prior-biologic	10.5%	8.1%	0%	0%	8.3%	13.5%

Assessment group comment:
Despite differences in licence and inclusion criteria, there appears to be sufficient overlap in key baseline characteristics

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*=ADA 0.8mg/kg; +=UST 0.75mg/kg; PLB=Placebo; ETA=Etanercept; UST=Ustekinumab; ADA=Adalimumab; MTX=Methotrexate;

Source: Assessment group report, table 4 (page 55)

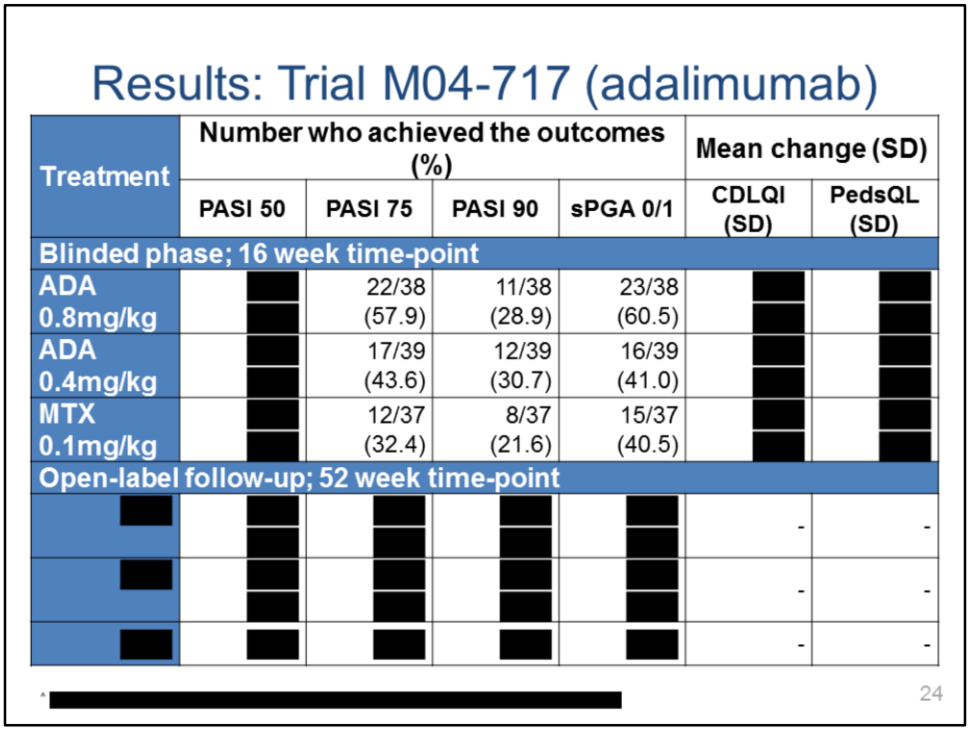
PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate;

*=ADA 0.8mg/kg

+=UST 0.75mg/kg

Assessment group noted 2 key differences which might have impacted differences at baseline:

- The age of the populations included in the trials differs across the RCTs and the interventions of interest have marketing authorisation for different age groups.
- The severity of plaque psoriasis is defined differently in the populations included in the RCTs and the interventions are licensed for different levels of severity in children and young people



Results: Trial M04-717 (adalimumab)

Treatment	Number who achieved the outcomes (%)				Mean change (SD)	
	PASI 50	PASI 75	PASI 90	sPGA 0/1	CDLQI (SD)	PedsQL (SD)
Blinded phase; 16 week time-point						
ADA 0.8mg/kg	[redacted]	22/38 (57.9)	11/38 (28.9)	23/38 (60.5)	[redacted]	[redacted]
ADA 0.4mg/kg	[redacted]	17/39 (43.6)	12/39 (30.7)	16/39 (41.0)	[redacted]	[redacted]
MTX 0.1mg/kg	[redacted]	12/37 (32.4)	8/37 (21.6)	15/37 (40.5)	[redacted]	[redacted]
Open-label follow-up; 52 week time-point						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-

[redacted]

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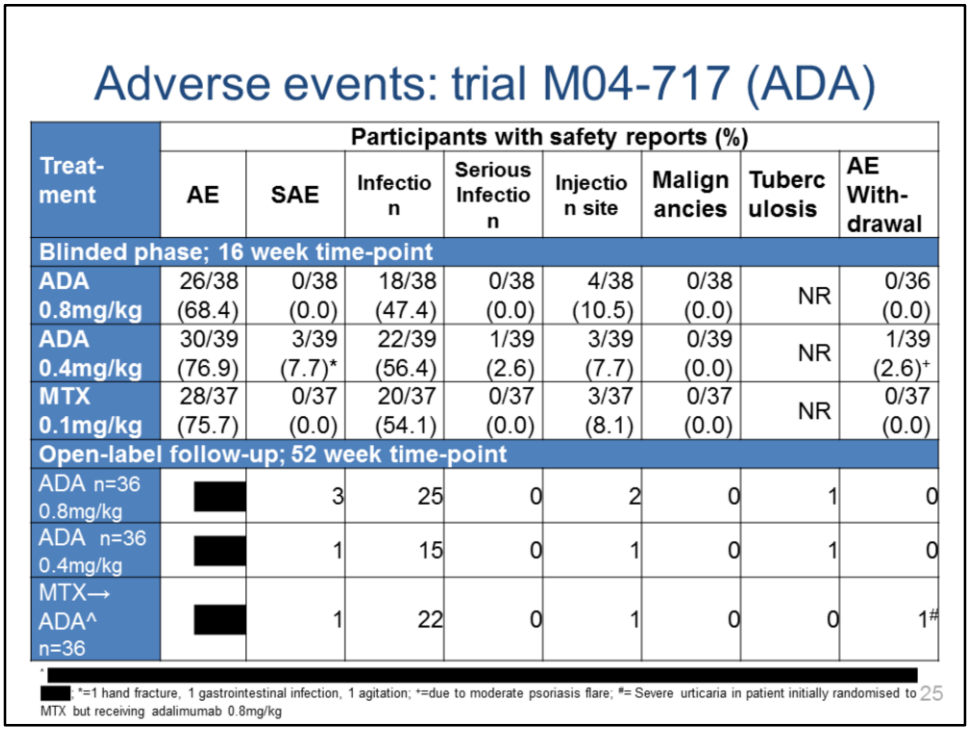
Source: Assessment group report, table 6 (page 62) and table 10 (page 67)

sPGA=Physician Static Global Assessment; CDLQI=Children's Dermatology Life Quality Index; Paediatric Quality of Life

^= [redacted]



Source: Assessment group report, table 11 (page 67) and table 12 (page 69)

^= [redacted]

*=1 hand fracture, 1 gastrointestinal infection, 1 agitation;

+=due to moderate psoriasis flare

#= Severe urticaria in patient initially randomised to MTX but receiving adalimumab 0.8mg/kg

Results: trial 20030211 (etanercept)

Blinded phase; 12 week time-point

Treatment	Number who achieved the outcomes (%)				Mean change (SD)	
	PASI 50	PASI 75	PASI 90	sPGA 0/1	CDLQI (SD)	PedsQL (SD)
ETA 0.8mg/kg	79/106 (74.5)	60/106 (56.6)	29/106 (27.4)	56/106 (52.8)	5.4 (5.6)	6.8 (17.6)
PLB	24/105 (22.9)	12/105 (11.4)	7/105 (6.7%)	14/105 (13.3)	3.1 (5.1)	3.8 (10.1)

Open-label ETA follow-up (weeks 48 to 312)

Week	Number who achieved the outcomes (%)				
	PASI 50	PASI 75	PASI 90	sPGA 0/1	sPGA 0 or 1
60	162/181 (89.5)	122/181 (67.4)	64/181 (35.4)	12/181 (13.3)	97/181 (53.6)
192	101/114 (88.6)	71/114 (62.3)	32/114 (28.1)	9/114 (7.9)	52/114 (45.6)
312	58/66 (87.9)	42/66 (63.6)	19/66 (28.8)	8/66 (12.1)	25/66 (37.9)

Source: Assessment group report, table 14 (page 73) and table 19 (page 77)

Adverse events: trial 20030211 (ETA)

Treatment	Participants with safety reports (%)						
	AE	SAE	Infection	Serious Infection	Injection site	Malignancies	AE With-drawal
Blinded phase; 12 week time-point							
ETA	68/106 (64.2)	NR	50/106 (47.2)	0/106 (0.0)	7/106 (6.6)	NR	1/106 (0.9)
PLB	62/105 (59.0)	NR	33/105 (31.4)	0/105 (0.0)	5/105 (4.8)	NR	0/105 (0.0)
Open-label follow-up; 48-312 week time-point							
ETA	161/181 (89.0)	7/181 (2.8)	140/181 (77.3)	2/181 (1.1)	16/181 (8.8)	NR	6/181 (3.3)*

*= 2 Crohn's disease, 1 glomerulonephritis, 1 psoriasis, sinusitis, and 1 nerve paralysis

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Source: Assessment group report, table 20 (page 77) and table 22 (page 79)

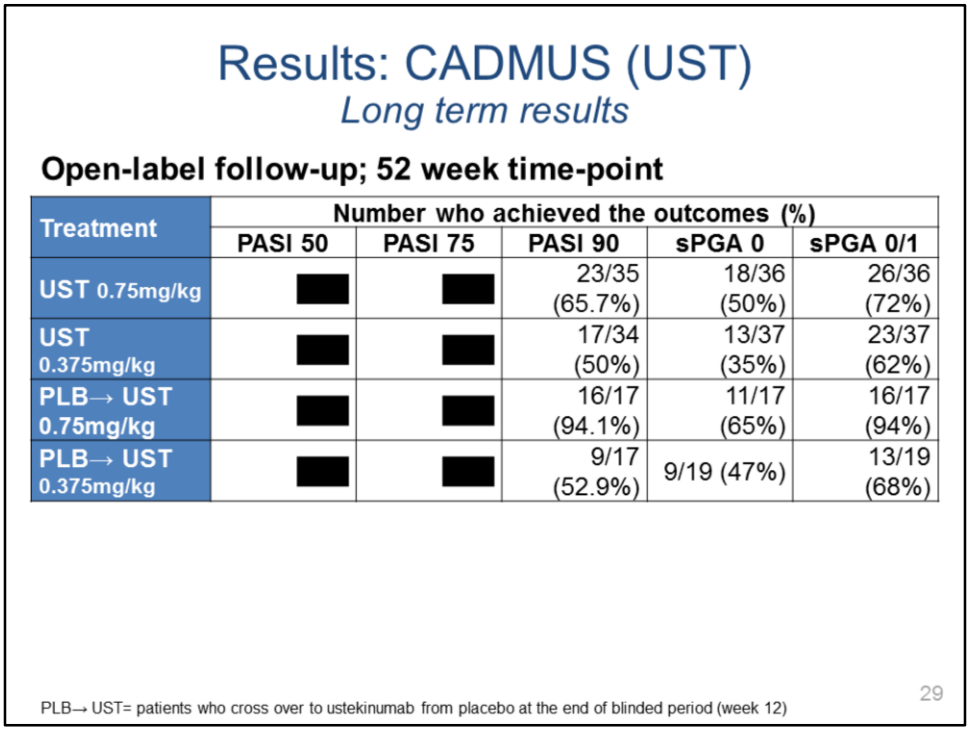
*= 2 Crohn's disease, 1 glomerulonephritis, 1 psoriasis, sinusitis, and 1 nerve paralysis

Results: CADMUS (ustekinumab)

Blinded phase; 12 week time-point

Treatment	Number who achieved the outcomes (%)					Mean change (SD)	
	PASI 50	PASI 75	PASI 90	sPGA 0/1	sPGA 0	CDLQI (SD)	PedsQL (SD)
UST n=36 0.75mg/kg	32/36 (88.9)	29/36 (80.6)	22/36 (61.1)	25/36 (69.4)	17/36 (47.2)	6.7 (5.6) n=32	8.03 (10.4) n=32
UST 0.375mg/kg	30/37 (81.2)	29/37 (78.4)	20/37 (54.1)	25/37 (67.6)	12/37 (32.4)	5.6 (6.4) n=35	10.81 (12.9) n=35
PLB	11/37 (29.7)	4/37 (10.8)	2/37 (5.4)	2/37 (5.4)	1/37 (2.7)	1.5 (3.2) n=32	3.35 (10.0) n=32

Source: Assessment group report, table 24 (page 85)



Source: Assessment group report, table 27 (page 88)

PLB→ UST= patients who cross over to ustekinumab from placebo at the end of blinded period (week 12)

Adverse events: CADMUS Trial (UST)

Treatment	Participants with safety reports (%)						
	AE	SAE	Infection	Serious Infection	Injection site	Malignancies	With-drawal
Blinded phase; 16 week time-point							
UST 0.75mg/kg	16/36 (44.4)	0/36 (0.0)	8/36 (22.2)	0/36 (0.0)	1/36 (2.8)	0/36 (0.0)	0/36 (0.0)
UST 0.375mg/kg	19/37(51.4)	1/37 (2.7)*	12/37 (32.4)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)
PLB	21/37 (56.8)	0/37 (0.0)	14/37 (37.8)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)
Open-label follow-up; 60 week time-point‡							
UST 0.75mg/kg	29/36 (80.6)	1/36 (2.8)^	24/36 (66.7)	1/36 (2.8)^	1/36 (2.8)	0/36 (0.0)	0/36 (0.0)
UST 0.375mg/kg	33/37 (89.2)	5/37+† (13.5)	26/37 (70.3)	1/37† (2.7)	0/37 (0.0)	0/37 (0.0)	2/37 (5.4)
PLB→ UST 0.75mg/kg	13/18 (72.2)	0/18 (0.0)	11/18 (61.1)	0/18 (0.0)	0/18 (0.0)	0/18 (0.0)	0/18 (0.0)
PLB→ UST 0.375mg/kg	15/19 (79.0)	0/19 (0.0)	13/19 (68.4)	0/19 (0.0)	0/19 (0.0)	0/19 (0.0)	2/19 (10.5)

*= one participant in the half ustekinumab dosage group was hospitalised for worsening of psoriasis; ‡incorporates week 12 and 40 data; ^ear infection; †pyelonephritis; +in addition to events recorded before week 60: 1 death due to automobile accident; 1 allergic contact dermatitis.

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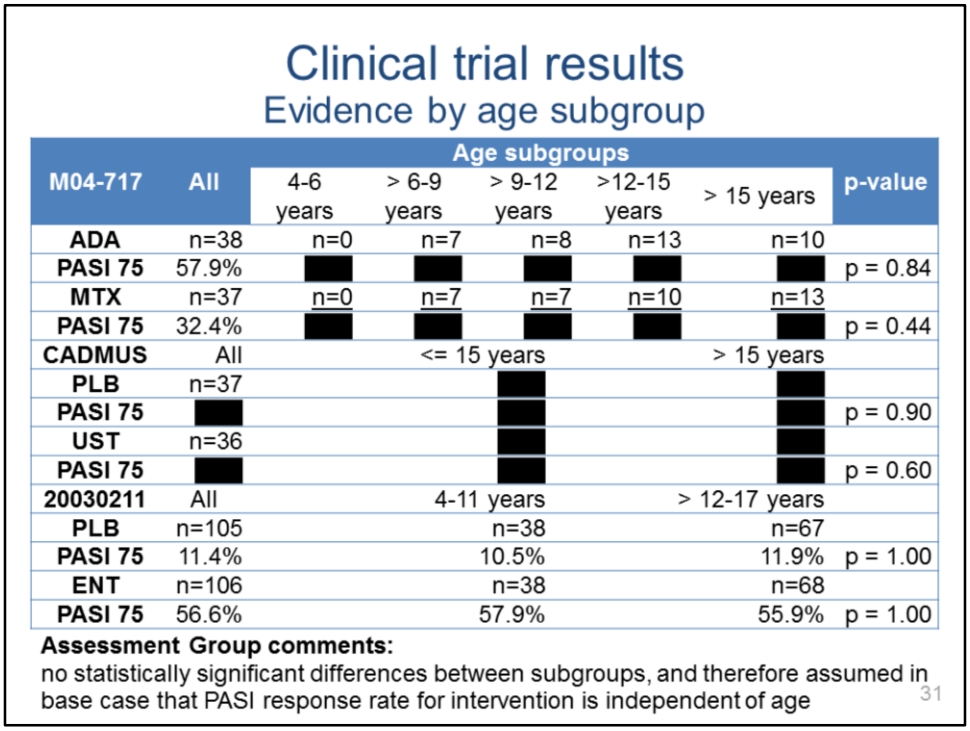
Source: Assessment group report, table 28 (page 89) and table 12 (page 69)

*= one participant in the half ustekinumab dosage group was hospitalised for worsening of psoriasis; ‡incorporates week 12 and 40 data; ^ear infection; †pyelonephritis; +in addition to events recorded before week 60: 1 death due to automobile accident; 1 allergic contact dermatitis.



Source: Assessment group report, table 28 (page 89) and table 12 (page 69)

- Due to variation in the age of the patient populations included in the RCTs adalimumab, etanercept and ustekinumab have marketing authorisation for different age groups in the population of children and young people (≥ 4 years for adalimumab, ≥ 6 years for etanercept, and ≥ 12 years for ustekinumab)
- To establish the relative efficacy of the interventions it is necessary to either i) assume that the PASI response rates for the treatments are independent of age within the full population of children and young people; or ii) consider outcomes in a subgroup population by age.
- Within each study, there were no statistically significant differences identified across the age subgroups for each of the PASI response rates of 50, 75 or 90. Therefore, in order to compare the relative efficacy of the interventions, the Assessment Group assumed that the PASI response rates for the treatments are independent of age within the full population of children and young people and that the studies are comparable for this population.

Assessment Group's comments

Clinical trial summary

- Risk of bias for all trials was low for most domains
- No head-to-head comparative data available for the 3 biologics
- Adalimumab trial used methotrexate as a comparator; placebo a common comparator for etanercept and ustekinumab trials
- PASI response rate, CDLQI and PedsQL consistently reported across trials
- Results from the blinded, RCT phase of the trials is used to inform the network-meta analysis

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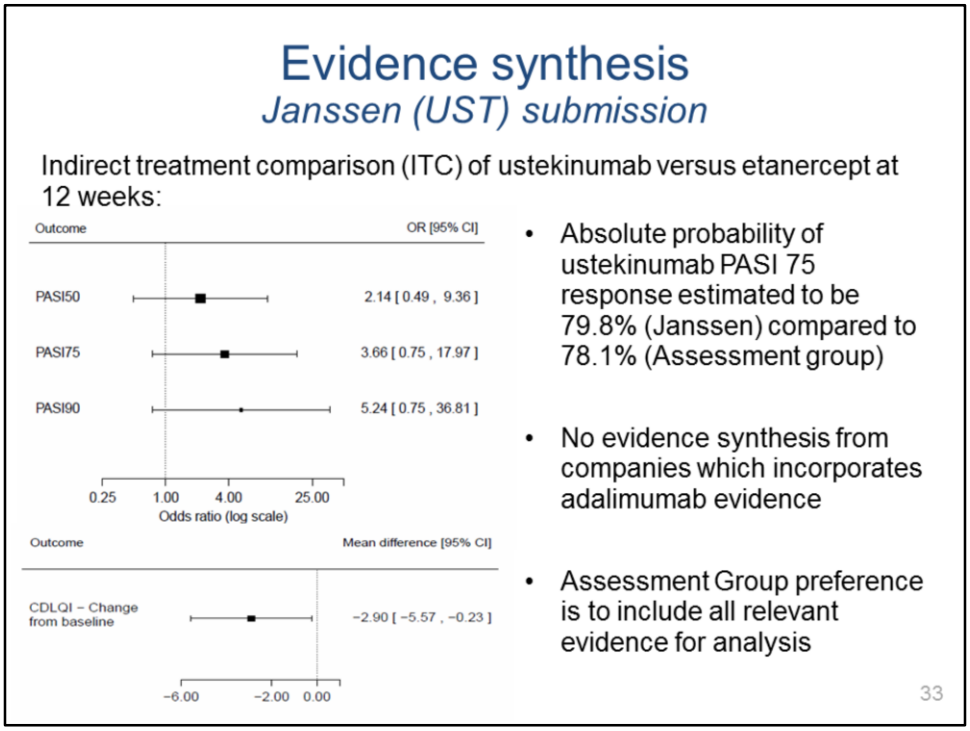


Source: Janssen company submission, figure 12 and 13 (page 54 and 55)

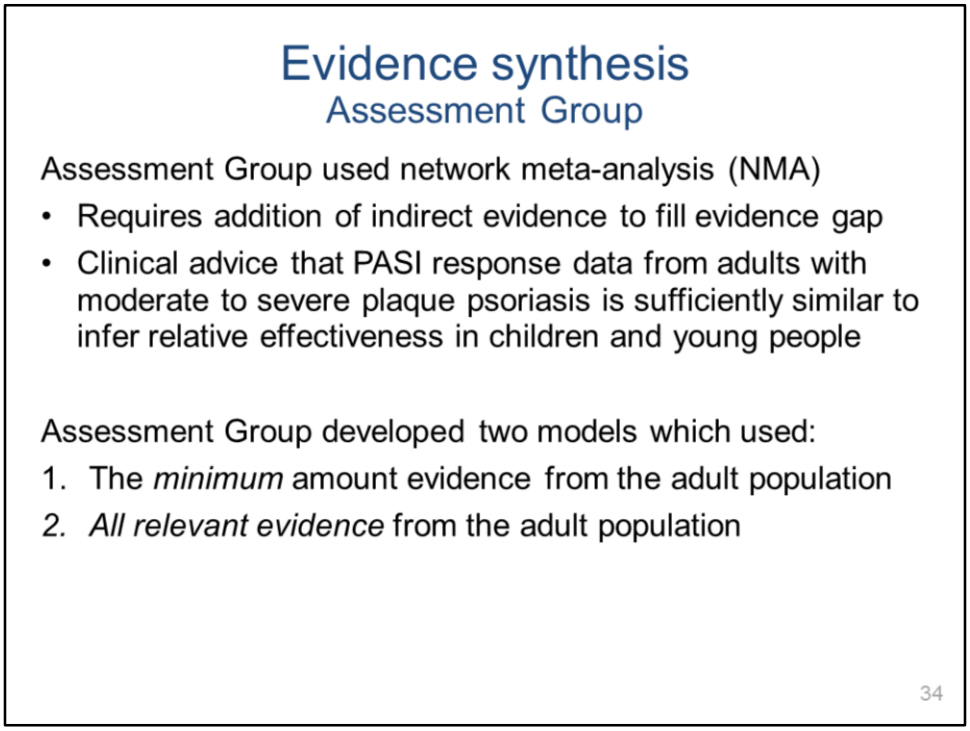
Rationale for not incorporating adalimumab evidence:

A meta-analysis neither feasible nor appropriate to conduct due to the differences in; study designs, comparators, inclusion/exclusion of study participants, variations in the outcome reporting, as well as outcome measures across the biologics studies.

Indirect comparison unfeasible due to the differences in the respective marketing authorizations, Lack of high quality studies and heterogeneity across the relevant studies

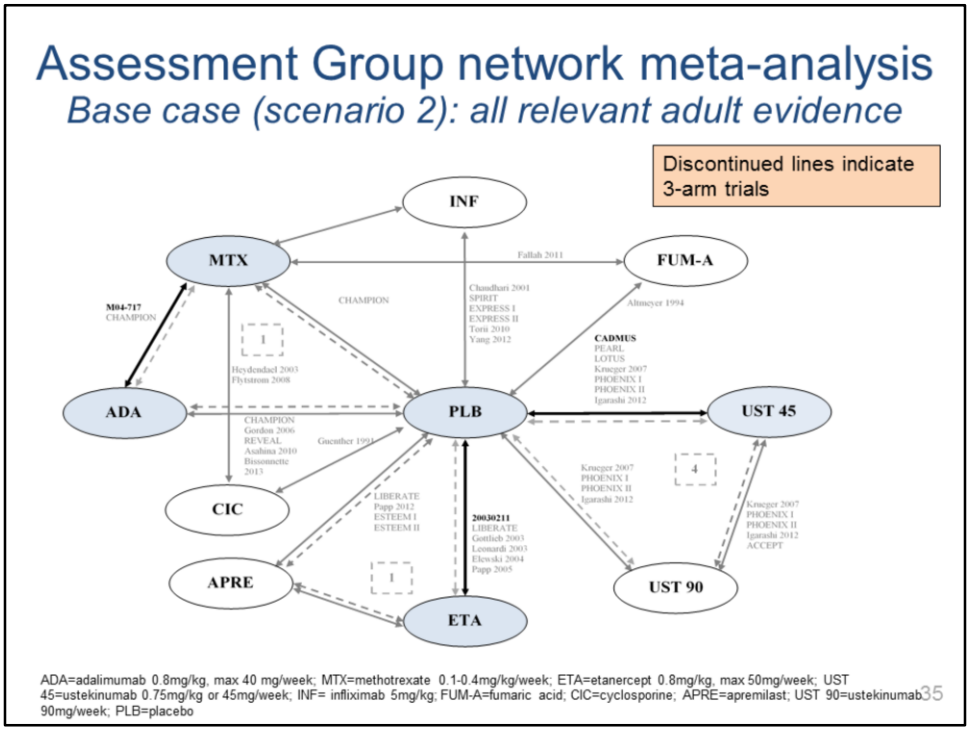
Assessment group highlight that indirect treatment analysis is limited :

- Draws conclusions only for short-term use of ustekinumab and etanercept from the corresponding trials;
- The placebo arms in study 20030211 (etanercept) and CADMUS assumed to be exchangeable;
- Inclusion criteria for age were different between the trials;
- There is uncertainty in both the within-trial and between-trial treatment effect estimates because of small sample sizes in the trials;
- differences between the trials in terms of baseline characteristics and trial design – these differences have been explored separately in Section 4;
- The indirect treatment comparison does not provide sufficient information to inform the economic analysis since the intervention of adalimumab has been excluded.



Assessment group highlight:

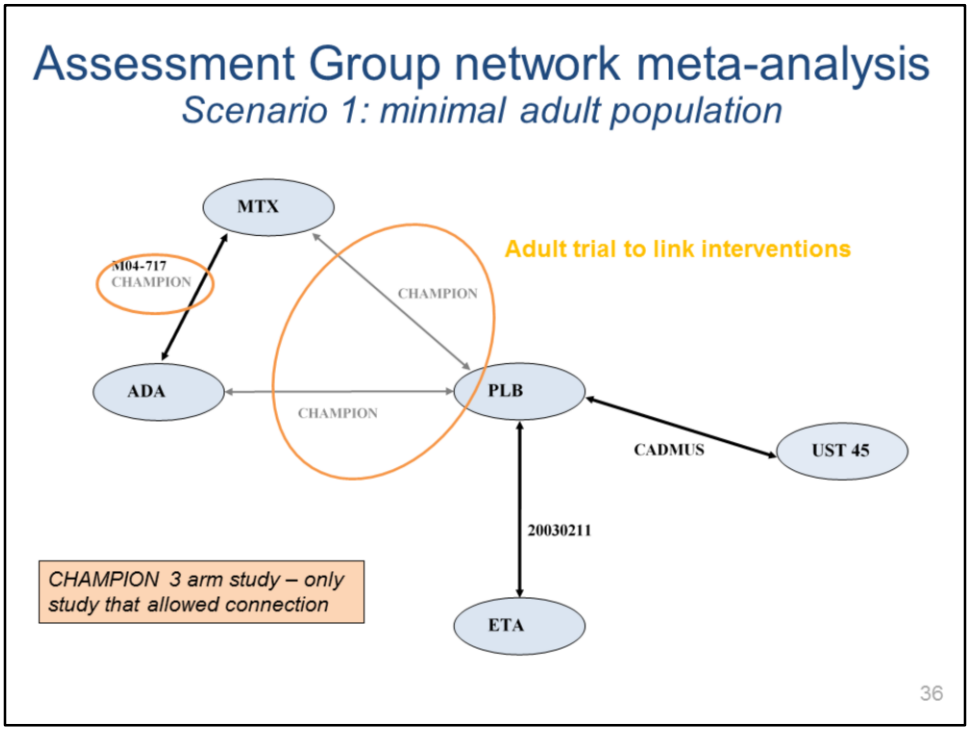
- This approach allows treatment specific estimates to be modelled in each population by drawing strength from the network of evidence available.
- The use of a NMA in preference to pairwise meta-analyses enables the inclusion of all relevant evidence, allowing for precise estimates of treatment effects to be calculated.
- The results from the NMA will feed directly into the economic model to provide the relevant cost-effectiveness of adalimumab, etanercept and ustekinumab against relevant comparators and each other.
- This approach has been used in previous NICE technology appraisals for the treatment of plaque psoriasis in adults (TA 103, 134, 146, 180, 350, and 368).



Source: Assessment group report, figure 5 (page 118)

ADA=adalimumab 0.8mg/kg, max 40 mg/week; MTX=methotrexate 0.1-0.4mg/kg/week; ETA=etanercept 0.8mg/kg, max 50mg/week; UST 45=ustekinumab 0.75mg/kg or 45mg/week; INF= infliximab 5mg/kg; FUM-A=fumaric acid; CIC=cyclosporine; APRE=apremilast; UST 90=ustekinumab 90mg/week; PLB=placebo.

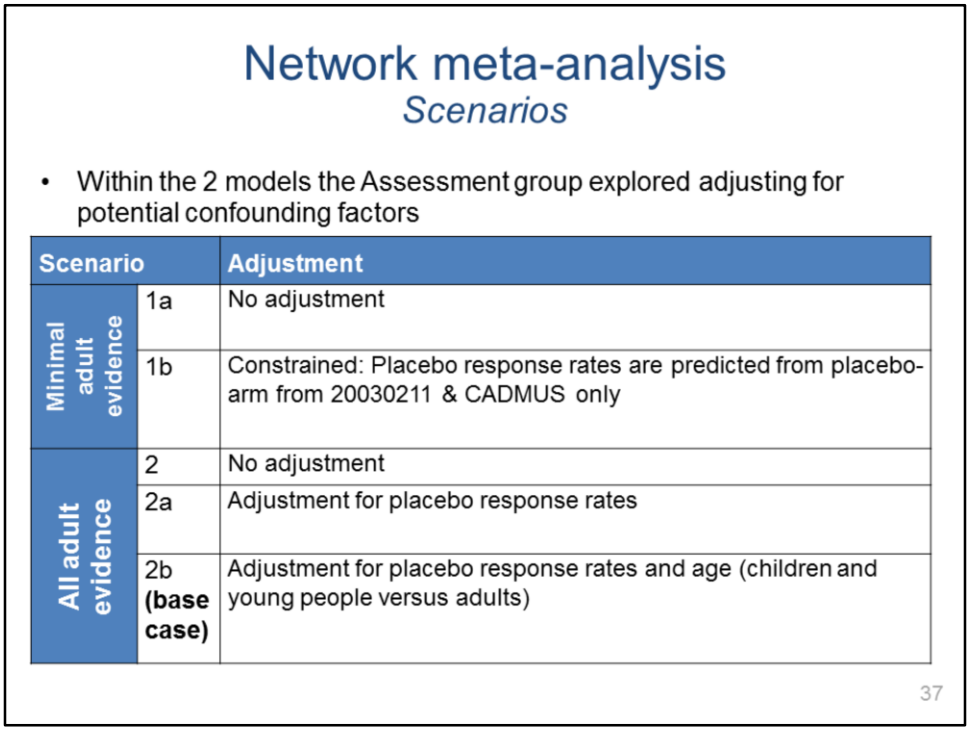
- Trial names are stated where trial evidence informs the network treatment link.
- Discontinued lines indicate where 3-arm trials inform the evidence network, with the number of 3-arm trials stated in a discontinued line box.



Source: Assessment group report, figure 4 (page 115)

The PASI 75 response rates for ADA and MTX in CHAMPION are similar in M04-717 for children and young people. There is a large observed placebo effect for the primary endpoint of PASI 75. In study 20030211 and CADMUS the proportion of PLB individuals achieving PASI 75 was approximately 11%, but approximately 19% in the CHAMPION study.

Therefore a baseline *constrained* prediction model was also considered, whereby placebo response rates are predicted based on the placebo-arm trials in children and young people only (i.e. study 20030211 and CADMUS) (analysis 1b). As the number of trials to inform each treatment effect is small, a fixed-effect model was used. The results of this analysis are presented in Section 5.4.3 (Results).



Source: adapted from Assessment group report, table 44 (page 120)

- For each NMA model fixed- and random-effects model approaches were investigated. The latter approach was shown to be preferable, highlighting that variability across trials was important to account for.
- The rate of placebo response was identified as a source of heterogeneity, which was adjusted for in the '*constrained'* and *'baseline adjusted'* models.
- *constrained* prediction model is where placebo response rates are predicted based on the placebo-arm trials in children and young people only
- Population adjusted models allowed obtaining subpopulation specific estimates for i) children and young people and ii) adults.

Network meta-analysis

Results: fit of the models

Analysis	1a & 1b		
	PASI 50	PASI 75	PASI 90
Residual deviance	46.6*	39.7	57.6
DIC	158.60		

Analysis	2			2a		
	PASI 50	PASI 75	PASI 90	PASI 50	PASI 75	PASI 90
Residual deviance	378.1*	355.6	404.0	381.7*	357.5	409.4
DIC	1241.07			904.5		

Analysis	2b – preferred by AG		
	PASI 50	PASI 75	PASI 90
Residual deviance	380.8*	356.2	408.6
DIC	1229.5		

Model 2b fits the data as well as model 2a, with similar average total residual deviance. DIC is substantially lower for 2a, suggesting the model is parsimonious

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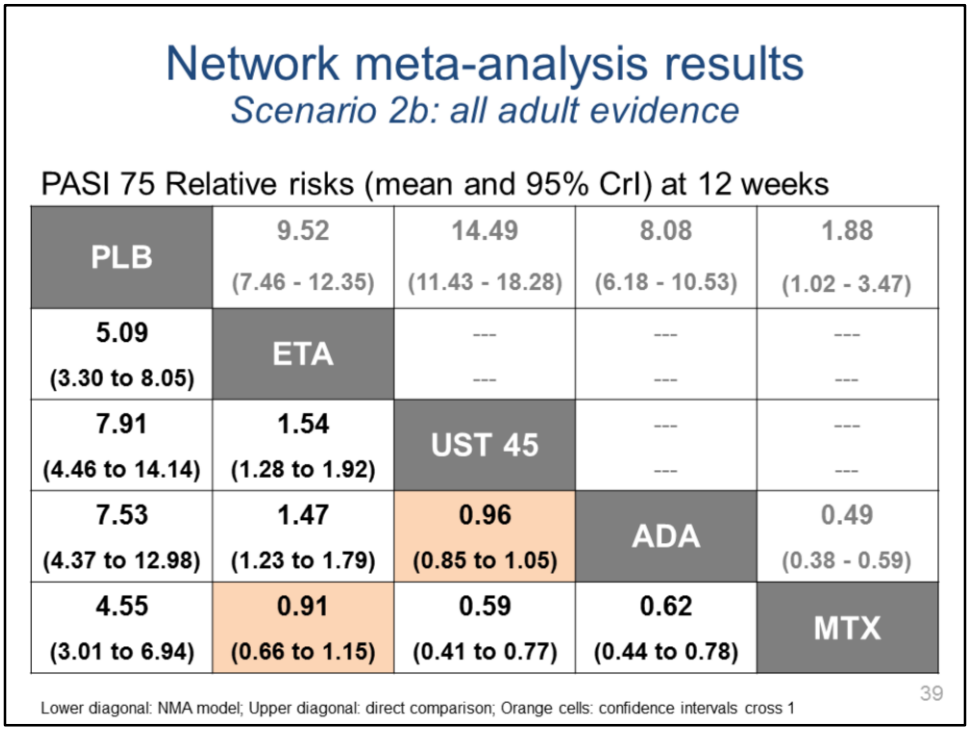
*=compared with 209 data points; DIC = deviance information criterion

Source: Assessment group report, table 44 (page 120)

- *=compared with 209 data points
- DIC=deviance information criterion
- The model from analysis 2b fits the data as well as model 2a, as both present similar average total residual deviance [380.8 (2b) vs. 381.7 (2a)]. However, DIC is substantially higher for 2b. This suggests that this model is being penalised due to issues of parsimony.
- Age and placebo adjusted model (analysis 2b) used for in the Assessment Group's base case.
- Parsimonious model: desired level of explanation or prediction with as few predictor variables as possible
- The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed



Source: Assessment group report, table 50 (page 129)

PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate;

- Lower diagonal: pooled RRs from NMA model.
- RRs above one favour the row agent;
- Upper diagonal: RRs from direct comparison (pooled using fixed-effects when multiple studies exist).
- RRs above one favour the column agent;
- non-significant differences in the relative effects between a pair of agents are shaded in orange.

Network meta-analysis results

Scenario 2b: Probability of PASI response

- **Inputs in Assessment Group's cost-effectiveness model**

Probability of PASI response (mean and 95% credible interval) at 12 weeks

	PASI 50	PASI 75	PASI 90
Placebo	0.265 (0.15 to 0.40)	0.115 (0.05 to 0.20)	0.029 (0.01 to 0.06)
Etanercept	0.752 (0.62 to 0.86)	0.544 (0.39 to 0.69)	0.279 (0.16 to 0.42)
Ustekinumab	0.934 (0.87 to 0.97)	0.824 (0.71 to 0.91)	0.594 (0.43 to 0.74)
Adalimumab	0.915 (0.83 to 0.97)	0.790 (0.64 to 0.90)	0.546 (0.37 to 0.72)
Methotrexate	0.708 (0.53 to 0.85)	0.492 (0.31 to 0.68)	0.240 (0.11 to 0.40)

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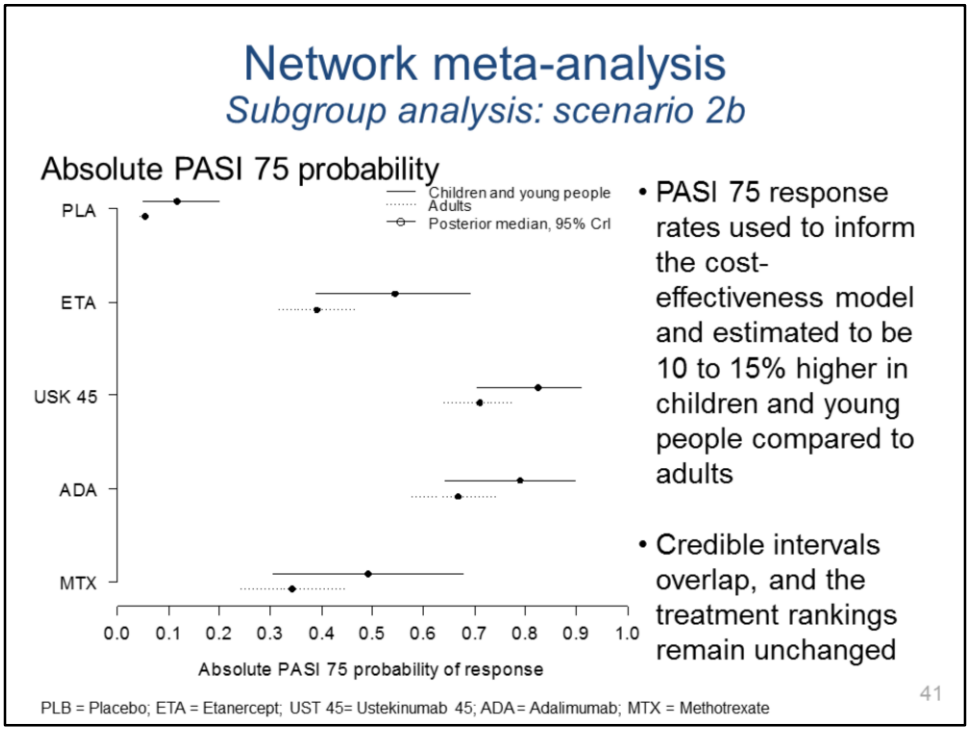
Source: Assessment group report, table 49 (page 127)



Source: Assessment group report, figure 7 (page 128)

PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate

Cost-effectiveness evidence

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Company submissions

AbbVie (adalimumab):

- No cost-utility analysis as there are considerable and unresolvable uncertainty
- There are limitations in utilities and natural history data that are required for modelling a life-time horizon in a paediatric population
- Provided results for an analysis on 'incremental cost per PASI-75 responder', where adalimumab incremental cost was £6,130 per PASI 75 responder

Janssen (ustekinumab)

- Provided a discussion of the known available evidence to help address uncertainties and aid the development of a model
- For further information see section 6.3 of the company submission

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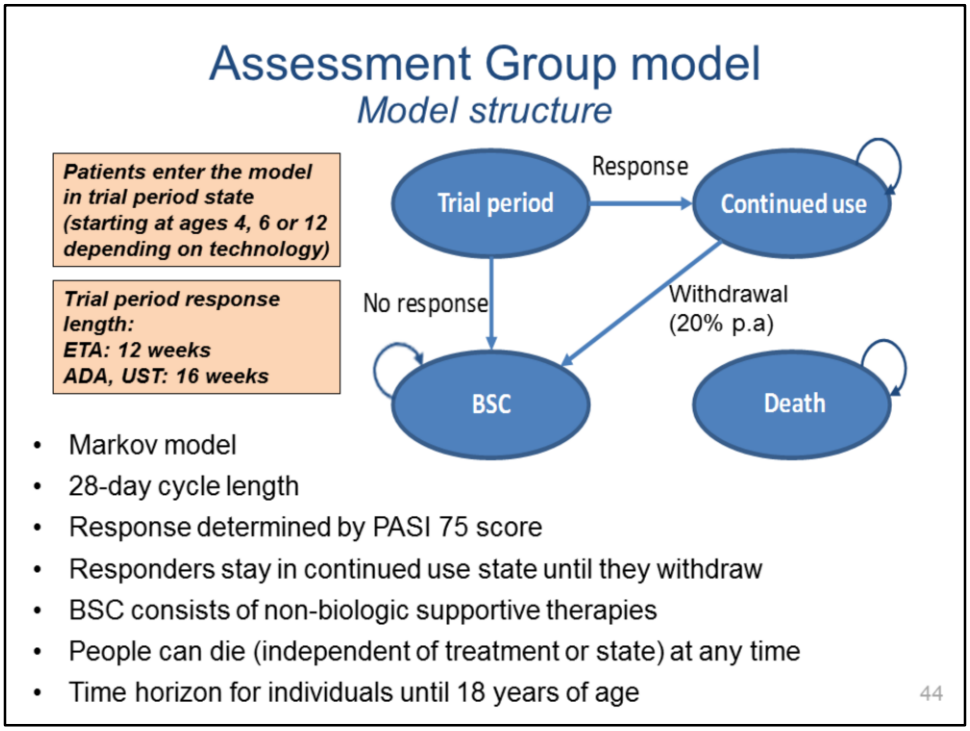
See section of 5 of AbbVie's company submission and section 6 of the Janssen's company submission

The incremental cost per PASI-75 responder based on this analysis was found to be £6,130 [£5,572 to £7,020] for adalimumab, £7,221 [£6,740 to £7,817] for ustekinumab, £7,570 [£7,091 to £8,101] for infliximab, £8,019 [£6,573 to 9,930] for etanercept 25 mg, and £10,188 [£9,007 to £11,544] for etanercept 50 mg



Source: Assessment group report, figure 10 (page 171)

BSC=best supportive care; p.a=per annuum

- Trial period corresponds to time-point in trials at which response to treatment is assessed: 12 weeks for etanercept; 16 weeks for adalimumab and ustekinumab.
- End of trial period people are classified as 'responders' or 'non-responders' to treatment based on PASI response rates.
- PASI response in the base-case analysis is taken to be PASI 75, i.e. response is assessed based on whether an individual achieves a 75% reduction in baseline PASI score.
- Continued use patients continue to receive the active therapy and are assumed to maintain their level of PASI response until treatment discontinuation due to any cause, such as lack of efficacy, the presence of adverse events or non-compliance to treatment (modelled together as an overall risk of all cause withdrawal).
- BSC was defined as per CG153, with the clinical input to assess the applicability of adult guidance for children and young people
- 'Death' is an all-cause mortality state, not conditioned on treatment or treatment

response. Mortality rates by age were sourced from life tables in England and Wales for the years 2013-15 and averaged across gender.

Assessment Group model

3 Populations in model

Population 1:

- 4 to 17 year olds whose disease is inadequately controlled by, or intolerant to topical therapy and phototherapies
  - Position: before systemic therapy (compared to methotrexate)
  - Interventions: adalimumab

Population 2:

- 6 to 11 year olds whose disease is inadequately controlled by, or intolerant to systemic therapies or phototherapies
  - Position: after systemic therapy (compared to best supportive care)
  - Interventions: adalimumab & etanercept

Population 3:

- 12 to 17 year olds whose disease is inadequately controlled by, or intolerant to systemic therapies or phototherapies
  - Position: after systemic therapy (compared to best supportive care)
  - Interventions: adalimumab, etanercept & ustekinumab

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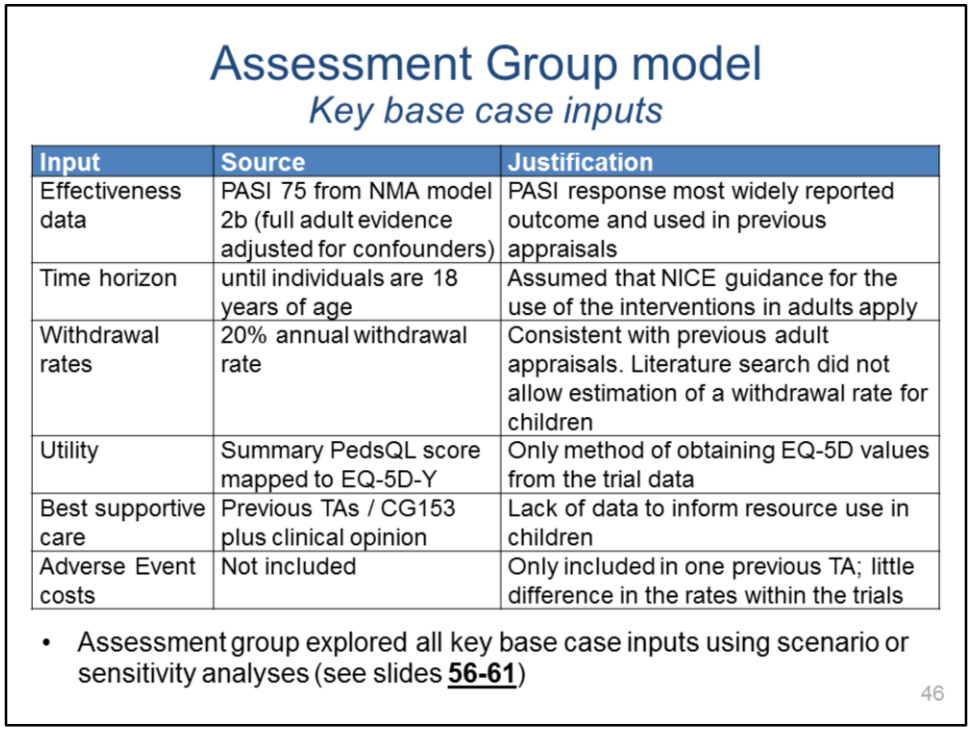

Assessment Group model

Key base case inputs

Input	Source	Justification
Effectiveness data	PASI 75 from NMA model 2b (full adult evidence adjusted for confounders)	PASI response most widely reported outcome and used in previous appraisals
Time horizon	until individuals are 18 years of age	Assumed that NICE guidance for the use of the interventions in adults apply
Withdrawal rates	20% annual withdrawal rate	Consistent with previous adult appraisals. Literature search did not allow estimation of a withdrawal rate for children
Utility	Summary PedsQL score mapped to EQ-5D-Y	Only method of obtaining EQ-5D values from the trial data
Best supportive care	Previous TAs / CG153 plus clinical opinion	Lack of data to inform resource use in children
Adverse Event costs	Not included	Only included in one previous TA; little difference in the rates within the trials

- Assessment group explored all key base case inputs using scenario or sensitivity analyses (see slides **56-61**)

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Effectiveness data

- Individuals who meet the threshold of PASI 75 are classified as responders at the end of the trial period and assumed to maintain their response until withdrawal
- PASI response for BSC are assumed equivalent to placebo in the NMA.
- Response rates are assumed to be constant per cycle in the model

20% annual withdrawal rate

- data indicated no significant predictive relationship for age and treatment continuation
- the UK BADBIR audit of adults is consistent with a withdrawal rate of 20%
- BADBIR audit suggests that there may be differences in the withdrawal rate by treatment, with UST having a significantly higher survival rate compared to ADA and ETA . However, the study does not distinguish between discontinuation due to a lack of treatment response in the short-term.

Time horizon

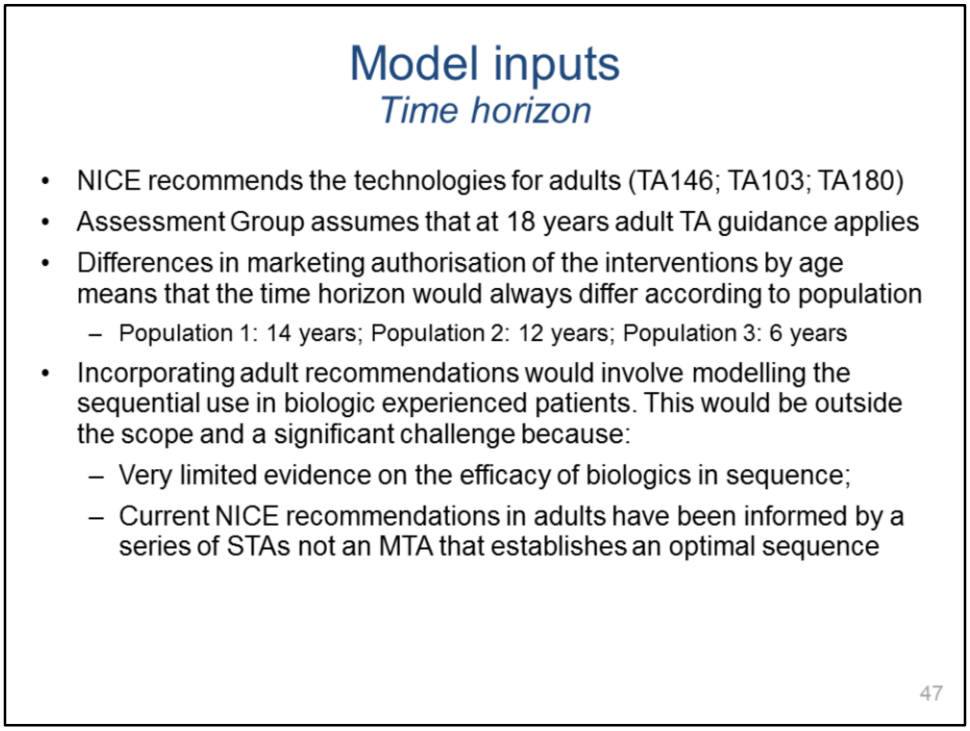
See slide **47**

Utility

- See slides **49-51**

Best supportive care

- See slide **52**



- TA 146, 103, 180 and 350 recommend adalimumab, etanercept, ustekinumab and secukinumab respectively as treatment options for adults with severe psoriasis who have not responded to, are intolerant to or contraindicated to standard systemic therapies such as ciclosporin, methotrexate or PUVA

Model inputs

Effectiveness over time and discontinuation rate

Effectiveness over time

- No evidence that PASI response rate varies with age (see slide **31**)
- Without access to individual patient data, no evidence to model time-varying transition probabilities

Discontinuation rate

- 20% withdrawal is consistent with previous adult appraisals
- Observational data generally suggests this is reasonable in adults but evidence from 1 adult registry that UST has a lower discontinuation rate (but no separation of trial period and long-term withdrawal).
- Evidence in children (2 registries) also suggests a consistent withdrawal is reasonable
- Insufficient evidence to change the assumption that 20% withdrawal is reasonable for all the technologies

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Model inputs

Health state utilities

- As per previous TAs the utility of an intervention is based on the proportion of patients in the different PASI response categories
- End of trial period people are classified as 'responders' or 'non-responders' to treatment based on achieving a PASI 75 response
- Responders continue the intervention and are assumed to maintain their level of PASI response until withdrawal (any cause) to the BSC state

Treatment	Health state in model		
	Trial period	Continued use (responders)	BSC (non-responders and withdrawals)
Adalimumab	0.9156	0.9261	0.8713
Etanercept	0.8974	0.9177	0.8713
Ustekinumab	0.9186	0.9274	0.8713
Methotrexate	0.8994	0.9164	0.8713
BSC	-	-	0.8713

Source: Assessment group report, table 63 (page 202)

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Model inputs
Utility

- Previous TAs estimate utility gain of PASI response either directly by EQ-5D score, or by mapping DLQI to EQ-5D
- The trials in this appraisal only report CDLQI and PedsQL. Assessment group literature search only found a single mapping algorithm, which maps to EQ-5D-Y scores
- Assessment Group mapped PedsQL scores from CADMUS
- Utility gains were smaller compared to previous appraisals
- BSC utility from PASI response for placebo of the NMA

Appraisal	Baseline	Utility gain by PASI response category			
		PASI<50	PASI 50-75	PASI 75-90	PASI ≥90
	0.8596	0.0036	0.0255	0.0340	0.0810
TA103	0.7**	0.050	0.170	0.190	0.210
TA146	NR***	0.063	0.178	0.178	0.308
TA180	0.692*	0.04	0.17	0.22	0.25

Source: Assessment group report, table 73 (page 202)

*DLQI>10; **Based on Revicki et al (2008), as it was not reported in the TAs; ***Constrained to this value, so that the absolute utility value would not go above one for patients undergoing the maximum utility increment.

- Assessment group used CADMUS trial because Janssen (ustekinumab) submitted aggregated summary data (mean and standard deviation) from the CADMUS trial for PedsQL subscale and total scale scores by treatment arm (placebo and ustekinumab standard dose) and PASI response categories at 12 weeks (<50, 50-75, 75-90, ≥90) for baseline,12, 28 and 52 weeks.

Model inputs – Utilities
Assessment Group comments

- Gains in CDLQI by PASI response category from the trials were smaller compared to DLQI in adults. This could be because:
  - Co-morbidities (e.g. mood disturbance) are more common in older people, psoriasis has less impact on quality of life in children compared to adults
  - Using a mapping algorithm to estimate utilities introduces uncertainty compared to direct EQ-5D measurement
  - The mapping algorithm has not been validated in children with psoriasis
  - PedsQL and CDLQI may not fully capture the disutility of the disease
  - The PedsQL data source (CADMUS) excluded children <12 years
  - CDLQI (children) and DLQI (adult) scores are not directly comparable
  - The number of observations is much smaller in the population of children and young people (n=73) compared with adult appraisals (TA180, n=1115)

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Model inputs

Best supportive care

- Best supportive care resource use has been identified as a source of uncertainty and key driver of cost-effectiveness in previous appraisals

	Current MTA/CG153	
	Resource use	Unit costs
Phototherapy	16% have 24 sessions a year	£95.53
Monitoring+	4 per year if on systemic treatment	£125.22 per visit
GFR	1 per year if on cyclosporine	£195.07 per GFR
Day centre visits	5 visits per year	£472.55 per visit
Outpatient visits	5 per year if not on systemic treatment	£119.99 per visit

- Clinical opinion identified where there should be a divergence from CG153

	CG153		Current MTA	
	Resource use	Unit costs	Resource use	Unit costs
Methotrexate	45%	£0.05/mg	61%*	£0.71/mg
Cyclosporine	45%	£0.02/mg	29%*	£0.02/mg
Hospitalisations	26.6 bed days	£271.17	0 bed days**	£295.80

- 1 UK observation study (Fonia et al) estimates hospitalisations at 6.49 bed days

* Data from a UK psoriasis audit; **alternative hospitalisation scenarios explored (Scenario 5); +CG153 included 0.04 liver biopsies and 4 PIIINP per year for patients on MTX not included in current MTA

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Source: Assessment group report, table 68 (page 190)

- BSC a source of uncertainty in previous appraisals
  - prior to CG153, BSC was restricted to outpatient visits and hospitalisations to manage symptoms of psoriasis (largely informed by clinical opinion)
  - After CG153, BSC included non-biologic systemic treatments, phototherapy and attendance at tertiary day centres
  - Both CG153 and Fonia et al thought in previous appraisals to overestimate hospitalisations because CG153 considers a high-need population with severe psoriasis, while Fonia describes care in a tertiary care centre known for treating the most severely affected individuals.
  - In recent adult appraisals, clinical experts indicated that hospitilisations for severe psoriasis has fallen over time and continues to fall
- Rationale for changes
  - Clinical opinion that children and young people are less likely to be managed with cyclosporine compared to adults due to the renal toxicity of the drug
  - Clinical advisor suggested that hospitalisations in children and young people are very rare. This is largely because children and young people have not yet developed co-morbidities which often lead to hospitalisation with psoriasis in adults

Base case results

Population 1: Alternative to systematic therapy

Base-case probabilistic results for adalimumab as an alternative to systemic therapy

	Mean costs (£)	Mean QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Population 1: Children and young people aged 4-17 years					
MTX	34,914	9.939	-	-	-
ADA	61,999	10.027	27,084	0.088	**308,329**

Incr. Costs = Incremental costs versus next best treatment; QALY = Quality adjusted life year; Incr. QALYS= Incremental QALYs versus next best treatment; ICER = incremental cost-effectiveness ratio

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Source: Assessment group report, table 72 (page 201)

Base case results

Populations 2 & 3: After failed systemic therapy

Base-case probabilistic results for interventions after failed systemic therapy

	Mean costs (£)	Mean QALYs	Incr. costs (£)	Incr. QALYs	Incr. ICER (£/QALY)
Population 2: Children and young people aged 6-11 years					
BSC	36,406	8.710	-	-	**-**
ETA	43,808	8.813	7,402	0.103	**71,903**
ADA	57,251	8.890	13,444	0.077	**174,519**
Population 3: Children and young people aged 12-17 years					
BSC	21,749	4.804	-	-	**-**
ETA	33,199	4.887	11,450	0.084	**ED ADA**
ADA	37,852	4.950	16,103	0.146	**110,430**
UST	39,975	4.960	2,123	0.011	**201,507**

54

Incr. ICER = Incremental ICER versus next best treatment; ED = extendedly dominated

Source: Assessment group report, table 73 (page 202)

Assessment Group's key scenario analyses

No.	Scenario	Description
1	Off-label use of biologics	No age or position constraints
2	Time horizon of model	Time horizon extended to 14 years
3	Evidence synthesis and treatment effectiveness	Assess the impact of using adult data or different PASI 50 scores
4	Utility values	Use the utility values from previous adult appraisals
5	Resource use associated with BSC	Where clinical opinion has informed an assumption use assumptions consistent with previous adult appraisals

For further details see section 7.5.2 of the Assessment group report

The Assessment Group also conducted scenarios which investigated:

- Costs associated with adverse events (scenario analysis 6)
- Sensitivity around overall treatment withdrawal rates (scenario analysis 7)
- Use of biosimilars (scenario analysis 8)

The impact of these scenarios was marginal, and not reported here. For further details see section 7.5.2.6 – 7.5.2.8 of the Assessment group report.

Scenarios 1 and 2

No age or position constraints

	Alternative to systematic therapy (ETA versus MTX)			After failed systemic therapy (ETA versus BSC)		
	Incr. costs	Incr. QALYs	Incr. ICER	Incr. costs	Incr. QALYs	Incr. ICER
Ages 4-17 years						
ETA	11,853	0.009	**ED ADA**	6,289	0.105	**59,924**
ADA	27,084	0.088	**ED UST**	15,231	0.079	**ED UST**
UST	29,512	0.101	**293,117**	23,948	0.013	**121,779**

Common time horizon of 14 years

	Population 2: Ages 6-11 years			Population 3: Ages 12-17 years		
	Incr. costs	Incr. QALYs	Incr. ICER	Incr. costs	Incr. QALYs	Incr. ICER
After failed systemic therapy; ETA versus BSC						
ETA	7,696	0.105	**73,153**	14,275	0.105	**ED ADA**
ADA	13,614	0.079	**172,000**	20,194	0.184	**109,531**
UST	-	-	-	2,299	0.012	**188,715**

Source: Assessment group report, tables 74, 75, and 76, (pages 206, 207 and 208)

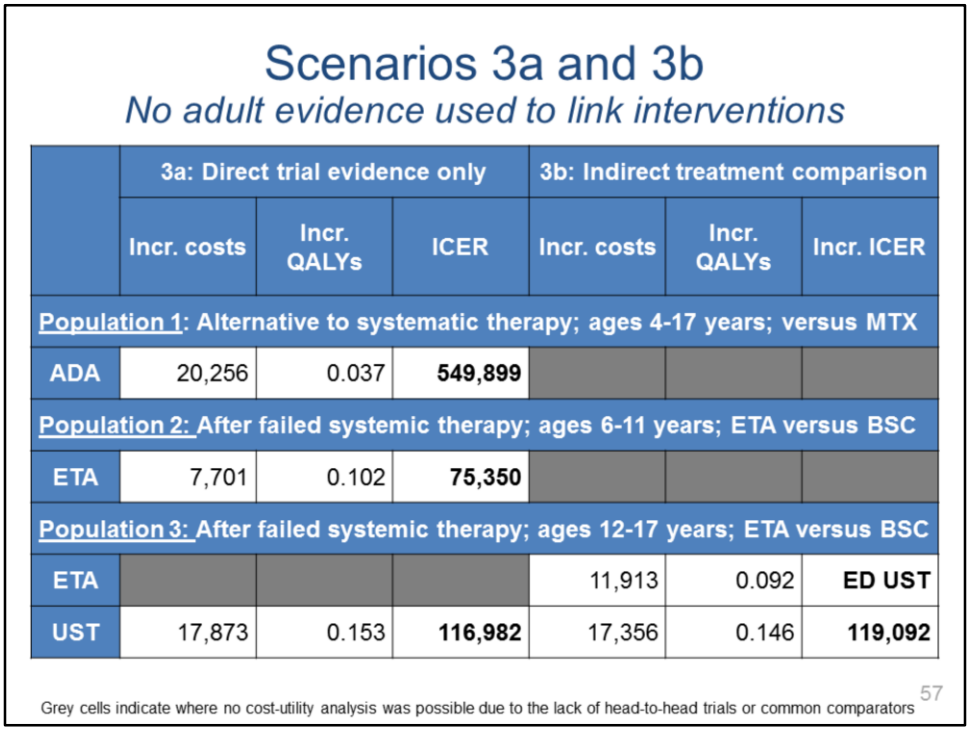
Scenario 1

In the absence of clinical effectiveness evidence in a systemic-naïve population, the same efficacy estimates as the base-case analysis is used in this scenario

Scenario 2

The time horizon of 14 years is sufficient to capture differences in costs and effects between the interventions under comparison because all individuals on each treatment in the model have moved to BSC by 14 years.

This time horizon is also greater than 10 years as used in previous TAs in adults.



Scenarios 3a and 3b

No adult evidence used to link interventions

	3a: Direct trial evidence only			3b: Indirect treatment comparison		
	Incr. costs	Incr. QALYs	ICER	Incr. costs	Incr. QALYs	Incr. ICER
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX						
ADA	20,256	0.037	**549,899**			
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC						
ETA	7,701	0.102	**75,350**			
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC						
ETA				11,913	0.092	**ED UST**
UST	17,873	0.153	**116,982**	17,356	0.146	**119,092**

Grey cells indicate where no cost-utility analysis was possible due to the lack of head-to-head trials or common comparators

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Source: Assessment group report, tables 77, 78 and 79 (pages 209, 210 and 211)

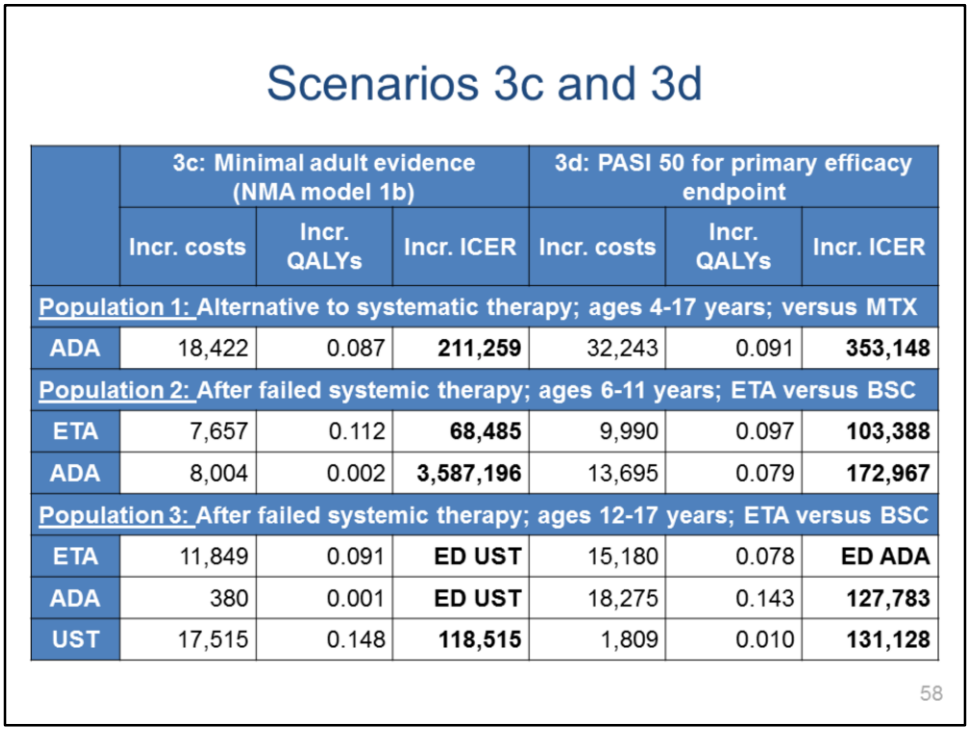
Scenario 3a

Direct trial evidence does not allow the relative cost-effectiveness of all three biologics to be assessed in the same analysis. However, it may give an indication of how much influence the wider network of evidence has on the individual pairwise comparisons.

Marginal impact on ICER as PASI 75 response rates estimated from the NMA for etanercept (54%), ustekinumab (82%) and placebo (11.5%) are very similar to the corresponding response rates from the individual trials (81% ustekinumab vs. 11% placebo, CADMUS; 57% etanercept vs. 11.4% placebo, study 20030211)

Scenario 3b

Indirect treatment comparison does not allow the relative cost-effectiveness of etanercept and ustekinumab to be compared with adalimumab due to the absence of a placebo arm in M04-717



	3c: Minimal adult evidence (NMA model 1b)			3d: PASI 50 for primary efficacy endpoint		
	Incr. costs	Incr. QALYs	Incr. ICER	Incr. costs	Incr. QALYs	Incr. ICER
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX						
ADA	18,422	0.087	**211,259**	32,243	0.091	**353,148**
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC						
ETA	7,657	0.112	**68,485**	9,990	0.097	**103,388**
ADA	8,004	0.002	**3,587,196**	13,695	0.079	**172,967**
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC						
ETA	11,849	0.091	**ED UST**	15,180	0.078	**ED ADA**
ADA	380	0.001	**ED UST**	18,275	0.143	**127,783**
UST	17,515	0.148	**118,515**	1,809	0.010	**131,128**

Source: Assessment group report, tables 80-83 (pages 213-215)

Scenario 3c

The CHAMPION study in adults, which was a three-arm trial comparing adalimumab, methotrexate and placebo, represented the best way to connect adalimumab to etanercept and ustekinumab using the least amount of evidence borrowed from the adult population

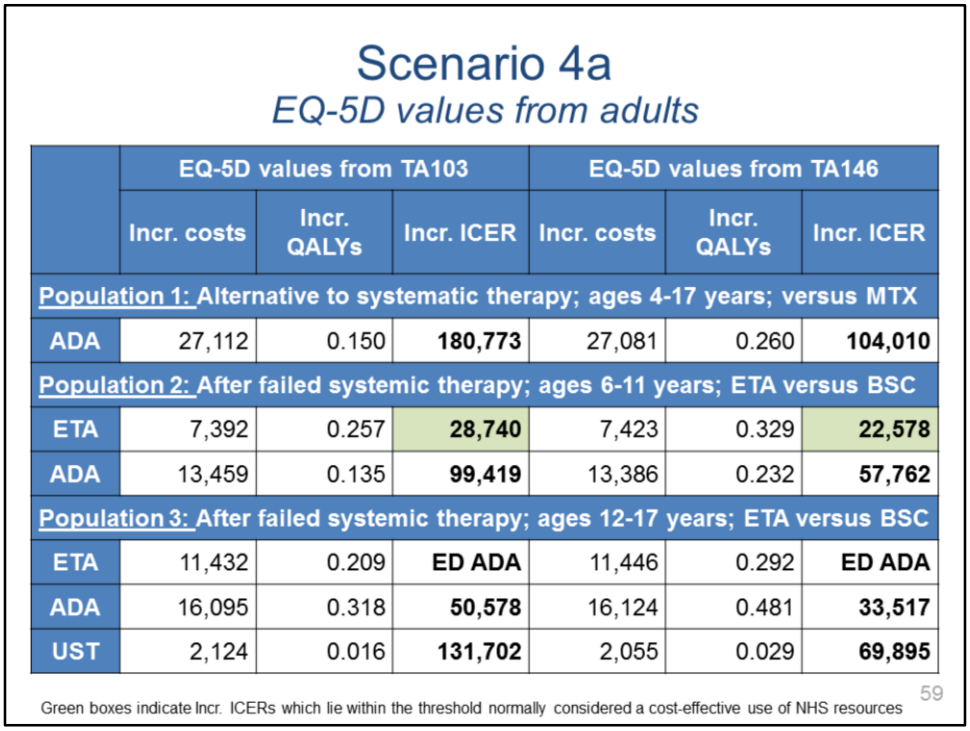
Alternative to systematic therapy very similar to base case because in the minimum NMA, the PASI response rates for placebo are greater than the full network. Therefore, the gain in utility associated with better efficacy is offset by a higher gain in utility associated with BSC

After failed systemic therapy the incremental costs and QALYs for etanercept and ustekinumab compared to BSC are similar to the base-case analysis, but the incremental costs and QALYs for adalimumab are reduced in both age groups.

Scenario 3d

ICER increases for all interventions because the total costs increase (a greater proportion of individuals continue treatment as responders) but QALY gain

decreases



Scenario 4a

EQ-5D values from adults

	EQ-5D values from TA103			EQ-5D values from TA146		
	Incr. costs	Incr. QALYs	Incr. ICER	Incr. costs	Incr. QALYs	Incr. ICER
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX						
ADA	27,112	0.150	**180,773**	27,081	0.260	**104,010**
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC						
ETA	7,392	0.257	**28,740**	7,423	0.329	**22,578**
ADA	13,459	0.135	**99,419**	13,386	0.232	**57,762**
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC						
ETA	11,432	0.209	**ED ADA**	11,446	0.292	**ED ADA**
ADA	16,095	0.318	**50,578**	16,124	0.481	**33,517**
UST	2,124	0.016	**131,702**	2,055	0.029	**69,895**

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Green boxes indicate Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources

Source: Assessment group report, tables 84 and 85 (pages 217 and 218)

- For EQ-5D values see slide ***50***
- Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green
- The estimated EQ-5D-Y utility gains from the PedsQL data were of a much smaller magnitude compared to the EQ-5D values used in previous TAs in adults. It was also noted that the gains in CDLQI by PASI response category were of a smaller magnitude compared to DLQI values reported in adults. It is not clear whether these smaller utility increments observed in children and young people is a reflection of less impact of severe psoriasis on quality of life in a paediatric population or a result of small sample sizes and limited data in this population.
- The scenario substantially improves ICERS for all interventions

Scenario 5
Alternative hospitalisation estimates

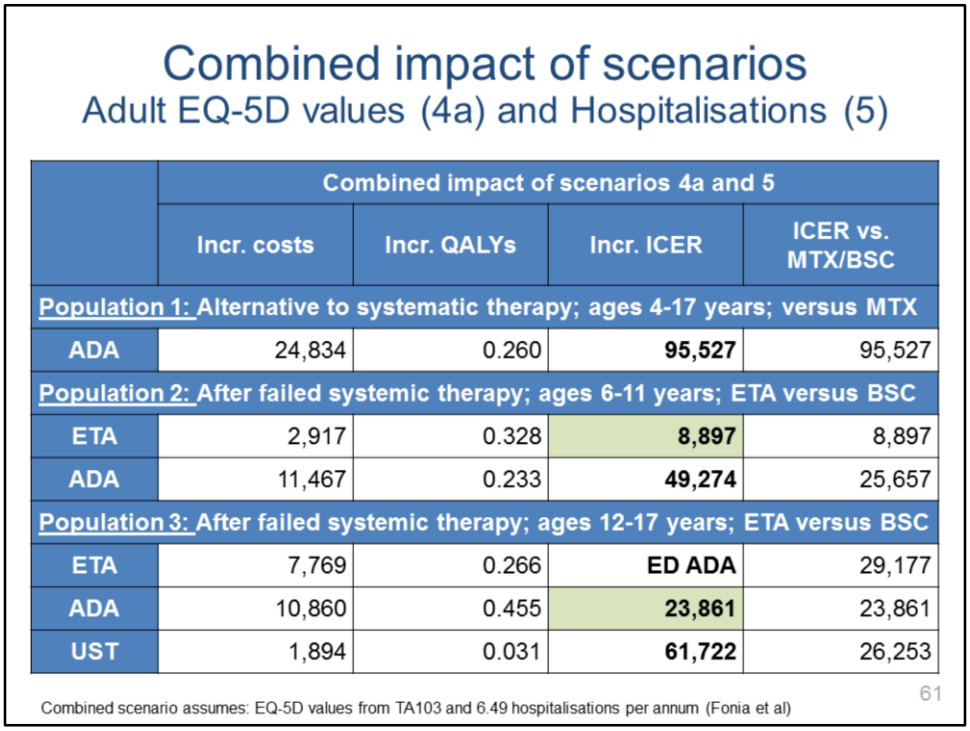
	Based on Fonia et al (2010)			Based on CG153		
	Incr. costs	Incr. QALYs	Incr. ICER	Incr. costs	Incr. QALYs	Incr. ICER
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX						
ADA	24,873	0.089	**281,029**	17,876	0.088	**202,571**
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC						
ETA	2,903	0.103	**28,286**	-5,500	0.180	**Dominant**
ADA	11,516	0.078	**148,586**	5,399	0.077	**69,797**
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC						
ETA	7,766	0.083	**ED ADA**	1,777*	-0.062*	**Dominated***
ADA	10,855	0.146	**74,501**	-	-	**Dominant**
UST	1,875	0.010	**186,634**	1,250	0.011	**118,665**

*: ETA versus ADA;
Green boxes indicate Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources

60

Source: Assessment group report, tables 88 and 89 (pages 221 and 222)

- Base case assumes children and young people in BSC have no hospitalisations
- Fonia et al assumes 6.49 hospitalisations per annum
- CG153 assumes 26.6 hospitalisations per annum
- As number of hospitalisations increase, the total cost of BSC increases. This improves the cost-effectiveness of all interventions, with a proportionally greater impact on the interventions after failed systemic therapy, as the comparator is BSC.
- Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green



Combined impact of scenarios
Adult EQ-5D values (4a) and Hospitalisations (5)

	Combined impact of scenarios 4a and 5			
	Incr. costs	Incr. QALYs	Incr. ICER	ICER vs. MTX/BSC
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX				
ADA	24,834	0.260	**95,527**	95,527
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC				
ETA	2,917	0.328	**8,897**	8,897
ADA	11,467	0.233	**49,274**	25,657
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC				
ETA	7,769	0.266	**ED ADA**	29,177
ADA	10,860	0.455	**23,861**	23,861
UST	1,894	0.031	**61,722**	26,253

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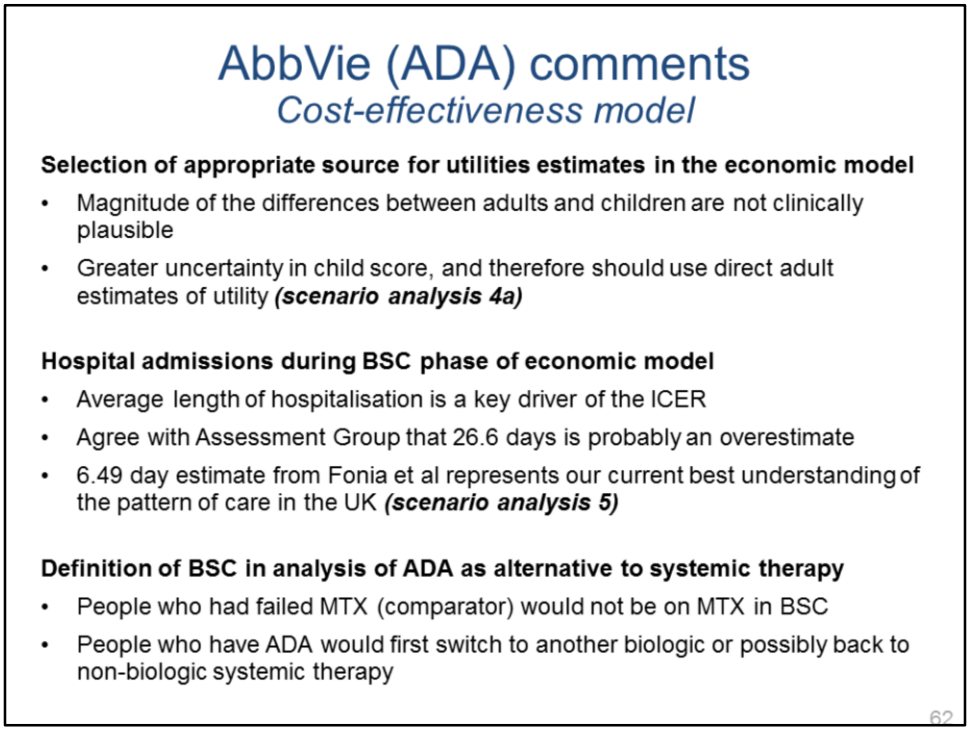
Combined scenario assumes: EQ-5D values from TA103 and 6.49 hospitalisations per annum (Fonia et al)

Source: Assessment group report, table 98 (page 233)

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green



For full details see the AbbVie's Response to the Assessment Group's Report

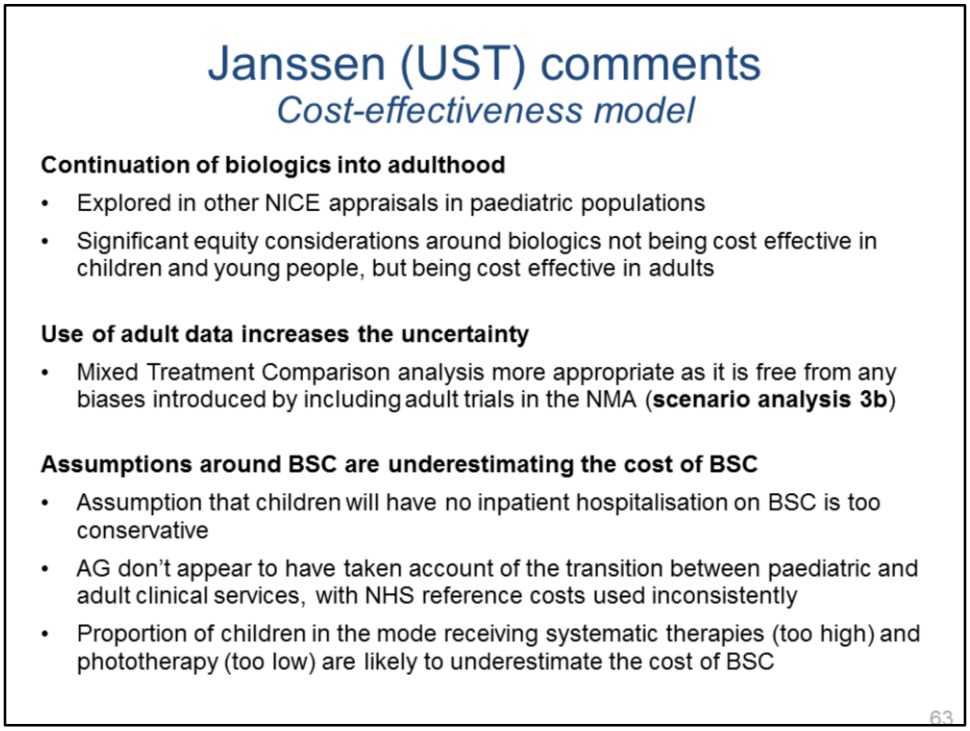
Source for utilities

Adult utility gains are 6.7-8.6 times greater than values estimated for adolescents for PASI 50-75, 5.3-6.5 times greater for PASI 75-90 and 2.6-3.8 times greater for PASI>90. Whilst some degree of quality of life difference between adolescents and adults is possible, incremental differences of this magnitude are not clinically plausible.

Underestimation of utility values in economic model

Fonia et al identified a mean LOS of 6.49 days in the year prior to treatment initiation, declining to 1.55 days in the year following treatment initiation. Although this patient group is not analogous to those who have failed biological therapy, and is limited to adult patients, it is probably the best estimate currently available to inform this model.

Difficult to justify the assumption of no admissions at all



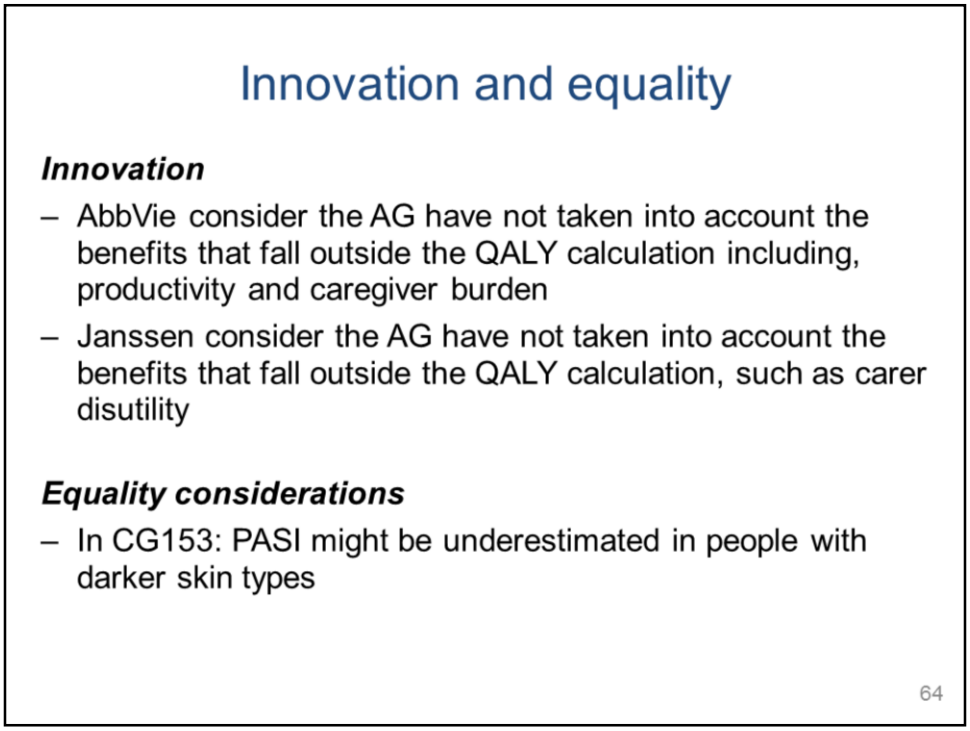
For full details see the Janssen's response to the Assessment Group's Report

Assumptions around BSC

- Underestimate the cost of BSC because of the low cost of the generic systematic medicines compared to patients receiving active management in an outpatient setting.
- Number of patients receiving phototherapy has been significantly underestimated currently (16%). Our clinical expert, suggests closer to 100% of patients
- 90% to be receiving systemic therapies based on the estimates used in NICE CG153 for an adult population is likely to be an overestimation because:
    - Methotrexate and cyclosporine are not licensed for use in children.
    - Drug survival rates in children are much lower than that seen in biologics in adults
    - Methotrexate has been associated with fertility concerns in paediatric patients and as the AG noted 'patients on cyclosporine will only receive treatment for a maximum of two years, because of increased risk of renal toxicity.
- In addition, patients on cyclosporine have no further cost attached to them after they discontinue at 2 years, and should instead be assumed to be having active management

Other concerns raised

- Exploration of higher doses of MTX which is seen in clinical practice should be explored
- There is evidence to suggest a difference in withdrawal rates in clinical practice for the different therapies, which has not been explored



Innovation

For further information see section 2.5 of the AbiVie's company submission and the AbiVie's company's response to AG Report

For further information see Janssen's company's response to AG Report

Authors

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Backup slides

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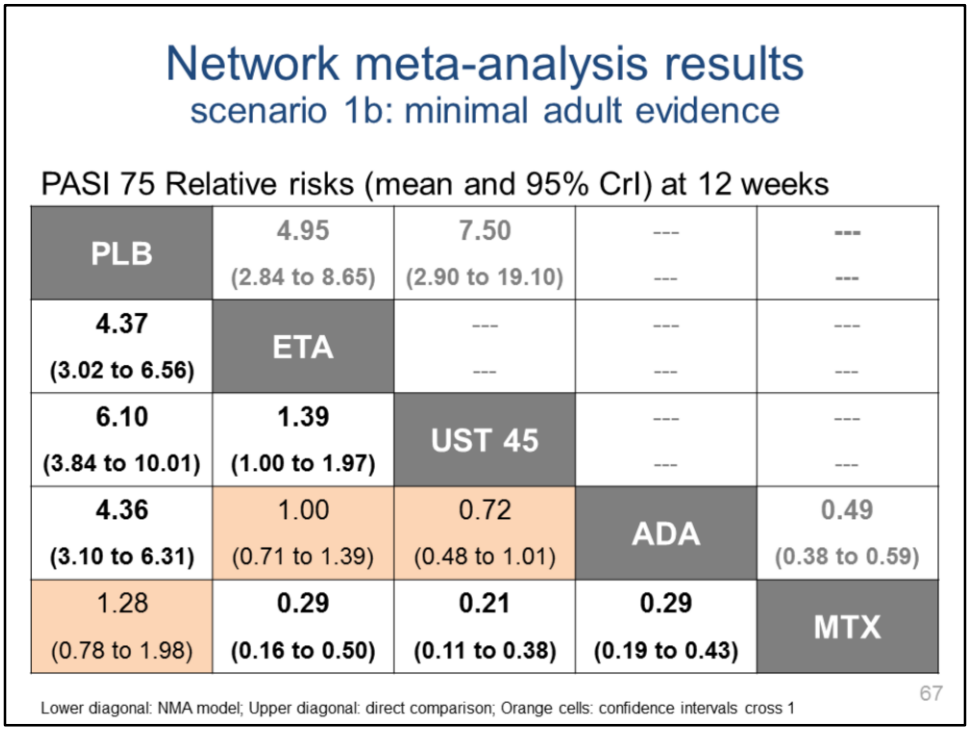
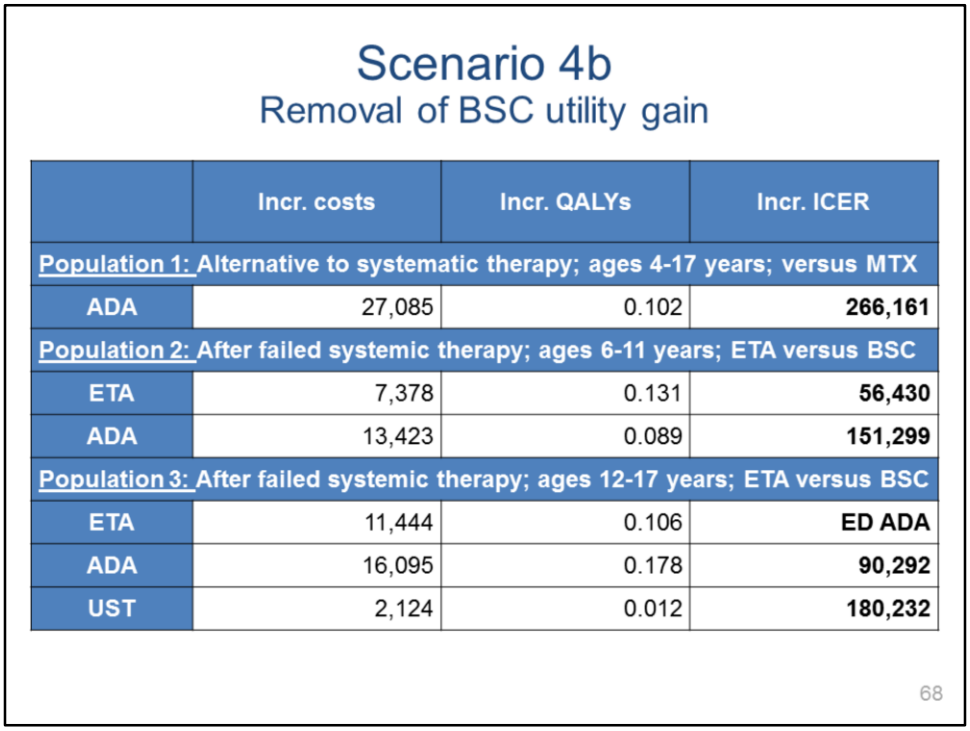


Source: Assessment group report, table 44 (page 120)

PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate;

- Lower diagonal: pooled RRs from NMA model.
- RRs above one favour the row agent;
- Upper diagonal: RRs from direct comparison (pooled using fixed-effects when multiple studies exist).
- RRs above one favour the column agent;
- non-significant differences in the relative effects between a pair of agents are shaded in orange.



Scenario 4b
Removal of BSC utility gain

	Incr. costs	Incr. QALYs	Incr. ICER
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX			
ADA	27,085	0.102	**266,161**
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC			
ETA	7,378	0.131	**56,430**
ADA	13,423	0.089	**151,299**
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC			
ETA	11,444	0.106	**ED ADA**
ADA	16,095	0.178	**90,292**
UST	2,124	0.012	**180,232**

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Source: Assessment group report, tables 86 and 87 (pages 219 and 220)

Scenario improves ICERS for all interventions

Pairwise ICER comparisons
Base case

	Incr. costs	Incr. QALYs	Incr. ICER	ICER vs. MTX/BSC
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX				
ADA	27,084	0.088	**308,329**	308,329
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC				
ETA	7,402	0.103	**71,903**	71,903
ADA	13,444	0.077	**174,519**	115,825
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC				
ETA	11,450	0.084	**ED ADA**	137,059
ADA	16,103	0.146	**110,430**	110,430
UST	2,123	0.011	**201,507**	116,568

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Source: Assessment group report, table 72 and 73 (page 201 and 202)

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

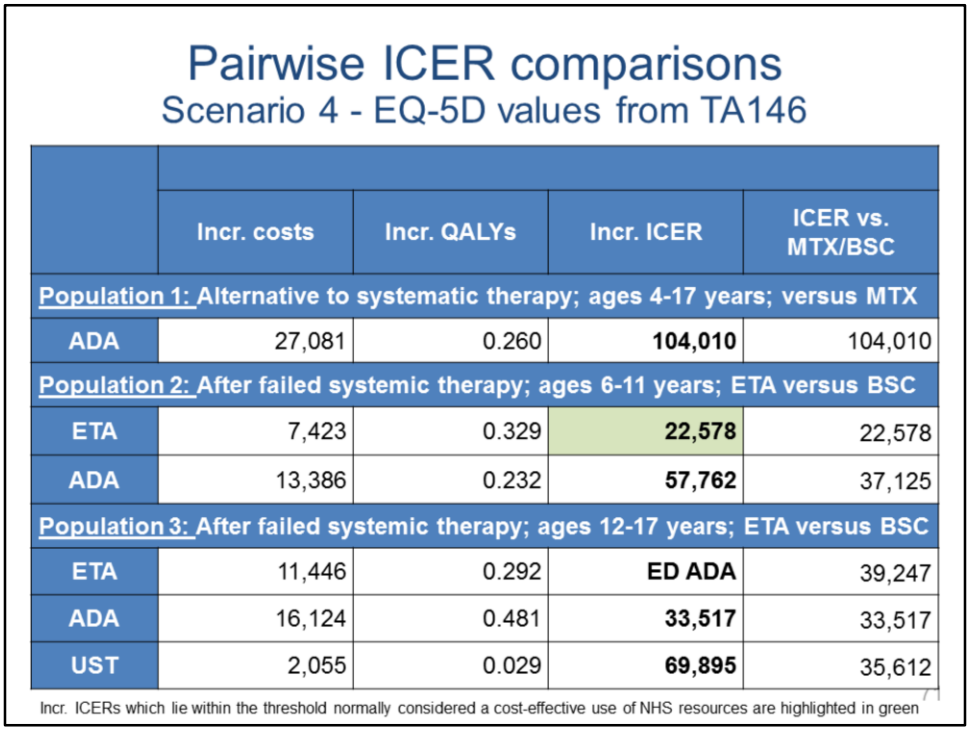
Pairwise ICER comparisons
Scenario 4 - EQ-5D values from TA103

	Incr. costs	Incr. QALYs	Incr. ICER	ICER vs. MTX/BSC
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX				
ADA	27,112	0.150	**180,773**	180,773
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC				
ETA	7,392	0.257	**28,740**	28,740
ADA	13,459	0.135	**99,419**	53,112
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC				
ETA	11,432	0.209	**ED ADA**	54,717
ADA	16,095	0.318	**50,578**	50,578
UST	2,124	0.016	**131,702**	54,491

70

Source: Assessment group report, tables 84 and 85 (pages 217 and 218)

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green



Pairwise ICER comparisons

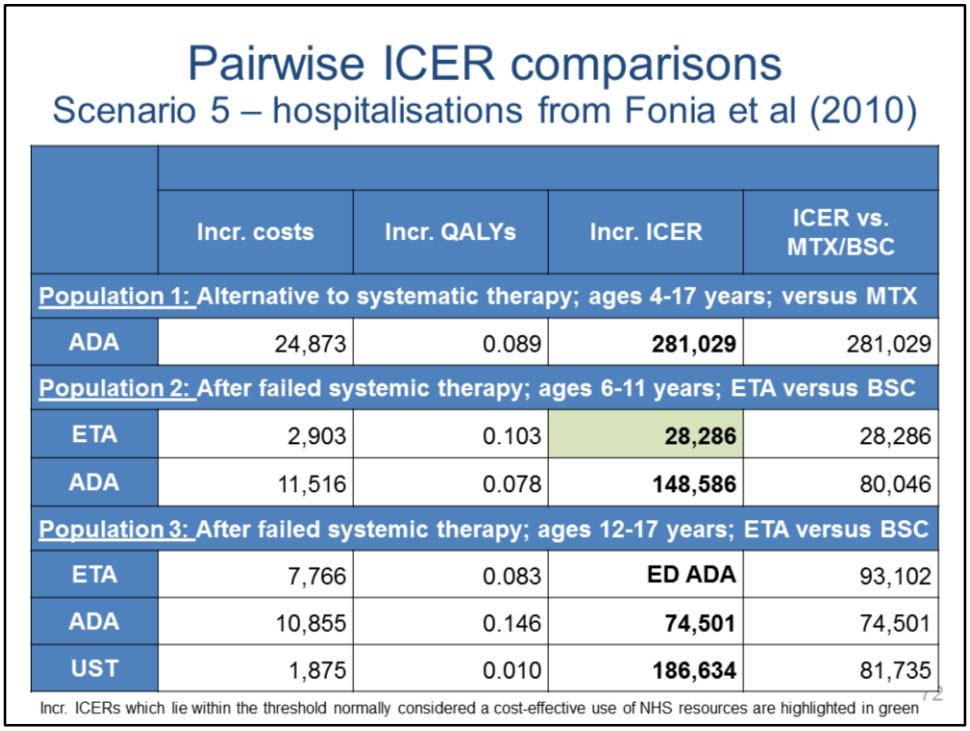
Scenario 4 - EQ-5D values from TA146

	Incr. costs	Incr. QALYs	Incr. ICER	ICER vs. MTX/BSC
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX				
ADA	27,081	0.260	**104,010**	104,010
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC				
ETA	7,423	0.329	**22,578**	22,578
ADA	13,386	0.232	**57,762**	37,125
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC				
ETA	11,446	0.292	**ED ADA**	39,247
ADA	16,124	0.481	**33,517**	33,517
UST	2,055	0.029	**69,895**	35,612

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

Source: Assessment group report, tables 84 and 85 (pages 217 and 218)

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green



Pairwise ICER comparisons

Scenario 5 – hospitalisations from Fonia et al (2010)

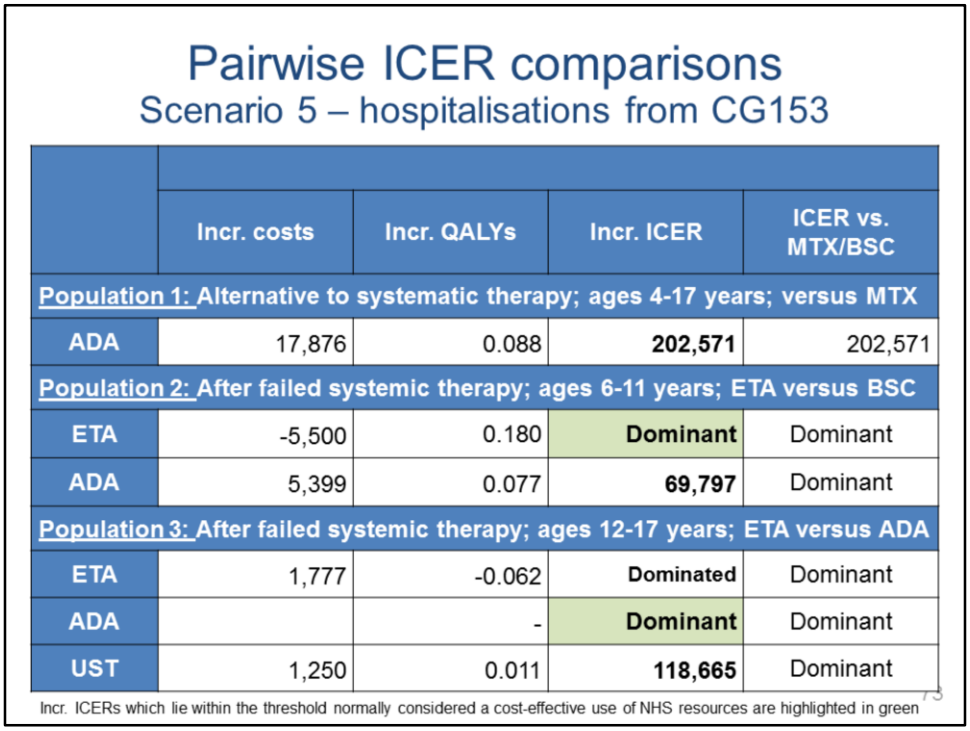
	Incr. costs	Incr. QALYs	Incr. ICER	ICER vs. MTX/BSC
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX				
ADA	24,873	0.089	**281,029**	281,029
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC				
ETA	2,903	0.103	**28,286**	28,286
ADA	11,516	0.078	**148,586**	80,046
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC				
ETA	7,766	0.083	**ED ADA**	93,102
ADA	10,855	0.146	**74,501**	74,501
UST	1,875	0.010	**186,634**	81,735

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

72

Source: Assessment group report, tables 88 and 89 (pages 221 and 222)

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green



Pairwise ICER comparisons

Scenario 5 – hospitalisations from CG153

	Incr. costs	Incr. QALYs	Incr. ICER	ICER vs. MTX/BSC
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX				
ADA	17,876	0.088	**202,571**	202,571
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC				
ETA	-5,500	0.180	**Dominant**	Dominant
ADA	5,399	0.077	**69,797**	Dominant
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus ADA				
ETA	1,777	-0.062	**Dominated**	Dominant
ADA		-	**Dominant**	Dominant
UST	1,250	0.011	**118,665**	Dominant

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

Source: Assessment group report, tables 88 and 89 (pages 221 and 222)

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

AG additional analyses in response to companies' comments

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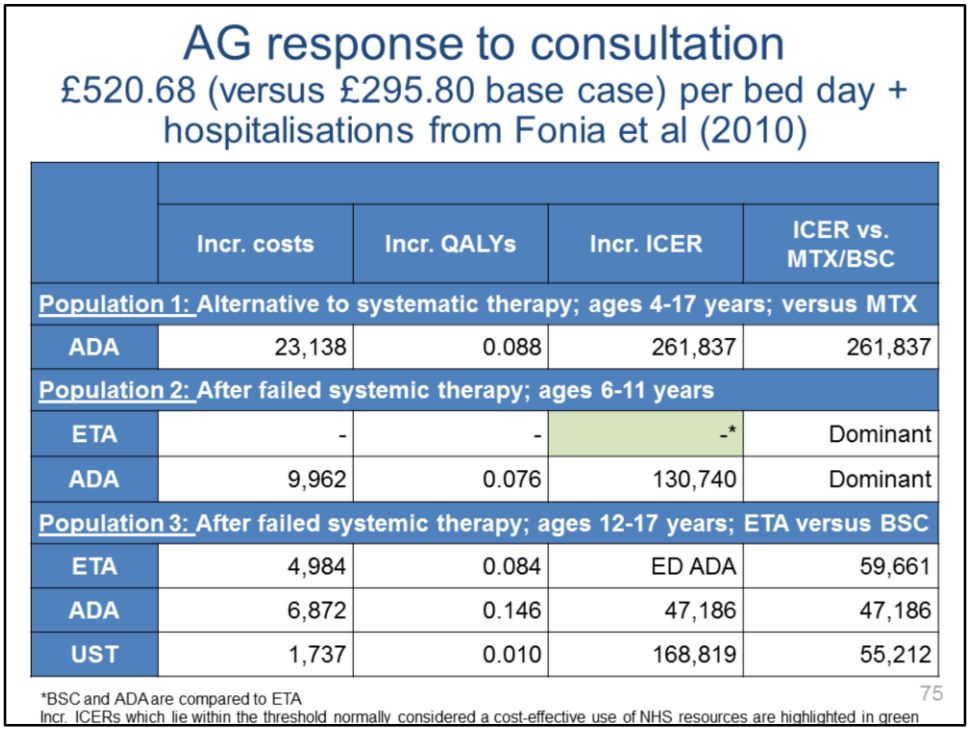

AG response to consultation

£520.68 (versus £295.80 base case) per bed day + hospitalisations from Fonia et al (2010)

	Incr. costs	Incr. QALYs	Incr. ICER	ICER vs. MTX/BSC
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX				
ADA	23,138	0.088	261,837	261,837
Population 2: After failed systemic therapy; ages 6-11 years				
ETA	-	-	-*	Dominant
ADA	9,962	0.076	130,740	Dominant
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC				
ETA	4,984	0.084	ED ADA	59,661
ADA	6,872	0.146	47,186	47,186
UST	1,737	0.010	168,819	55,212

*BSC and ADA are compared to ETA
Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

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Source: Assessment group response (Janssen), tables 2a and 2b (page 11)

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

The unit cost selected for inpatient bed day (£295.80) corresponds to the average unit cost of a non-elective excess bed day in the NHS across all HRG codes (see Index sheet on the NHS reference costs 2014-15). This unit cost is not specific to adults or skin conditions, as it is estimated from the totality of HRGs. The AG chose not to use a paediatric specific skin disorder unit cost for inpatient stay since it is unclear whether this unit cost also includes costs related to treatment. Treatment costs are included separately in the cost of BSC via its other components (drugs, monitoring, and phototherapy costs). The unit cost estimate for inpatient stay used in the AG scenario is very similar to that used in CG153 (£271.17), which appears to be an average unit cost of a non-elective excess bed day in the NHS.

We have been unable to identify the cost suggested by Janssen for an activity

weighted average across the Paediatric skin disorders HRG codes for non-elective excess bed day (£496.83). The paediatric inpatient stay unit cost based on an activity weighted average for Paediatric Skin disorders (currency codes PJ35A-D) is £520.68 per bed day. This value is almost twice as high as the average unit cost of a non-elective excess bed day in the NHS across all HRG codes.

AG response to consultation

£520.68 (versus £295.80 base case) per bed day + hospitalisations from CG153

	Incr. costs	Incr. QALYs	Incr. ICER	ICER vs. MTX/BSC
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX				
ADA	10,718	0.089	120,686	120,686
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC				
ETA	658	-0.077	Dominated	Dominant
ADA	-	-	Dominant	Dominant
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus ADA				
ETA	6,024	-0.073	Dominated	Dominant
ADA	-	-	-*	Dominant
UST	621	0.010	62,100	Dominant

*BSC and ADA are compared to ETA
Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

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Source: Assessment group response (Janssen), tables 2a and 2b (page 11)

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

AG response to consultation

£622.29 (versus £472.55 base case) per day centre visit

	Incr. costs	Incr. QALYs	Incr. ICER	ICER vs. MTX/BSC
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX				
ADA	18,963	0.088	216,034	216,034
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC				
ETA	5,665	0.103	54,963	54,963
ADA	12,616	0.076	165,268	101,896
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC				
ETA	10,002	0.083	ED ADA	119,924
ADA	14,066	0.146	96,418	96,418
UST	1,988	0.010	199,378	103,005

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

Source: Assessment group response (Janssen), tables 3a and 3b (page 13)

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

The day centre cost included in the AG model refers to skin disorders without interventions (£472.55). The cost of treatment (e.g. phototherapy sessions) is considered separately in the cost of BSC. In the currency codes specific to children there is no separation between skin disorders with and without interventions and, therefore, the possibility of double counting cannot be excluded from the company's suggested value of £622.29.

AG response to consultation

100% (versus 16% base case) receive phototherapy

	Incr. costs	Incr. QALYs	Incr. ICER	ICER vs. MTX/BSC
Population 1: Alternative to systematic therapy; ages 4-17 years; versus MTX				
ADA	24,799	0.088	280,738	280,738
Population 2: After failed systemic therapy; ages 6-11 years; ETA versus BSC				
ETA	2,907	0.103	28,236	28,236
ADA	11,476	0.077	79,937	79,937
Population 3: After failed systemic therapy; ages 12-17 years; ETA versus BSC				
ETA	7,753	0.083	ED ADA	92,960
ADA	10,857	0.146	74,378	74,378
UST	1,863	0.010	188,841	81,623

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

Source: Assessment group response (Janssen), tables 4a and 4b (page 14 and 15)

Incr. ICERs which lie within the threshold normally considered a cost-effective use of NHS resources are highlighted in green

The proportion of patients on systemic therapies (Table 68, p189) was informed by our clinical advisor. Although methotrexate and ciclosporin are not licensed in children and young people they are currently used in this population, as recorded in BADBIR and confirmed by our clinical advisor – see Burden-Teh E, Lam ML, Taibjee SM, Taylor A, Webster S, Dolman S, et al. How are we using systemic drugs to treat psoriasis in children? An insight into current clinical UK practice. British Journal of Dermatology. 2015;173(2):614-8.

The proportion of patients on phototherapy was also verified by our clinical advisor. She stated that clinicians are more reluctant to deliver phototherapy to children and young people compared to adults due to the associated risks with lifetime exposure to radiation.

CONFIDENTIAL UNTIL PUBLISHED
Assessment Group's Report
Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people

Produced by CRD and CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York, Heslington, York YO10 5DD

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None.

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Rider on responsibility for report

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Contributions of authors

Ana Duarte contributed to the protocol, the development of the economic model, the review of economic analyses, the interpretation of the results and the writing of the report.

Teumzghi Mebrahtu contributed to the protocol, study selection, data extraction, validity assessments and synthesis of the included studies. He also contributed to the interpretation of the results and the writing of the report.

Pedro Saramago Goncalves contributed to the protocol and conducted the network meta-analyses. He also contributed to the interpretation of the results and the writing of the report.

Melissa Harden developed the search strategies, conducted a range of searches to locate studies, and wrote the sections of the report relating to the literature searches.

Ruth Murphy provided expert clinical advice, contributed to the protocol, interpretation of the results and commented on drafts of the report.

Stephen Palmer contributed to the protocol, advised on the economic analysis, the interpretation of the results and commented on drafts of the report.

Nerys Woolacott contributed to the protocol, advised on the clinical evidence review, the interpretation of the results and commented on drafts of the report.

Mark Rodgers contributed to the protocol, study selection, data extraction, validity assessments and synthesis of the included studies. He also contributed to the interpretation of the results and the writing of the report. He took overall responsibility for the clinical effectiveness section.

Claire Rothery had overall responsibility for the cost-effectiveness sections. She contributed to the development of the protocol, the network meta-analyses, the economic model, and the economic analyses. She also contributed to the interpretation of the results and the writing of the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

Keywords

Psoraisis; children; young people; adalimumab; etanercept; ustekinumab; clinical effectiveness; cost-effectiveness

Abstract

Background

Psoriasis is a chronic inflammatory disease that predominately affects the skin. Adalimumab, etanercept and ustekinumab are the three biologics currently licensed for psoriasis in children.

Objective

To determine the clinical and cost-effectiveness of adalimumab, etanercept and ustekinumab within their respective licensed indications, for the treatment of plaque psoriasis in children and young people.

Design

Systematic review and economic model

Data sources

Searches of the literature and regulatory sources, contact with European psoriasis registries, company submissions and clinical study reports from manufacturers, previous NICE Technology Appraisals' documentation.

Methods

Included studies were summarised and subjected to detailed critical appraisal. A network meta-analysis incorporating adult data was developed to connect the effectiveness data in children and young people and populate a *de novo* decision analytic model.

The model estimated the cost-effectiveness of adalimumab, etanercept and ustekinumab to each other and to either methotrexate or best supportive care (BSC) depending on the position of the intervention in the management pathway.

Results

Nine studies (three RCTs and six observational studies) were included in the review of clinical effectiveness and safety.

Etanercept and ustekinumab lead to significantly greater improvements in psoriasis symptoms than placebo at 12 weeks' follow-up. The magnitude and persistence of effects beyond 12 weeks is less certain. Adalimumab lead to significantly greater improvements in psoriasis symptoms than methotrexate for some, but not all measures at 16 weeks. Observed quality of life benefits were inconsistent across different measures.

There was limited evidence of excess short-term adverse events. However, the relatively small number of observations and limited length of follow-up mean the possibility of rare events cannot be excluded.

Based on the economic assessment, the majority of incremental cost-effectiveness ratios for the use of biologics in children and young people exceeded NICE's usual range of cost-effectiveness and were reduced significantly only when combined assumptions that align with those for the management of psoriasis in adults were adopted.

Conclusions

The paucity of clinical and economic evidence to inform the cost-effectiveness of biological treatments in children and young people imposed a number of strong assumptions and uncertainties. Health-related quality of life (HRQoL) gains associated with treatment and the number of hospitalisations in children and young people are areas of considerable uncertainty. Findings suggest that biological treatments may not be cost-effective for the management of psoriasis in children and young people at £30,000 per QALY, unless a number of strong assumptions on HRQoL and costs of BSC are combined.

Future work recommendations

Adequately powered randomised trials are needed to inform the effectiveness of biological treatments in biologic-experienced populations of children and young people, particularly in younger children. Such trials should establish the impact of biological therapies on HRQoL in this population, ideally by collecting direct estimates of EQ-5D-Y.

Biologic registry data would help determine safety, patterns of treatment switching, and long-term withdrawal rates. Resource use and costs associated with BSC is another area requiring further research.

Study registration

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Plain English Summary

Psoriasis is an inflammatory disease that predominately affects the skin. It can greatly reduce a person's quality of life. A range of treatments are used in psoriasis, including the relatively new 'biologic' therapies. NICE currently recommends a number of biologic therapies for treating severe psoriasis in adults. The purpose of this project was to assess the benefits, harms and the cost-effectiveness of three biologic therapies that can be used in children – adalimumab, etanercept, and ustekinumab.

We identified and analysed all the data from relevant clinical trials. The results showed that adalimumab, etanercept and ustekinumab all improve the symptoms of psoriasis but the small amount of evidence from children mean that the longer-term effects are not so clear. The only way to estimate which treatment was best was to include extra evidence about the effects of these drugs when used in adults.

The economic assessment found that the use of biologics in children and young people would probably only be good value for NHS money if various circumstances and consequences of biologic treatment in children are considered to be the same as those in adults.

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List of abbreviations

ADA	Adalimumab
AEs	Adverse Events
AG	Assessment Group
APRE	Apremilast
AWMSG	All Wales Medicines Strategy Group
BAD	British Association of Dermatologist
BADBIR	British Association of Dermatologists Biologic Interventions Register
BIW	Bi-weekly
BNF	British National Formulary
BSA	Body Surface Area
BSC	Best Supportive Care
CDLQI	Children Dermatology Life Quality Index
CEA	Cost-effectiveness Analysis
CEACs	Cost-effectiveness acceptability curves
CG	Clinical Guideline
CI	Confidence Interval
CLAD	Censored Least Absolute Deviations
CRD	Centre for Reviews and Dissemination
CS	Cyclosporine
CSR	Clinical Study Report
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing & Allied Health
DARE	Database of Abstracts of Reviews of Effects
GDG	Guideline Development Group
DIC	Deviance Information Criterion
DLQI	Dermatology Life Quality Index
DMARDs	Disease-modifying anti-rheumatic drugs
EFA	Efalizumab
EMEA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions questionnaire
EQ-5D-Y	European Quality of Life-5 Dimensions questionnaire for Youth
ERG	Evidence Review Group
ETA	Etanercept

FDA	Food and Drugs Agency
FE	Fixed Effect
FUM-A	Fumaric Acid
GLiMs	Generalised Linear Models
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
HRQoL	Health Related Quality of life
ICER	Incremental Cost-effectiveness Ratio
IL	Inter-leucine
IPD	Individual level Patient Data
INF	Infliximab
IVR	Interactive Voice Response
IWR	Interactive Web Response
ITT	Intent-to-treat
LOCF	Last Observation Carried Forward
LOS	Length of Stay
MCID	Minimally Clinical Important Difference
MCMC	Markov Chain Monte Carlo
MIMS	Monthly Index of Medical Specialities
MTA	Multiple Technology Appraisal
MTX	Methotrexate
NHS	National Health Services
NMA	Network Meta-Analysis
NICE	National Institute for Care and Excellence
NRI	Non-responder Imputation
OLS	Ordinary Least Squares
ONS	Office of National Statistics
PASI	Psoriasis Area and Severity Index
PedsQL	Paediatrics Quality of Life
PGA	Physician Global Assessment
PLB	Placebo
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted Life Year

RCT	Randomised Controlled Trials
RE	Random Effects
RR	Relative Risk
SAEs	Serious Adverse Events
SD	Standard deviation
SEC	Secukinumab
SF-6D	Short Form–6 Dimension
sPGA	Physician Static Global Assessment
SPC	Summary of Product Characteristics
STA	Single Technology Appraisals
TA	Technology Appraisal
T-QoL	Teenager's Quality of Life Index
TNF-α	Alpha Tumour Necrosis Factor
UST	Ustekinumab
WHO	World Health Organisation

Glossary

Adverse effect: An abnormal or harmful effect caused by and attributable to exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism, or increases the susceptibility of the organism to other chemical or biological stress.

Between-study variance: Between-study variance is a measure of statistical heterogeneity that depends on the scale of the outcome measured. It represents the variation in reported study effects over and above the variation expected given the within-study variation.

Biological therapies (biologic): Any pharmaceutical product derived from biological sources. In PsA treatment these are generally monoclonal antibodies which bind to and inactivate immune cell signalling molecules (e.g. tumour necrosis factor and interleukins) thereby dampening the inflammatory response.

Biosimilar: An imitation biological medical product (such as an anti-TNF) usually marketed by a different manufacturer to the original biological product, once a patent has expired. The biosimilar should be similar to the original licensed product in terms of safety and efficacy.

Cyclosporin: A medication originally developed to prevent the immune system from rejecting transplanted organs, but which has also proved helpful in treating psoriasis.

Confidence Interval (CI): The typical ('classical' or 'frequentist') definition is the range within which the 'true' value (e.g. size of effect of an intervention) would be expected to lie if sampling could be repeated a large number of times (e.g. 95% or 99%).

Cost-benefit analysis: An economic analysis that converts the effects or consequences of interventions into the same monetary terms as the costs and compares them using a measure of net benefit or a cost–benefit ratio.

Cost-effectiveness analysis: An economic analysis that expresses the effects or consequences of interventions on a single dimension. This would normally be expressed in 'natural' units (e.g. cases cured, life-years gained). The difference between interventions in terms of costs and effects is typically expressed as an incremental cost-effectiveness ratio (ICER) (e.g. the incremental cost per life-year gained).

Cost–utility analysis: The same as a cost-effectiveness analysis, but the effects or consequences of interventions are expressed in generic units of health gain, usually quality-adjusted life-years (QALYs).

Credible interval: In Bayesian statistics, a credible interval is a posterior probability interval estimation that incorporates problem-specific contextual information from the prior distribution. Credible intervals are used for the purposes similar to those of confidence intervals in frequentist statistics.

Crohn's disease: An inflammatory condition of the digestive tract; rheumatic diseases are often associated with it and ulcerative colitis is related to it.

Deviance Information Criterion (DIC): A model fit statistics and used for Bayesian model comparison. The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed.

Disease-modifying anti-rheumatic drugs (DMARDs): DMARDs are drugs capable of modifying the progression of rheumatic disease. The term is, however, applied to what are now considered to be traditional (or conventional, cDMARDS) disease modifying drugs, in particular sulphasalazine, methotrexate and ciclosporin, as well as azathioprine, cyclophosphamide, antimalarials, penicillamine and gold. The newer agent leflunomide is also a DMARD. Biologics are not generally referred to as DMARDs, though occasionally bDMARD may be used.

European Quality of Life-5 Dimensions questionnaire (EQ-5D): A standardised instrument for measuring generic health-related quality of life, used in computation of the QALY.

Fixed-effect model: A statistical model that stipulates that the units under analysis (e.g. people in a trial or study in a meta-analysis) are the ones of interest, and thus constitute the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed effect model.

Health Assessment Questionnaire (HAQ): HAQ is a self-administered questionnaire measuring an individual's physical disability and pain. HAQ scores ability to perform various activities between 0 (without any difficulty) and 3 (unable to do), it is reported as an average of all activity scores.

Heterogeneity: In systematic reviews heterogeneity refers to variability or differences between studies in the estimates of effects. A distinction is sometimes made between "statistical heterogeneity"

(differences in the reported effects), "methodological heterogeneity" (differences in study design) and "clinical heterogeneity" (differences between studies in key characteristics of the participants, interventions or outcome measures).

Intention-to-treat (ITT): An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not.

Methotrexate (MTX): One of the oldest chemotherapy drugs used in treatment of cancer and autoimmune diseases such as rheumatoid and psoriatic arthritis.

Network meta-analysis (NMA) (synonym: mixed treatment comparison - MTC, indirect treatment comparison - ITC): Used when there is insufficient direct evidence linking two interventions, a meta-analysis comparing three or more different treatments using both direct comparison within RCTs and indirect comparison between trials based on a common comparator (such as placebo).

Placebo: An inactive substance or procedure administered to a patient, usually to compare its effects with those of a real drug or other intervention, but sometimes for the psychological benefit to the patient through a belief that s/he is receiving treatment.

Plaque psoriasis: The most common form of psoriasis, also known as psoriasis vulgaris, recognised by red, raised lesions covered by silvery scales. About 80% of patients with psoriasis have this type.

Psoriasis: A chronic skin disease characterised by inflammation and scaling. Scaling occurs when cells in the outer layer of skin are produced faster than normal and build up on the skin's surface. It is thought to be caused by a disorder of the immune system.

Psoriasis Area and Severity Index (PASI) score: A number representing extent of skin coverage, redness, scaliness and thickness of a person's psoriasis. PASI response is presented as PASI 50, PASI 75, PASI 90. This represents the reduction of the individual's PASI score from baseline as a percentage.

Psoriatic arthritis (PsA): A disease characterised by stiffness, pain, and swelling in the joints, especially of the hands and feet. It affects about 30% of people with psoriasis. Early diagnosis and treatment can help inhibit the progression of joint deterioration.

Quality Adjusted Life Year (QALY): An index of health gain where survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Quality of Life: A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity as well as other factors which might affect their physical, mental and social well-being.

Random effects model: A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

Randomised controlled trial (RCT) (synonym: randomised clinical trial): An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared.

Relative risk (RR) (synonym: risk ratio): The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability, or rate) is the ratio of people with an event in a group to the total number in the group. A RR of one indicates no difference between comparison groups. For undesirable outcomes, an RR of <1 indicates that the intervention was effective in reducing the risk of that outcome.

Residual deviance: An analysis used for model comparison and goodness-of-fit. The residual deviance is equal to the deviance for a given model minus the deviance for a saturated model. A saturated model is one where all of the predictions from the model are equal to the observed data values. Total residual deviance should approximate the number of data points for a good fit.

Rheumatoid arthritis (RA): A chronic autoimmune disease characterised by pain, stiffness, inflammation, swelling, and, sometimes, destruction of joints.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Statistical significance: An estimate of the probability of an association (effect) as large as or larger than what is observed in a study occurring by chance, usually expressed as a p-value.

Tumour necrosis factor alpha (TNF, TNFα): A cell signalling molecule (cytokine) involved in the inflammatory response pathway, known to be fundamental to the pathological processes causing psoriasis and psoriatic arthritis. It plays a key role in onset and persistence of joint and skin inflammation.

1 Scientific Summary

1.1 Background

Psoriasis is a chronic inflammatory disease of the skin and joints and typically features red, scaly and flaky skin also known as plaque psoriasis.

The prevalence of psoriasis in the UK is estimated to be around 0.4% and 2.2% for children (including adolescents) and adults, respectively, with both genders equally affected.

The impact of psoriasis encompasses functional, psychological, and social dimensions. Factors that contribute to this include skin symptoms, psoriatic arthritis, treatment related problems, and the effect of living with a highly visible, disfiguring skin disease.

Existing psoriasis guidance for all age groups (NICE guideline CG153 in England), states that traditional topical therapies can be prescribed as a first-line therapy. Second-line therapies include phototherapy and non-biological systemic agents such as ciclosporin, methotrexate and acitretin. Third-line therapy includes systemic biological therapies. While there is currently no childhood-specific treatment pathway, CG153 highlights special considerations for children (e.g. referral to a specialist at presentation; avoidance of very potent corticosteroids, PUVA, and acitretin).

Adalimumab (Humira, AbbVie) etanercept (Enbrel, Pfizer) and ustekinumab (Stelara, Janssen) are the three biologics currently licensed in children, though the exact populations and ages for these licenses vary.

1.2 Objectives

The aim of the study was to determine the clinical effectiveness and cost-effectiveness of adalimumab, etanercept and ustekinumab within their respective licensed indications, for the treatment of plaque psoriasis in children and young people.

1.3 Methods

1.3.1 Methods of clinical review and network meta-analysis

Studies were identified through searches of the literature and regulatory sources and requests for clinical study reports from the relevant manufacturers. Registry data were identified though literature searches and direct contact with European psoriasis registries.

Studies of children and/or young people with moderate to severe plaque psoriasis, in whom topical, systemic or phototherapies were inadequate, inappropriate or not tolerated were eligible for inclusion.

Relevant interventions were adalimumab, etanercept and ustekinumab, and relevant comparators included: alternative biologic therapies with relevant marketing authorisation (adalimumab, etanercept or ustekinumab); non-biological systemic therapy; topical therapy; biologic treatments used outside of their marketing authorisation (including adalimumab, etanercept or ustekinumab if used outside of the constraints of the relevant marketing authorisation in children and young people); and biosimilars of etanercept, adalimumab, or ustekinumab.

Data on the effectiveness, adverse effects, patient-centred outcome measures, costs to the health service, and cost-effectiveness were eligible for inclusion.

RCTs were eligible for the review of clinical efficacy. To address longer-term measures of efficacy and drug survival, published analyses based on large and long-term data sets were also considered. Two reviewers independently selected studies for inclusion, with all extraction and quality assessment undertaken by one reviewer and checked by a second.

The results of included studies were presented in a series of structured tables, summarised narratively and subjected to detailed critical appraisal. A naive indirect treatment comparison of adalimumab and etanercept was initially conducted based solely on the available placebo-controlled RCT data in children with psoriasis. In order to populate the economic model, a network meta-analysis (NMA) framework incorporating adult data was developed to allow connecting the effectiveness data in children and young people.

1.3.2 Methods of cost-effectiveness review

A systematic review was undertaken to identify published evidence on the cost-effectiveness of adalimumab, etanercept and ustekinumab, and relevant comparators, for psoriasis in children and young people. This included the company submissions from Janssen (ustekinumab) and AbbVie (adalimumab); Pfizer (etanercept) did not submit. Additional hand-searching of published documents associated with previous NICE Technology Appraisals of psoriasis in adults was carried out. The aim was to examine existing decision-analytic models, to identify important structural assumptions, highlight key areas of uncertainty and outline the potential issues associated with generalising evidence from the adult population to a population of children and young people.

1.3.3 Methods of economic modelling

A de novo decision analytic model was developed to estimate the cost-effectiveness of adalimumab, etanercept and ustekinumab to each other and to either, methotrexate or best supportive care (BSC) depending on the position of the intervention in the management pathway. Before systemic therapy, methotrexate was considered the relevant comparator (as the current standard of care), whereas after systemic therapy BSC was considered the most relevant comparator. The cost-effectiveness model takes the form of a cohort Markov model and the time horizon extends until individuals reach 18 years old, when separate NICE recommendations for the use of the interventions in adults apply. Outcomes are expressed using quality-adjusted life years (QALYs) and costs take the perspective of the NHS and Personal Social Services.

In order to reflect differences in marketing authorisation by age and positioning of treatment in the pathway, the cost-effectiveness analysis considers three separate populations:

1. Children and young people **aged 4-17 years** with **adalimumab** as the only licensed intervention for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **topical therapy and phototherapies, i.e. as an alternative to systemic therapies.**
2. Children and young people **aged 6-11 years** with **adalimumab** and **etanercept** for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **systemic therapies or phototherapies.**
3. Children and young people **aged 12-17 years** with **adalimumab, etanercept** and **ustekinumab** for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **systemic therapies or phototherapies.**

1.4 Results of clinical effectiveness review

A total of nine studies (three RCTs and six observational studies) were included.

1.4.1 Efficacy data from pivotal RCTs

Three randomised clinical trials (RCTs) were retrieved – one for each of the three biologics of interest. The etanercept and ustekinumab trials had 12 weeks of follow-up and used placebo as a comparator, whilst the adalimumab trial was of 16 weeks' duration and included methotrexate as the comparator. Risk of bias was low for most domains in each study.

While only older children and adolescents (12-17 years of age) were included in the ustekinumab trial, the median age of children did not differ greatly across the three trials as relatively few younger children were included in the adalimumab and etanercept trials. Across the three RCTs, just four children aged under 6 years received biologic treatment (etanercept in all cases).

All three trials used a composite measure of disease severity incorporating baseline PASI, PGA and BSA measurements. Average PASI scores ranged from 18.3 to 21.2, with 93-100% of participants having a PGA score exceeding 3 ("mild/moderate disease"). Though adalimumab and etanercept are licenced for "severe chronic plaque psoriasis" and ustekinumab for "moderate-to-severe plaque psoriasis", on average, measures of disease duration and the component measures of severity did not appear to differ markedly between the three trials.

29.8% of participants in the adalimumab trial had received prior systemic therapy, compared with 42.7% of participants in the ustekinumab trial. 56.8% of participants in the etanercept trial had received either prior systemic therapy or phototherapy.

A similar proportion of participants in the adalimumab and ustekinumab trials had received some form of biologic treatment prior to enrolment (9.6% and 10.8% respectively). No participants recruited to the etanercept trial had previously been treated with a biologic.

1.4.1.1 Adalimumab

One multicentre RCT (M04-717) found that adalimumab at the licenced dose of 0.8mg/kg (up to 40mg) lead to significantly greater responses than methotrexate for the outcomes of PASI 50 and PASI 75, but not PASI 90 at 16 weeks. PGA 0/1 response rates were non-significantly higher for adalimumab 0.8mg/kg than methotrexate. The benefits of half-dose adalimumab were not statistically greater than those for methotrexate. Evidence on quality of life was inconsistent across different measures, possibly due to baseline imbalance on PedsQL. In children and young people, adalimumab did not appear to be associated with an increase in adverse effects relative to methotrexate over 16 weeks, though the possibility of rare adverse events cannot be entirely excluded. The trial did not provide evidence for children aged 4 to 6 years of age.

[redacted]

1.4.1.2 Etanercept

One multicentre RCT (20030211) found etanercept to be significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50, 75 and 90, and PGA 0/1 response rates at 12 weeks. Improvements in health-related quality of life were larger for etanercept than placebo, but only reached statistical significance when measured by CDLQI.

Adverse events rates were mostly similar in etanercept and placebo groups at 12 weeks with no serious adverse events observed for either treatment. However, a higher observed rate of infections among participants receiving etanercept was of borderline statistical significance. Relatively few young children (9% aged under 8 years; 4.3% aged under 6 years) were included in study.

Up to six years open-label follow-up (20050111) found that the proportion of PASI and PGA responders were stable over time, though only 36% of participants were available at the latest follow-up point. The proportion of participant withdrawing due to lack of efficacy is unknown. Through 264 weeks of follow-up, withdrawals due to adverse events were infrequent, and no deaths or malignancies were observed.

1.4.1.3 Ustekinumab

One multicentre trial (CADMUS) in children 12 to 17 years of age found both the standard dosage and half dosage of ustekinumab were significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50, 75 and 90 and PGA 0/1 responses at 12 weeks. Both ustekinumab dosages also lead to significantly greater improvements in health-related quality of life (CDLQI and PedsQL).

Among participants originally allocated to ustekinumab, PASI and PGA effects observed at 12 weeks appeared to be largely sustained at 52 weeks, with few withdrawals due to lack of efficacy.

There were no notable adverse effects associated with ustekinumab, though the number of observations was small and longest the follow-up time was just 60 weeks. Few participants withdrew due to adverse effects.

1.4.2 Efficacy data from network meta-analyses

The treatment effects for the interventions were assumed to be exchangeable across age since no statistically significant differences were identified in PASI response outcomes by age within the trials.

The wider network including evidence from adult trials facilitated an indirect comparison of adalimumab, etanercept and ustekinumab. The network meta-analysis results – adjusted for differences in population and placebo response rates – demonstrated that ustekinumab is the most effective intervention, followed by adalimumab, etanercept and methotrexate.

1.5 Results of cost-effectiveness evaluation

1.5.1 Cost-effectiveness reported in existing published studies and manufacturer submissions

No previously published cost-effectiveness studies of adalimumab, etanercept or ustekinumab for psoriasis in children and young people were identified. One economic model of psoriasis in this population was discussed as part of the All Wales Medicines Strategy Group (AWMSG) advice No.138 for the use of etanercept within NHS Wales.

None of the companies participating in this appraisal submitted an economic model.

1.5.2 Cost effectiveness results from de novo modelling

The *de novo* model generated incremental cost-effectiveness ratios (ICERs) for the three populations above according to age and position of the intervention in the pathway of treatment. Results were generated for a base case and for separate scenarios. The base case ICERs were:

1. For the evaluation of adalimumab as an alternative to systemic therapy, the ICER for adalimumab compared to methotrexate is £308,329 per QALY gained.
2. For the evaluation of adalimumab and etanercept after failed systemic therapy in ages 6-11 years, adalimumab is the more effective but also more costly treatment compared to etanercept and BSC. Based on a fully incremental analysis, the ICER for etanercept compared to BSC is £71,903 per QALY, while the ICER for adalimumab compared to etanercept is £174,519 per QALY. The individual pairwise ICER for adalimumab compared to BSC is £115,825 per QALY.
3. For the evaluation of ustekinumab, adalimumab and etanercept after failed systemic therapy in ages 12-17 years, ustekinumab is the most effective and most costly treatment, followed by adalimumab, etanercept and BSC. Based on a fully incremental analysis, etanercept is extendedly dominated by adalimumab (i.e. etanercept produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy of adalimumab), the ICER of adalimumab compared to BSC is £110,430 per QALY, and the ICER of ustekinumab compared to adalimumab is £201,507 per QALY. The individual

pairwise ICERs for etanercept, adalimumab and ustekinumab compared to BSC are £137,059, £110,430 and £116,568 per QALY, respectively.

The model was also used to explore a number of uncertainties through scenario analyses. The scenarios which had the most impact on the cost-effectiveness results were: (i) the utility estimates based on an adult population; (ii) the health benefits associated with BSC; and (iii) the average number of hospitalisations per annum for BSC. Using utility values from an adult population brings the ICER of etanercept compared to BSC under a threshold of £30,000 per QALY in children and young people aged 6-11 years. The ICERs for ustekinumab and adalimumab are reduced significantly but remain above £30,000 per QALY threshold. Under the assumption of no health benefits for BSC, the ICERs are reduced substantially but remain quite high with the lowest ICER of £56,430 per QALY gained for etanercept compared to BSC. If the average number of hospitalisations per annum is increased from 0 days to 6.49 days based on a study inadults, the ICERs for the interventions reduce significantly; however, the only ICER which falls below £30,000 is for the use of etanercept compared to BSC in children and young people aged 6-11 years. If the average number of hospitalisations per annum is increased significantly to 26.6 days per annum based on a very high need adult population, the biological treatments compared to BSC are all considered cost-effective in individuals who have failed systemic therapy.

1.6 Discussion

While the total number of included participants and average length of follow-up was limited, this systematic review included the best available evidence on the efficacy and short- to medium-term safety of adalimumab, etanercept and ustekinumab directly relevant to the decision problem.

Very little evidence of efficacy or safety was available for young children. The ustekinumab trial (CADMUS) restricted inclusion to participants aged over 12 years, and the adalimumab and etanercept studies included few children aged under 8 years. Just nine 4 to 5 year-olds were included across all RCTs of biologics for psoriasis.

The review of cost-effectiveness evidence in this population, and the absence of economic models from the companies, highlights the challenges involved in evaluating the cost-effectiveness of biological interventions in children and young people with plaque psoriasis. The fundamental challenge is the limited clinical evidence base for short- and long-term outcomes. A key strength of this evaluation was that it went beyond the scope of the appraisal by bringing together evidence from

the adult population in order to support an economic evaluation in children and young people. However, inevitably the results aresubject to a number of uncertainties.

1.7 Conclusions

The paucity of clinical and economic evidence to inform the cost-effectiveness of biological treatments in children and young people has imposed a number of strong assumptions and uncertainties. Health-related quality of life gains associated with treatment and number of hospitalisations in children and young people are areas of considerable uncertainty.

Based on the economic assessment, the majority of ICERs for the use of biologics in children and young people are in excess of NICE's usual range of cost-effectiveness and are reduced significantly only when combined assumptions that align with those for the management of psoriasis in adults are adopted.

1.8 Suggested research priorities

- Adequately powered randomised trials are needed to inform the effectiveness of biological treatments in biologic-experienced populations of children and young people, i.e. treatment response rates conditional on prior treatment are required. Evidence for the clinical effectiveness and safety of adalimumab and etanercept in younger children in particular is currently lacking.
- Further research is needed to establish the impact of biological therapies on improving the health-related quality of life of children and young people. Future trials should consider collecting direct estimates of EQ-5D-Y.
- With the introduction of biological treatments in the population of children and young people continued collection of data through biologic registries for individuals younger than 18 years is warranted in order to investigate safety, patterns of treatment switching, and long-term withdrawal rates.
- Resource use and costs associated with best supportive care is an area of further research.

1.9 Study Registration

PROSPERO: CRD42016039494

1.10 Funding

Health Technology Assessment programme of the National Institute for Health Research

2 Background

2.1 Description of the health problem

2.1.1 Epidemiology

Psoriasis is a chronic but non-contagious inflammatory disease of the skin and joints.[1] The disease predominantly affects body parts like the scalp, elbows, knees and lower back that features a typical red, scaly and flaky skin also known as plaque psoriasis.[2] Plaque psoriasis is the most common type of psoriasis, although there are also other types of psoriasis such as *guttate* psoriasis (mostly in the trunk area), flexural psoriasis (affects the flexures), palmoplantar pustulosis psoriasis (affects the palms), and psoriatic nail diseases.[2] In children, plaque lesions appear most frequently on the scalp followed by the extensor surfaces of the extremities and the trunk.[3]

Psoriasis can appear at any age although it predominantly starts during adulthood.[1, 2, 4] The prevalence of psoriasis varies across the world ranging from 0-2.1% in children and 0.91-8.5% in adult population.[5] The prevalence of psoriasis in the UK is estimated to be around 0.4% and 2.2% for children (including adolescents) and adults, respectively, with both genders equally affected.[6]

2.1.2 Aetiology, pathology and prognosis

The aetiology of psoriasis remains largely unknown; however, genetic predisposition and environmental factors are believed to be the key players.[7, 8] It is estimated that the heritability of psoriasis is 60-90%, however, a worldwide positive family history of psoriasis ranges between 4.5% to 88%.[9] Among environmental factors: alcohol consumption, infection, emotional stress, medications, obesity and smoking may be risk factors for psoriasis.[1, 9]

The natural history of psoriasis varies by clinical subtype, that is, it may present as chronic, stable plaques with intermittent remissions and exacerbations, or acutely with a rapid progression and widespread involvement.[1] Plaque psoriasis usually manifests as a chronic disease with intermittent remissions and in some cases joints and eyes can be involved.[1] In contrast to adults, plaque psoriasis in children is less scaly and the lesions are often smaller and thinner; this can result in delayed diagnosis of the disease.[3] Also in children, plaques appear most frequently on the scalp and may lead to hair loss (psoriatic alopecia) if severe.[3]

2.1.3 Significance in terms of ill health

The impact of psoriasis encompasses functional, psychological, and social dimensions. [10] Factors that contribute to this include symptoms specifically related to the skin (for example, chronic itch, bleeding, scaling and nail involvement), problems related to treatments (mess, odour, inconvenience

and time), psoriatic arthritis, and the effect of living with a highly visible, disfiguring skin disease (difficulties with relationships, difficulties with securing employment and poor self-esteem). Even people with minimal involvement (less than the equivalent of three palm areas) state that psoriasis has a major effect on their life. The combined costs of long-term therapy and social costs of the disease have a major impact on healthcare systems and on society in general.[11]

Mortality primarily due to psoriasis is not common; however the chronic and incurable nature of psoriasis means that associated morbidity is significant.[11] Studies show that a significant proportion of childhood psoriasis cases (12-37%) don't grow out of it,[12] which implies that childhood psoriasis has a substantial long-term social and economic impact on individuals and the community.[13]

Some reports also suggest that adult psoriasis patients who were diagnosed during childhood have worse lifetime quality of life than those diagnosed during adulthood,[14, 15] although this claim is not supported by others.[16]

2.1.4 Assessment and management of psoriasis in children

Currently, there is no treatment pathway specific to psoriasis in children in the UK. Treatment depends to some extent on the extent and severity of an individual's disease, local custom and practice. Existing psoriasis guidance for all age groups (NICE guideline CG153 in England) states that traditional topical therapies (such as corticosteroids, vitamin D and analogues, dithranol and tar preparations) can be prescribed as a first-line therapy. Second-line therapies can include, phototherapy, broad- or narrow-band ultraviolet [UV] B light, with or without supervised application of complex topical therapies such as dithranol in Lassar's paste or crude coal tar and photochemotherapy, psoralen plus UVA light [PUVA], and non-biological systemic agents such as cyclosporine, methotrexate and acitretin. Third-line therapy includes systemic biological therapies that use molecules designed to block specific molecular steps important in the development of psoriasis such as the TNF antagonists, and anti-IL12-23 monoclonal antibodies. However, this guideline highlights special considerations for children (e.g. avoidance of very potent corticosteroids, PUVA, and acitretin) and recommends that children and young people with any type of psoriasis should be referred to a specialist at presentation.

2.1.5 Assessment of treatment response and quality of life

In children, there are a variety of clinical scales used to assess treatment response in psoriasis, including the Physician Global Assessment (PGA), Psoriasis Area and Severity Index (PASI), Children's Dermatology Life Quality Index (CDLQI) and Paediatrics Quality of Life (PedsQL)[17, 18]

2.1.5.1 The Physician global assessment (PGA)

The PGA is an instrument that provides a subjective overall evaluation of plaque psoriasis severity using a scale of seven categories ('clear', 'almost clear', 'mild', 'mild to moderate', 'moderate', 'moderate to severe', 'severe'.[19] There are two primary forms: a static form (physician static global assessment (sPGA)), which measures the physician's impression of the disease at a single point, and a dynamic form (physician dynamic global assessment (dPGA) in which the physician assesses the global improvement from baseline.[17]

The sPGA assumes seven scaled scores based on the severity of the disease, that is, 0='clear', 1='almost clear', 2='mild', 3='mild to moderate', 4='moderate', 5='moderate to severe', 6='severe'.[17, 20] The dPGA, on the other hand, uses six scaled scores to describe either improvement or deterioration of disease. For an improvement, the scores would be: +1= mild;+2=moderate; +3=moderate to large; +4=large; and, +5=very large improvement. For a disease deterioration: -1=mild; -2=moderate; -3=moderate to large; -4=large; and, -5=very large deterioration. A score of zero indicates no or minimal change.

The sPGA scoring system is simpler to use than dPGA; since physicians have to record the severity of psoriasis at baseline in order to evaluate the change in disease status after a follow-up period when they use dPGA, the sPGA has become widely used treatment response assessment tool in practice.[17] However, the sPGA does not discriminate small changes and the range scores are not robust.[17]

2.1.5.2 Psoriasis Area and Severity Index (PASI)

In clinical trials of patients with psoriasis, assessment of the response to treatment is usually based on the Psoriasis Area and Severity Index (PASI). Although it is widely used, the PASI measure also has a number of deficiencies: its constituent parameters have never been properly defined; it is insensitive to change in mild-to-moderate psoriasis; estimation of disease extent is notoriously inaccurate; and the complexity of the formula required to calculate the final score further increases the risk of errors. It combines an extent and a severity score for each of the four body areas (head, trunk, upper extremities and lower extremities). The extent score of 0–6 is allocated according to the percentage of skin involvement (e.g. 0 and 6 represent no psoriasis and 90%–100% involvement, respectively). The severity score of 0–12 is derived by adding scores of 0–4 for each of the qualities of erythema (redness), induration and desquamation representative of the psoriasis within the affected area. It is probable, but usually not specified in trial reports, that most investigators take induration to mean plaque thickness without adherent scale and desquamation to mean thickness of scale rather than severity of scale shedding. The severity score for each area is multiplied by the extent score and the

resultant body area scores, weighted according to the percentage of total BSA that the body area represents (10% for head, 30% for trunk, 20% for upper extremities and 40% for lower extremities), are added together to give the PASI score. Although PASI can theoretically reach 72, scores in the upper half of the range (>36) are not common even in severe psoriasis. Furthermore, it fails to capture the disability that commonly arises from involvement of functionally or psychosocially important areas (hands, feet, face, scalp and genitalia), which together represent only a small proportion of total BSA. However, PASI-based measures have discriminatory capability and are generally accepted for the assessment of treatment effects. However, clinical expert opinion is that PASI is not widely used in clinical practice.

Despite the fact that it has not been validated in children, PASI has been chosen as the primary outcome variable of psoriasis in the economic evaluation because it is used in the majority of randomised controlled trials (RCTs). Typically this is reported as a dichotomous measure indicating a 50%, 75%, or 90% reduction in PASI score from baseline (PASI 50, PASI 75, and PASI 90 respectively).

2.1.5.3 Childhood Dermatology Quality of Life Index (CDLQI)

The CDLQI is a 10 item questionnaire that aims to measure the quality of life of children (4-16 years of age) based on how much they have been affected by a skin problem over the week preceding the date of questioning.[21] The 10 items cover six areas of daily activities, including: symptoms and feelings, leisure, school or holidays, personal relationships, sleep and treatment.[22, 23] Usually children alone, or with the help of their parents, choose one of the four possible replies (scored 0-3) for a maximum overall score of 30, with a high score corresponding to low quality of life and vice versa.[23]

CDLQI scores can be divided into scoring bands: band 0 (score = 0-1), band 1 (score = 2-6), band 2 (score= 7-12), band 3 (score=13-18) and band 4 (score=19=30) that respectively correspond to no, small, moderate, very large or extremely large effects on the child's quality of life.[23]. However, the CDLQI is not considered appropriate for use as health-related quality of life assessment tool beyond the age of 16 years.

2.1.5.4 Pediatric Quality of Life (PedsQL)

The PedsQL is a modular instrument for measuring of health-related quality of life in children and adolescents (2 to 18 years of age). It has 23 items in four domains: a) physical functioning (8 items); b) emotional functioning (5 items); c) social functioning (5 items); and, d) school functioning (5 items). Each item receives a score 0-4 (0 = never a problem; 1 = almost never a problem; 2 =

sometimes a problem; 3 = often a problem; 4 = almost always a problem) and are reverse-scored and linearly transformed to a 0 to 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better HRQOL.[24] Paediatric self-report is measured in children and adolescents ages 5-18 years, and parent proxy-report of child HRQOL is measured for children and adolescents ages 2-18 years.

2.1.5.5 Teenager's Quality of Life Index (T-QoL)

Built on qualitative data from patients, the T-QoL is a validated tool to quantify the impact of skin disease on adolescents' quality of life. The index contains 18 items categorised into three domains: 'Self-image', 'Physical wellbeing and the future', and 'Psychological impact and relationships'. The authors have proposed the T-QoL as an outcome measure in both clinical practice and in clinical research.[25]

2.1.5.6 General issues with quality of life measurement in childhood psoriasis

Quality of life measurements may not be particularly meaningful in younger children who are less good at articulating how much the disease is bothering them. In the case of younger children, proxy measurements may more accurately reflect parental perception or concern. There is only moderate correlation between PASI/PGA response measures and CDLQI;[26]some children with relatively mild disease can have very poor HRQoL scores, while others with more severe disease can have acceptable HRQoL. As well as disease symptoms and consequences, frequency of injections can be an important quality of life consideration in children.

2.2 Description of technology under assessment

"Biological therapies" or "biologics" are agents extracted or semi-synthesised from biological sources, used for treating specific medical conditions, including auto-immune diseases. They are frequently produced using recombinant DNA technology and designed to act on specific parts of human immune system. For example, biologics such as certolizumab, etanercept, adalimumab, infliximab and golimumab block Tumour Necrosis Factor (TNF) alpha; and, ustekinumab and secukinumab inhibit interleukin 12/23 and interleukin 17-A, respectively. Such biologics are indicated for a range of conditions, including psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease.

Three biologics (adalimumab, etanercept and ustekinumab) have regulatory approval for the treatment of plaque psoriasis in children and young people.

Adalimumab (Humira, AbbVie) is a fully human immunoglobulin G1 monoclonal antibody that inhibits the activity of tumour necrosis factor alpha (TNFα). It has a marketing authorisation in the UK for treating severe chronic plaque psoriasis in children and adolescents from 4 years of age who have an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Etanercept (Enbrel, Pfizer) is a recombinant human TNFα receptor fusion protein that inhibits the activity of TNFα. It has a marketing authorisation in the UK for treating chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Ustekinumab (Stelara, Janssen) is a fully human monoclonal antibody that acts as a cytokine inhibitor by targeting interleukin‑12 and interleukin‑23. It has a marketing authorisation for treating moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Table 1 Summary of drug properties and marketing authorisations

Treatment	Age range	Disease status	Mechanism of action	Dose / frequency	Treatment pathway
Adalimumab	4 years and older	Severe chronic plaque psoriasis	TNF-α inhibitor	0.8mg/kg up to a maximum of 40 mg at weeks 0 and 1, then every 2 weeks thereafter	Where topical therapy and phototherapies are inadequate or inappropriate
Etanercept	6 years and older	Severe chronic plaque psoriasis	TNF-α inhibitor	0.8mg/kg up to a maximum of 50 mg weekly for up to 24 weeks	Where systemic therapies or phototherapies are inadequate or not tolerated
Ustekinumab	12 years and older	Moderate to severe plaque psoriasis	IL-12/IL-23 inhibitor	0.75mg/kg for bodyweight <60kg; 45mg for bodyweight 60-100kg; 90mg for bodyweight >100kg at weeks 0 and 4 then every 12 weeks thereafter	Where systemic therapies or phototherapies are inadequate or not tolerated

More recently, versions of biologic drugs have become available that are manufactured after the expiry of an original innovator agent's patent. These "biosimilars" are developed to be highly similar to the existing biologic agent physicochemical and biological terms and are typically cheaper than the original agent. Biosimilar medicines are usually licensed for all indications specified in the licence of the originator biological medicine, but this requires appropriate scientific justification on the basis of demonstrated or extrapolated equivalence. Benepali, a biosimilar of etanercept, has been approved in Europe for use in adults with moderate to severe rheumatoid arthritis, psoriatic arthritis, severe ankylosing spondylitis, severe non-radiographic axial spondyloarthritis, and moderate-to-severe plaque psoriasis. Currently, three biosimilars of infliximab (Inflectra, Remsima, Flixabi) are approved for use in ankylosing spondylitis, Crohn's disease, psoriatic arthritis, psoriasis, rheumatoid arthritis, and ulcerative colitis.

3 Definition of decision problem

According to NICE guideline CG153 in England, psoriasis patients are treated in three stages.[11] First-line therapy includes traditional topical therapies (such as corticosteroids, vitamin D and vitamin D analogues, dithranol and tar preparations). Second-line therapy includes phototherapies narrow-band ultraviolet B light and psoralen plus UVA light [PUVA]) and systemic non-biological agents such as cyclosporine, methotrexate and acitretin are administered. Systemic biological therapies such as the tumour necrosis factor antagonists: adalimumab, etanercept and infliximab, and the monoclonal antibody ustekinumab that targets interleukin-12 (IL-12) and IL-23 can be provided as third-line therapy.[11]

The three biologics (adalimumab, etanercept and ustekinumab) that have regulatory approval for the treatment of plaque psoriasis in children and young people have not yet been appraised by NICE and no NICE technology appraisal guidance is available for treating children and adolescents in the UK for these treatments in this indication

3.1 Objectives

The aim of the study is to determine the clinical effectiveness and cost-effectiveness of adalimumab, etanercept and ustekinumab within their respective licensed indications, for the treatment of plaque psoriasis in children and young people.

4 Assessment of clinical effectiveness

4.1 Methods for synthesis of evidence of clinical effectiveness

A systematic review of the clinical effectiveness was performed following the general principles recommended in CRD's guidance and the PRISMA statement while a protocol was registered with PROSPERO.[27]

4.1.1 Literature searching – adalimumab, etanercept and ustekinumab

The literature search for the clinical effectiveness review aimed to systematically identify relevant randomised controlled trials (RCTs) of adalimumab, etanercept and ustekinumab for children and young people with plaque psoriasis.

The search strategy was developed in MEDLINE (Ovid) and included search terms for:

- psoriasis
- adalimumab, etanercept, ustekinumab or biosimilars
- children or young people

The 3 sets of terms were combined using the Boolean operator AND. Search terms were developed through discussion with the review team, use of database thesauri and online drug information resources. No language, date, geographical or study design limits were applied. The MEDLINE strategy was adapted for use in the other resources searched.

The searches were carried out on 24th/25th May 2016 and updated during September 2016. The following databases were searched: MEDLINE (including: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Cumulative Index to Nursing & Allied Health (CINAHL Plus), Database of Abstracts of Reviews of Effects (DARE), EMBASE, Health Technology Assessment (HTA) database, PubMed, and the Science Citation Index.

In addition, the following resources were searched for on-going, unpublished or grey literature: ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, PROSPERO and the WHO International Clinical Trials Registry Platform portal.

A search for guidelines on psoriasis in children or young people was carried out via the following guideline websites: National Guideline Clearinghouse, NICE Clinical Knowledge Summaries (CKS), NHS Evidence, NICE Evidence summaries: new medicines, and the NICE website.

In addition to utilising other published and unpublished data resources, requests for clinical study reports (CSRs) relating to adalimumab, etanercept and ustekinumab were made to Abbvie, Pfizer and Janssen respectively.

The search results were imported into EndNote x7 (Thomson Reuters, CA, USA) and deduplicated. Full search strategies can be found in appendix 12.1.

4.1.2 Literature searching – network meta-analysis

4.1.2.1 Alternative treatments in children and young people

A search was undertaken to identify relevant RCTs of systemic non-biological (acitretin, methotrexate, and cyclosporine) and other biological therapies (infliximab, secukinumab) in children and young people with plaque psoriasis to inform the network meta-analysis. No language, date, geographical or study design limits were applied to the search.

This search was carried out on 31st May 2016 on the following databases: MEDLINE (including: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Cumulative Index to Nursing & Allied Health (CINAHL Plus), Database of Abstracts of Reviews of Effects (DARE), EMBASE, Health Technology Assessment (HTA) database, PubMed, and the Science Citation Index.

In addition, the following resources were searched for on-going, unpublished or grey literature: ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, PROSPERO and the WHO International Clinical Trials Registry Platform portal.

The search results were imported into EndNote x7 (Thomson Reuters, CA, USA) and de-duplicated. The search was updated in September 2016 to capture more recent studies.

4.1.2.2 Registry data

In order to identify longer-term follow-up evidence, a literature search was conducted within the MEDLINE database for the search terms “psoriasis AND regist*”. The results of this search were screened for publications from psoriasis registries, secondary analyses of registry data, and systematic

reviews of broader dermatological and psoriasis registries. The list of registries generated through these searches was compared against three relevant systematic reviews[28-30] to verify those studies included and to identify any which had been overlooked. Twenty patient registries for psoriasis treatment were identified in this way, 14 of which were located in European countries, three were international in scope, and two were based in the USA and one in Malaysia. Each registry name was then separately used as a search term in MEDLINE, and any publications referencing these which had not been found in the initial searches were retrieved.

In addition, representatives of the 14 psoriasis registries from European countries (Austria, Australia, Czech Republic, Denmark, France, Germany, Italy, Netherlands, Portugal, Slovenia, Spain, Sweden, Switzerland and UK) were contacted and asked to provide any relevant information on psoriasis treatment for three biologics (adalimumab, etanercept and ustekinumab) in children and young people.

4.1.3 Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full manuscripts of any titles/abstracts that could be relevant were obtained where possible and the relevance of each study was assessed by two reviewers according to the criteria below. Any discrepancies were resolved by consensus and, if necessary, a third reviewer was consulted. Studies available only as abstracts were included and attempts were made to contact authors for further data.

4.1.3.1 Study design

RCTs (including any open-label extensions of RCTs) were eligible for the review of clinical efficacy.

Information on adverse events was also sought from regulatory sources where appropriate. Registries and observational studies were included where relevant outcome data were available.

To address longer-term measures of efficacy and drug survival, published analyses based on large and long-term data sets (including studies of registry data) were also considered.

4.1.3.2 Participants

Studies of children and/or young people who have moderate to severe plaque psoriasis were included. Studies of guttate, erythrodermic, and pustular psoriasis were excluded, as were studies of psoriatic arthritis.

Studies in children or young people with psoriasis in whom topical, systemic or phototherapies were inadequate, inappropriate or not tolerated were eligible for inclusion. Participants aged below 12 years were considered children, with those aged 12-17 years considered young people.

4.1.3.3 Interventions

The relevant interventions were adalimumab, etanercept and ustekinumab.

4.1.3.4 Comparators

Relevant comparators are:

- Alternative biologic therapies with relevant marketing authorisation (adalimumab, etanercept or ustekinumab)
- Non-biological systemic therapy (including, but not limited to, cyclosporine and methotrexate)
- Topical therapy (for people in whom non-biological systemic therapy is not suitable), i.e. best supportive care
- Biological treatments used outside of their marketing authorisation (such as infliximab, adalimumab, etanercept or ustekinumab if used outside of the constraints of the relevant marketing authorisation in children and young people)
- Biosimilars of etanercept, adalimumab, or ustekinumab

4.1.3.5 Outcomes

Data on the effectiveness, adverse effects, patient-centred outcome measures, costs to the health service, and cost-effectiveness were eligible for inclusion, including the following outcomes:

- Severity of psoriasis such as body surface area (BSA), Physician's Global Assessment (PGA) score
- Response and remission rates (such as PASI 50/75/90 response)

- Relapse rate
- Rates of treatment discontinuation and withdrawal
- Short and long-term adverse effects of treatment (such as injection site and allergic reactions, serious infections, re-activation of infections including tuberculosis, malignancy)
- Health-related quality of life (such as CDLQI, PedsQL, EQ-5D)

4.1.4 Data extraction

Data relating to both study design and quality were extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus, and if necessary, a third reviewer was consulted. Data from studies with multiple publications were extracted and reported as a single study.

4.1.5 Quality assessment

The quality of RCTs was assessed using the Cochrane risk of bias tool, with additional assessments made for baseline imbalance of important prognostic indicators.[31, 32] Relevant prognostic and treatment response indicators were identified from both published research and clinical advice. Risk of bias assessment was performed by one reviewer, and independently checked by a second. Disagreements were resolved through consensus, and if necessary, a third reviewer was consulted.

The quality of non-randomised studies was assessed using a checklist based on CRD Guidance[27] and used in previous technology assessments for NICE.[33] This assesses study eligibility criteria and recruitment methods, baseline similarity of comparison groups, blinding of allocation, completeness of follow-up, and outcome reporting.

4.1.6 Methods of data synthesis

The analysis and synthesis of clinical data in this review were conducted in distinct sections. In the absence of sufficient trials to conduct pairwise meta-analysis, the results of included studies are presented in a series of structured tables and summarised narratively and subjected to detailed critical appraisal.

In order to assess the relative clinical effectiveness of the three biologics (i.e. adalimumab, etanercept and ustekinumab) syntheses of both pairwise (head-to-head) and indirect comparative data were planned. Where possible, treatment response (PASI) outcomes were to be synthesized using Bayesian network meta-analysis methods. Bayesian statistical methods provide information on the benefits of the active treatments relative to the appropriate comparators and each other.[34] Meta-analysis using

mixed treatment comparisons enables the estimation of different parameters from several studies with similar comparisons to be combined when direct evidence on comparisons of interest is absent or sparse.[35] For example, should active treatments being evaluated have a common comparator of placebo, this would allow a network to be established between them, providing information on the benefits of these treatments relative to placebo and to each other.

However, the available trials conducted in children precluded the construction of the necessary network. To inform the economic evaluation, trials conducted in adults were included in a network meta-analysis. Full details of the methods and results are presented in Section 5.

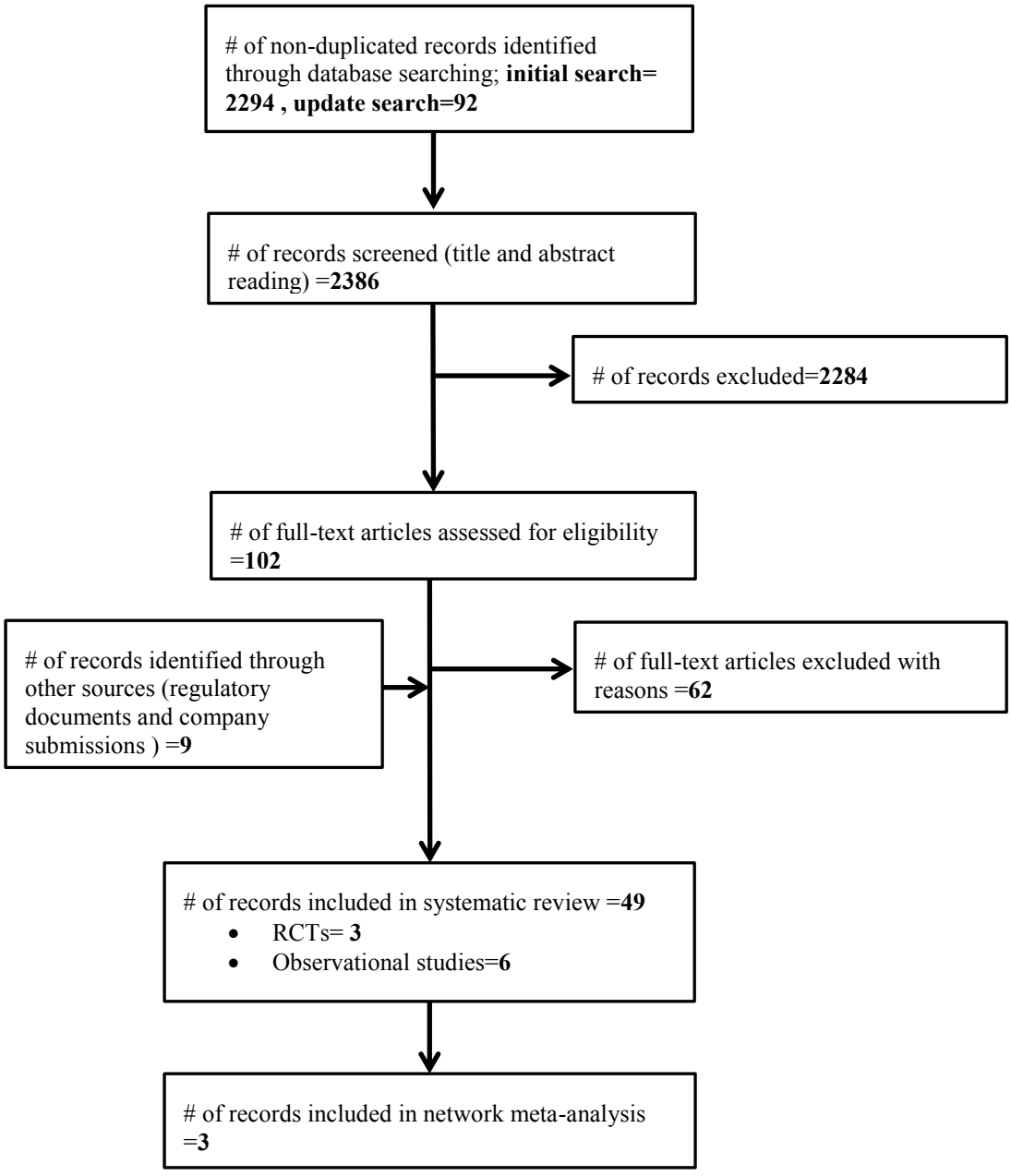
4.2 Results

4.2.1 Quantity of identified evidence

A total of 2386 non-duplicate records were identified from the clinical effectiveness database searches. Of these, 2284 records were excluded after title or abstract screening. In addition, eight relevant regulatory documents were retrieved. Thus, a total of 111 records were read in full, resulting in 62 records being excluded and a total of 48 records being included in the review. A total of nine studies (3 RCTs and 6 open-label or observational follow-up of RCTs) were included in the review of clinical effectiveness, see **Figure 1**. The included records are summarised in appendix 12.2. Appendix 12.3 also lists the excluded studies and reasons of exclusion.

Searches for relevant registry data identified 685 publications. Three publications from two registries were found to include children with psoriasis who were treated with biologics. Of the 14 national psoriasis registry representatives contacted, seven responded but no relevant additional data were available.

Figure 1 PRISMA flow diagram of studies in children and young people



4.2.2 Characteristics of studies included

Three randomised clinical trials (RCTs) were retrieved – one for each of the three biologics of interest (i.e. adalimumab, etanercept and ustekinumab). The RCTs investigated short term clinical efficacy and adverse events. The etanercept and ustekinumab trials had 12 weeks of follow-up and used placebo as a comparator, whilst the adalimuimab trial was of 16 weeks' duration and included methotrexate as the comparator. Each RCT also incorporated an open-label phase (**Table 3**). These open-label or observational periods investigated longer-term efficacy and adverse events, incorporating withdrawal and/or re-treatment phases. The adalimumab, etanercept and ustekinumab trials had 52, 312, and 60 weeks of follow-up data available, respectively.

4.2.2.1 Patients' baseline characteristics

The baseline characteristics are presented in **Table 4**. While only older children and adolescents (12-17 years of age) were included in the ustekinumab trial, the median age of children across the three trials did not differ greatly; since it appears relatively few younger children were included in the adalimumab and etanercept trials.

All three trials used a composite measure of disease severity incorporating baseline PASI, PGA and BSA measurements. When used in isolation, a PASI score between 10 and 20 is considered to indicate moderate to severe psoriasis, while severe psoriasis has a score above 20. Across the included studies, average PASI scores ranged from 18.3 to 21.2, with 93-100% of participants having a PGA score exceeding 3 ("mild/moderate disease"). Though adalimumab and etanercept are licenced for "severe chronic plaque psoriasis" and ustekinumab for "moderate-to-severe plaque psoriasis", on average, measures of disease duration and the component measures of severity did not appear to differ markedly between the three trials. The degree of psoriasis affecting high-impact and difficult to treat sites (e.g. face, scalp, palms, soles, flexures and genitals) across the three studies was less clear.

A key difference in the licences between the three agents is the availability of adalimumab for patients for whom topical and phototherapy are inadequate or inappropriate. Unlike the licences for etanercept and ustekinumab, there is no mention of prior non-biologic systemic treatment. However, the baseline characteristics of the included studies indicate that a substantial minority of participants in the adalimumab trial (29.8%) had received prior systemic therapy, compared with 42.7% of participants in the ustekinumab trial. 56.8% of participants in the etanercept trial had received either prior systemic therapy or phototherapy (separate data were not reported).

A similar proportion of participants in the adalimumab and ustekinumab trials had received some form of biologic treatment prior to enrolment (9.6% and 10.8% respectively). As etanercept was the first

TNF-α inhibitor to be approved for psoriasis, none of the participants recruited to the etanercept trial had previously been treated with a biologic.

While there were noticeable differences in participant characteristics between trials, these were not as clear as the respective licences of the three treatments might suggest. Notwithstanding methodological differences, there appears to be sufficient overlap in populations to discuss these three trials together.

4.2.2.2 Length of follow-up and early escape

The initial randomised treatment period was 12 weeks in the etanercept and ustekinumab trials and 16 weeks in the adalimumab trial. Twelve week outcome data were not available for the adalimumab trial, though clinical advice suggested that the difference in length of follow-up between treatments was acceptable.

All three trials allowed participants to "escape" from the randomised treatment period before 12/16 week follow-up. The criteria and statistical handling of early escape data are discussed separately for each trial in sections 4.3 to 4.5.

Post randomised treatment periods are briefly summarised in **Table 3**.

4.2.2.3 Outcomes

The adalimumab and etanercept trials considered PASI 75 response to be the primary outcome measures, whereas the ustekiniumab trial used a primary measure of PGA score of 0 or 1 ("clear" or "almost clear"). However, all three trials reported PASI, PGA and some measure of HRQoL (CDLQI and/or PedsQL), all of which are presented in the following sections.

Table 2 Inclusion and exclusion criteria for included RCTs

Adalimumab (Trial M04-717)	Etanercept (Trial 20030211)	Ustekinumab (CADMUS Trial)

Inclusion Criteria:
• Subject is ≥ 4 years and < 18 years of age;
• Participant weighs ≥ 13 kg;
• Participant must have failed to respond to topical therapy;
• Participant must need systemic treatment to control his/her disease and meet one of the following:
  • Physician's Global Assessment (PGA) ≥ 4
  • Body surface area (BSA) involved > 20%
  • Very thick lesions with BSA > 10% - Psoriasis Area and Severity Index (PASI) > 20
  • PASI > 10 and at least one of the following:
  • Active psoriatic arthritis unresponsive to non-steroid anti-inflammatory drugs (NSAIDs)
  • Clinically relevant facial involvement
  • Clinically relevant genital involvement
  • Clinically relevant hand and/or foot involvement
  • Children's Dermatology Life Quality Index (CDLQI) > 10
• If participant is < 12 years of age and resides in a geographic region where heliotherapy is practical, participant must have failed to respond, be intolerant, or have a contraindication to heliotherapy, or is not a suitable candidate for heliotherapy;
• If ≥12 years of age, participant must have failed to respond, be intolerant, or have a contraindication to phototherapy, or is not a suitable candidate for phototherapy;
	Inclusion criteria:
	• age 4 to 17 years;
	• stable, moderate-to-severe plaque psoriasis at screening, defined as a psoriasis area-and-severity index (PASI) score of at least 12 (PASI scores range from 0 to 72, with higher scores indicating worse condition;
	• A static physician's global assessment of at least 3 (where 0 indicates clear and 5 severe psoriasis), and psoriasis involvement of at least 10% of the body-surface area;
	• A history of psoriasis for at least 6 months; and,
	• Previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids) or psoriasis considered by the investigator as poorly controlled with topical therapy.
	Exclusion criteria:
	• Pregnancy or lactation (sexually active patients were required to use contraception);
	• Guttate, erythrodermic, or pustular psoriasis;
	• Skin conditions that would interfere with study evaluations;
	• Previous treatment with anti-TNF agents;
		Inclusion Criteria:
		• Age 12 to 17 years, (inclusive),
		• Had a diagnosis of moderate-to-severe plaque psoriasis (ie, baseline Psoriasis Area and Severity Index [PASI] ≥12, a Physician's Global Assessment [PGA] ≥3; and ≥10% body surface area involved with psoriasis) for ≥6 months,
		• Candidates for phototherapy or systemic treatment, or had psoriasis that was poorly controlled with topical therapy
		• Have a diagnosis of plaque-type psoriasis with or without psoriatic arthritis (PsA) for at least 6 months
		Exclusion Criteria:
		• Currently have nonplaque forms of psoriasis (e.g. erythrodermic, guttate, or pustular) or drug-induced psoriasis (e.g. a new onset of psoriasis or an

• Participant must have a clinical diagnosis of psoriasis for at least 6 months as determined by the participant's medical history and confirmation of diagnosis through physical examination by the Investigator; 8. Participant must have stable plaque psoriasis for at least 2 months prior to Baseline **Exclusion Criteria:** • Prior biologic use other than prior treatment with etanercept; • Treatment with etanercept therapy within 4 weeks prior to the Baseline visit; • Methotrexate (MTX) use within the past year or prior MTX use at any time where the participant did not respond, or did not tolerate MTX; • Contraindication for treatment with MTX during the study; • Erythrodermic Ps, generalized or localized pustular Ps, medication-induced or medication exacerbated Ps or new onset guttate Ps; • Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit; • Treatment of Ps with topical therapies such as corticosteroids, vitamin D analogs, or retinoids within 7 days prior to the Baseline visit; • Treatment of Ps with UVB phototherapy, excessive sun exposure, or the use of tanning beds within 7 days prior to the Baseline visit; • Treatment of Ps with PUVA phototherapy, non-biologic systemic therapies for the treatment of Ps, or systemic therapies known to improve Ps within 14 days prior to the Baseline visit;	• Major concurrent medical conditions; • Treatment with psoralen and ultraviolet A (PUVA), ultraviolet A, ultraviolet B, systemic psoriasis medications, oral or parenteral corticosteroids, topical corticosteroids, topical vitamin A or D analogue preparations, anthralin, or calcineurin inhibitor within a 14-day washout period before the study; and, • Treatment with biologic agents within a 30-day washout period before the study. Patients could use low-to-moderate-potency topical steroids on the scalp, axillae, or groin	exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) • Have used any therapeutic agent targeted at reducing interleukin-12 (IL-12) or interleukin-23 (IL-23), including but not limited to ustekinumab and briakinumab • Received conventional systemic therapies or phototherapy within the last 4 weeks • Received biologic therapies within the last 3 months

Table 3 Trial durations (including open-label extensions) and dosing regimens

Study reference	Relevant dosing and regimens used	Duration of randomised and blinded phase	Post-randomised period design details	Latest time point with available result data	Anticipated time to response: information from Summary of Product Characteristics (SPC)
M04-717 Adalimumab	Adalimumab standard dose (initial 0.8mg/kg up to a maximum to 40mg, followed by 0.8mg/kg weekly) or half-dose.	16 weeks	• After the primary treatment phase (Period A-Blinded period), responders from period A were withdrawn from active treatment for up to 36 weeks and monitored for loss of disease control —Withdrawal Phase or Period B. • Participants from period B who had experienced loss of disease control were treated with adalimumab for up to 16 weeks—Re-treatment phase or Period C. • Participants from periods A, B, and C who met entry criteria to long-term follow-up phase or Period D received adalimumab or were observed off-treatment (if disease remained under control during Period B)	52 weeks	Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.
20030211 Etanercept	Etancercept at a dose of 0.8mg per kilogram of body weight up to a maximum of	12 weeks	A 24-week, open-label treatment period (weeks 13 to 36) to assess the efficacy of etanercept therapy in all patients; and a 12-week, randomized, double-blind, withdrawal–retreatment period (weeks 37 to	312 weeks	The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with

	intended dose of 50 mg		48) to examine the effects of withdrawal of study drug and subsequent retreatment		Enbrel is indicated, the above guidance on treatment duration should be followed.
CNTO1275 PSO3006 CADMUS Ustekinumab	Ustekinumab standard dose (0.75mg/kg up to 60kg; fixed 45mg for 60-100kg; fixed 90mg >100kg) or half-dose at 0, 4 and every 12 weeks subsequently	12 weeks	After the double blinded period (12 weeks), the placebo group were allowed to cross over to receive either standard or half-dose ustekinumab at weeks 12 and 16 and then every 12 weeks. Participants were followed for efficacy and safety through weeks 52 and 60, respectively.	60 weeks	Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Table 4 Baseline patients' characteristics of RCTs

	M04-717-Adalimumab			20030211- Etanercept		CNTO1275PSO3006 CADMUS-Ustekinumab		
	ADA 0.8mg/kg	**ADA 0.4mg/kg**	**MTX**	**ETA 0.8mg/kg**	**PLB**	**UST 0.75mg/kg**	**UST 0.375mg/kg**	**PLB**
Study duration	16 weeks	16 weeks	16 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
Number of patients	38	39	37	106	105	36	37	37
Median age (range) in years	[redacted]	[redacted]	[redacted]	14 (4-17)	13 (4-17)	15.0 (12-17)	15.0 (12-17)	16 (12-17)
Mean (SD) age in years	13.0 (3.3)	12.6 (4.4)	13.4 (3.5)	-	-	14.8 (1.7)	15.1 (1.7)	15.6 (1.5)
Male %	44.7	53.8	29.7	52	50	44.4	48.6	54.1
Mean (SD) duration of psoriasis (yrs)	5.0 (3.8)	4.8 (3.3)	5.1 (3.8)	-	-	5.6 (3.8)	5.9 (4.0)	6.2 (5.0)
Median (range) duration of psoriasis (yrs)	[redacted]	[redacted]	[redacted]	6.8 (0.3-17.9)	5.8 (0.3-15.8)	[redacted]	[redacted]	[redacted]
Mean (SD) weight (kg)	-	-	-	-	-	62 (17.1)	68.2 (24.5)	64.7 (14.7)

	M04-717-Adalimumab			**20030211- Etanercept**		**CNTO1275PSO3006 CADMUS-Ustekinumab**		
	ADA 0.8mg/kg	**ADA 0.4mg/kg**	**MTX**	**ETA 0.8mg/kg**	**PLB**	**UST 0.75mg/kg**	**UST 0.375mg/kg**	**PLB**
Median (range) weight (kg)	48.5 (17-95)	53 (15-108)	52 (20-87)	59.6 (17.7-168.3)	59.8 (17.2-131.5)	[redacted]	[redacted]	[redacted]
Mean (SD) height (cm)	-	-	-	-	-	163.9 (9.2)	168 (11.0)	169.7 (11.3)
Median (range) height (cm)	156.5 (104-185)	157 (121-182)	157 (121-182)	159 (104-188)	158 (104-191)	[redacted]	[redacted]	[redacted]
Mean (SD) BSA% affected	27.7 (20.4)	26.0 (16.2)	30.3 (21.2)	-	-	31.9 (23.2)	33.6 (21.4)	27.4 (16.4)
Median (range) BSA% affected	[redacted]	[redacted]	[redacted]	21 (10 - 90)	20 (10 - 95)	-	-	-
Median (range) PASI score	15.3 (10.2-50.4)	15.6 (6.1-29.4)	17.5 (5-51.4)	16.7 (12.0 - 51.6)	16.4 (12.0 - 56.7)	16.8	19.5	19.6
Mean (SD) PASI score	18.9 (10)	16.9 (5.8)	19.2 (10)	18.5 (6.7)	18.6 (6.8)	21.7 (10.4)	21.0 (8.5)	20.8 (8.0)
PGA of at least 3 (%)	92	90	97	99	99	[redacted]	[redacted]	[redacted]

	M04-717-Adalimumab			20030211- Etanercept		CNTO1275PSO3006 CADMUS-Ustekinumab		
	ADA 0.8mg/kg	**ADA 0.4mg/kg**	**MTX**	**ETA 0.8mg/kg**	**PLB**	**UST 0.75mg/kg**	**UST 0.375mg/kg**	**PLB**
PsA (%)	0	2.6	0	5	13	[redacted]	[redacted]	[redacted]
Previous use of topical therapy (%)	100	100	100	-	-	91.7	83.8	91.9
Previous use of phototherapy (%)	44.7	59	51.4	-	-	38.9	48.6	29.7
Previous use of systemic therapy (%)	36.8	28.2	24.3	55 *	59 *	47.2	37.8	43.2
Previous use of biologic therapy (%)	10.5	10.3	8.1	0	0	8.3	10.8	13.5
Mean (SD) CDLQI	10.9 (6.6)	11.6 (7.9)	11.4 (5.6)	8.7 (6.0)	10 (6.4)	10.3 (6.6)	9.4 (6.5)	9.1 (6.4)
Median (range) CDLQI	10 (1-23)	10.5 (0-27)	12 (1-23)	7.0 (0-26)	9.5 (0-29)	9.0 (1.0-26.0)	10.5 (0.0-24.0)	10.0 (1.0-26.0)
Mean (SD) PedsQL	70.4 (14.2)	70.4 (21.3)	78.8 (14.9)	74.8 (17.8)	76.1 (16.9)	[redacted]	[redacted]	[redacted]

	M04-717-Adalimumab			**20030211- Etanercept**		**CNTO1275PSO3006 CADMUS-Ustekinumab**		
	ADA 0.8mg/kg	**ADA 0.4mg/kg**	**MTX**	**ETA 0.8mg/kg**	**PLB**	**UST 0.75mg/kg**	**UST 0.375mg/kg**	**PLB**
Median (range) PedsQL	72.3 (41.3-93.5)	75 (5.4-100)	84.8 (38.98.9)	77.2 (5.4-100)	79.9 (79.9-100)	[redacted]	[redacted]	[redacted]

Note: ADA= Adalimumab, ETA=etanercept, PLB=Placebo, UST=Ustekinumab, *= phototherapy or systemic therapy

4.3 Efficacy and safety of adalimumab

One multicentre RCT (M04-717), comparing two doses of adalimumab against methotrexate, met the selection criteria. While this has not been published in a peer-reviewed journal, data were available from regulatory documentation, conference proceedings, and a clinical study report (CSR) provided by the manufacturer. [36-42, 43, 2015, 44, 45]

The M04-717 study was separated into four periods:

- Period A: Double blind randomised controlled trial of initial treatment (16 weeks)
- Period B: Observational study of treatment withdrawal (up to 36 weeks)
- Period C: Double-blind re-treatment study based on original randomisation in Period A (16 weeks)
- Period D: Long-term follow-up (up to 52 weeks)

The double-blind RCT ('Period A') recruited paediatric patients (ages 4 to 17 years, weighing at least 13kg) with severe chronic psoriasis from 42 centres across 13 countries. Severe chronic psoriasis was defined as failure to respond to topical therapy, requiring systemic treatment to control disease and one of the following: (a) sPGA≥4, (b) BSA>20%, (c) very thick lesions with BSA>10%, (d) PASI>20, or (e) PASI>10, plus one of the following (i) active PsA unresponsive to nonsteroidal anti-inflammatory drugs; (ii) Clinically relevant facial involvement; (iii) Clinically relevant genital involvement; (iv) Clinically relevant hand and/or foot involvement or (v) Children's Dermatology Life Quality Index (CDLQI) >10.

A total of 114 participants were randomised: 38 to standard dose adalimumab (subcutaneous; initial 0.8mg/kg up to a maximum to 40mg, followed by 0.8mg/kg eow); 39 to low dose adalimumab (subcutaneous; initial 0.4mg/kg up to a maximum to 20mg, followed by 0.4mg/kg eow); and 37 to methotrexate (oral; initial 0.1mg/kg up to a maximum to 7.5mg, followed by weekly dose of up to 0.4mg/kg, up to a maximum dose of 25mg/week). To maintain blinding, participants allocated to adalimumab received placebo tablets and participants allocated to methotrexate received placebo injection following the adalimumab schedule. As methotrexate is a folic acid antagonist, all participants received folic acid (0.8 to 1.0mg/day) as a dietary supplement (to maintain study blinding).

Previous therapy received by trial participants included topical therapy (100%), phototherapy (52%), non-biologic systemic therapy (30%), and biologic therapy (10%; all etanercept).

4.3.1 Risk of bias assessment

The risk of bias for the trial was low for most domains, with appropriate methods used for allocation of participants, blinding, handling of missing data, and reporting of outcomes (on the basis of information reported in the CSR; see **Table 5.** Baseline characteristics were mostly balanced across treatment groups, with the exception of male sex, which appeared to be lower in the methotrexate arm. It should be noted that only six of the 114 children randomised were aged less than seven years at recruitment, all of whom were randomised to the low dose adalimumab group. This means that, despite adalimumab having marketing authorisation in children aged 4 years and older, this particular trial does not provide any efficacy data on the licenced standard dose of adalimumab in children aged 4-6 years.

16 of the 114 participants received the wrong medication. Regulatory documents indicate that the incidence of the error ”wrong medication” occurred at single time points and were unlikely to have affected the results of the study.

Table 5 Risk of bias assessment using Cochrane tool of bias for M04-717 RCT (“Period A”)

Assessment criterion	Risk of bias judgement	Support for judgement
Sequence generation	Low	“Participants were randomized by interactive voice/web response system to receive adalimumab 0.8 mg/kg, adalimumab 0.4 mg/kg, or MTX in a 1:1:1 ratio, respectively. Randomization was stratified by prior treatment with etanercept.”
Allocation concealment	Low	Participants were randomized by interactive voice/web response (IVR/IWR) system
Baseline comparability	Moderate	Higher proportion of female participants in MTX group than adalimumab groups. Only six children aged <7 years included in the trial, all of whom were in the 0.4mg/kg adalimumab group. Higher baseline PedsQL score in MTX group.
Blinding of participants, personnel, and outcome assessors	Low	“All AbbVie personnel with direct oversight of the conduct and management of the trial, (with the exception of the AbbVie Drug Supply Management Team), the PI, study site personnel, and the participant were to remain blinded to each participant's treatment throughout the blinded period of the study. The IVR/IWR system was to provide access to blinded participant treatment information in the case of medical emergency.” There was 1 participant for whom the blind was broken due to an SAE of

		proctocolitis that occurred on Day 195 of Period B and was thus nontreatment-emergent.
Incomplete outcome data	Low	Eight participants "early escaped" by week 8 of Period A: Five initially randomised to MTX, two randomised to low dose adalimumab, one randomised to standard dose adalimumab. [redacted]
Selective reporting	Low	All outcomes from clinicaltrials.gov protocol NCT01251614 reported in CSR

Primary efficacy endpoints for the randomised controlled period were ≥PASI 75 response at week 16 and sPGA rating of "cleared" or "minimal" (0 or 1) at week 16. Secondary outcomes included PASI 50, 90 and 100 responses, PGA score or 0, CDLQI and PedsQL scores.

Participants were evaluated at all visits for worsening of psoriasis. Up to and including the Week 8 visit, participants were eligible for "early escape" if they met the following criteria: (1) PASI scores increased by 50% relative to baseline at Week 4; or (2) PASI scores increased by 25% relative to baseline and by at least 4 points at each of two consecutive study visits (prior to or at Week 8). After Week 8, participants were to continue in the trial until the Week 16 visit.

Participants entering "early escape" were permitted to enter a longer-term observational study period (Period D; see below) in which they would receive open-label adalimumab at a dose of 0.8 mg/kg every other week (up to a maximum of 40 mg).

Primary efficacy analyses were conducted in the intent-to-treat (ITT) population (i.e. all randomised participants). Participants with missing or incomplete data at week 16 (including those entering "early escape") were imputed to be non-responders for categorical variables (non-responder imputation method; NRI), and had last observation carried forward (LOCF) for continuous variables. Analyses using per-protocol and "as observed" data were also reported in the CSR. The safety analysis was conducted in the safety population (i.e. all participants who received at least one dose of study medication).

4.3.2 Efficacy of adalimumab at 16 weeks

The absolute and relative results for PASI, sPGA, CDLQI and PedsQL outcomes at week 16 are shown in **Table 6** and **Error! Reference source not found.**)

Table 6 Results of key outcomes of adalimumab (Trial M04-717) at 16 weeks

Treatment	Dichotomous outcomes (ITT; NRI)				Continuous outcomes (ITT; LOCF)	
	PASI 50	PASI 75	PASI 90	sPGA 0 or 1	CDLQI mean change (SD)	PedsQL mean change (SD)
ADA 0.8mg/kg	[redacted]	22/38 (57.9%)	11/38 (28.9%)	23/38 (60.5%)	[redacted]	[redacted]
ADA 0.4mg/kg	[redacted]	17/39 (43.6%)	12/39 (30.7%)	16/39 (41.0%)	[redacted]	[redacted]
MTX 0.1mg/kg	[redacted]	12/37 (32.4%)	8/37 (21.6%)	15/37 (40.5%)	[redacted]	[redacted]

ADA=Adalimumab; CDLQI= Childhood Dermatology Quality of Life Index; ITT= Intention to Treat; LOCF=Last observation carried forward; NRI=non responder imputation; PASI=Psoriasis Area and Severity Index; PedsQL=Pediatric Quality of Life; sPGA=Physician static Global Assessment.

Table 7 Relative risks of key outcomes of adalimumab (Trial M04-717) at 16 weeks

Treatment	Relative risk and 95% CI				Mean Difference (MD) and 95% CI	
	PASI 50	PASI 75	PASI 90	sPGA 0 or 1	CLDQI	PedsQL

ADA 0.8mg/kg	[redacted]	1.79 (1.04 to 3.06)	1.34 (0.61 to 2.95)	1.49 (0.94 to 2.38)	1.6 (-1.44 to 4.64)	8.9 (2.94 to 14.86)
ADA 0.4mg/kg	[redacted]	1.34 (0.75 to 2.42	1.42 (0.65 to 3.08)	0.81 (0.46 to 1.41)	-0.1 (-3.14 to 2.94)	7.6 (2.42 to 12.78)
MTX 0.1mg/kg (reference)	[redacted]	1.00	1.00	1.00	0.00	0.00

4.3.2.1 PASI response

[redacted]PASI 75 response rates at 16 weeks were significantly greater for standard dose adalimumab (0.8mg/kg) than for methotrexate [redacted] 58% vs 32% [redacted]. Low dose adalimumab (0.4mg/kg) did not show a statistically significant improvement over methotrexate on these outcomes ([redacted]44% vs 32%). PASI 90 response rates did not differ significantly between the three treatment arms.

[redacted]

4.3.2.2 Physicians Global Assessment (PGA)

The proportion of participants achieving a sPGA score of 0 or 1 ('clear' or 'minimal') at 16 weeks was greater for standard dose adalimumab than low dose adalimumab or methotrexate (61% vs 41% vs 41%), though this difference was not statistically significant.

[redacted]

4.3.2.3 Quality of life

Two health related quality of life measures, CDLQI and PedsQL, were reported at 16 weeks. All three treatment groups showed improvements from baseline in the dermatology-specific quality of life measure (CDLQI), exceeding the published minimally clinical important difference (MCID) of a 2.5 point change from baseline. [46] However, these improvements were similar across the three treatment groups, with no significant difference between either dose of adalimumab or methotrexate ([redacted]).

Unlike CDLQI, improvements on the generic health related quality of life measure (PedsQL) significantly favoured both doses of adalimumab over methotrexate (mean changes of [redacted] and [redacted] for standard and low dose adalimumab respectively vs [redacted] for methotrexate). The mean changes in the adalimumab groups both exceed the published MCID of 4.4 for PedsQL.[24]

It is unclear why PedsQL scores would increase in the absence of dermatology-related QoL benefits as measured by CDLQI. However, both mean and median PedsQL scores at baseline were noticeably higher at baseline for methotrexate than adalimumab treatment arms (see **Table 4Error! Reference source not found.**), so the observed PedsQL change scores in the adalimumab arms may be overestimates due to regression to the mean.[47]

Table 8 PASI and sPGA response by age subgroups at 16 weeks

Subgroup	Treatment	PASI 50	PASI 75	PASI 90	sPGA 0 or 1
4 to 6 years of age	ADA 0.8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 0.4 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	MTX	[redacted]	[redacted]	[redacted]	[redacted]
>6 to 9 years of age	ADA 0.8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 0.4 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	MTX	[redacted]	[redacted]	[redacted]	[redacted]
>9 to 12 years of age	ADA 0.8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 0.4 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	MTX	[redacted]	[redacted]	[redacted]	[redacted]

>12 to 15 years of age	ADA 0.8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 0.4 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	MTX	[redacted]	[redacted]	[redacted]	[redacted]
>15 years of age	ADA 0.8 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 0.4 mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
	MTX	[redacted]	[redacted]	[redacted]	[redacted]

4.3.3 Longer term efficacy of adalimumab

4.3.3.1 Period B: Withdrawal

[redacted]

4.3.3.2 Period C: Retreatment

[redacted]

[redacted]

[redacted]

[redacted]

Table 9 Reported PASI responses during retreatment phase (week 16 of period C)

	PASI 50	PASI 75	PASI 90	sPGA 0/1
Participants from Period B who had experienced loss of disease control, retreated with originally randomised dose of adalimumab 0.8mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
Participants from Period B who had experienced loss of disease control, retreated with originally randomised dose of adalimumab 0.4mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
Participants from Period B who had experienced loss of disease control, who were initially randomised to methotrexate, retreated with adalimumab 0.8mg/kg	[redacted]	[redacted]	[redacted]	[redacted]

4.3.3.3 Period D: Long-term follow-up

[redacted]

[redacted]

Table 10 Reported PASI responses during long-term follow-up phase (week 52 of period D)

	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.3.4 Safety of adalimumab

4.3.4.1 Adverse events at 16 weeks

Adverse event rates were comparable among the three treatment groups (**Error! Reference source ot found.**). Three serious adverse events considered unrelated to treatment (hand fracture, gastrointestinal infection due to food poisoning, and agitation due to alcohol overtake) were reported, all of which occurred in participants receiving adalimumab 0.4 mg/kg. One participant in the same treatment arm withdrew due to an adverse event (moderate psoriasis flare).

Table 11 Reported safety outcomes of Adalimumab (Trial M04-717) at week 16

Treatment	Participants with safety reports (%)						
	AE	SAEs	Infections	Serious infections	Injection site reactions	Malignancies	Withdrawals due to adverse events
ADA 0.8mg/kg	26/38 (68.4)	0/38 (0.0)	18/38 (47.4)	0/38 (0.0)	4/38 (10.5)	0/38 (0.0)	0/36 (0.0)
ADA 0.4mg/kg	30/39(76.9)	3/39 (7.7)*	22/39 (56.4)	1/39 (2.6)	3/39 (7.7)	0/39 (0.0)	1/39 (2.6) [+]
MTX	28/37 (75.7)	0/37 (0.0)	20/37 (54.1)	0/37 (0.0)	3/37 (8.1)	0/37 (0.0)	0/37 (0.0)

AE= Adverse Events; SAE=Serious Adverse events. *=1 hand fracture, 1 gastrointestinal infection, 1 agitation; [+]=due to moderate psoriasis flare

4.3.4.2 Longer-term safety of adalimumab

Table 12 shows the overall numbers of adverse events during patient follow-up across all four study periods to be similar across treatment arms. A total of nine SAEs were reported in eight participants. In terms of episodes per 100 patient years (E/100 PYs), the total rate of SAEs was 5.9 E/100 PYs for all participants ever treated with adalimumab 0.8 mg/kg from the first dose of adalimumab 0.8 mg/kg and 7.4 E/100 PYs for all participants treated with adalimumab (0.4 mg/kg and 0.8 mg/kg) from the first dose of adalimumab 0.8 mg/kg.

One SAE of hemorrhagic ovarian cyst occurred in Period B in a participant who had been initially randomized to adalimumab 0.8 mg/kg.

Five SAEs occurred during Period D, including one death due to an accidental fall, one tendon injury in a participant receiving adalimumab 0.4 mg/kg, one rash maculopapular in a participant receiving adalimumab 0.8 mg/kg, one chest pain in a participant randomized to MTX but receiving adalimumab 0.8 mg/kg, and one eye nevus in a participant receiving adalimumab 0.8 mg/kg (Table 12). All SAEs were considered by investigators to be unrelated or probably unrelated to study drug with the exception of eye nevus, which was assessed as possibly related.

In addition to the participant who discontinued treatment due to a moderate event of psoriasis flare in Period A, one participant initially randomized to MTX but receiving adalimumab 0.8 mg/kg during Period D discontinued due to an event of severe urticaria.

The rate of all infections reported by participants receiving adalimumab 0.8 mg/kg was 170.4 E/100 PY. Only two events of tuberculosis occurred, both during period D.

Table 12 Reported safety outcomes of adalimumab (Trial M04-717) for the follow-up periods

		Participants with safety reports							
		AE	**SAEs**	**Infections**	**Serious infections**	**Injection site reactions**	**Malignancies**	**Tuberculosis**	**Withdrawals due to adverse events**
Period B	ADA 0.8mg/kg (n=23)	[redacted]	[redacted]	[redacted]	0	0	0	0	0
	ADA 0.4mg/kgmg/kg (n=18)	[redacted]	[redacted]	[redacted]	0	0	0	0	0
	MTX (n=13)	[redacted]	[redacted]	[redacted]	0	0	0	0	0
Period C	ADA 0.8mg/kg (n=19)	[redacted]	[redacted]	[redacted]	0	0	2	0	0
	ADA 0.4mg/kgmg/kg (n=11)	[redacted]	[redacted]	[redacted]	0	0	0	0	0
	MTX (n=8)	[redacted]	[redacted]	[redacted]	0	0	0	0	1
Period D	ADA 0.8mg/kg (n=36)	[redacted]	3	25	0	2	0	1	0
	ADA 0.4mg/kgmg/kg (n=36)	[redacted]	1	15	0	1	0	1	0
	MTX (n=36)	[redacted]	1	22	0	1	0	0	1*

*= Severe urticaria in patient initially randomised to MTX but receiving adalimumab 0.8mg/kg

4.3.5 Summary of the efficacy and safety of adalimumab

- There is evidence from one 16-week randomised controlled trial comparing adalimumab to methotrexate in children and young people with severe chronic psoriasis.
- The trial does not provide evidence for children aged 4 to 6 years of age.
- Adalimumab at the licenced dose of 0.8mg/kg (up to 40mg) leads to significantly greater responses than methotrexate for the outcomes of PASI 50, PASI 75, but not PASI 90.
- PGA 0/1 response rates were higher for adalimumab 0.8mg/kg than methotrexate, though the difference was not statistically significant.

- The benefits of half-dose adalimumab were not statistically greater than those observed for methotrexate.
- Evidence on quality of life was inconsistent across different measures, possibly due to baseline imbalance on PedsQL.
- [redacted]
- [redacted]
- In children and young people adalimumab does not appear to be associated with an increase in adverse effects relative to methotrexate over 16 weeks, [redacted]
- However, due to the small numbers of observed participants, the possibility of rare adverse events cannot be entirely excluded.

4.4 Efficacy and safety of etanercept

One multicentre RCT (20030211) comparing etanercept with placebo met the selection criteria. Data on short-term safety and efficacy (blinded period) were available from published peer-reviewed journal papers,[46, 48-52] conference proceedings [53-59]and regulatory documentations [60-70].

The double-blind RCT recruited children between 4 to 17 years of age from 42 sites in the United States and Canada who had stable, moderate-to-severe plaque psoriasis at screening. Moderate-to-severe plaque psoriasis was defined as a psoriasis area-and-severity index (PASI) score of at least 12 (PASI scores range from 0 to 72, with higher scores indicating worse condition); a static physician's global assessment of at least 3 (where 0 indicates clear and 5 severe psoriasis), and psoriasis involvement of at least 10% of the body-surface area; a history of psoriasis for at least 6 months; and previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids) or psoriasis considered by the investigator as poorly controlled with topical therapy.

Within each age stratum, participants were randomized to either etanercept 0.8 mg/kg once weekly up to maximum dose of 50 mg once weekly or placebo in a 1:1 ratio. A total of 106 and 105 participants were randomized to etanercept and placebo arms, respectively.

The primary outcomes measures used in the RCT was PASI 75 response, defined as a 75% or greater decrease in PASI score (i.e., improvement) from baseline at week 12. The secondary outcome measures were: PASI 50 response, PASI 90 response, clear or almost clear status of sPGA (Static Physician Global Assessment of psoriasis), and percentage improvement from baseline in CDLQI (Children's Dermatology Life Quality Index) at week 12.

A total of 264 participants were screened and 211 children were randomised to etanercept or placebo. At baseline, both groups were similar in terms of age and gender composition, BSA, PASI and PGA scores , though the placebo group had a slightly higher proportion of patients with psoriatic arthritis (13% vs. 5%). There was no previous use of biologic therapy in either group (see Table 4). It should be noted that just 19 (9%) of children included in study were under the age of 8 years, and only 9 (4.3%) were under 6 years old.

At or after Week 4, participants with >50% increase or an absolute increase of at least 4 points in PASI score from baseline were allowed to enter an “escape” arm to receive open-label etanercept every week through Week 12. During this initial 12-week comparative period, a higher number of participants from the placebo group (27 out of 105) than the etanercept group (5 out of 106) entered early escape. Participants who entered the escape arm were recorded as non-responder at the time they entered the escape arm. Data for those participants from before they entered the escape arm were not changed. For participants who had missing data, their missing data were imputed as non-responder but their existing data were included as observed.

4.4.1 Risk of bias assessment

The trial had a low overall risk of bias for most domains, with appropriate methods used for randomisation, handling of missing data, and reporting of outcomes (see Table 13). The study was described as ‘double-blinded’, though the methods used to achieve blinding were not described.

Table 13 Risk of bias assessment using Cochrane tool of bias for 20030211 RCT

Assessment criterion	Risk of bias judgement	Support for judgement

Sequence generation	Low	Interactive voice or web response system was used
Allocation concealment	Low	Interactive voice or web response system was used during randomisation
Baseline comparability	Low	No obvious baseline imbalance, though slightly higher PsA rate (13% vs 5%) in placebo group.
Blinding of participants and personnel	Unclear	Although double blinded initially, patients could enter to escape group and receive open-label etanercept. 27/105 placebo-allocated patients entered escape group vs. 5/106 etanercept-allocated patients. For binary endpoints, efficacy measures taken after entering the escape group were imputed as non-responses. Blinding methods not described.
Blinding of outcome assessment	Unclear	Participants, caregiver, investigator and outcomes assessor were blinded, though method of blinding was not described.
Incomplete outcome data	Low	For binary measures, missing post-baseline data were imputed as non-responses. Continuous measures were imputed to have baseline values.
Selective reporting	Low	The reported treatment response and health quality outcomes match those described in the study protocol.

4.4.2 Efficacy of etanercept at week 12

Data on the outcomes of treatment response for the 20030211 RCT were available from publications and regulatory documents. PASI and PGA scores are reported in Table 14 and Table 15.

4.4.2.1 PASI response

PASI 50, 75 and 90 for the etanercept group were 74.5%, 56.6% and 27.4%, respectively. Response rates for the placebo group were 22.9%, 11.4% and 6.7%. When translated into relative risk values, the etanecept group had significantly higher probability of achieving PASI 50, 75 and 90, with respective RRs of 3.26 (95% CI 2.26 to 4.71), 4.95 (95% CI 2.84 to 8.65) and 4.10 (95% CI 1.88 to 8.95).

Table 14 Reported treatment response and health quality of life outcomes of Etanercept (Trial 20030211) at week 12

Treatment	Dichotomous outcomes				Continuous outcomes	
	PASI 50	**PASI 75**	**PASI 90**	**sPGA 0 or 1**	**CDLQI (SD)***	**PedsQL (SD)***
ETA 0.8mg/kg	79/106 (74.5%)	60/106 (56.6%)	29/106 (27.4%)	56/106 (52.8%)	5.4 (5.6)	6.8 (17.6)
PLB	24/105 (22.9%)	12/105 (11.4%)	7/105 (6.7%)	14/105 (13.3%)	3.1 (5.1)	3.8 (10.1)

Note: *= mean change from baseline

Table 15 Relative effects of reported outcomes of Etanercept (Trial 20030211) at week 12

Treatment arms	Relative risk and 95% CI				Mean difference (95% CI)	
	PASI 50	**PASI 75**	**PASI 90**	**sPGA 0 or 1**	**CDLQI**	**PedsQL**
ETA 0.8mg/kg	3.26 (2.26 to 4.71)	4.95 (2.84 to 8.65)	4.10 (1.88 to 8.95)	3.96 (2.36 to 6.66)	2.3 (0.85 to 3.74)	3.0 (-0.87 to 6.87)
PLB (reference)	1.00	1.00	1.00	1.00	0.00	0.00

4.4.2.2 Physicians Global Assessment (PGA)

The proportion of participants achieving a PGA score of 0 or 1 ('clear' or 'minimal') at 12 weeks was significantly greater for etanercept than placebo (52.8% vs 13.3%), equating to a relative risk of 3.96 (95% CI 2.36 to 6.66).

4.4.2.3 Quality of life

Data for two health related quality of life measures, CDLQI and PedsQL, were available at 12 weeks (**Table 14**). Both etanercept and placebo treatment groups showed improvements from baseline in CDLQI scores, exceeding the published minimally clinical important difference (MCID) of a 2.5

point change from baseline,[46]PedsQL though the improvement in the etanercept group was statistically significantly greater than in the placebo group (mean difference: 2.3, 95% CI:0.85 to 3.74).

Both treatment groups also showed improvements in the PedsQL, though for the placebo group this fell below the published MCID of 4.4. The mean change in PedsQL from baseline, while favouring etanercept, was not statistically significantly different between the treatment groups (mean difference: 3.0, 95% CI: -0.87 to 6.87).

4.4.2.4 Sub-group outcomes

Age-based subgroup analysis results of PASI responses for the Trial 20030211 were available (see **Table 16**). A higher proportion of the etanercept treatment group achieved PASI 50, 75 and 90 responses than the placebo group in all age categories. Imputation of treatment failure for participants entering early escape reduced the magnitude of the difference between treatments, though these differences remained formally statistically significant for all comparisons, with the exception of PASI 90, which was of borderline statistical significance (p=0.054).

Table 16 Sub-group PASI responses at week 12 (published results)[49]

		PASI 50	PASI 75	PASI 90
Age				
≥ 8 years	Etanercept	70/95* (73.7%)	52/95* (54.7%)	26/95* (27.4%)
	Placebo	23/97* (23.7%)	11/97* (11.3%)	6/97* (6.2%)
4-11 years	Etanercept	29/38 (76.3%)	22/38 (57.9%)	N/A
		30/38 (78.9%)†	22/38 (57.9%)†	12/38 (31.6%)†
	Placebo	8/38 (21.1%)	4/38 (10.5%)	N/A
		16/38 (42.1%)†	10/38 (26.3%)†	5/38 (13.2%)†
12-17 years	Etanercept	50/68 (73.5%)	38/68 (55.9%)	N/A
		51/68 (75.0%)†	38/68 (55.9%)†	17/68 (25.0%)†
	Placebo	16/67 (23.9%)	8/67 (11.9%)	N/A
		21/67 (31.3%)†	11/67 (16.4%)†	4/67(5.6%)†

*back-calculated from reported percentages, so integers may not be entirely accurate; N/A= not available; †ITT with treatment failure imputation extracted from EMEA document[62]

4.4.3 Longer-term efficacy of etanercept

4.4.3.1 Weeks 12-36: Open-label etanercept treatment

At the end of the 12-week double-blind period, a total of 208 participants (105 and 103 from the original etanercept and placebo groups respectively) entered to an open-label treatment phase (i.e. all were treated with etanercept) and followed-up until week 36.

Patients who did not achieve PASI 50 at week 24 were given the option to discontinue the study or to enter the incomplete-responder arm. Participants in the incomplete-responder arm had the option to receive topical psoriasis therapy according to the standard of care in addition to receiving open-label etanercept (see Figure 2).

By weeks 24 and 36 (i.e. 12 and 24 weeks of open-label etanercept), participants who were originally randomised to the placebo during the double-blind period achieved a similar PASI and PGA responses as participants receiving etanercept throughout (see Table 17).

Table 17 Results of key outcomes of Etanercept (Trial 20030211) between 12 and 36 weeks

		PASI 50	PASI 75	PASI 90
Week 24	ETA/ETA	92/105 (88%)	72/105 (68%)	39/105 (37 %)
	PLB/ETA	80/103 (78%)	64/103 (62%)	37/103 (37%)
Week 36	ETA/ETA	91/105 (87%)	71/105 (68%)	43/105 (41%)
	PLB/ETA	89/103 (86%)	67/103 (65%)	39/103 (38%)

ETA/ETA= participants randomised to etanercept and received etanercept after double-blind period (12 weeks); PLB/ETA=participants randomised to placebo but received etanercept after double-blind period.

4.4.3.2 Weeks 36-48: Re-randomised 'withdrawal-retreatment' period

At week 36, 138 patients who had achieved PASI 50 at week 24 or PASI 75 at week 36 were randomised 1:1 to receive either etanercept or placebo in a double-blinded fashion and followed-up for further 12 weeks until week 48.

During the follow-up, 42 participants from the ITT population (29/69 and 13/69 from the placebo and etanercept arms respectively) lost PASI 75 response and so were allocated to receive etanercept in open-label fashion until week 48.

Overall, 52 out of 65 (80%) participants who received etanercept throughout the withdrawal-retreatment period maintained PASI 75. 85% of those re-randomised to placebo and did not lose PASI 75 during follow-up retained response at week 48. Only 36% of those who were retreated with open-label etanercept after losing PASI75 response on placebo had regained response by week 48 (Table 18). The use of PASI75 as both a retreatment rule and as an outcome makes these results difficult to interpret; however, a relatively high rate of late cross-over from placebo to etanercept could partly explain a lack of response among these participants on PASI and PGA measures.

Table 18 Results of key outcomes of Etanercept (Trial 20030211) at week 48 (observed data)

	PASI 75	sPGA 0 or 1
Re-randomised to etanercept and received blinded etanercept (no loss of PASI 75 response) or open-label etanercept (after loss of PASI 75 response)	52/65 (80%)	38/65 (58%)
Re-randomised to placebo and stayed on blinded placebo until week 48 (no loss of PASI 75 response)	34/40 (85%)	27/40 (68%)
Re-randomised to placebo but received open label etanercept after loss of PASI 75 response	10/28 (36%)	8/28 (29%)

4.4.3.3 Weeks 48-312 (Study 20050111)

194 participants completed 48 weeks of follow-up in the 20030211 trial (57 participants who received etanercept and topical therapy starting from the open-label treatment phase, 95 participants who were randomised to etanercept and placebo arms and continued to receive blinded drug, and 42 participants who were randomised to either etanercept or placebo but did not achieve PASI 75 and were re-treated with etanercept until the end of the study).

Of the 194 participants who completed the 20030211 trial, 182 were enrolled in an open-label extension study (20050111) to establish long-term safety of etanercept. Participants received etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) subcutaneously once weekly for a further 264 weeks. 63 participants (34.6%) completed 264 weeks of follow-up.

During the 264 weeks of further follow-up, the probability of achieving of PASI 50, 75 and 90 was similar across all the outcome recoding points. However, it should be noted that by week 264, 63.6% of the participants (115/181) withdrew from the study (Table 19) and reasons for withdrawal were unavailable.

Table 19 Reported efficacy outcomes during long-term follow-up period (study 20050111)

Week	≥PASI 50 (%)	≥PASI 75 (%)	≥PASI 90 (%)	sPGA 0 (%)	sPGA 0 or 1 (%)
12	162/181(89.5)	122/181 (67.4)	64/181 (35.4)	12/181 (13.3)	97/181 (53.6)
48	150/168 (89.3)	113/168 (67.3)	55/168 (32.7)	18/168 (10.7)	82/168 (48.8)
96	123/138 (89.1)	84/138 (60.9)	41/138 (29.7)	16/139 (11.5)	66/139 (47.5)
144	101/114 (88.6)	71/114 (62.3)	32/114 (28.1)	9/114 (7.9)	52/114 (45.6)
192	80/92 (87)	64/92 (69.6)	3392 (35.9)	19/92 (20.7)	44/92 (47.8)
240	68/74 (91.9)	48/74 (64.9)	27/74 (36.5)	13/74 (17.6)	37/74 (50)
264	58/66 (87.9)	42/66 (63.6)	19/66 (28.8)	8/66 (12.1)	25/66 (37.9)

4.4.4 Safety of Etanercept

4.4.4.1 Adverse events at 12 weeks

The number of adverse events reported during the 12 week period was similar for etanercept and placebo (68 vs. 62). There were 50 infections and seven injection site reactions in the etanercept group, compared with 33 infections and 5 injection site reactions in the placebo group. While difference in rate of infections fell short of formal statistical significance, there were noticeably more infections in the etanercept treatment arm (47.2% vs 31.4%; p=0.0683). One participant in the etanercept group withdrew due to an adverse effect (no further details available). No serious adverse events were observed during the 12-week randomised phase.

Table 20 Reported safety outcomes of Etanercept (Trial 20030211) at week 12

Treatment	Participants with safety reports(%)						
	AE	SAEs	Infections	Serious infections	Injection site reactions	malignancies	Withdrawals due to adverse events

ETA	68/106 (64.2)	NR	50/106 (47.2)	0/106 (0.0)	7/106 (6.6)	NR	1/106 (0.9)
PLB	62/105 (59.0)	NR	33/105 (31.4)	0/105 (0.0)	5/105 (4.8)	NR	0/105 (0.0)

NR=Not reported

4.4.4.2 Adverse events weeks 12-36

Through week 36, 282 infections were reported during treatment with etanercept (238.18 events per 100 person-years). The most common infections were upper respiratory tract infection, nasopharyngitis, influenza, pharyngitis, streptococcal pharyngitis, and viral upper respiratory infection (59.97, 33.79, 16.05, 15.20, 8.45, and 8.45 events per 100 participant-years, respectively). During the same period, a single serious non-infectious adverse event (due to benign ovarian mass) and one serious infection of gastroenteritis with dehydration were observed.

Through week 36, a total of 2.4% (5/208) withdrew due to adverse events: three participants were withdrawn because of non-infectious adverse events (psoriasis, atopic dermatitis and muscle cramps) and two participants because of infections (pneumonia and skin infection), see Table 21.

Table 21 Reported safety outcomes of Etanercept (Trial 20030211) through week 36

Participants with safety reports (%)							
AE	**SAEs**	**Infections**	**Serious infections**	**Injection site reactions**	**Malign-ancies**	**Withdrawals due to adverse events**	**Deaths**
584.48 events per 100 person-years	1/208 (0.4)	238.18 events per 100 person-years	1/208 (0.4)	26/208 (12.5)	0	5/208 (2.4)*	0/208 (0.0)

*= psoriasis, atopic dermatis, muscle cramps, pnuemonia and skin infection

4.4.4.3 Adverse events weeks 48 to 312

A total of 161 participants (89.0%) reported at least one adverse event during the study through week 264 of follow-up study 20050111. Seven participants (3.9%) reported serious adverse events with each participant reporting a single event: anxiety, cellulitis, infectious mononucleosis, post-operative intestinal obstruction, osteonecrosis, and thyroid cyst; a seventh participant underwent an elective

abortion (Table 22) However, of the seven serious adverse events, only the cellulitis infection was considered by the investigator to be related to etanercept treatment.

Six participants (3.3%) withdrew from the study due to either an infectious or non-infectious adverse event: Two participants withdrew due to Crohn's disease, and one participant each withdrew due to glomerulonephritis (secondary to infection), psoriasis, sinusitis, and nerve paralysis. Glomerulonephritis and one of the cases of Crohn's disease were considered to be related to treatment.

No serious adverse event led to study withdrawal. No opportunistic infections or deaths occurred during the study and no malignancies were reported.

Table 22 Reported safety outcomes of Etanercept (Trial 20030211) through week 264

Treatment	Participants with safety reports (%)						
	AE	SAEs	Infections	Serious infections	Injection site reactions	Malignancies	Withdrawals due to adverse events
ETA	161/181 (89.0)	7/181 (2.8)	140/181 (77.3)	2/181(1.1)	16/181 (8.8)	NR	6/181 (3.3)*

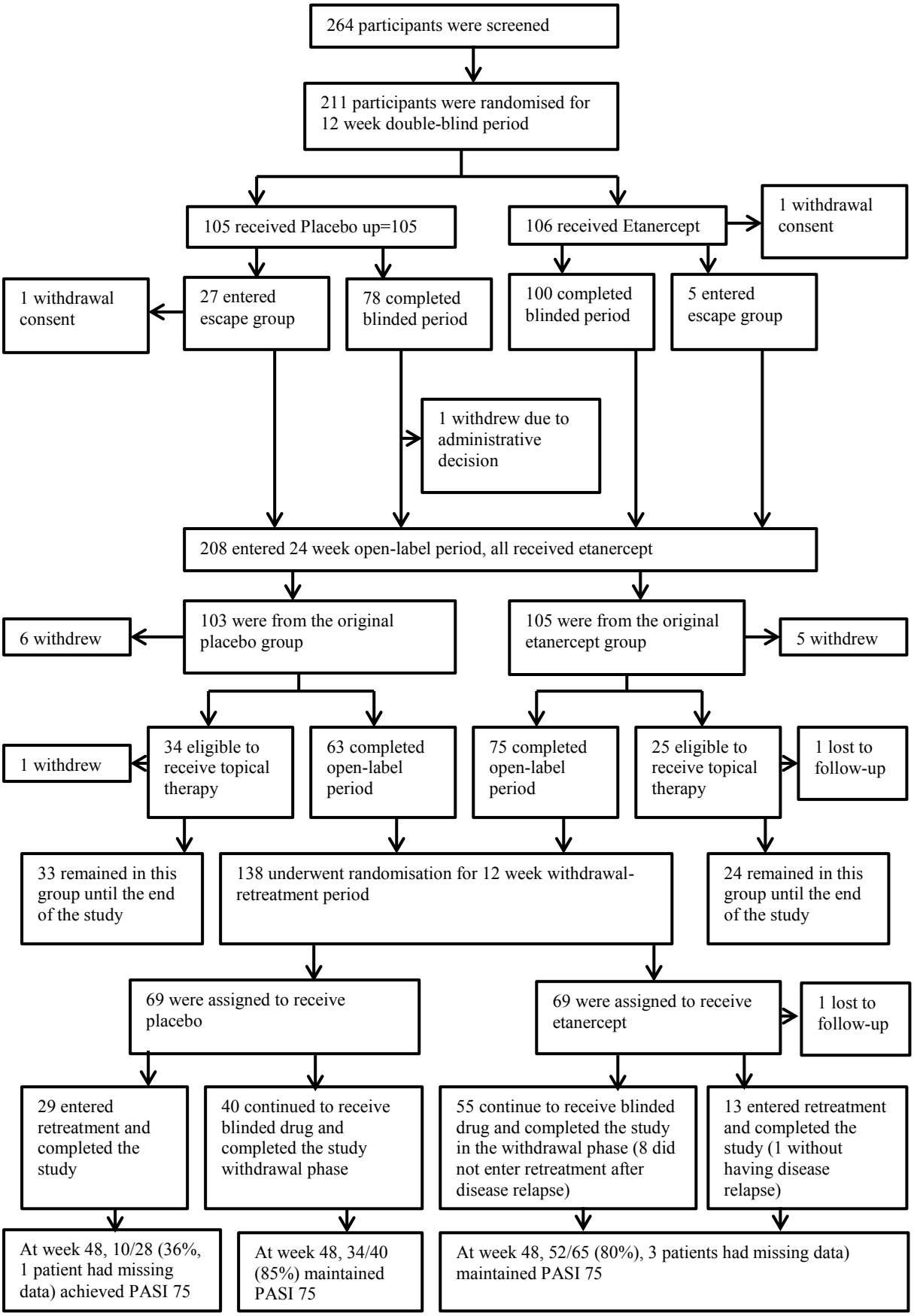
NR=Not reported; * = 2 Crohn's disease, 1 glomerulonephritis, 1 psoriasis, sinusitis, and 1 nerve paralysis

4.4.5 Summary of the efficacy and safety of etanercept

- One multicentre RCT (20030211) compared etanercept versus placebo in children aged 4 to 17 years of age with moderate-to-severe plaque psoriasis.
- Relatively few young children (9% aged under 8 years; 4.3% aged under 6 years) were included in study
- At 12 weeks, etanercept was significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50, 75 and 90, and PGA cleared or minimal scores.
- Improvements in health-related quality of life were larger for etanercept than placebo, but only reached statistical significance for CDLQI.
- Adverse events rates were similar between etanercept and placebo groups at 12 weeks with no serious adverse events observed for either treatment. However, observed higher rate of infections among participants receiving etanercept was of borderline statistical significance.

- A subsequent open-label extension study followed-up participants for up to six years from entry into the original RCT. The proportion of PASI and PGA responders were stable over time, though only 36% of participants were available at the latest follow-up point. The proportion of participant withdrawing due to lack of efficacy is unknown. These longer-term uncontrolled observational response data may therefore overestimate the efficacy of etanercept.
- Through 264 weeks of additional follow-up, withdrawals due to adverse events were infrequent, and no deaths or malignancies were observed.

Figure 2 Short-term and long-term participant follow-up flow chart of etanercept trial



4.5 Efficacy and safety of ustekinumab

One multicentre RCT (1275PSO3006; CADMUS) comparing standard and half dosages of ustekinumab (0.75mg/kg and 0.375mg/kg, respectively) with placebo met the selection criteria. Data on safety and efficacy (blinded period) were available from one peer-reviewed journal paper,[71] conference proceedings,[72] regulatory documentation,[73, 74] and a clinical study report provided by the manufacturer.

The CADMUS RCT was a double-blind, placebo-controlled study in adolescent participants (≥12 to <18 years of age) ,who had a diagnosis of moderate-to-severe plaque psoriasis for at least 6 months, conducted at multiple sites in Europe (Belgium, France , Germany , Hungary , Portugal , Russia, Sweden , Ukraine and United Kingdom) and Canada. Moderate-to-severe disease was defined as Psoriatic Area and Severity Index (PASI) ≥12, Physician's Global Assessment (PGA) ≥3, and body surface area (BSA) involvement ≥10%.

A total of 157 participants were screened. One hundred ten participants were eligible and randomized (37 participants to placebo, 37 participants to ustekinumab half-standard dosage and 36 participants to ustekinumab standard dosage). The standard dosage of ustekinumab was 0.75 mg/kg for participants ≤60 kg of weight, 45mg for participants weighing 60kg to 100 kg, and 90mg for participants weighing >100 kg. The half-standard dosage ustekinumab was 0.375 mg/kg weighing 60kg to 100 kg, and 45mg for participants weighing >100 kg. Randomization was stratified by investigational site and baseline weight (≤60 kg or >60 kg).

The study had three periods:

- Controlled period (0-12weeks): participants received either ustekinumab (full or half doses) or placebo. In the ustekinumab groups, participants were allowed to early escape at week 8 to have moderate-to-high potency topical steroid preparations through Week 12 if their PASI scores increased by ≥50% from baseline. However no participants entered the escape route during this period.
- Placebo crossover and active treatment period (12-52 weeks): participants randomised to placebo during the controlled period were allowed to crossover to the full or half-dose of ustekinumab at week 12.
- Follow-up period (52-60 weeks): participants continued to be followed for safety analysis.

To preserve blinding, participants in the half-standard dosage and standard dosage groups received ustekinumab at Week 0 and Week 4 followed by doses every 12 weeks until Week 40. Participants in

the placebo group also received placebo at Week 0 and Week 4, crossed over to receive either half-standard dosage or standard dosage ustekinumab at Week 12 and Week 16, followed by 12 weekly doses of either a half-standard dosage or standard dosage ustekinumab, with the last dose at Week 40. All participants were followed for efficacy through Week 52 and for safety through Week 60.

The primary outcome measure was the proportion of participants who achieved sPGA score of 'cleared' or 'minimal' at Week 12. Data from all randomized participants were analysed according to their assigned treatment group. Participants who met treatment failure criteria prior to Week 12 or who entered early escape were considered non-responders at Week 12. In addition, participants who had a missing PGA score at Week 12 were considered as not achieving the primary endpoint at Week 12.

The secondary outcome measures were the PASI 50, 75 and 90 at Week 12 based on all randomized participants, and changes from baseline in CDLQI at Week 12 based on efficacy evaluable participants.

4.5.1 Risk of bias assessment

Based on the Cochrane risk of bias assessment tool, the CADMUS RCT double-blind period had a low risk of bias: appropriate randomisation and blinding techniques were implemented, no obvious difference of baseline characteristics between treatment arms was apparent, missing data were handled appropriately and that all protocol-stated outcome measures were reported (see Table 23).

Table 23 Risk of bias assessment using Cochrane tool of bias for Ustekinumab RCT (CADMUS)

Assessment criterion	Risk of bias judgement	Support for judgement
Sequence generation	Low	"Dynamic central randomization was implemented in conducting this study. Participants were randomly assigned to 1 of 4 treatment groups based on an algorithm implemented in the Interactive Voice/Web Response System (IVRS or IWRS) before the study"
Allocation concealment	Low	Based on the algorithm, the IVRS/IWRS assigned a unique treatment code, which dictated the treatment assignment.
Baseline comparability	Low	No obvious difference in baseline characteristics
Blinding of participants, personnel and outcome assessors	Low	"The Sponsor, investigative study sites, and participants remained blinded to treatment assignment until the last participant enrolled completed the Week 60 evaluations and the database was locked"
Incomplete outcome data	Low	"Participants who discontinued study treatment due to lack of efficacy, an adverse event (AE) of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could affect their psoriasis were considered as treatment failures. A participant who met 1 or more treatment failure criteria was considered as a treatment failure from that point onward. The baseline values were used for all directly measured endpoints regardless of the actual measurements. Zeros were assigned to improvements and percent improvements, and nonresponder status was assigned to binary response variables. " "Participants who used a moderate to high potency topical steroid as a result of being eligible to early escape were considered as nonresponders at Week 12 for binary endpoints and their continuous outcomes at Week 12 were imputed by the last value at or prior to Week 8. The analysis at Week 16 was the observed data without imputation. After Week 16, if participants continued to use a moderate to high potency topical steroid, treatment failure rules were applied to those participants.
Selective reporting	Low	Primary and secondary outcomes reported match the study protocol

4.5.2 Efficacy of ustekinumab

4.5.2.1 Efficacy at week 12

Data on treatment response (PASI and PGAs) and health quality of life (CDLQI and PedsQL) outcomes for CADMUS RCT are presented in Table 24 and Table 25 below.

Table 24 Results of key outcomes of Ustekinumab (Trial CNTO1275PSO3006 CADMUS) at week 12

Treatment	Number of participant who achieved the outcomes (%)					Mean change (SD)	
	PASI 50	PASI 75	PASI 90	sPGA 0 or 1	sPGA 0	CDLQI	PedsQL
UST 0.75mg/kg	32/36 (88.9)	29/36 (80.6)	22/36 (61.1)	25/36 (69.4)	17/36 (47.2)	-6.7 (5.6) n=32	8.03 (10.4) n=32
UST 0.375mg/kg	30/37 (81.2)	29/37 (78.4)	20/37 (54.1)	25/37 (67.6)	12/37 (32.4)	-5.6 (6.4) n=35	10.81 (12.9) n=35
PLB	11/37 (29.7)	4/37 (10.8)	2/37 (5.4)	2/37 (5.4)	1/37 (2.7)	-1.5 (3.2) n=32	3.35 (10.0) n=32

Table 25 Relative effects of Ustekinumab (Trial CNTO1275PSO3006 CADMUS) at week 12

Treatment	Relative risks and 95% CI					Mean Difference (MD) and 95% CI	
	PASI 50	PASI 75	PASI 90	sPGA 0/1	sPGA 0	CDLQI	PedsQL
UST 0.75mg/kg	2.99 (1.79 to 4.97)	7.5 (2.9 to 19.1)	11.0 (2.8 to 43.5)	12.9 (3.3 to 50.3)	17.5 (2.5 to 124.5)	5.2 (2.96 to 7.44)	8.9 (2.46 to 15.34)
UST 0.375mg/kg	2.72 (1.62 to 4.48)	7.3 (2.8 to 18.6)	10.0 (2.5 to 39.8)	12.5 (3.2 to 49)	12.0 (1.6 to 87.7)	4.1 (1.7 to 6.5)	7.6 (2.16 to 13.04)
PLB	1.00	1.00	1.00	1.00	1.00	0.00	0.00

Physicians Global Assessment (PGA)

Significantly greater proportions of participants in the standard dosage and the half-standard dosage groups (69.4% and 67.6%, respectively) achieved PGA scores of cleared (0) or minimal (1) at Week 12 compared with the placebo group (5.4%). The proportions of participants who achieved PGA scores of cleared (0) were also higher in the standard dosage and half-standard dosage groups (47.2% and 32.4%, respectively) than the placebo groups (2.7%). The relative risks for these outcomes are shown in Table 25

PASI response

Higher proportions of participants in the standard dosage and the half-standard dosage groups achieved PASI 50, 75 and 90 than the placebo group. For example, whilst 80.6% and 78.4% of the standard dosage and half-standard dosage groups, respectively, achieved a PASI 75 response at week 12, only 10.8% the placebo group achieved the same PASI response (see Table 24). The relative risk values also show that both ustekinumab dosage groups had significantly higher probabilities of achieving the PSAI 50, 75 and 90 responses than the placebo group (Table 25)

Health-related quality of life

Changes from baseline in CDLQI were significantly greater in both the standard dosage and half-standard dosage groups (mean of -6.7 and -5.6, respectively) compared with the placebo group (-1.5). Whilst both ustekinumab treatment groups showed improvements from baseline in the CDLQI that exceed the published minimally clinical important difference (MCID) of a 2.5 point change from baseline, this was not the case for the placebo group. The mean difference values indicate that CDLQI changes were significantly greater for both ustekinumab dosage groups than the placebo group (mean difference: 5.2, 95% CI: 2.96 to 7.44 and mean difference: 4.1, 95% CI: 1.7 to 6.5, respectively; see **Table 25**).

Participants in both the standard dosage and half-standard dosage groups (mean of 8.03 and 10.81, respectively) showed significantly larger improvements in the PedsQL total scale scores than participants in the placebo group (3.35). The mean changes for the half dosage and standard dosage were above the published MCID of 4.4 while changes for the placebo group was below the MCID figure. Mean differences at 12 weeks indicate that standard dosage and half dosage groups had significantly higher improvement in PedsQL than the placebo group (mean difference: 8.9, 95% CI: 2.46 to 15.34 and mean difference: 7.6, 95% CI: 2.16 to 13.04, respectively).

Sub-group efficacy outcomes

Sub-group efficacy results of PASI 75 and PGA 0 or 1 were available from the CSR (Table 26) [redacted]

Table 26 Sub-group efficacy outcomes of Ustekinumab (Trial CNTO1275PSO3006 CADMUS) at week 12

		PASI 75*	sPGA 0 or 1*
Age <=15			
	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]

	Placebo	[redacted]	[redacted]
Age >15 years			
	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
Sex			
Male	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
Female	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
Weight			
≤60kg	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
>60-≤100kg	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
>100kg	UST 0.75mg/kg	[redacted]	[redacted]
	UST 0.375mg/kg	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]

*back-calculated from reported percentages, so values may not be entirely accurate.

4.5.3 Longer term efficacy of ustekinumab

4.5.3.1 PASI response

Among participants continuing ustekinumab treatment, PASI responses observed in week 12 appeared to be sustained at week 52, with few participants lost to follow-up (one participant was lost from the standard dose arm and two from the half-dose arm).

Participants who were randomised to placebo and crossed over to standard ustekinumab dosage (0.75mg/kg) achieved better PASI responses than those who crossed over to half-standard dosage (0.375mg/kg), see Table 27.

4.5.3.2 PGA response

A similar pattern of responses as can be seen for PGA response data, with similar response rates at week 52 as at week 12 among participants continuing ustekinumab treatment, and a large improvement between weeks 12 and 52 for participants crossing over to active treatment from placebo (Table 27).

Table 27 Reported PASI and PGA response outcomes at week 52

	PASI 50	PASI 75	PASI 90	sPGA 0	sPGA 0 or 1
UST 0.75mg/kg	[redacted]	[redacted]	23/35 (65.7%)	18/36 (50%)	26/36 (72%)
UST 0.375mg/kg	[redacted]	[redacted]	17/34 (50%)	13/37 (35%)	23/37 (62%)
PLB→ UST 0.75mg/kg	[redacted]	[redacted]	16/17 (94.1%))	11/17 (65%)	16/17 (94%)
PLB→ UST 0.375mg/kg	[redacted]	[redacted]	9/17 (52.9%))	9/19 (47%)	13/19 (68%)

4.5.4 Safety of ustekinumab

4.5.4.1 Adverse events at week 12

Total reported adverse events did not significantly differ between the ustekinumab treatment (44.4% standard and 51.4% half-dose) and placebo groups (56.8%; Table 28) There were no serious adverse events reported in the standard ustekinumab dosage or placebo groups, while one participant in the ustekinumab half-dosage group was hospitalised for worsening of psoriasis (see Table 28). There were no reported malignancies or withdrawals due to adverse events.

One participant in the standard dosage ustekinumab group had a mild injection site reaction. There were no incidences of serious infection, tuberculosis, malignancy or withdrawals due to adverse events during the initial 12-week treatment period.

Table 28 Reported safety outcomes of Ustekinumab (Trial CNTO1275PSO3006 CADMUS) at week 12

Treatment	Participants with safety reports (%)						
	AE	SAEs	Infections	Serious infections	Injection site reactions	Malignan-cies	Withdrawals due to adverse events
UST 0.75mg/kg	16/36 (44.4)	0/36 (0.0)	8/36 (22.2)	0/36 (0.0)	1/36 (2.8)	0/36 (0.0)	0/36 (0.0)
UST 0.375mg/kg	19/37(51.4)	1/37 (2.7) *	12/37 (32.4)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)
PLB	21/37 (56.8)	0/37 (0.0)	14/37 (37.8)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)	0/37 (0.0)

*= one participant in the half ustekinumab dosage group was hospitalised for worsening of psoriasis

4.5.4.2 Discontinuation through week 40

Through Week 40, 8.2% (9/110) of participants discontinued the trial. The most common reasons for discontinuation were lack of efficacy and adverse events (Table 29). Five participants (13.5%) who were originally randomised to half-standard dosage ustekinumab group discontinued the trial compared with two participants (5.6%) in the standard dosage group. Two patients who crossed over from placebo to half-dose ustekinumab withdrew due to adverse events.

Table 29 Reported number of participants discontinuing ustekinumab treatment (CADMUS) through week 40

Treatment	Participants with safety reports (%)			
	Total discontinued	Due to AEs	Due to death	Due to lack of efficacy
UST 0.75mg/kg	2/36 (5.6)	0/36 (0.0)	0/36 (0.0)	2/36 (5.6)
UST 0.375mg/kg	5/37 (13.5)	1/37 (2.7)	1/37 (2.7)	3/37 (8.1)
PLB→ UST 0.75mg/kg	0/18 (0.0)	0/18 (0.0)	0/18 (0.0)	0/18 (0.0)
PLB→ UST 0.375mg/kg	2/19 (10.5)	2/19 (10.5)	0/19 (0.0)	0/19 (0.0)

4.5.4.3 Adverse events through week 60

Through Week 60, 81.8% (90/110) of participants in the ustekinumab combined group reported one or more AEs. Of the 74 participant recorded infections, 18 (24%) were considered reasonably related to ustekinumab treatment.

A total of 5.5% (6/110) of participants in the ustekinumab combined group (5 participants in the half-standard dosage group and 1 participant in the standard dosage group) reported SAEs (Table 30). Four (one due to worsening of psoriasis) of the 110 of participants in the ustekinumab combined group discontinued the trial due to an adverse event by week 60.

Table 30 Reported safety outcomes of Ustekinumab (Trial CNTO1275PSO3006 CADMUS) through week 60‡

Treatment	Participants with safety reports(%)						
	AE	**SAEs**	**Infections**	**Serious infections**	**Injection site reactions**	**Malignancies**	**Withdrawals due to adverse events**
UST 0.75mg/kg	29/36 (80.6)	1/36 (2.8)*	24/36 (66.7)	1/36 (2.8)*	1/36 (2.8)	0/36 (0.0)	0/36 (0.0)
UST 0.375mg/kg	33/37 (89.2)	5/37[+†] (13.5)	26/37 (70.3)	1/37† (2.7)	0/37 (0.0)	0/37 (0.0)	2/37 (5.4)
PLB→ UST 0.75mg/kg	13/18 (72.2)	0/18 (0.0)	11/18 (61.1)	0/18 (0.0)	0/18 (0.0)	0/18 (0.0)	0/18 (0.0)
PLB→ UST 0.375mg/kg	15/19 (79.0)	0/19 (0.0)	13/19 (68.4)	0/19 (0.0)	0/19 (0.0)	0/19 (0.0)	2/19 (10.5)

‡incorporates week 12 and 40 data; * ear infection; †pyelonephritis; [+]in addition to events recorded before week 60: 1 death due to automobile accident; 1 allergic contact dermatitis; 1 laboratory values for ALC, ANC and white blood cells of: 0.53, 0.87 and 1.62 x 103/μL, respectively while undergoing treatment with acyclovir for a concurrent AE of herpes simplex

4.5.5 Summary of the efficacy and safety of ustekinumab

In this multicentre trial (CADMUS) of children 12 to 17 years of age:

- Both the standard dosage and half dosage of ustekinumab were significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50,75 and 90, PGA cleared or minimal and PGA cleared scores at 12 weeks.
- Both ustekinumab dosages also lead to significantly greater improvements in health-related quality of life measurements (CDLQI and PedsQL) at 12 weeks than the placebo group.
- Among participants originally allocated to ustekinumab, PASI and PGA effects observed at 12 weeks appeared to be largely sustained at 52 weeks, with few withdrawals due to lack of efficacy.
- Participants originally allocated to placebo showed substantial improvements in PASI and PGA response at 52 weeks, after crossing over to ustekinumab treatment at week 12. There

was some indication that the gains were greater among those received standard dosage ustekinumab than those received half-standard dosage treatment.

- There were no notable differences between the ustekinumab and placebo in terms of short-term and longer-term adverse events, though the number of observations was small and longest the follow-up time was just 60 weeks. Few participants withdrew due to adverse effects.

4.6 Additional observational evidence

4.6.1 Retrospective case series

Two retrospective case series reported the use of adalimumab, etanercept and ustekinumab from 4 to 165 weeks in children with moderate-to-severe psoriasis.[75, 76] Key characteristics and results from these studies are reported in Table 31.

Garber et al reported a retrospective chart review of 27 participants (19 males, 8 females) attending a single US general dermatology clinic from 2008-2014. Insufficient details were reported to establish how many patients received more than one biologic over this period. Clearance rates (defined as 99% reduction on the simple measure for assessing psoriasis severity; S-MAPA) were reported (see Table 31). No serious adverse events were reported. Though the authors concluded that adalimumab, etanercept and ustekinumab are safe and efficacious in paediatric psoriasis, this study provides insufficient data on the efficacy or safety profiles of these agents in practice.

Klufas et al similarly reported a retrospective case series evaluating 51 children with moderate to severe psoriasis treated with systemic therapies for adverse event occurrence and PGA-measured disease response. For all biologics (alone or in combination with methotrexate), mean PGA values fell at 5-7 months follow-up. 29 adverse events were reported in relation to 80 treatment data points (some patients received more than one biologic); most were minor subjective side effects, with no infections or SAEs reported. Again, limitations in the sample size and study design preclude strong inferences being drawn from these data.

Table 31 Retrospective case series of adalimumab, etanercept, or ustekinumab in children and young people with psoriasis

Study (Year) Country	Treatment (dose)	Number of	Treatment duration (weeks)	Median age (range)	Mean PGA at baseline	Reported outcomes / key adverse events
Garber et al (2015) **USA**	Adalimumab (40mg eow)	7	146	-	-	4/6 achieved clearance; 3 secondary failure, 1 injection site reaction, 3 minor infections†
	Etanercept (50mg weekly)	13	87	-	-	6/9 achieved clearance; 1 injection site reaction, 6 secondary failure, 3 lack of response, 4 minor infections*
	Ustekinumab (45mg at weeks 0 and 4, then every 12 weeks)	3	165	-	-	1/3 achieved clearance
	Adalimumab + Methotrexate	2	11	-	-	1/2 achieved clearance
	Etanercept + Methotrexate	2	121	-	-	2/2 achieved clearance
	Etanercept + Cyclosporine	1	20	-	-	-
Klufas et al (2016) **USA**	Adalimumab (40mg eow)	11	3-134	16.5 (7.0-18.0)	2.4	Mean PGA‡ 0.7; 1 injection site reaction
	Etanercept (25 or 50 mg once or twice weekly)	23	8-135	14.0 (8.0-18.0)	3.0	Mean PGA‡ 1.5; 2 injection site reactions
	Ustekinumab (45mg or 90mg at weeks 0 and 4, then every 12 weeks)	6	4-72	16.5 (7.0-18.0)	2.6	Mean PGA ‡1.5
	Adalimumab (40mg eow) + Methotrexate (7.5 to 15mg weekly)	9	8-118	15.0 (11.0-17.0)	2.4	Mean PGA‡ 1.0; 1 injection site reaction
	Etanercept (50mg once or twice weekly + Methotrexate (7.5 to 15mg weekly)	5	4-30	15.0 (13.0-17.0)	3.1	Mean PGA‡ 1.8

Ustekinumab (45mg at weeks 0 and 4, then every 12 weeks) + Methotrexate (12.5mg weekly)	2	NR	16.5 (16.0-17.0)	3.8	Mean PGA‡ 1.3

*across all participants who received etanercept (n=16); †across all participants who received adalimumab (n=9), ‡at 5-7 months

4.6.2 Registry data

Published findings or papers detailing study design were identified for 16 registries. Information on biologic drug safety in their psoriasis cohorts was published by nine registries, where 11 published articles on biologic efficacy and nine included drug survival data. This does not necessarily mean the other registries did not record these outcomes, but they were not covered in the identified literature output.

4.6.2.1 Registry data for children

Further screening was carried out to find publications with explicit reference to children with psoriasis within each registry; specifically on information on survival of biologic treatment. Two registries (Child-CAPTURE and DERMBIO) were found to include children with psoriasis who were treated with biologics. Child-CAPTURE (Netherlands) contained 7 children treated with etanercept,[77] but did not differentiate between biologic and non-biologic therapies in drug survival analyses. We identified from the 2014 annual report by the DERMBIO (Denmark) registry that there are 37 children enrolled who are undergoing treatment with adalimumab, etanercept, or ustekinumab, though data for this group were not reported separately. Cox regression modelling of covariates in two studies found no significant predictive relationship between patient age and drug survival, suggesting treatment withdrawal rates among children were similar to those in adults.[78, 79]

4.6.2.2 Wider registry data

In one 2015 DERMBIO study following 1277 (predominately adult) psoriasis patients for up to 10 years, median drug survival in etanercept was 30 months (CI 25.1 - 34.9), which was significantly lower than for adalimumab (59 months, CI 45.6 – 72.4) and ustekinumab (median not reached).[78] Year-on-year survival for etanercept (estimated from Kaplan-Meier curve) was 0.7 at one year, 0.53 at year two, and 0.3 at year five, compared to 0.85 after one year, 0.78 at two, and 0.65 at year five for ustekinumab (**Table 32**). Loss of efficacy was the most likely reason for drug discontinuation, but this was of greater significance proportionally in etanercept than in the other biologics analysed.

Findings from the British Association of Dermatologists Biologic Interventions Register (BADBIR) were broadly similar to those seen in the Danish cohort. A study by Warren *et al*. on drug survival over three years in 3523 biologic-naïve patients found that 77% of patients remained on biologic treatment over the first year, falling to 53% by the third year.[80] There were again significant differences in the treatment withdrawal rates between biologics; ustekinumab exhibited the highest first-course survival rate at 0.89 for year one and 0.75 at year three. Adalimumab showed the highest survival of the anti-TNFα drugs, at 0.79 after one year and 0.59 after three. Disregarding the very small population of patients on infliximab, etanercept was consistently the worst-performing in terms of treatment withdrawal; with a one year survival rate of 0.70, dropping to 0.40 at three years (Table 33). Etanercept was also found to be a significant predictor of discontinuation of therapy due to loss of efficacy. Other significant predictors of treatment withdrawal were female gender, smoking status, and a higher baseline DLQI.

Table 32 Survival of first biologic in the DERMBIO registry

Biologic	Drug survival		
	1 year	2 years	5 years
Adalimumab (n=567)	0.77	0.67	0.48
Etanercept (n=364)	0.70	0.53	0.30
Infliximab (n=176)	0.75	0.62	0.43
Ustekinumab (n=170)	0.85	0.78	0.65

Table 33 Survival of first biologic in the BADBIR registry

Biologic	Drug survival		
	1 year	2 years	3 years
Adalimumab (n=1879)	0.79	0.67	0.59
Etanercept (n=1098)	0.70	0.51	0.40
Infliximab (n=96)	0.65	0.50	0.35

Ustekinumab (n=450)	0.89	0.82	0.75

4.7 Overview of RCT results

Despite differences in inclusion criteria, the relative lack of younger children in the in the adalimumab and etanercept trials meant that the median age of children across the three trials did not differ greatly. Similarly, measures of disease duration and the component measures of severity did not appear to differ markedly between the three trials. Few participants in any trial had prior experience of biologic treatment.

The biologics and their respective comparators in relevant RCTs in children and young people are summarised in Table 34.

Table 34 summary of biologics and their comparators based on RCTs

Treatment	Class of therapy	Dosage	Comparator
Adalimumab (ADA)	Anti TNF-α	• Standard (0.8mg/kg) • Half-standard (0.4mg/kg)	Methotrexate
Etanercept (ETA)	Anti TNF-α	• Standard (0.8mg/kg)	Placebo
Ustekinumab (UST)	Anti IL-12/IL-23	• Standard (0.75mg/kg) • Half-standard (0.375mg/kg)	Placebo

However, there were no head-to-head comparative data available for the three biologics. In addition, while the etanercept and ustekinumab trials had a placebo as a common comparator, the adalimumab trial used methotrexate as a comparator.

Table 35 shows the relative effects for all three biologics from the three RCTs. However, an implicit comparison is not useful for the purposes of the decision analytic modelling required for the economic evaluation. Section 5 therefore describes a formal evidence synthesis to inform the relative efficacy of these interventions.

Table 35 Relative risks of PASI outcomes for biologic trials in children

Trial	Relative risk and 95% CI		
	PASI 50	**PASI 75**	**PASI 90**
Adalimumab vs. Methotrexate (M04-717); 16 weeks			
Standard dosage (0.8mg/kg)	[redacted]	1.79 (1.04 to 3.06)*	1.34 (0.61 to 2.95)
Half-standard dosage (0.4mg/kg)	[redacted]	1.34 (0.75 to 2.42*	1.42 (0.65 to 3.08)
Etanercept vs. placebo (20030211); 12 weeks			
Standard dosage (0.8mg/kg)	3.26 (2.26 to 4.71)	4.95 (2.84 to 8.65)*	4.10 (1.88 to 8.95)
Ustekinumab vs. placebo (CADMUS); 12 weeks			
Standard dosage (0.75mg/kg)	2.99 (1.79 to 4.97)	7.5 (2.9 to 19.1)	11.0 (2.8 to 43.5)
Half-standard dosage (0.375mg/kg)	2.72 (1.62 to 4.48)	7.3 (2.8 to 18.6)	10.0 (2.5 to 39.8)

*stated as primary outcome

5 Evidence synthesis to inform the relative efficacy of the interventions

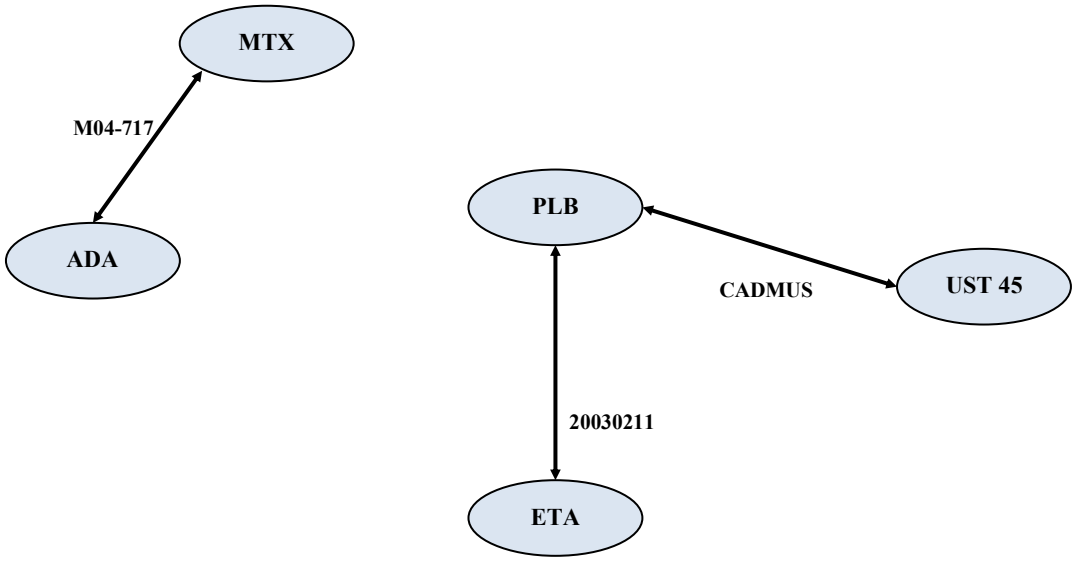
5.1 Overview

RCTs of the effectiveness of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people have been discussed and summarised in Section 4. The efficacy endpoint consistently reported across the trials was PASI response rates, which is the key efficacy parameter used in the economic analysis. In order to determine the relative efficacy of the interventions, it would be ideal to have the results from good quality adequately powered RCTs comparing the active treatments with one another in the population of children and young people. However, the evidence base presents a number of challenges for informing the relative efficacy of the interventions in this population. Firstly, the interventions of interest have not been directly compared in head-to-head RCTs. Secondly, no common comparator (e.g. placebo) exists across all the RCTs. Thirdly, the age of the populations included in the trials differs across the RCTs and the interventions of interest have marketing authorisation for different age groups. Fourthly, the severity of plaque psoriasis is defined differently in the populations included in the RCTs and the interventions are licensed for different levels of severity in children and young people. These challenges mean that a number of assumptions are required in order to inform the benefits of the active treatments relative to the appropriate comparators and each other.

Meta-analysis using mixed treatment comparisons enables the estimation of different parameters from several studies with similar comparisons to be combined when direct evidence on comparisons of interest is absent or sparse. The statistical synthesis method of network meta-analysis (NMA) enables the comparison of multiple treatment options using both direct comparisons of interventions from RCTs and indirect comparisons across trials based on a common comparator. [81, 82] As suggested by the term, NMA needs a 'network of evidence' to be established between all of the interventions of interest. However, with neither direct comparisons nor a common comparator in the evidence base for children and young people from which to derive indirect comparisons of comparator treatments, the evidence base is structured as a 'disconnected network').

In the following sections we build on the challenges listed above by firstly exploring the treatment efficacy by age subgroup and by performing a naive indirect treatment comparison of adalimumab and etanercept, highlighting the limitations of such analysis. Furthermore, a framework of analysis is described that uses different levels of evidence from the adult population to specifically address the issue of having a disconnected network structure.

Figure 3 Network of evidence for children and young people



ADA=adalimumab 0.8mg/kg, max 40 mg/week; MTX=methotrexate 0.1-0.4mg/kg/week; ETA=etanercept 0.8mg/kg, max 50mg/week; UST 45 =ustekinumab 0.75mg/kg or 45mg/week; PLB=placebo. Trial names are stated where trial evidence informs the network treatment link.

5.2 Efficacy differences by age subgroup

Adalimumab, etanercept and ustekinumab have marketing authorisation for different age groups in the population of children and young people (≥ 4 years for adalimumab, ≥ 6 years for etanercept, and ≥ 12 years for ustekinumab). This is the result of variation in the age of the patient populations included in the RCTs for these interventions. Furthemore, the trial population for etanercept also includes patients younger than the licensed age group (i.e. the inclusion criteria for the etanercept trial is children and adolescents aged 4-17 years old and 9 children were included in the trial who were younger than the subsequent licensed age group of 6 years old and over). In order to establish the relative efficacy of the interventions it is necessary to either i) assume that the PASI response rates for the treatments are independent of age within the full population of children and young people; or ii) consider outcomes in a subgroup population by age.

Section 4 presents the PASI response rates for each study by age subgroup. On inspection of the PASI response rates, there does not appear to be a pattern across the efficacy outcomes for the different age subgroups within the same study which could explain any differences in efficacy as a result of age. This would seem to suggest that the PASI response rates for the study as a whole are reflective of the outcomes expected in a particular subpopulation by age. This was examined further by using standard parametric statistical tests to assess equality of proportions (i.e. probability of PASI 50/75/90 response rates) across different age subgroups within each study. Within each study, there were no statistically

significant differences identified across the age subgroups for each of the PASI response rates of 50, 75 or 90 (see Table 36). Therefore, in order to compare the relative efficacy of the interventions, it is assumed that the PASI response rates for the treatments are independent of age within the full population of children and young people and that the studies are comparable for this population.

Table 36 Hypothesis testing results of age subgroup PASI response by study and by treatment arm

Study: M04-717	**All**	**Age subgroups**					**Hypothesis test of equality of proportions, p-value**
		4-6 years	**> 6-9 years**	**> 9-12 years**	**>12-15 years**	**> 15 years**	
Adalimumab	**n=38**	**n=0**	**n=7**	**n=8**	**n=13**	**n=10**	
PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.72**
PASI 75	57.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.84**
PASI 90	28.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.47**
Methotrexate	**n=37**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**------**
PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.91**
PASI 75	32.4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.44**
PASI 90	21.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**p = 0.77**
Study: CADMUS	All	**Age subgroups**					**Hypothesis test of equality of proportions, p-value**
		<= 15 years		**> 15 years**			
Placebo	**n=37**	[redacted]		[redacted]			
PASI 50	[redacted]	N/A		N/A			N/A
PASI 75	[redacted]	[redacted]		[redacted]			**p = 0.90**
PASI 90	[redacted]	N/A		N/A			N/A
Ustekinumab	**n=36**	[redacted]		[redacted]			**------**
PASI 50	[redacted]	N/A		N/A			N/A
PASI 75	[redacted]	[redacted]		[redacted]			**p = 0.60**
PASI 90	[redacted]	N/A		N/A			N/A
Study: 20030211	**All**	**Age subgroups**					**Hypothesis test of equality of proportions, p-value**
		4-11 years		**> 12-17 years**			
Placebo	**n=105**	**n=38**		**n=67**			
PASI 50	22.9%	21.1%		23.9%			**p = 0.93**
PASI 75	11.4%	10.5%		11.9%			**p = 1.00**
PASI 90	6.7%	N/A		N/A			N/A
Etanercept	**n=106**	**n=38**		**n=68**			**------**
PASI 50	74.5%	76.3%		73.5%			**p = 0.93**
PASI 75	56.6%	57.9%		55.9%			**p = 1.00**
PASI 90	27.4%	N/A		N/A			N/A

Adalimumab 0.8mg/kg, max 40 mg/week; Methotrexate 0.1-0.4mg/kg/week; Etanercept 0.8mg/kg, max 50mg/week; Ustekinumab 0.75mg/kg or 45mg/week. N/A= not available

5.3 Indirect treatment comparison

Figure 3 shows that there is no common comparator arm between the adalimumab trial (M04-717) and the trials of etanercept (study 20030211) and ustekinumab (CADMUS), where the former trial is compared against methotrexate (MTX) and the latter trials against placebo. Therefore, it is not possible to establish an indirect comparison between adalimumab and etanercept or ustekinumab without drawing on evidence from other sources (e.g. evidence on the relative efficacy of the interventions in adults) or by creating a common comparator (e.g. assuming that MTX and placebo response rates are exchangeable between the trials). In this section, attention is focused on the indirect comparison that can be established between etanercept and ustekinumab.

An indirect treatment comparison of PASI response rates at 12 weeks was performed between the licensed dose of etanercept (0.8mg/kg up to a maximum dose of 50mg) and ustekinumab (standard dose) using placebo as a common comparator. A Bayesian indirect treatment comparison was undertaken using a probit model for ordered multinomial outcomes of PASI response rates (using a fixed-effect model with multinomial likelihood and a probit link, see appendix 12.8. Table 37 presents the absolute probability of PASI 50, 75 and 90 for etanercept and ustekinumab, while Table 38 presents the relative treatment effect expressed as a relative risk, with 95% Bayesian credible intervals (CrI).

The results demonstrate that ustekinumab appears more effective than etanercept in this population. The PASI 75 absolute probability of response for ustekinumab at 12 weeks is estimated to be 78% (95% CrI 63% to 90%), while for etanercept it is estimated to be 57% (95% CrI 44% to 69%). The 95% credibility intervals are wide and overlap, which reflects the small sample size and limited number of data points used in this analysis. The pooled relative risk (RR) presented in Table 38 for ustekinumab compared to etanercept is 1.41, but is not statistically significant with 95% CrI including 1. The indirect comparison results are in line with the direct evidence from the clinical trials.

Table 37 Absolute probabilities of PASI 50/75/90 results of the indirect treatment comparison for etanercept and ustekinumab

	PASI 50	PASI 75	PASI 90
	Mean (95% CrI)	Mean (95% CrI)	Mean (95% CrI)
Placebo	0.265 (0.190 to 0.346)	0.131 (0.082 to 0.191)	0.042 (0.021 to 0.073)
Etanercept	0.744 (0.631 to 0.841)	0.565 (0.437 to 0.688)	0.330 (0.218 to 0.454)
Ustekinumab SD	0.896 (0.797 to 0.962)	0.781 (0.632 to 0.898)	0.571 (0.395 to 0.742)

SD= Standard dose

Table 38 Relative effect estimates (as relative risks, RR, mean and 95% CrI) for each treatment combination for PASI 75 of the direct trial comparisons (upper diagonal) and of the indirect treatment comparison for etanercept and ustekinumab (lower diagonal)

PLB	**4.95 (2.84 to 8.65)**	**7.50 (2.90 to 19.10)**
4.48 (2.99 to 6.64)	**ETA**	--- ---
6.27 (3.80 to 10.00)	1.41 (0.99 to 1.93)	**UST SD**

PLB = Placebo; ETA = Etanercept 0.8mg/kg, max 50mg/week; USK SD = Ustekinumab 0.75mg/kg or 45mg/week; Lower diagonal: pooled RRs from NMA model. RRs above one favour the row agent; Upper diagonal: RRs from direct comparison. RRs above one favour the column agent; Significant differences in the relative effects between a pair of agents are given in bold.

The company submission for ustekinumab presented a similar indirect treatment comparison for ustekinumab vs. etanercept. The company's analysis produced results for the full population and for a subgroup aged 12-17 years. The results of the company's full population NMA are broadly similar to the results from the AG analysis, e.g. ustekinumab PASI 75 response was estimated to be 79.8% compared to 78.1% in Table 37.

It is important to note that this analysis is limited for a number of reasons:

- It only draws conclusions regarding short-term use of ustekinumab and etanercept in the population of children and young people from the corresponding trials;
- The placebo arm in study 20030211 and CADMUS is assumed to be exchangeable between the trials;
- Inclusion criteria for age were different between the trials;

- There is uncertainty in both the within-trial and between-trial treatment effect estimates due to small sample sizes in the trials;
- There are differences between the trials in terms of baseline characteristics and trial design – these differences have been explored separately in Section 4;
- The indirect treatment comparison does not provide sufficient information to inform the economic analysis since the intervention of adalimumab has been excluded from the analysis due to a lack of common comparator.

As a consequence of the above limitations, in particular, the exclusion of the adalimumab trial evidence (M04-717 study), the results in Table 37 could not be used to assess the relative cost-effectiveness of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people.

5.4 Framework of analysis for informing the relative efficacy of the interventions

Due to the lack of a common comparator arm between the adalimumab trial (M04-717) and the ustekinumab (CADMUS) and etanercept (study 20030211) trials, an analysis plan was developed which entailed exploring the possibility of using PASI response data from adults with moderate to severe plaque psoriasis to fill the evidence gap in the population of children and young people. The use of data from the adult population was supported by our clinical advisor who did not see any reason that precluded the use of the relative effectiveness of the interventions in adults to infer relative effectiveness in children and young people, especially in the absence of evidence in the latter population.

A framework of analysis was thus developed for the NMA approach which allowed all available and relevant evidence to be included was pursued. The framework explored two separate networks which differed according to the extent of evidence utilised from the adult trials:

- The network of trials in children and young people was connected by bringing the *minimum* amount of evidence required from the adult population in order to link the adalimumab trial with the other trials in the disconnected network of Figure 3;
- The network of trials in children and young people was connected by bringing together *all relevant evidence* on the efficacy of all the interventions in adults.

This approach allows treatment specific estimates to be modelled in each population by drawing strength from the network of evidence available. The use of a NMA in preference to pairwise meta-analyses enables the inclusion of all relevant evidence, allowing for precise estimates of treatment effects to be calculated. In addition, the results from the NMA will feed directly into the economic

model to provide the relevant cost-effectiveness of adalimumab, etanercept and ustekinumab against relevant comparators and each other. This approach has been used in previous NICE technology appraisals for the treatment of plaque psoriasis in adults (TA 103, 134, 146, 180, 350, and 368).[83-89]

In each of the NICE technology appraisals in adults the evidence network was updated with new studies reported since the previous appraisal. Therefore we took the most recent single technology appraisals in adults (TA 368 and TA 350) as the starting point for developing a network of studies which could potentially connect the adalimumab trial in children and young people to the other interventions. The Evidence Review Groups (ERGs) for these appraisals generally rated the systematic reviews underpinning the identification of trials for inclusion in the NMA as appropriate, and the evidence networks were subsequently used to inform NICE recommendations in these appraisals. Therefore, it was assumed that the vast majority of relevant evidence for the interventions in adults has been captured in the most recent appraisals in 2015. Relevant adult trials were identified based on the indirect comparison and/or multiple treatment comparisons reported within these appraisals. Lists of excluded trials and reasons for exclusion were also reviewed and relevant trials identified. To supplement this review, the results of a recently published systematic review and NMA, which adjusted for cross-trial differences in the comparative efficacy of biologic treatments for moderate to severe psoriasis in adults, was also examined to cross-check that the majority of relevant studies had been identified in the previous appraisals [90]. Furthermore, we also considered studies reported in the original multiple technology appraisal in adults (TA 103) which included interventions such as methotrexate and cyclosporine. The key inclusion and exclusion criteria used to identify relevant trials for the NMA are shown in Table 39. A list of excluded trials (n=18) and reasons for exclusion can be found in appendix 12.9. Table 40 presents a summary of the trials in adults and the comparator agents in each trial, which was used to inform the NMA.

Table 39 Key inclusion and exclusion criteria for adult studies

Inclusion criteria	Exclusion criteria
• RCT adult studies that considered one or more of the three treatments of interest in recommended dosages: adalimumab, etanercept and ustekinumab; • RCT adult studies that considered the systemic treatment methotrexate - a key comparator in the M04-717 study; • RCT adult studies that directly or indirectly inform comparisons between agents or comparator of interest (adalimumab, etanercept, ustekinumab and methotrexate) or of these against placebo/best supportive care	• RCT adult studies and/or arms that considered irrelevant doses or comparators; • RCT adult studies that reported PASI outcome data at irrelevant time points.

Table 40 Summary of trials in adults selected to inform the NMA

No. trials	Trial reference	Adalimumab (dose)	Etanercept (dose)	Ustekinumab (dose)	Methotrexate	Apremilast	Cyclosporine	Fumaric Acid	Infliximab	Placebo
5	Saurat 2008 [91] (CHAMPION)	✓ (40)			✓					✓
	Gordon 2006 [92]	✓ (40)								✓
	Menter 2008 [93] (REVEAL)	✓ (40)								✓
	Asahina 2010 [94]	✓ (40)								✓
	Bissonnette 2013 [95]	✓ (40)								✓
6	Gottlieb 2003 [96]		✓ (50)							✓
	Leonardi 2003 [97]		✓ (50)							✓
	Elewski 2004 [98]		✓ (50)							✓
	Papp 2005 [99]		✓ (50)							✓
	Van de Kerkhof 2008 [100]		✓ (50)							✓
	PSOR-010 [101] (LIBERATE)		✓ (50)			✓				✓
7	Tsai 2011 [102] (PEARL)			✓ (45)						✓
	Zhu 2013 [103] (LOTUS)			✓ (45)						✓
	Krueger 2007 [104]			✓ (45,90)						✓
	Leonardi 2008 [105] (PHOENIX I)			✓ (45,90)						✓
	Papp 2008 [106] (PHOENIX II)			✓ (45,90)						✓
	Igarashi 2012 [107]			✓ (45,90)						✓

No. trials	Trial reference	Adalimumab (dose)	Etanercept (dose)	Ustekinumab (dose)	Methotrexate	Apremilast	Cyclosporine	Fumaric Acid	Infliximab	Placebo
	Griffiths 2010 [108] (ACCEPT)			✓ (45,90)						
4	Heydendael 2003 [109]				✓		✓			
	Flytstrom 2008 [110]				✓		✓			
	Barker 2011 [111] (RESTORE I)				✓				✓	
	Fallah 2011 [112]				✓			✓		
3	Papp 2012 [113]					✓				✓
	Papp 2015 [114] (ESTEEM I)					✓				✓
	Paul 2015 [115] (ESTEEM II)					✓				✓
2	Guenther 1991 [116]						✓			✓
	Meffert 1997 [117]						✓			✓
1	Altmeyer 1994 [118]							✓		✓
6	Chaudhari 2001 [119]								✓	✓
	Gottlieb 2004 [120] (SPIRIT)								✓	✓
	Reich 2005 [121] (EXPRESS I)								✓	✓
	Menter 2007 [122] (EXPRESS II)								✓	✓
	Torii 2010 [123]								✓	✓
	Yang 2012 [124]								✓	✓

Thirty-four trials in adults with moderate to severe plaque psoriasis were found to be relevant for the NMA; twenty-nine of these considered a placebo arm and six were three-arm trials. As described in the ERG reports for the previous technology appraisals, selected studies were mostly comparable in

terms of their inclusion criteria regarding prior and concomitant medication use. The majority of studies included patients who had failed or had an insufficient response to prior topical therapy and conventional systemic agents such as cyclosporine or methotrexate. Some studies included only biologic-naïve individuals, whereas others allowed prior biologic therapy use. Almost all of the studies did not allow concomitant treatment with systemic agents or phototherapy. A few studies did not mention their criteria regarding concomitant medication use.

The full set of interventions and comparators include adalimumab, etanercept, ustekinumab 45mg, ustekinumab 90mg, apremilast, methotrexate, cyclosporine, fumaric acid, infliximab and placebo. PASI response rates for PASI 50, 75 and 90 from the selected trials were identified and extracted, together with sample size and key baseline patient characteristics by treatment arm. Table 41 presents a summary of the data extracted together with the corresponding data from the three trials in children and young people.

Table 41 Summary of PASI response data used in the NMA and key baseline patient characteristics by treatment arm.

Study reference	Treatment / weekly dose	Population	Time point (weeks)	N	Age (mean years)	Male (%)	PASI 50 (n)	PASI 50 (%)	PASI 75 (n)	PASI 75 (%)	PASI 90 (n)	PASI 90 (%)
20030211 [46, 48-70]	Placebo	Children and young people	12	105	---	50	24	22.9	12	11.4	7	6.7
	Etanercept 0.8mg/kg (max 50mg)		12	106	---	52	79	74.5	60	56.6	29	27.4
CADMUS 2015 [71-74]	Placebo	Children and young people	12	37	16	54	11	29.7	4	10.8	2	5.4
	Ustekinumab SD (max 45mg)		12	36	15	44	32	88.9	29	80.6	22	61.1
M04-717 [36-45]	Adalimumab 0.8mg/kg (max 40mg)	Children and young people	16	37	13	45	30	78.9	22	57.9	11	28.9
	Methotrexate		16	38	13	30	20	54.1	12	32.4	8	21.6
Guenther 1991 [116]	Placebo	Adults	10	11	---	---	1	9.0	---	---	---	---
	Cyclosporine		10	12	---	---	12	100.0	---	---	---	---
Altmeyer 1994 [118]	Placebo	Adults	16	51	---	---	---	---	1	2.0	---	---
	Fumaric acid		16	49	---	---	---	---	12	24.5	---	---
Meffert 1997 [117]	Placebo	Adults	10	43	---	---	---	---	2	4.7	---	---
	Cyclosporine		10	41	---	---	---	---	4	9.8	---	---
Chaudhari 2001 [119]	Placebo	Adults	10	11	45	73	---	---	2	18.2	---	---
	Infliximab 5mg/kg		10	11	51	64	---	---	9	81.8	---	---

Study reference	Treatment / weekly dose	Population	Time point (weeks)	N	Age (mean years)	Male (%)	PASI 50 (n)	PASI 50 (%)	PASI 75 (n)	PASI 75 (%)	PASI 90 (n)	PASI 90 (%)
Gottlieb 2003 [96]	Placebo	Adults	12	55	47	67	6	10.9	1	1.8	0	0.0
	Etanercept 50mg		12	57	48	58	40	70.2	17	29.8	6	10.5
Heydendael 2003 [109]	Methotrexate	Adults	16	43	42	65	---	---	26	60.5	---	---
	Cyclosporine		16	42	38	69	---	---	30	71.4	---	---
Leonardi 2003 [97]	Placebo	Adults	12	166	46	63	24	14.5	6	3.6	1	0.6
	Etanercept 50mg		12	162	45	67	94	58.0	55	34.0	19	11.7
Elewski 2004 [98]	Placebo	Adults	12	193	45	64	18	9.3	6	3.1	1	0.5
	Etanercept 50mg		12	196	45	65	126	64.3	67	34.2	2	1.0
Gottlieb 2004 [120] (SPIRIT)	Placebo	Adults	10	51	45	61	11	21.6	3	5.9	1	2.0
	Infliximab 5mg/kg		10	99	44	74	96	97.0	87	87.9	57	57.6
Papp 2005 [99]	Placebo	Adults	12	193	44	64	18	9.3	6	3.1	1	0.5
	Etanercept 50mg		12	196	46	65	126	64.3	67	34.2	21	10.7
Reich 2005 [121] (EXPRESS)	Placebo	Adults	10	77	44	79	6	7.8	2	2.6	1	1.3
	Infliximab 5mg/kg		10	301	43	69	274	91.0	242	80.4	172	57.1
Gordon 2006 [92]	Placebo	Adults	12	52	43	65	7	13.5	2	3.8	0	0.0
	Adalimumab 40mg		12	45	46	71	34	75.6	24	53.3	11	24.4
Krueger 2007 [104]	Placebo	Adults	12	64	44	72	7	10.9	1	1.6	1	1.6
	Ustekinumab 45mg		12	64	45	61	59	92.2	43	67.2	28	43.8

Study reference	Treatment / weekly dose	Population	Time point (weeks)	N	Age (mean years)	Male (%)	PASI 50 (n)	PASI 50 (%)	PASI 75 (n)	PASI 75 (%)	PASI 90 (n)	PASI 90 (%)
	Ustekinumab 90mg		12	64	44	81	59	92.2	52	81.3	33	51.6
Menter 2007 [122] (EXPRESS II)	Placebo	Adults	10	208	44	69	---	---	4	1.9	1	0.5
	Infliximab 5mg/kg		10	314	45	65	---	---	237	75.5	142	45.2
Flytstrom 2008 [110]	Methotrexate	Adults	12	37	48	76	24	64.9	9	24.3	4	10.8
	Cyclosporine		12	31	45	87	27	87.1	18	48.6	9	24.3
Leonardi 2008 [105] (PHOENIX I)	Placebo	Adults	12	255	45	72	26	10.2	8	3.1	5	2.0
	Ustekinumab 45mg		12	255	46	69	213	83.5	171	67.1	106	41.6
	Ustekinumab 90mg		12	256	45	68	220	85.9	170	66.4	94	36.7
Menter 2008 [93] (REVEAL)	Placebo	Adults	16	398	45	65	60	15.1	28	7.0	8	2.0
	Adalimumab 40mg		16	614	44	67	667	81.9	578	71.0	366	45.0
Papp 2008 [106] (PHOENIX II)	Placebo	Adults	12	410	47	69	41	10.0	15	3.7	3	0.7
	Ustekinumab 45mg		12	409	45	69	342	83.6	273	66.7	173	42.3
	Ustekinumab 90mg		12	411	47	67	367	89.3	311	75.7	209	50.9
Saurat 2008 [91] (CHAMPION)	Placebo	Adults	16	53	41	66	16	30.2	10	18.9	6	11.3
	Adalimumab 40mg		16	108	43	65	95	88.0	86	79.6	55	50.9
	Methotrexate		16	110	42	66	68	61.8	39	35.5	15	13.6
Van de Kerkhof 2008 [100]	Placebo	Adults	12	46	44	54	4	8.7	1	2.2	1	2.2
	Etanercept 50mg		12	96	46	62	66	68.8	36	37.5	13	13.5

Study reference	Treatment / weekly dose	Population	Time point (weeks)	N	Age (mean years)	Male (%)	PASI 50 (n)	PASI 50 (%)	PASI 75 (n)	PASI 75 (%)	PASI 90 (n)	PASI 90 (%)
Asahina 2010 [94]	Placebo	Adults	16	46	44	89	9	19.6	2	4.3	0	0.0
	Adalimumab 40mg		16	43	44	83	35	81.4	27	62.8	17	39.5
Griffiths 2010 [108] (ACCEPT)	Ustekinumab 45mg	Adults	12	209	45	64	182	87.1	141	77.5	76	53.9
	Ustekinumab 90mg		12	347	45	67	319	91.9	256	80.3	155	60.5
Torii 2010 [123]	Placebo	Adults	10	19	43	74	2	10.5	0	0.0	0	0.0
	Infliximab 5mg/kg		10	35	47	63	29	82.9	26	68.6	19	54.3
Barker 2011 [111] (RESTORE I)	Methotrexate	Adults	16	215	42	69	130	60.5	90	41.9	41	19.1
	Infliximab 5mg/kg		16	653	44	67	567	86.8	508	77.8	356	54.5
Fallah 2011 [112]	Methotrexate	Adults	12	27	41	59	15	55.6	6	22.2	2	7.4
	Fumaric acid		12	27	43	74	11	40.7	5	18.5	1	3.7
Tsai 2011 [102] (PEARL)	Placebo	Adults	12	60	40	88	8	13.3	3	5.0	1	1.7
	Ustekinumab 45mg		12	61	41	82	51	83.6	41	67.2	30	49.2
Igarashi 2012 [107]	Placebo	Adults	12	31	49	84	4	12.9	2	6.5	1	3.2
	Ustekinumab 45mg		12	64	45	83	53	82.8	38	59.4	21	32.8
	Ustekinumab 90mg		12	62	44	76	52	83.9	42	67.7	27	43.5
Papp 2012 [113]	Placebo	Adults	16	88	44	60	22	25.0	5	5.7	1	1.1
	Apremilast		16	88	44	57	53	60.2	36	40.9	10	11.4
Yang 2012 [124]	Placebo	Adults	10	45	40	78	6	13.2	1	2.2	0	0.0

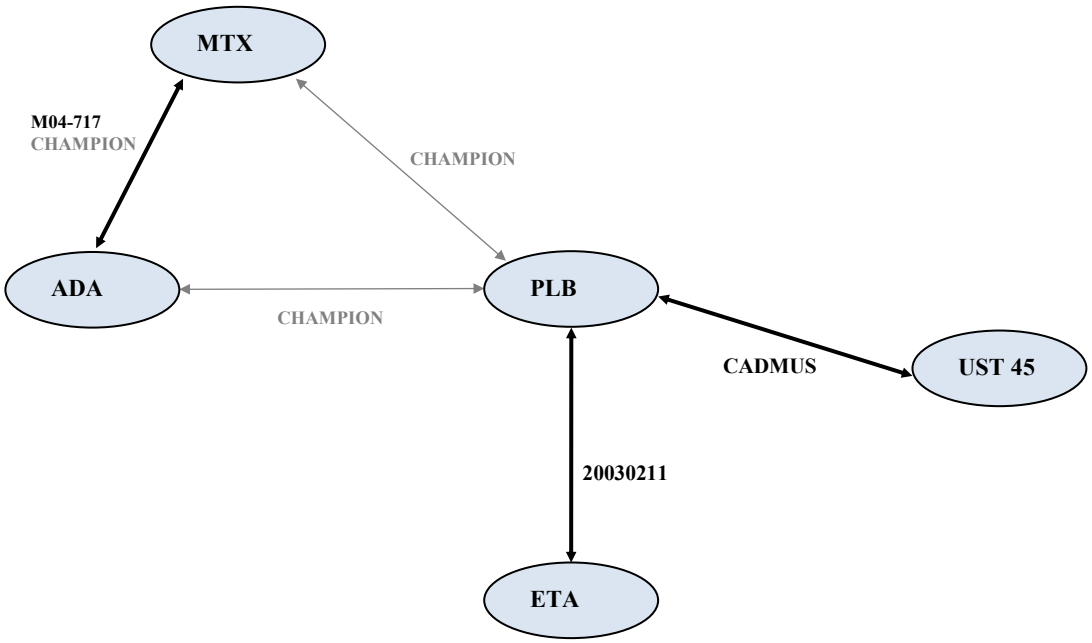
Study reference	Treatment / weekly dose	Population	Time point (weeks)	N	Age (mean years)	Male (%)	PASI 50 (n)	PASI 50 (%)	PASI 75 (n)	PASI 75 (%)	PASI 90 (n)	PASI 90 (%)
	Infliximab 5mg/kg		10	84	39	71	79	94.0	68	81.0	48	57.1
Bissonnette 2013 [95]	Placebo	Adults	16	10	57	60	---	---	2	20.0	---	---
	Adalimumab 40mg		16	20	56	85	---	---	14	70.0	---	---
Zhu 2013 [103] (LOTUS)	Placebo	Adults	12	162	40	78	32	19.8	18	11.1	5	3.1
	Ustekinumab 45mg		12	160	49	84	146	91.3	132	82.5	107	66.9
Papp 2015 [114] (ESTEEM I)	Placebo	Adults	16	282	47	69	48	17.0	15	5.3	1	0.4
	Apremilast		16	562	46	67	330	58.7	186	33.1	55	9.8
Paul 2015 [115] (ESTEEM II)	Placebo	Adults	16	137	46	73	27	19.7	8	5.8	1	0.7
	Apremilast		16	274	45	64	152	55.5	79	28.8	24	8.8
PSOR-010 [101] (LIBERATE)	Placebo	Adults	16	84	---	---	28	33.3	10	11.9	---	---
	Etanercept 50mg		16	83	---	---	69	83.1	40	48.2	---	---
	Apremilast		16	83	---	---	---	---	33	39.8	---	---

Outcome data measured at weeks 10-16 was generally used with preference for data at 12 weeks if outcomes were reported at multiple time points. SD = standard dose

5.4.1 NMA using minimum evidence from the adult population

The disconnected network of evidence in children and young people was connected in the first instance by bringing together the minimum amount of evidence required from the adult population in order to link the adalimumab trial with the other trials (Figure 4). Among the studies presented in **Table 40**, there was only one trial in adults which could directly connect methotrexate with placebo and adalimumab with placebo (CHAMPION [91]). There were a number of trials comparing adalimumab with placebo alone but inclusion of these trials would mean that methotrexate is only connected indirectly through adalimumab and placebo, potentially undermining the evidence from M04-717 on this agent. Therefore, the CHAMPION study represented the best way to connect adalimumab and methotrexate to etanercept and ustekinumab using the least amount of evidence drawn from the adult population.

Figure 4Network of evidence using minimum evidence from the adult population



ADA=adalimumab 0.8mg/kg, max 40 mg/week; MTX=methotrexate 0.1-0.4mg/kg/week; ETA=etanercept 0.8mg/kg, max 50mg/week; UST 45 =ustekinumab 0.75mg/kg or 45mg/week; PLB=placebo. Trial names are stated where trial evidence informs the network treatment link.

In the CHAMPION study, the primary efficacy endpoint was the proportion of individuals achieving PASI 75 at 16 weeks. Adalimumab was found to have significantly greater efficacy (79.6% achieving PASI 75) compared with either methotrexate (35.5%) or placebo (18.9%). PASI outcome data and

key baseline characteristics for the CHAMPION study can be found in Table 41. The average age of patients recruited in CHAMPION was approximately 42 years of age. CHAMPION is a larger trial compared to the trials in children and young people (n=271 vs. n=75 (M04-717)), with approximately 10-20% higher proportion of males.

The PASI 75 response rates for adalimumab and methotrexate in CHAMPION are similar to those reported in study M04-717 in children and young people. An important difference between the CHAMPION study and the trials in children and young people is the observed placebo effect for the primary endpoint of PASI 75. While for study 20030211 and CADMUS the proportion of individuals achieving PASI 75 in the placebo arms was approximately 11%, the proportion observed in placebo-treated patients in the CHAMPTION study was approximately 19%. The authors of the CHAMPION study identified two reasons for this anomalous placebo response: i) placebo response rates are generally greater in European studies; and ii) that the observed placebo response may partly have resulted from the correction of an underlying folate deficiency following folate supplementation, which was mandatory for all study patients.

Given that the CHAMPION study connects the adalimumab trial in children and young people (M04-717) to etanercept and ustekinumab through placebo, it is important to ensure that the differences in placebo response rates do not 'artificially' inflate or deflate the PASI response outcomes for the interventions of interest. Therefore, as well as using a baseline *unconstrained* prediction model, whereby baseline risk (placebo response rates) is predicted using evidence from all studies included in the network (analysis 1a), a baseline *constrained* prediction model was also considered, whereby placebo response rates are predicted based on the placebo-arm trials in children and young people only (i.e. study 20030211 and CADMUS) (analysis 1b). As the number of trials to inform each treatment effect is small, a fixed-effect model was used. The results of this analysis are presented in Section 5.4.3 (Results).

5.4.2 NMA using full evidence from the adult population

The second approach to the NMA involved connecting the evidence from the adalimumab trial in children and young people to the evidence from the other trials (study 20030211 and CADMUS) by drawing strength from the full network of evidence available in adults. The relative efficacy of adalimumab, etanercept and ustekinumab has been evaluated extensively in adults with moderate to severe plaque psoriasis. Given the limited evidence base in children and young people, and the expectation that the difference in response rates between the interventions is predominantly due to the relative efficacy of the biologics rather than age or other patient characteristics, it would seem appropriate to combine the weight of evidence from all relevant trials and comparators, including

those in adults. This wider network of evidence can be used to facilitate an indirect comparison of adalimumab with etanercept and ustekinumab by examining the relationships that exist between the different treatments and study populations and drawing strength from the full network of evidence.

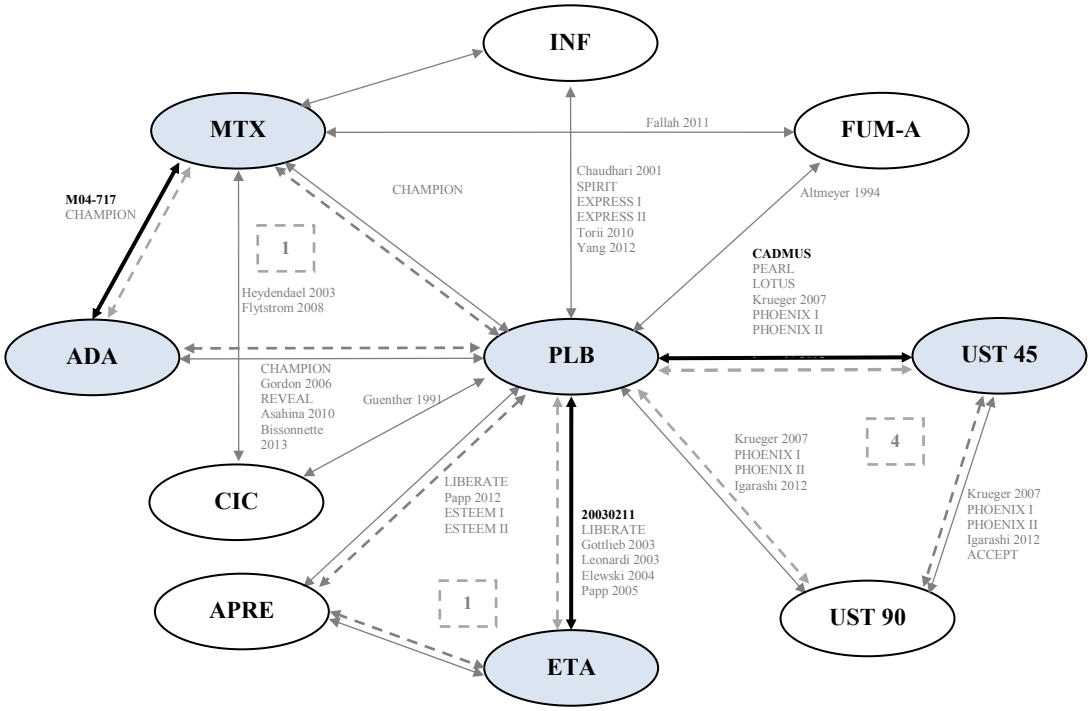
Figure 5 presents the full network of evidence in both populations. This wider network considers 9 active treatments and placebo, which encompass 37 RCTs in total (3 in children and young people and 34 in adults) with 6 of these being three-arm trials. The majority of network links ('head-to-head trial comparisons') are populated by more than one study.

A Bayesian evidence synthesis approach was employed which draws on the relationships that exist between treatments and populations, while also preserving differences that exist across populations by adjusting for age and placebo response rates. NMA meta-regression models on baseline risk (i.e. placebo response) were explored. [90] These models impose a common interaction effect between baseline risk and relative effectiveness that account for variation in reference arm response across trials. NMA meta-regression models that explore variability caused by age effects were also implemented. These models impose an age group interaction effect at the study level (binary variable: 1 if study is from a children or young adult population, 0 otherwise) that attempts to explain the heterogeneity between treatment effects when considering both adult treatment response data and data from children and young people. The age adjusted meta-regression models provided pooled PASI response rates by treatment for both children and young people and adults. A common treatment by age interaction effect was imposed. The common interaction assumption is the least data demanding (i.e. only one extra parameter is needed to be estimated), but it also imposes the strongest assumption as it implies that the same age group effect exists regardless of treatment (excluding placebo).[125] For example, if the age interaction effect (of children and young people vs. adults) is estimated to be positive and of average magnitude 25% on the absolute PASI scale, PASI response rates in children and young people will be approximately 25% higher, on average, relative to adults, irrespective of treatment. Further details on the implemented synthesis models and their assumptions, including WinBUGS code can be found in appendix 12.9.

Fixed- and random-effects analyses were explored for two separate scenarios: (a) meta-regression model with adjustment for baseline risk (i.e. placebo response rates); and (b) meta-regression model with adjustment for baseline risk and age. Irrespective of scenario and according to deviance information criterion (DIC) and total residual deviance statistics, the random-effects approach provided a better fit to the data than the fixed-effect counterpart. Therefore, only results from the random-effects model are presented and discussed herein. Results from the fixed-effect model can be found in appendix 12.10.

Table 42 provides a summary of the models implemented together with the key modelling assumptions. As no evidence was found to support the existence of a class effect, all models considered treatments to be independent of each other. Models in analyses 2a and 2b assume treatments are independent of each other, but treatment effects are adjusted with the trial-specific baseline effects assuming a common interaction term. In addition, models in analysis 2b adjust for trial-specific age effects, also assuming a common interaction term. This age adjustment enables the estimation of treatment effects separately by age populations (adults and children and young people). All implemented synthesis models assumed fixed effects on PASI response cut-off points.

Figure 5 Wider network of evidence in children and young people and adult populations



ADA=adalimumab 0.8mg/kg, max 40 mg/week; MTX=methotrexate 0.1-0.4mg/kg/week; ETA=etanercept 0.8mg/kg, max 50mg/week; UST 45=ustekinumab 0.75mg/kg or 45mg/week; INF= infliximab 5mg/kg; FUM-A=fumaric acid; CIC=cyclosporine; APRE=apremilast; UST 90=ustekinumab 90mg/week; PLB=placebo. Trial names are stated where trial evidence informs the network treatment link. Discontinued lines indicate where 3-arm trials inform the evidence network, with the number of 3-arm trials stated in a discontinued line box.

Table 42 Summary of models implemented and key modelling assumptions.

Analysis	Study	Meta-regression	Baseline prediction
1a	FE	No adjustment	Unconstrained
1b	FE	No adjustment	Constrained to studies of children and young people

2	RE	No adjustment	Unconstrained
2a	RE	Common interaction term for baseline effect	Unconstrained; baseline adjusted
2b	RE	Common interaction term for baseline effect and for age effect	Unconstrained; baseline adjusted

5.4.3 Results

5.4.3.1 Analysis 1 – Results using minimum evidence from the adult population

Table 43 summarises the results of the NMA in terms of absolute PASI response rates for the unconstrained (no explicit adjustment for differences in placebo response rates across the trials) and constrained (placebo response rates are predicted based on the placebo-arm trials in children and young people only) models. The results of both sets of analyses show that all active treatments are more effective than placebo. In terms of mean response rates, ustekinumab is estimated to have the highest probability of achieving PASI 50 (90%, 95% CrI: 81% to 96%), PASI 75 (79%, 95% CrI: 64% to 90%) and PASI 90 (57%, 95% CrI: 39% to 74%) compared to any of the other treatments, suggesting that it is the most effective intervention. This is followed by adalimumab, etanercept and methotrexate in both sets of analyses, i.e. the ranking of treatments based on mean response rates is unchanged by the different models.

The unconstrained baseline model (analysis 1a), however, predicts a placebo effect for PASI 75 of 20.3% (95% CrI: 14% to 27%) compared to 13.1% (95% CrI: 8% to 19%) for the constrained baseline model. This difference is driven by the CHAMPION study which had a substantially higher placebo response rate of approximately 19% for PASI 75 compared to the placebo response rates observed in the trials of children and young people (approximately 11% in study 20030211 and CADMUS). The constrained baseline model (analysis 1b) adjusts the baseline predictions to consider only placebo effect evidence from trials in the younger population. In this analysis, the mean PASI 75 response rate for placebo is reduced and closer to the observed response in the children and young people trials.

Table 43 NMA results of absolute PASI response for analysis 1a and 1b: probability of achieving PASI 50/75/90

Analysis	1a				1b			
	PASI 50 Mean (95% CrI)	**PASI 75** Mean (95% CrI)	**PASI 90** Mean (95% CrI)	r	**PASI 50** Mean (95% CrI)	**PASI 75** Mean (95% CrI)	**PASI 90** Mean (95% CrI)	r

Placebo	0.371 (0.29 to 0.46)	0.203 (0.14 to 0.27)	0.071 (0.04 to 0.11)	5	0.267 (0.19 to 0.35)	0.131 (0.08 to 0.19)	0.039 (0.02 to 0.07)	5
Etanercept	0.830 (0.73 to 0.91)	0.676 (0.54 to 0.79)	0.431 (0.30 to 0.57)	3	0.747 (0.63 to 0.84)	0.566 (0.43 to 0.69)	0.321 (0.21 to 0.44)	3
Ustekinumab	0.941 (0.87 to 0.99)	0.859 (0.73 to 0.95)	0.677 (0.49 to 0.85)	1	0.901 (0.81 to 0.96)	0.787 (0.64 to 0.90)	0.569 (0.39 to 0.74)	1
Adalimumab	0.832 (0.74 to 0.91)	0.678 (0.56 to 0.79)	0.433 (0.31 to 0.56)	2	0.746 (0.60 to 0.87)	0.567 (0.40 to 0.73)	0.324 (0.19 to 0.49)	2
Methotrexate	0.432 (0.33 to 0.54)	0.251 (0.17 to 0.34)	0.096 (0.06 to 0.15)	4	0.323 (0.20 to 0.47)	0.170 (0.09 to 0.28)	0.057 (0.02 to 0.11)	4
Residual deviance	46.6*	39.7	57.6		46.6*	39.7	57.6	
DIC		158.60				158.60		

r-– ranking of treatments according to point estimates; FE-fixed effect; *Compared with 27 data points. DIC and total residual deviance are marginally lower in analysis 1b than in 1a, implying a better fitting model.

As shown by the credible intervals around the mean response rates, which are wide and overlap, there is uncertainty around these response rates. This is also shown in terms of the relative risks of each treatment compared with placebo and their credibility intervals for the best fitting model 1b (Table 44).

Table 44 Relative effect estimates (as relative risks, RR, mean and 95% CrI) for each treatment combination for PASI 75 of the direct trial comparisons (upper diagonal) and of the NMA results of analysis 1b (lower diagonal)

PLB	**4.95 (2.84 to 8.65)**	**7.50 (2.90 to 19.10)**	--- ---	--- ---
4.37 (3.02 to 6.56)	**ETA**	--- ---	--- ---	--- ---
6.10 (3.84 to 10.01)	**1.39 (1.00 to 1.97)**	**UST 45**	--- ---	--- ---
4.36 (3.10 to 6.31)	1.00 (0.71 to 1.39)	0.72 (0.48 to 1.01)	**ADA**	**0.49 (0.38 to 0.59)**
1.28 (0.78 to 1.98)	**0.29 (0.16 to 0.50)**	**0.21 (0.11 to 0.38)**	**0.29 (0.19 to 0.43)**	**MTX**

PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate; Lower diagonal: pooled RRs from NMA model. RRs above one favour the row agent; Upper diagonal: RRs from direct comparison (pooled using fixed-effects when multiple studies exist). RRs above one favour the column agent; Significant differences in the relative effects between a pair of agents are given in bold.

5.4.3.2 Analysis 2 – Results using all relevant evidence from the adult population

Table 45 summarises the absolute PASI response rates from the NMA which uses the full network of evidence in both populations for the unadjusted random-effects model (analysis 2). Relative treatment effects for analysis 2 and for PASI 75 response are presented in Table 46. The random-effects approach outperformed the fixed-effect one in terms of model fit, suggesting that accounting for between-study heterogeneity is an important factor ($\tau^2 = 0.02$).

The results of this analysis suggest that ustekinumab is the most effective intervention with the highest mean probability of PASI response (PASI 75: 73%, 95% CrI: 67% to 79%), followed by adalimumab (PASI 75: 63%, 95% CrI: 55% to 70%), etanercept (PASI 75: 40%, 95% CrI: 34% to 47%) and methotrexate (PASI 75: 34%, 95% CrI: 25% to 42%). Ustekinumab is statistically significantly more effective than any other agent based on relative effect estimates for PASI 75 (vs. etanercept, RR 1.78, 95% CrI 1.50 to 2.12; vs. adalimumab, RR 1.15, 95% CrI 1.01 to 1.35) and adalimumab is statistically significantly more effective than etanercept (RR 1.54, 95% CrI 1.25 to 1.88). The estimated pooled placebo absolute effect is in line with that observed, on average, across all studies in all populations.

These unadjusted results, however, do not consider an explicit adjustment for differences in placebo response rates across trials or differences across the populations (i.e. children and young people compared to adults). In the following sections, the results from the adjusted analyses are presented.

Table 45 NMA results of absolute PASI response for analysis 2: probability of achieving PASI 50/75/90

Analysis	2			
	PASI 50 Mean (95% CrI)	**PASI 75** Mean (95% CrI)	**PASI 90** Mean (95% CrI)	r
Placebo	0.141 (0.12 to 0.16)	0.049 (0.04 to 0.06)	0.010 (0.01 to 0.01)	5
Etanercept	0.633 (0.57 to 0.70)	0.404 (0.34 to 0.47)	0.172 (0.13 to 0.22)	3
Ustekinumab	0.885 (0.85 to 0.92)	0.732 (0.67 to 0.79)	0.466 (0.40 to 0.53)	1
Adalimumab	0.818 (0.76 to 0.87)	0.629 (0.55 to 0.70)	0.354 (0.28 to 0.43)	2
Methotrexate	0.562 (0.47 to 0.65)	0.336 (0.25 to 0.42)	0.130 (0.08 to 0.18)	4
Residual deviance	378.1*	355.6	404.0	
DIC		1241.07		

r-– ranking of treatments according to point estimates; *Compared with 209 data points.

Table 46 Relative effect estimates (as relative risks, RR, mean and 95% CrI) for each treatment combination for PASI 75 of the direct trial comparisons (upper diagonal) and of the NMA results of analysis 2 (lower diagonal)

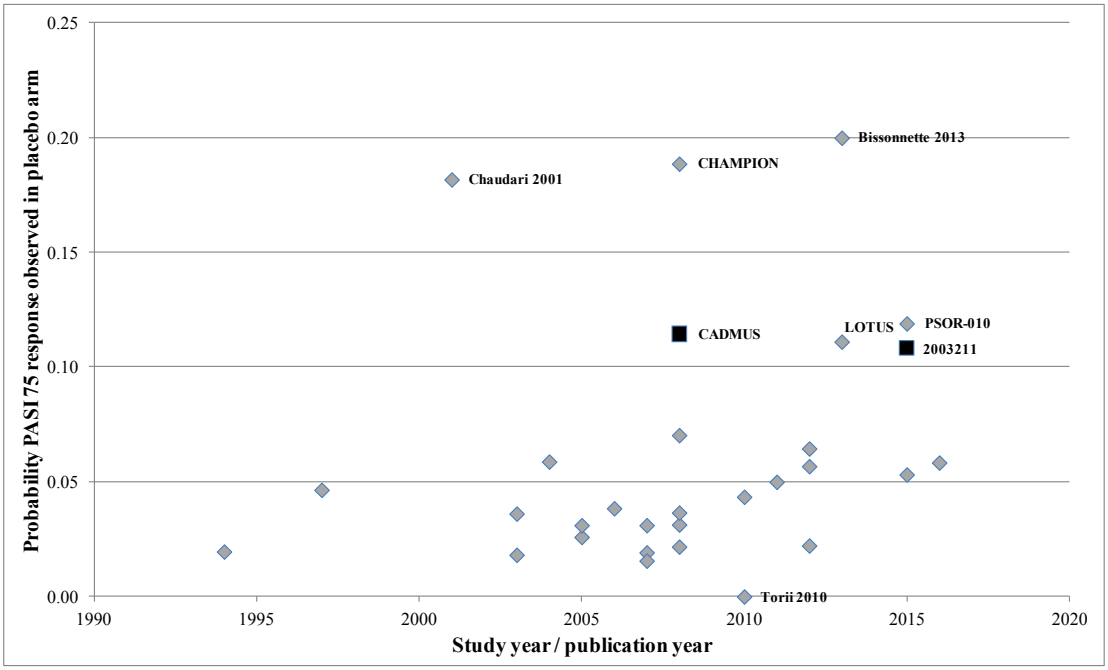
PLB	**9.52 (7.46 to 12.35)**	**14.49 (11.43 to 18.28)**	**8.08 (6.18 to 10.53)**	**1.88 (1.02 to 3.47)**
8.03 (6.61 to 9.64)	**ETA**	--- ---	--- ---	--- ---
14.24 (12.17 to 16.58)	**1.78 (1.50 to 2.12)**	**UST 45**	--- ---	--- ---
12.34 (10.10 to 14.82)	**1.54 (1.25 to 1.88)**	**0.87 (0.74 to 0.99)**	**ADA**	**0.49 (0.38 to 0.59)**
6.72 (4.83 to 8.90)	0.84 (0.60 to 1.11)	**0.47 (0.35 to 0.60)**	**0.55 (0.42 to 0.68)**	**MTX**

PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate; Lower diagonal: pooled RRs from NMA model. RRs above one favour the row agent; Upper diagonal: RRs from direct comparison (pooled using fixed-effects when multiple studies exist). RRs above one favour the column agent; Significant differences in the relative effects between a pair of agents are given in bold.

5.4.3.3 Adjustment for differences in placebo response rates across the trials

The NMA in the full population compares treatment outcomes across a large number of separate clinical trials. The reliability of these comparisons depends on the cross-trial similarity of the patient populations included in the network. An important difference between the included trials is the observed PASI response rates in the placebo arms of the trials, which is a common reference treatment across the majority of the trials. Table 41 showed that the PASI response rates in the placebo arm of the trials ranged from zero to 20% (0% in Torii et al [123] and 20% in Bissonnette et al [95]). All of the trials varied by design, eligibility criteria, prior medication use, average age and other characteristics. All of these variations could contribute to differences in placebo response rates and, therefore, to differences in the relative efficacy of the intervention to placebo. However, there is no systematic way to identify the reasons for these differences. A 'placebo creep' phenomenon has been discussed in the literature, which identifies a relationship between placebo response rates and time since publication of trial results. [126] However, such a phenomenon has not been identified in the trials considered in the NMA (Figure 6). The average PASI 75 response rate in the placebo arm across all trials is 6.2%, while the average rate is 5.9% in studies of adult populations and 11.1% in studies of children and young people. Three adult studies, [91, 95, 119] including CHAMPION, have substantially higher placebo response rates of approximately 18-20% compared to the other studies. Four studies, which include the two trials in children and young people and two in adults [101, 103], have approximately double the average placebo rate.

Figure 6 Probability of PASI 75 response in placebo arms of trials in NMA by study year



It is not clear exactly how these varying placebo rates affect treatment effects; however, it is clear that any differences will affect the relative efficacy of the interventions compared to placebo. Therefore, a potential relationship between baseline risk and relative treatment effect was explored [90] in analysis 2a.

Table 47 and Table 48 present the results of a model that adjusts for differences in placebo response rates. As for the unadjusted analysis (i.e. analysis 2), the baseline adjusted random-effects model was found to fit the data considerably better than the fixed-effect counterpart [DIC: 1303.7 (FE) vs. 1177.6 (RE); total residual deviance: 473.5 (FE) vs. 380.9 (RE)]. Furthermore, the 95% credible intervals for the estimated mean baseline effect derived in the baseline adjusted model do not include zero (-0.93, 95% CrI: -0.97 to -0.88). This suggests that adjusting for baseline risk heterogeneity is important to explain existing between-study variation.

Table 47 NMA results of absolute PASI response for analyses 2a: probability of achieving PASI 50/75/90

Analysis	**2a**			
	PASI 50	**PASI 75**	**PASI 90**	
	Mean (95% CrI)	Mean (95% CrI)	Mean (95% CrI)	r

Placebo	0.151 (0.13 to 0.17)	0.053 (0.04 to 0.06)	0.010 (0.01 to 0.01)	5
Etanercept	0.642 (0.57 to 0.71)	0.414 (0.35 to 0.49)	0.180 (0.12 to 0.25)	3
Ustekinumab	0.882 (0.84 to 0.92)	0.727 (0.66 to 0.79)	0.461 (0.37 to 0.56)	1
Adalimumab	0.839 (0.78 to 0.89)	0.660 (0.58 to 0.74)	0.349 (0.25 to 0.45)	2
Methotrexate	0.570 (0.46 to 0.67)	0.344 (0.25 to 0.44)	0.178 (0.10 to 0.28)	4
Residual deviance	381.7*	357.5	409.4	
DIC		904.5		

r-– ranking of treatments according to point estimates; *Compared with 209 data points.

Table 48 Relative effect estimates (as relative risks, RR, mean and 95% CrI) for each treatment combination for PASI 75 of the direct trial comparisons (upper diagonal) and of the NMA results of analysis 2a (lower diagonal)

PLB	**9.52 (7.46 to 12.35)**	**14.49 (11.43 to 18.28)**	**8.08 (6.18 to 10.53)**	**1.88 (1.02 to 3.47)**
7.86 (6.46 to 9.44)	**ETA**	--- ---	--- ---	--- ---
13.82 (11.70 to 16.32)	**1.77 (1.48 to 2.11)**	**UST 45**	--- ---	--- ---
12.53 (10.34 to 15.01)	**1.60 (1.31 to 1.95)**	0.91 (0.78 to 1.04)	**ADA**	**0.49 (0.38 to 0.59)**
6.52 (4.68 to 8.55)	0.84 (0.58 to 1.12)	**0.47 (0.34 to 0.61)**	**0.52 (0.38 to 0.67)**	**MTX**

PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate. Lower diagonal: pooled RRs from NMA model. RRs above one favour the row agent; Upper diagonal: RRs from direct comparison (pooled using fixed-effects when multiple studies exist). RRs above one favour the column agent; Significant differences in the relative effects between a pair of agents are given in bold.

The results of analysis 2a suggests that ustekinumab is the most effective intervention with the highest mean probability of PASI response (PASI 75: 73%, 95% CrI: 66% to 79%), followed by adalimumab (PASI 75: 66%, 95% CrI: 58% to 74%), and etanercept (PASI 75: 41%, 95% CrI: 35% to 49%) and methotrexate (PASI 75: 34%, 95% CrI: 25% to 44%). Ustekinumab is statistically significantly more effective than etanercept based on relative effect estimates for PASI 75 (RR 1.77, 95% CrI 1.48 to 2.11), but not when compared to adalimumab (RR 1.10, 95% CrI 0.96 to 1.28). Adalimumab is also statistically significantly more effective than etanercept (RR 1.60, 95% CrI 1.31 to 1.95).

5.4.3.4 Adjusting for differences in population and placebo response rates

While evidence from trials in both children and young people and adults contributed to the full network of evidence (effectively assuming independence between age and treatment effectiveness), it is important to recognise that the age of the population could contribute to differences in treatment efficacy. Therefore, analysis 2b adjusts for differences in population and differences in placebo response rates (since the placebo response rates were considerably different in the trials of children and young people compared to adults). Table 49 summarises the results of this analysis in terms of PASI response outcomes for both populations. Table 50 presents the corresponding relative risks for PASI 75 for children and young people.

The model from analysis 2b fits the data as well as model 2a, as both present similar average total residual deviance [380.8 (2b) vs. 381.7 (2a)]. However, DIC is substantially higher for 2b. This suggests that this model is being penalised due to issues of parsimony. The children and young people subgroup effect is estimated not to be statistically significantly different from the adults' subgroup effect, implying that PASI absolute effect distributions of these populations overlap. This is not unexpected due to the limited number of existing studies in the population of children and young people.

The adjustment for population resulted in similar treatment rankings for children and young people when compared with the whole population results (Table 47). The pooled placebo response rate for children and young people is estimated to be higher than for adults (PASI 75: 12%, 95% CrI 5% to 20% in children and young people vs. 5%, 95% CrI 4% to 6% in adults), reflecting the higher placebo response rates observed in the trials for children and young people. This impacts on the efficacy of treatments by substantially increasing the estimated absolute PASI response rates across all treatments, but affecting the relative effects to a smaller extent. On average, PASI 75 response rates are estimated to be 10 to 15% higher in children and young people compared to adults. The treatment rankings, however, remain unchanged. This is consistent with clinical opinion, where efficacy rates are expected to be generally higher in children and young people compared to adults, since the biological interventions tend to work better in individuals with a lower body weight. Also children and young people tend to have less comorbidities and generally get more UV light from participating in outside activities. The credible intervals for PASI 75 for children and young people and adults overlap as shown in Figure 7.

The results of analysis 2b in children and young people suggests that ustekinumab is the most effective intervention with the highest mean probability of PASI response (PASI 75: 82%, 95% CrI:

71% to 90%), followed by adalimumab (PASI 75: 79%, 95% CrI: 64% to 90%), etanercept (PASI 75: 54%, 95% CrI: 39% to 69%) and methotrexate (PASI 75: 49%, 95% CrI: 31% to 68%). The relative efficacy of ustekinumab and adalimumab is similar based on relative effectiveness estimates for PASI 75 (ADA vs. UST 45, RR: 0.96, 95% CrI 0.85 to 1.05). In children and young people, ustekinumab (RR 1.47, 95% CrI 1.28 to 1.92) and adalimumab (RR 1.47, 95% CrI 1.23 to 1.79) are statistically significantly more effective than etanercept.

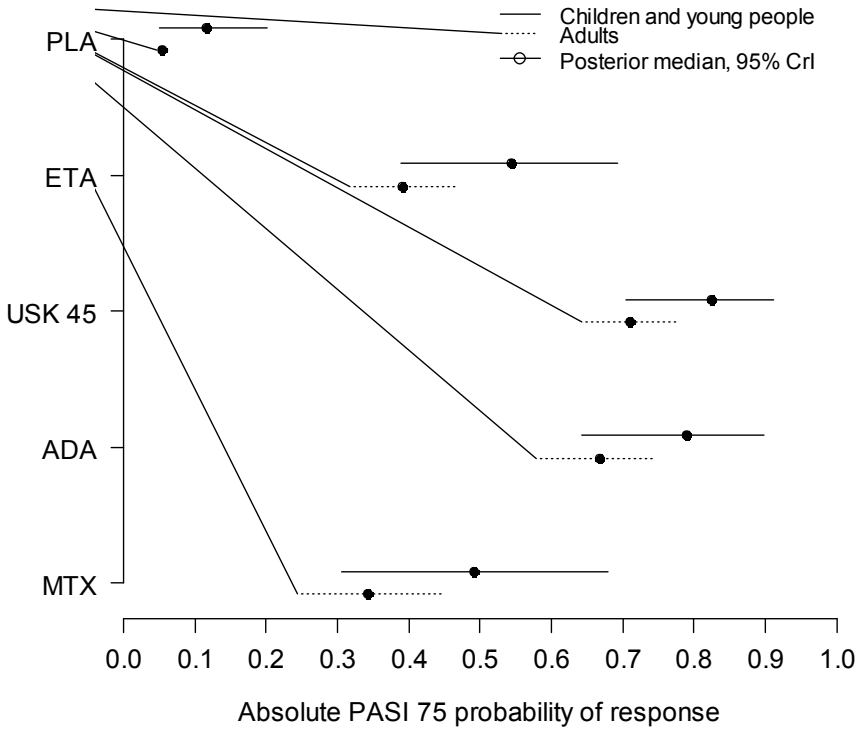
Table 49 NMA results of PASI response for analysis 2bii: probability of achieving PASI 50/75/90 for children and young people and adults

Analysis	Children and young people population				Adults			
	PASI 50	**PASI 75**	**PASI 90**		**PASI 50**	**PASI 75**	**PASI 90**	
2b	Mean (95% CrI)	Mean (95% CrI)	Mean (95% CrI)	r	Mean (95% CrI)	Mean (95% CrI)	Mean (95% CrI)	r

Placebo	0.265 (0.15 to 0.40)	0.115 (0.05 to 0.20)	0.029 (0.01 to 0.06)	5	0.151 (0.13 to 0.17)	0.053 (0.04 to 0.06)	0.010 (0.01 to 0.01)	5
Etanercept	0.752 (0.62 to 0.86)	0.544 (0.39 to 0.69)	0.279 (0.16 to 0.42)	3	0.619 (0.54 to 0.69)	0.390 (0.32 to 0.47)	0.162 (0.12 to 0.22)	3
Ustekinumab	0.934 (0.87 to 0.97)	0.824 (0.71 to 0.91)	0.594 (0.43 to 0.74)	1	0.872 (0.83 to 0.91)	0.711 (0.64 to 0.78)	0.441 (0.36 to 0.52)	1
Adalimumab	0.915 (0.83 to 0.97)	0.790 (0.64 to 0.90)	0.546 (0.37 to 0.72)	2	0.844 (0.78 to 0.90)	0.667 (0.58 to 0.75)	0.393 (0.30 to 0.48)	2
Methotrexate	0.708 (0.53 to 0.85)	0.492 (0.31 to 0.68)	0.240 (0.11 to 0.40)	4	0.567 (0.45 to 0.68)	0.342 (0.24 to 0.45)	0.134 (0.08 to 0.20)	4
Residual deviance	380.8*	356.2	408.6		380.8*	356.2	408.6	
DIC		1229.5				1229.5		

r-– ranking of treatments according to point estimates; *Compared with 209 data points.

Figure 7 Absolute PASI 75 probability of response for children and young people and adult population from NMA model 2b



PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate.

Table 50 Relative effect estimates (as relative risks, RR, mean and 95% CrI) for each treatment combination for PASI 75 of the direct trial comparisons (upper diagonal) and of the NMA results of analysis 2b in the children and young people subgroup of the population (lower diagonal)

PLB	**9.52 (7.46 to 12.35)**	**14.49 (11.43 to 18.28)**	**8.08 (6.18 to 10.53)**	**1.88 (1.02 to 3.47)**
5.09 (3.30 to 8.05)	**ETA**	--- ---	--- ---	--- ---
7.91 (4.46 to 14.14)	**1.54 (1.28 to 1.92)**	**UST 45**	--- ---	--- ---
7.53 (4.37 to 12.98)	**1.47 (1.23 to 1.79)**	0.96 (0.85 to 1.05)	**ADA**	**0.49 (0.38 to 0.59)**
4.55 (3.01 to 6.94)	0.91 (0.66 to 1.15)	**0.59 (0.41 to 0.77)**	**0.62 (0.44 to 0.78)**	**MTX**

PLB = Placebo; ETA = Etanercept; UST 45= Ustekinumab 45; ADA = Adalimumab; MTX = Methotrexate. Lower diagonal: pooled RRs from NMA model. RRs above one favour the row agent; Upper diagonal: RRs from direct comparison (pooled using fixed-effects when multiple studies exist). RRs above one favour the column agent; Significant differences in the relative effects between a pair of agents are given in bold.

A consistency assessment was undertaken which involved excluding the trials of children and young people from the evidence network. This assessment indicated that the results were consistent across populations – see appendix 12.12 for further details.

5.4.4 Summary of findings of relative efficacy from NMA

There is no direct trial evidence that allows establishing the relative effectiveness of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people. Furthermore, there is no common comparator across the three trials, which precludes establishing an indirect comparison between all the interventions without drawing on evidence from other sources, namely from a different age population (i.e. adults).

In this section several NMA analyses were conducted to overcome the challenges in formally assessing the relative efficacy of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people.

First, statistical testing was performed on age subgroup efficacy data from the clinical trials in children and young people to establish whether it is reasonable to assume that the PASI response rates for the treatments are independent of age within the full population of children and young people, as the trials included participants in different age ranges. An indirect treatment comparison based solely

on children and young people trial data for etanercept and ustekinumab was then performed and results presented. However, this analysis was of limited use for the economic analysis as the network did not incorporate the full set of relevant interventions. Finally, a framework of analysis using different levels of evidence from the adult population was developed to address the issue of having a disconnected network structure. Previously appraised adult trial evidence was reviewed and extracted, and assumed exchangeable with children and young adult evidence for inclusion in the evidence base. Two main approaches were considered, one where the network of trials in children and young people was connected by bringing the *minimum* amount of evidence required from the adult population in order to link the three existing trials, and another where *all relevant efficacy evidence* identified in adults was incorporated in the network. For each NMA model fixed- and random-effects model approaches were investigated. The latter approach was shown to be preferable, highlighting that variability across trials was important to account for. The rate of placebo response was identified as a source of heterogeneity. Also, population adjusted models allowed obtaining subpopulation specific estimates for i) children and young people and ii) adults. The different model adjustments were explored and the age and placebo adjusted model identified as the best fitting model. For comparison and comprehensiveness, unadjusted and adjusted model results were also presented.

PASI response results were generally consistent across the different models, adjusted and unadjusted. Ustekinumab was identified as the most efficacious treatment followed by adalimumab and etanercept. Methotrexate was the least efficacious active agent, followed by placebo. The economic model in Section 7 uses the results for the children and young people subgroup of the placebo and population random-effects adjusted NMA (2b, Table 49) to inform the effectiveness estimates. This NMA model was considered to provide the most appropriate set of efficacy estimates to inform the economic analysis because: a) it considers all relevant evidence; b) it adjusts for placebo heterogeneity; c) it adjusts for age effects; and d) it enables the estimation of age subgroup-specific effects. Scenario analyses are also conducted where the results from the unadjusted baseline constrained model with minimum adult evidence (1b, Table 43) are applied in the model. Partial comparisons with direct trial data and the indirect comparison reported in Section 5.3 are also incorporated in a scenario analysis for completeness.

6 Assessment of existing cost-effectiveness evidence

6.1 Introduction

This section aims to provide an overview of existing evidence on the cost-effectiveness of adalimumab, etanercept, ustekinumab and relevant comparators for the treatment of plaque psoriasis in children and young people. The overview includes the company submissions from Janssen (ustekinumab) and AbbVie (adalimumab), while Pfizer (etanercept) did not submit a company submission. An overview of cost-effectiveness evidence from related NICE Technology Appraisals (TAs) for the treatment of plaque psoriasis in adults (TA 103, 134, 146, 180, 350, and 368) is also presented. The differences in the model structures and assumptions used across the studies are examined in order to identify any important differences in approaches and areas of uncertainty. The findings from the review provide the basis for the development of a new decision-analytic model in children and young people reported in Section 7.

6.2 Methods

Systematic searches of the literature were conducted to identify potentially relevant studies for inclusion in the assessment of cost-effectiveness of the interventions against any comparator in children and young people. A broad range of studies was considered for inclusion in the assessment of cost-effectiveness, including economic evaluations conducted alongside clinical trials and modelling studies. Only full economic evaluations that compared two or more options and considered both costs and consequences in children and/or young people were considered. The inclusion criteria allowed for studies in adults as long as data were reported separately for a subpopulation of children and/or young people. The searches were not restricted to biologic therapy or level of disease severity, as a dearth of evidence was anticipated in the population of children and young people.

The following resources were searched for relevant published literature: MEDLINE, MEDLINE In-Process, PubMed, Cumulative Index to Nursing & Allied Health (CINAHL), EMBASE, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, and Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was the same as that reported for the systematic review described in Section 4 (see Appendix 12.1) but was restricted to include studies with ‘cost’ in the title or abstract. Titles and abstracts were assessed independently by two reviewers for inclusion and any discrepancies were resolved by consensus. Additional hand-searching of related TAs in adults was undertaken.

6.3 Results

6.3.1 Identified published studies

A total of 293 unique records were identified from the systematic literature review of existing cost-effectiveness evidence in children and young people, of which only one study subsequently met the inclusion criteria [127]. This study was from the All Wales Medicines Strategy Group (AWMSG) advice for the use of etanercept for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years in NHS Wales who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies [127].

One previous NICE MTA appraisal (TA 103) [88, 89] and five STA appraisals (TA 134, 146, 180, 350, and 368) [84-87, 128] were identified in adults with chronic plaque psoriasis..

6.3.2 Review of existing published cost-effectiveness studies

This review starts with an overview of the AWMSG cost-effectiveness model for the assessment of etanercept in children and adolescents from the age of 8 years and then considers the cost-effectiveness evidence submitted by the companies for ustekinumab and adalimumab in children and young people. The final section provides an overview of the cost-effectiveness modelling used in the previous TAs in adults.

6.3.3 Etanercept AWMSG cost-effectiveness model in children and young people

The only economic model identified in published studies was that reported as part of the AWMSG advice No. 138 for the use of etanercept within NHS Wales for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years. The cost-effectiveness evidence presented was deemed insufficient for AWMSG to recommend the use of etanercept in NHS Wales. The cost-effectiveness modelling is not reported in sufficient detail to be very informative. The AWMSG considered that it was not possible to judge whether or not the analysis presented by the company (Pfizer) in their submission represented the most plausible estimate of the cost-effectiveness of etanercept compared to placebo in this population. This was due to a number of limitations of the economic evidence and decision analytic model submitted by the company.

The economic model was a Markov model with a 28-day cycle length to represent intermittent treatment with etanercept compared to placebo/non-systemic therapy over a 10-year time horizon. The perspective of the evaluation was NHS Wales. For treatment with etanercept 0.8 mg/kg weekly (up to a maximum of 50 mg), individuals were modelled to receive initial therapy for a 'trial period' of 12 weeks, after which their PASI 50 response was used to determine whether or not they were considered responders or non-responders to treatment. Those who achieved a PASI 50 response were considered

responders and continued treatment with continuous etanercept up until week 24. At week 24, those who did not achieve a PASI 50 response discontinued treatment, while those with a PASI response between 50 and 75 remained on continuous etanercept. Of those with PASI 75 response, 25% were assumed to remain on continuous etanercept and the remainder received intermittent etanercept (comprising of a treatment-free period, with treatment reinitiated in those who experience relapse). Non-responders at 12 and 24 weeks were assumed to discontinue treatment.

The effectiveness evidence was sourced from a placebo controlled RCT of etanercept in children and adolescents aged 4-17 years with moderate to severe psoriasis and with previous or current treatment with phototherapy or systemic therapies, or psoriasis considered by the investigator as poorly controlled with topical treatments [56]. The AWMSG estimated that only 57% of the trial population met the licensed indication for etanercept at the time of the submission.

The Health-related quality of life (HRQoL) estimates applied in the model were derived from adult studies of etanercept through the mapping of adult Dermatology Quality of Life Index (DLQI) scores to EQ-5D utility values. The utility gains from baseline were assumed to be independent of treatment and varied according to severity of disease based on PASI response rates. The AWMSG noted that there was no discussion of the uncertainty surrounding the use of utility values from adults to inform the population of children and adolescents.

The drug costs of etanercept were based on the doses used in the RCT in children and adolescents, at 0.8 mg/kg body weight up to a maximum dose of 50mg and delivered in pre-filled syringes. However, the AWMSG noted discrepancies between that reported and the doses used in the model, with a lower dose of 25 mg weekly used in the model for all patients instead of 44% of patients receiving the maximum dose of 50 mg per week and 56% of patients receiving a weekly dose of 0.8 mg/kg in the trial. The median weight in the trial was approximately 60 kg which equates to a median dose closer to 50 mg per week than 25 mg per week. The AWMSG noted that the model was very sensitive to the assumed weekly cost of etanercept.

The number of clinic visits was informed by the British Association of Dermatologist (BAD) guidelines and length of hospital stay for patients who failed treatment was sourced from TA103 for adults. A number of other model parameters were not discussed in the company's submission but appeared to have been sourced from the original NICE MTA (TA 103) in adults. The use of adult data to populate the model and the implications of assuming transferability of adult data to inform the decision problem in children and adolescents did not appear to have been discussed by the company during the AWMSG appraisal.

The results of the company's model showed that etanercept was both less expensive and more effective (i.e. etanercept was the dominant treatment strategy) compared to placebo in children and adolescents of age 8 years and older. Sensitivity analysis was poorly reported and it was uncertain whether probabilistic sensitivity analysis had been performed. The AWMSG considered it impossible to establish whether the base-case analysis represented the most plausible estimate of the cost-effectiveness of etanercept in this population based on the limited information provided in the company's submission. As a result, the AWMSG were unable to recommend etanercept for children and young people due to the uncertainties inherent in the economic model.

6.3.4 Janssen submission for ustekinumab in children and young people

Within their submission supporting this appraisal, Janssen explored the possibility of constructing an economic model to assess the cost-effectiveness of ustekinumab for the treatment of moderate to severe psoriasis in children and young people. However, given the limited clinical evidence identified in their systematic review of effectiveness, Janssen decided not to pursue the development of an economic model. Janssen noted that the only previous economic evaluation in this population (i.e. etanercept for AWMSG) resulted in an adaptation of an adult model in psoriasis and relied on simplifying assumptions for the cost-effectiveness analysis. Therefore, due to the limitations of the evidence base, they concluded that any estimation of the cost-effectiveness of biologics in children and young people with psoriasis will be subject to a number of insuperable uncertainties and will largely be based upon a number of assumptions taken from the adult population. Janssen's submission does, however, provide an overview of the available evidence in children and adults to aid the development of an economic model by the Assessment Group. However, no cost-effectiveness results are presented in Janssen's submission for children and young people.

6.3.5 AbbVie submission for ustekinumab in children and young people

AbbVie undertook a targeted review to identify publications and major HTA bodies that report cost-effectiveness analyses for adalimumab in children and young people with plaque psoriasis. Their submission indicates that only one relevant study was identified (Langley et al 2014).[129] This study estimated the number needed to treat to achieve PASI 75 response based on a Bayesian network meta-analysis of efficacy outcomes for adalimumab, etanercept, infliximab and ustekinumab and evaluated the incremental cost per PASI 75 responder for biologic treatments during the first 10 to 16 weeks of treatment. Based on the results of this study, AbbVie indicates that adalimumab was found to be the most cost-effective treatment option in terms of incremental cost per PASI 75 responder compared to the other biologics. However, the Assessment Group notes that the study by Langley et al 2014 is not based on a population of children and young people and does not present cost-effectiveness of the

biologics in terms of costs and quality-adjusted life years (QALYs) over a time horizon sufficiently long to capture differences between the interventions. Furthermore, the study is only presented in the form of an abstract rather than a full publication, therefore limited details are available to adequately critique the study. AbbVie's submission did not include an economic model for the assessment of adalimumab in children and young people.

6.4 Cost-effectiveness models in adults

6.4.1 Overview

Given that the literature review only identified one unpublished model assessing the cost-effectiveness of etanercept in children and young people and that this model was adapted from TA 103 in adults and largely populated with adult data, additional hand-searching of published documents associated with the previous NICE TAs of plaque psoriasis in adults was carried out. The aim was to examine existing decision-analytic models, to identify important structural assumptions, highlight key areas of uncertainty and outline the potential issues associated with generalising evidence from the adult population to a population of children and young people.

The first NICE TA on biologic therapies for the treatment of psoriasis was a Multiple Technology Appraisal (MTA) examining the cost-effectiveness of etanercept and efalizumab within their licensed indications in adults (TA 103 published in July 2006).[88, 89] As part of this appraisal, the York Assessment Group developed a *de novo* cost-effectiveness model, which was subsequently referred to as 'the York model'. Six subsequent Single Technology Appraisals (STAs) followed TA 103:

- TA 134 – Infliximab for the treatment of adults with psoriasis (published in January 2008);[87]
- TA 146 – Adalimumab for the treatment of adults with psoriasis (published in June 2008);[86]
- TA 180 – Ustekinumab for the treatment of adults with moderate to severe psoriasis (published in September 2009);[85]
- TA 350 - Secukinumab for the treatment of adults with moderate to severe plaque psoriasis (published in July 2015);[84]
- TA 368 - Apremilast for the treatment of adults with moderate to severe plaque psoriasis (published in November 2015).[128]

All of these STAs employed a similar modelling approach to the original York model in TA 103. The only study identified which deviated from the original model was the most recent STA of apremilast (TA 368) which included the modelling of sequences of treatment. Therefore, the main differences between the TAs lies in the evidence base, intervention and comparators rather than any major structural

differences in the modelling approach used. A summary of the York model and the key differences between the assumptions and evidence base used in subsequent adaptations of the model are described in the following section. Table 51 provides an overview of the NICE TAs in adults

Table 51 Overview of NICE TAs for psoriasis in adults

Appraisal	**Etanercept and efalizumab** **TA103**	**Infliximab** **TA134**	**Adalimumab** **TA146**	**Ustekinumab** **TA180**	**Secukinumab** **TA350**	**Apremilast** **TA368**
Modelling approach	Markov model, which became known as the 'York model'	Based on the York model	Based on the York model	Based on the York model	Based on the York model, but explicitly incorporates a decision tree for trial period followed by a Markov model	Based on the York model but with treatment sequences
Intervention	EFA ETA 25 mg BIW continuous ETA 50 mg BIW intermittent	INF	ADA	UST 45 mg UST 90 mg	SEC	Primary analysis: APR→ADA→ ETA → BSC Subgroup analysis: APR → BSC Scenario analysis APR→ADA→ ETA/UST → BSC
Comparators	Primary analysis: BSC Secondary analysis: CS, fumaderm, MTX, INF	EFA ETA 25 mg BIW continuous ETA 25 mg BIW intermittent ETA 50 mg BIW intermittent BSC	INF EFA ETA 25 mg BIW continuous ETA 25 mg BIW intermittent ETA 50 mg BIW intermittent BSC	ADA INF EFA ETA 25 mg BIW continuous ETA 25 mg BIW intermittent ETA 50 mg BIW intermittent BSC	ADA UST INF ETA BSC	Primary analysis: ADA→ ETA → BSC Subgroup analysis: BSC Scenario analysis ADA→ ETA/UST → BSC
Time horizon & justification	10 years NR	10 years Sufficient time for all future costs and	10 years Based on the York model	10 years Based on the York model	10 years Time horizon reflective of treatment duration of	10 years

Appraisal	**Etanercept and efalizumab** **TA103**	**Infliximab** **TA134**	**Adalimumab** **TA146**	**Ustekinumab** **TA180**	**Secukinumab** **TA350**	**Apremilast** **TA368**
		outcomes to be included			moderate to severe plaque psoriasis	Maintain consistency with previous analyses and in the base case majority of patients are on BSC by the end of 10 years
Cycle length	12 months (not explicit)	12 months	12 months	3 months	12 months	28 days
Discount rates	6.0% on costs, 1.5% on QALYs	3.5%	3.5%	3.5%	3.5%	3.5%
Mortality	Not considered	Not considered	Not considered	Not considered	Not considered	All-cause mortality incorporated
HRQoL instrument	DLQI mapped to EQ-5D	Utilities from York model	EQ-5D	DLQI mapped to EQ-5D; SF-6D in sensitivity analysis	EQ-5D	Utilities from York model & EQ-5D; DLQI mapped to EQ-5D
Link between utility and clinical efficacy	EQ-5D mapped from ΔDLQI by ΔPASI (coefficients not reported)	Base-case used the estimates from the York model, but only for those in the 4th quartile of DLQI (worst HRQoL). Additional analyses used utility values estimated by mapping SF-36 data collected in EXPRESS I and II to EQ-5D using an	Trial collected EQ-5D association with DLQI and changes in PASI	EQ-5D mapped from ΔDLQI by ΔPASI (used a mapping algorithm based on the published scatter-plot in the York model): EQ-5D = -0.0162*DLQI + 0.8554	Changes in EQ-5D from baseline at a given time point as function of: - PASI response at that time point - baseline DLQI difference from the pooled mean baseline DLQI - interaction between these terms	Changes in utility associated with changes from baseline PASI were taken from the York model for the DLQI>10 population. For the DLQI≤10, EQ-5D data collected in trials was used; direct link between %ΔPASI and ΔEQ5D in patients with DLQI≤10 The same baseline utility

Appraisal	**Etanercept and efalizumab** **TA103**	**Infliximab** **TA134**	**Adalimumab** **TA146**	**Ustekinumab** **TA180**	**Secukinumab** **TA350**	**Apremilast** **TA368**
		unpublished mapping algorithm.				score (0.7) from a published study was used for both populations.
Total costs	Incremental vs. supportive care: Supportive Care: £0 ETA 25 mg: £7,743 EFA £9,382 ETA 25 mg Continuous: £9,665 ETA 50 mg: £14,860	Incremental vs. supportive care: Continuous ETA 25 mg: £1,531 INF: £4,562	Incremental vs. supportive care: - MTX £-3,844 - Cyclosporine £-1,987 - Supportive Care £0 - ETA intermittent £4,114 - ETA High Intermittent £4,699 - EFA £4,942 - ADA £4,993 - ETA £5,058 - INF £7,736	Incremental vs. supportive care: - Supportive care £0 - EFA £5,264 - ETA 25 mg intermittent £3,989 - ETA 25 mg continuous £4,829 - ETA 50 mg continuous £5,333 - ADA £4,660 - UST £4,615 - INF £6,327	Standard of care: £73,610 ETA 25 mg BIW: £75,788 SEC 300 mg:£76,361 ADA 40 mg: £76,981 UST 45 mg: £79,544 UST 90 mg: £79,732 INF 5 mg/kg: £93,539	DLQI>10 Apremilast sequence: £89,374 Comparator sequence: £92,589
Total QALYs	Supportive Care: 0 ETA 25 mg: 0.116 EFA: 0.112 ETA 25mg continuous: 0.116 ETA 50 mg: 0.123	Continuous ETA 25 mg: 0.089 INF: 0.205	Incremental vs supportive care - MTX 0.129 - Cyclosporine 0.079 - ETA intermittent 0.11	Incremental vs. supportive care: - EFA 0.1308 - ETA 25 mg intermittent 0.1325 - ETA 25 mg continuous 0.1409	Standard of care: 0.97 ETA 25 mg BIW: 1.13 SEC 300 mg: 1.36 ADA 40 mg: 1.22 UST 45 mg: 1.30	DLQI>10 Apremilast sequence: 6.83 Comparator sequence: 6.69

Appraisal	**Etanercept and efalizumab** **TA103**	**Infliximab** **TA134**	**Adalimumab** **TA146**	**Ustekinumab** **TA180**	**Secukinumab** **TA350**	**Apremilast** **TA368**
			- ETA high intermittent 0.123 - EFA 0.124 - ADA 0.164 - ETA 0.134 - INF 0.182	- ETA 50 mg continuous 0.1483 - ADA 0.1502 - UST 0.156 - INF 0.1616	UST 90 mg: 1.33 INF 5 mg/kg: 1.36	

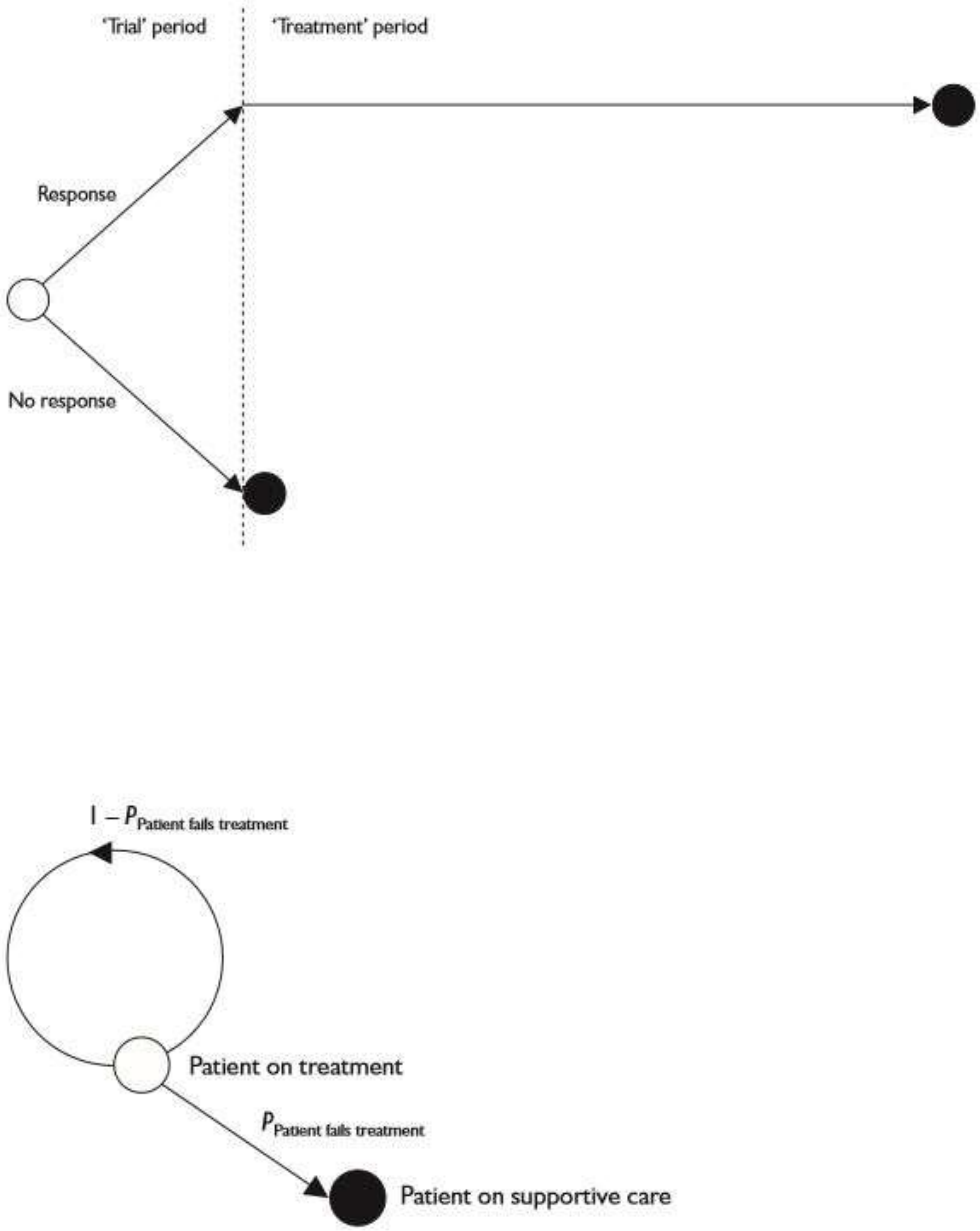
ADA, adalimumab; APR, apremilast; BIW, twice weekly; BSC, Best supportive care; CS, cyclosporine; EFA, efalizumab; ETA, etanercept; INF, infliximab; MTX, methotrexate; NR, not reported; SEC, secukinumab; SF-6D, Short Form–6 Dimension; UST, ustekinumab.

6.4.2 Summary of the York model (TA 103) and subsequent adaptations (TA 134, 146, 180, 350, 368)

The York model was a cohort Markov model, which was developed to estimate the costs and QALYs of etanercept and efalizumab compared to best supportive care (BSC) over a time horizon of 10 years (primary analysis). A secondary analysis was also conducted to compare the interventions with additional systemic therapies of cyclosporine, fumaderm, methotrexate and infliximab. The model adopted the perspective of the UK NHS. The price year for costs was 2004-2005 and an annual discount rate of 6% for costs and 1.5% for outcomes was applied (in line with NICE Guidance at the time of the appraisal).

The model consisted of a two part structure: a 'trial' period for initial response and a 'treatment' period for long-term response to treatment (see Figure 8). The initial response period was used to determine initial response rates and the decision to continue treatment. The duration of the trial period was based on the period over which response was assessed in the efficacy trials for each treatment – this was 12 weeks for etanercept and efalizumab and between 10 and 16 weeks for the other systemic therapies. Individuals with a PASI 75 response were considered 'responders' and continued treatment after the trial period (i.e. they entered the treatment period), while individuals who were 'non-responders' discontinued treatment and received best supportive care. The treatment duration for responding individuals was based on an annual withdrawal rate of 20%. Upon withdrawal, individuals were assumed to receive BSC.

Figure 8 Structure of the York model (Source: TA 103)



The base case analysis considered a single line of therapy consisting of a biologic treatment (etanercept or efalizumab) followed by BSC. While specific sequences of treatments were not considered in the York model, an analysis showing the expected costs and QALYs associated with each treatment option compared to BSC was used to determine the most 'cost-effective order' in which to give the treatments, which varied according to the cost-effectiveness threshold.

The same model structure based on a single line of treatment was used in subsequent TAs of TA 134, 146, 180 and 350, and to a lesser extent in TA 368, where it was only used for the subpopulation of

patients with DLQI ≤ 10. The only difference in the modelling approach across the appraisals was a variation in the cycle length of the Markov model (12 months in TA 134, 146, 350; 3 months in TA 180; and 28 days in TA 368), which was adapted to reflect the different length of the trial periods when treatment response was assessed. All appraisals used a time horizon of 10 years in their base case analysis and used additional scenarios to show the implications of a change in the time horizon.

In TA 368, the company adapted the model structure to allow a comparison of treatment sequences, with up to five sequential lines of treatment. The model structure followed the same approach as the York model but if treatment response was considered inadequate at the end of the trial period, individuals moved into the trial period of the next line of treatment (or to BSC if the end of the treatment sequence had been reached). The company's original economic model only considered apremilast as first treatment in the sequence and compared different treatment sequences with apremilast as an additional line of therapy, rather than replacing an existing biological therapy in the sequence. However, following the Evidence Review Group critique additional analyses were presented which compared the use of apremilast at different positions within a sequence.

6.4.3 Clinical effectiveness evidence in the York model and subsequent appraisals

The response rates used in the York model were based on a Bayesian network meta-analysis comparing the interventions to a broad range of comparators including systemic therapies. An ordered probit model was used to predict PASI 50, PASI 75 and PASI 90 response rates, with PASI 75 used as the primary measure of response at the end of the trial period. If the trial only reported PGA 0/1 (clear or almost clear) as the endpoint, it was assumed to be equivalent to PASI 75 response. A similar Bayesian network meta-analysis was used in subsequent appraisals but was updated with additional evidence as more interventions and comparators became available. There were some differences across the appraisals in terms of how heterogeneity was accounted for in the meta-analysis and whether any adjustment had been made for differences in placebo response rates across the trials.

The effectiveness data was considered to be an area of uncertainty in the previous appraisals, mainly due to the lack of direct head-to-head comparisons between the biologic treatments and the paucity of longer-term data. Although the evidence base expanded over time with many more RCTs included in the network meta-analysis, other concerns were raised relating to differences between the trial populations in the network (e.g. exposure to prior therapies and severity of disease). The definition of placebo or best supportive care across the different trials included in the network meta-analysis was also a contentious issue.

6.4.4 Health-related quality of life in the York model and subsequent appraisals

The utility values associated with treatment in the York model were based on the proportion of patients in the different PASI response categories (<50, 50-75, 75-90, ≥90) and the change in utility from baseline associated with the PASI response category. Utility values were estimated based on a two stage process:

- Mean change in DLQI score between baseline and week 12 in the etanercept trials was estimated for patients with different levels of PASI response and different baseline DLQI scores. This analysis was facilitated by access to patient-level data from the trials, and the placebo and treatment groups were pooled.
- The DLQI data collected in the etanercept trials was then mapped onto EQ-5D values. This was achieved through access to data from the Health Outcomes Data Repository (HODaR), which included patients who had completed both the DLQI and EQ-5D. This data was used to map the change in DLQI associated with PASI responses to changes in EQ-5D utility values.

The two-stage process estimated average EQ-5D gains in utility from baseline for the different PASI response categories: 0.05 for PASI <50, 0.17 for PASI 50-75, 0.19 for PASI 75-90 and 0.21 for PASI ≥90. Estimated gains in utility were also presented for individuals in the fourth quartile of baseline DLQI, i.e. for patients with the worst baseline quality of life. The utility values from the York model were applied directly in TA 368 for the population with DLQI >10 and in TA 134 (values for the fourth quartile of baseline DLQI). For TA 146, TA 350, and TA 368 (scenario analysis), the company had access to EQ-5D data collected in the trials, which were pooled across treatment groups and reported by PASI response category. For TA 180, a similar modelling approach was used but the mapping algorithm used in the York model was applied to ustekinumab trial data to generate utility gains by PASI response category based on DLQI scores in the trial. The utility values applied in the TAs are summarised in Table 52.

None of the TAs included a disutility associated with adverse events from treatment. Only one TA considered a disutility from flare-ups associated with time off treatment with intermittent etanercept (TA 146); however the value applied was not reported in the published documentation.

The modelling approach used in the previous TAs assume that:

- PASI response is a perfect proxy for the change in utility arising from treatment. In other words, by conditioning on PASI response, utility is independent of treatment;
- Similarly, if utility is conditioned on DLQI change, then utility is independent of PASI response;

- The relationship between DLQI and utility is linear;
- The impact of adverse events on health-related quality of life is unimportant.

The main critique of the approach used in the York model relates to the uncertainty introduced by mapping from DLQI to EQ-5D, based on a small sample of 86 patients. The NICE Appraisal Committees favoured the use of EQ-5D data collected directly from the trials when available. Scenario analysis in TA 103 showed that the cost-effectiveness results were very sensitive to the selection of utility values, with greater QALY gains from treatment in the fourth quartile of baseline DLQI (subgroup with worse baseline HRQoL) compared to the overall trial population. Furthermore, since the utility values were conditioned on PASI response at the end of the trial period, these values were extrapolated over the time horizon of the model, which is a key driver of differences between the treatments.

Table 52 Summary of utility values applied in previous TAs

	TA 103		TA 134**	TA 146			TA 180		TA 350***	TA 368			
Population*	All	4th qtl DLQI	4th qtl DLQI	All	DLQI >10	DLQI≤10	DLQI≥10	DLQI≥10	All	DLQI>10		DLQI≤10	
Analysis	BC	SA	BC	SA	BC	SA	BC	SA	BC	BC	SA	BC	SA
BL PASI	-	-	-	-	-	-	-	-	0.642	0.7	0.7	0.7	0.7
Source	NR	NR	NR	NR	NR	NR	NR	NR	RCT	Revicki et al, 2008 [130]			
Incremental gain in utility from baseline													
PASI<50	0.050	0.120	0.120	0.054	0.063	0.045	0.04	0.0016	0.109	0.05	0.0134	0	-0.0024
PASI50-75	0.170	0.290	0.290	0.140	0.178	0.102	0.17	0.0424	0.193	0.17	0.0537	0.02	0.0275
PASI75-90	0.190	0.380	0.380				0.22	0.0970	0.226	0.19	0.1150	0.03	0.0256
PASI>90	0.210	0.410	0.410	0.219	0.308	0.130	0.25	0.1276	0.264	0.21	0.1333	0.07	0.0704
Source	Trial collected DLQI data by PASI category, mapped to EQ-5D		TA103	Pooled trial EQ-5D data. Relationship with PASI established by mixed model.			Trial DLQI data by PASI category, mapped to EQ-5D	RCT sourced SF-6D data by PASI	Pooled trial EQ-5D data and a statistical model predicted	TA103	Pooled trial EQ-5D data by PASI respons	Pooled trial EQ-5D data by PASI respons	Pooled trial EQ-5D data by PASI response category. Includes all available

				using TA103's mapping algorithm.	response category	the change in HRQoL from BL by categories of PASI response.		e category .	e category .	apremilast trial data available

BC; base-case; BL, baseline; NR, not reported; qtl, quartile; RCT, randomised clinical, trial; SA, scenario analysis

*Populations are defined based on baseline DLQI HRQoL; **A scenario analysis with utilities estimates from the all population in TA103 was also conducted; ***A scenario analysis with utilities estimates from the all population in TA146 was also conducted.

6.4.5 Resource use and costs in the York model and subsequent appraisals

Resource use and costs included in the York model and subsequent appraisals consisted of drug acquisition costs, administration and monitoring, outpatient visits and inpatient hospitalisation stay. The cost of tests to assess eligibility for biologic treatment was excluded. All treatments with the exception of infliximab were assumed to be self-administered. Drug costs were sourced from the most recent information in the British National Formulary (BNF). A range of monitoring and laboratory costs were considered, including full blood count, liver function tests and regular physician visits. No adverse event costs associated with treatment were included in the York model. TA 350 was the only appraisal where costs of adverse events were considered. The rates of adverse events applied were sourced from the secukinumab trials and published literature and included non-melanoma skin cancer, other malignancies and severe infections.

Resource use and costs included in the earliest TAs (TA 134, TA 146 and TA 180) mostly followed the assumptions of the York model and sourced their resource use and unit costs from TA 103. There were small differences in resource use for drug monitoring and administration between the TAs but these differences had only a minor impact on the cost-effectiveness results. Later TAs (TA 350, TA 368) based their resource use and cost estimates on the NICE Clinical Guideline on psoriasis (CG 153) for the cost-effectiveness of second-line biologics and on the accompanying costing report. .[131, 132] The CG 153 included the same categories of costs as the York model but expanded upon them to better characterise the costs of BSC. The costs associated with BSC were identified as a key driver of the cost-effectiveness results in TA 103 and were considered to be an area of substantial uncertainty in subsequent TAs.

In all of the appraisals, non-responders to treatment were assumed to receive BSC (with the exception of TA 368 where sequential use of treatments was considered and non-responders only moved to BSC when all other treatment options were exhausted). The costs associated with BSC differ across the appraisals as there is no clear guidance on what BSC consists of. Table 53 details the elements of cost for BSC included in each of the TAs, as well as those reported in CG 153.

Table 53 Summary of resource use and costs for best supportive care included in the previous TAs and NICE guidance

Study	Treatments included as part of BSC	Outpatient visits (annual)	Day centre care (annual)	Hospitalisations (annual)	Reported total annual cost of BSC
TA 368	45% of patients on MTX 45% of patients on continuous CS 16% of patients have 24 sessions of NBUVB per year	10% of patients have 5 visits	All patients have 5 visits	82% of patients (high need) have one hospitalisation with a 20.8 days mean LOS, 18% (very high need) have 2.55 hospitalisations with a 53.04 days mean LOS. On average 26.6 days.	£11,542.73
TA 350	45% of patients on MTX 15 mg/week 45% of patients on continuous CS 300 mg/day for a maximum of 2 years 3.84 sessions of NBUVB per year	4	5	10.7	£9,015.00
CG 153	45% of patients on MTX 45% of patients on continuous CS for a maximum of 2 years 16% of patients have 24 sessions of NBUVB per year	10% of patients have 5 visits	All patients have 5 visits	82% of patients (high need) have one hospitalisation with a 20.8 days mean LOS, 18% (very high need) have 2.55 hospitalisations with a 53.04 days mean LOS. On average 26.6 days.	£10,730.00
TA 180	No treatments	2	0	21	£6,209.54

TA 146	No treatments	2	0	21	£5,493.00
TA 134	No treatments	18*	0	21	£7,365.00
TA 103	No treatments	2	0	0/21**	£113.20/£5,327.71

BSC, Best supportive care; CS, cyclosporine; LOS, length of stay; MTX, methotrexate; NBUVB, narrow band UVB therapy.

*Non-responders that switch to BSC, responders have 2 outpatient visits; **Zero in the base-case analysis and 21 days in a scenario analysis.

The cost of BSC for non-responders in the York model was limited to two annual outpatient visits in the base-case analysis, but included one annual hospitalisation with a 21 day length of stay (LOS) in a scenario analysis. The rate of hospitalisation for patients on BSC was based on expert opinion with LOS sourced from Hospital Episode Statistics (HES) data and two local surveys. Subsequent TAs (TA 134, TA 146, TA 180) used the 21 days of inpatient stay for BSC in their base-case analysis. In each of these appraisals it was assumed that no treatments were given as part of BSC.

The NICE Clinical Guideline CG 153 departed from this definition of BSC (see Appendix P of the guideline) because they believed that it does not reflect what currently happens in clinical practice for patients who require a second line biologic. They assumed that 45% of patients would receive treatment with methotrexate, 45% would receive continuous cyclosporine for a maximum of 2 years, and 16% would have 24 sessions of narrow band UVB therapy per year, while on BSC. Furthermore, it was reported in CG 153 that patients meeting the eligibility criteria for biologic therapy are generally high-need patients who utilise sizeable health care resources through inpatient admissions, lengthy hospital stays, frequent visits to day clinics for specialist-applied topical treatments and UVB, and require monitoring for toxicity due to the use of systemic treatments. The NICE Guideline Development Group (GDG) sourced the resource use estimates for BSC from two published cohorts of patients with high need (i.e. those with severe psoriasis), which were conducted in tertiary dermatology units in the UK (n=76) [130] and the Netherlands (n=67). [133]. Both of these studies estimated mean inpatient days in the year preceding initial treatment with biologic therapy. In addition, estimates of LOS from a multicentre prospective service review based on four specialist dermatology centres in the UK [134] were used in a scenario analysis. The GDG for CG 153 emphasised that there is substantial variability in the long-term costs reported for patients with psoriasis. As a result, CG 153 included extensive sensitivity analyses for the elements of cost associated with BSC. These included variations in number of hospitalisations per year and average LOS by level of need. The cost-effectiveness of second line biologic therapy compared to BSC in CG 153 was highly sensitive to the assumptions about BSC.

The more recent TAs (TA 368 and TA 350) largely followed the resource use reported in CG 153 for BSC (see Table 54). The NICE Appraisal Committees for TA 350 and TA 368 noted that in both cases the costs of BSC were likely to have been overestimated. The committees considered that the patient population in CG 153 and Fonia et al (2010) did not match that of the appraisals and reflected a sicker group of patients. In particular, Fonia et al (2010) described care in a tertiary care centre, which is known to be associated with treating the most severely affected cases of psoriasis. Furthermore, during consultation of TA 368, the company provided NHS hospital episode statistics data that showed that the average length of hospital stay associated with BSC was 3.5 days. However, this was argued by the

company to be an underestimate as it includes patients with different disease severities and patients receiving concomitant medication. The duration of hospital stay for BSC in adults with moderate to severe psoriasis remains highly uncertain.

Table 54 Summary of CG 153 assumptions for scenario analysis

Severity of psoriasis	Proportion of patients	Number of admissions (annual)	Assumed average LOS (days)	Patient days in hospital	Number of bed days per annum in the model	Base-case assumptions and variations in scenario analysis
High need	82%	1	20.8	20.8		**Base case:** Proportion of patients by level of need sourced from Driessen et al, 2010. Average LOS taken from Wood et al, 2008 for patients with baseline PASI of 10-20 (20.8 days). Number of hospitalisations calculated to match Driessen et al, 2010, average LOS for very high need patients in the year prior to biologic therapy (53 days).
Very high need	18%	2.55	20.8	53.0	26.6	
High need	82%	1	**23.7**	23.7		**Scenario 1:** Average LOS taken from Wood et al 2008 for patients with baseline PASI greater than 20 (23.7 days).
Very high need	18%	2.55	**23.7**	60.4	30.3	
High need	**70%**	1	20.8	20.8		**Scenario 2:** 30% very high need
Very high need	**30%**	2.55	20.8	53.0	30.5	
High need	**95%**	1	20.8	20.8		**Scenario 3:** 5% very high need
Very high need	**5%**	2.55	20.8	53.0	22.4	
High need	82%	**0.25**	20.8	5.2		**Scenario 4 –** Aims to match Driessen et al, 2010, estimates of average LOS (53 days for patients with LOS equal or greater than 30 days and 14.9 days for the full study population) by changing the number of hospitalisations per year. However, the number of hospitalisations per year for the high need patients would have to be 0.75 to yield an average of 14.9 days LOS as reported in the study.
Very high need	18%	2.55	20.8	53.0	13.8	
High need	82%	**0.5**	20.8	10.4		**Scenario 5:** 0.5 hospitalisations for high need and 2 hospitalisations for very high need
Very high need	18%	**2**	20.8	41.6	16.0	
High need	82%	**1**	20.8	20.8		**Scenario 6:** 1 hospitalisation for all
Very high need	18%	**1**	20.8	20.8	20.8	

High need	82%	**0.312**	20.8	6.49	6.5	**Scenario 7:** Aims to match Fonia et al, 2010 estimate of average LOS (6.49 days) by changing the number of hospitalisations per year.
Very high need	18%	**0.312**	20.8	6.49		

Elements varied in sensitivity analysis are shown in bold; all of the variations result in a different estimate for number of bed days per annum applied in the model.

6.4.6 Cost-effectiveness results from the York model and subsequent appraisals

The cost-effectiveness results for the base-case analysis in previous NICE TAs in adults are summarised in Table 55, alongside the drivers of cost-effectiveness stated in the TAs documentation. The results reported for TA 134, 146, 180, 350 and 368 correspond to those in the company submissions.

Table 55 Summary of cost-effectiveness results and key drivers of cost-effectiveness for previous adult TAs

Appraisal	**Etanercept and efalizumab** **TA 103**	**Infliximab** **TA 134**	**Adalimumab** **TA 146**	**Ustekinumab** **TA 180**	**Secukinumab** **TA 350**	**Apremilast** **TA 368**
Base-case analysis results ICERs (/QALY)	Incremental analysis: ETA 25 mg vs BSC: £66,703 EFA: dominated ETA 25mg continuous: dominated ETA 50 mg vs ETA 25 mg : £1,035,121 ICER vs Supportive care: ETA 25 mg: £66,703 EFA: £84,018 ETA 25 mg continuous: £83,258 ETA 50 mg £120,855	Incremental analysis: - ETA 25 mg vs BSC: £8,044 -EFA: dominated - ETA 25mg continuous vs ETA 25 mg: £17,208 - ETA 50 mg: Extendedly dominated - INF vs ETA 25mg continuous: £ £26,095 ICER relative to supportive care: - INF: £22,240	Incremental analysis: (biologics only): ETA Intermittent: extendedly dominated ETA High Intermittent: extendedly dominated EFA: extendedly dominated ADA compared to BSC: £30,538 ETA: Dominated Infliximab: £147,906 ICER relative to supportive care: - MTX: £-29,759 - CS: £-25,135 - ETA Intermittent: £37,284 - ETA High Intermittent: £38,358 - EFA: £39,948 - ADA: £30,538	ICERs vs. supportive care: - EFA: £40,250 - ETA 25 mg intermittent: £30,111 - ETA 25 mg continuous: £34,281 - ETA 50 mg continuous: £35,964 - ADA: £31,022 - UST:£29,587 - INF: £39,153 ICER UST vs other treatments: - Supportive care: £29,587 - EFA: UST dominant - ETA 25 mg intermittent: £26,637 - ETA 25 mg continuous: UST dominant	Incremental analysis: ETA 25 mg BIW compared to BSC: £13,948[a] SEC compared to BSC: £2,464 ADA 40 mg: Dominated by SEC UST 45 mg: Dominated by SEC UST 90 mg: Dominated by SEC INF: Dominated by SEC	Apremilast sequence dominated the comparator sequence.

			- ETA: £37,676 - INF: £42,492	- ETA 50 mg continuous: UST dominant - ADA: UST dominant - INF vs. UST: £304,566		
Stated drivers of cost-effectiveness	Identified by scenario analysis in the AG report: - Source of utility gain by PASI response: use of estimates from subgroup with lower baseline HRQoL (higher DLQI) improves the cost-effectiveness of biologic drugs. - Inclusion of 21 days of hospitalisation on the costs of non-responders favours the cost-effectiveness of the more effective drugs	Identified by one way sensitivity analysis in the MS: - Non-responders' inpatient LOS - Mean patient weight in the model - Response rates to treatment for infliximab - Utility gain for responders	Identified by scenario analysis in the MS: - Source of utility gain by PASI response: use of estimates from subgroup with lower baseline HRQoL (higher DLQI) improves the cost-effectiveness of biologic drugs. - Annual length of inpatient stays for non-responders	Identified by one way sensitivity analysis in the MS: - Number of hospital days for BSC - Estimated cost of dosing for intermittent ETA 25 mg - SF-6D utility scores instead of EQ-5D (mapped from DLQI)	Identified by scenario analysis in the MS: - Costs assumed for BSC including hospitalisation costs, day care costs and, to a lesser extent costs of phototherapy. - Small changes in incremental health benefits between different biological treatments, thus ICERs could vary considerably with small QALY changes	Differences in costs (mostly because of hospitalisation LOS for those on BSC) and outcomes with APR compared with BSC were the main driver, given high assumed costs of BSC and the assumption of no PASI response for BSC

[a] ETA extendedly dominated by SEC.

ADA, adalimumab; AG, Assessment Group; APR, apremilast; BIW, twice weekly; BSC, Best supportive care; CS, cyclosporine; EFA, efalizumab; ETA, etanercept; ICER, incremental cost-effectiveness ratio; INF, infliximab; LOS, length of stay; MS, manufacturer's submission; MTX, methotrexate; SEC, secukinumab; SF-6D, Short Form–6 Dimension; UST, ustekinumab.

In the base-case full incremental analysis for TA 103, which compared etanercept in three dosing regimens (25 mg intermittent, 50 mg intermittent and 50 mg continuous), efalizumab and BSC, and with the assumed no hospitalisations for non-responders to biologic treatment, BSC was the most cost-effective strategy at cost-effectiveness thresholds below £66,703 per QALY gained. At a threshold equal or greater than £66,703 per additional QALY, intermittent etanercept 25 mg would be the cost-effective intervention, dominating (i.e. being less costly and more effective than) continuous etanercept 25 mg and efalizumab. Intermittent etanercept at 50 mg had an ICER exceeding £1 million per QALY gained compared to etanercept at a lower dose (25 mg intermittent).

Inclusion of 21 days of hospitalisation for the non-responders to biologic drugs, reduced the ICER of intermittent etanercept 25 mg compared to BSC to £29,420 per additional QALY. When in addition to the 21 hospitalisation days, the estimates of utility gains per PASI response were sourced from the subgroup of patients at the highest (worst HRQoL) quartile of baseline DLQI in the analysis (group with the highest gain in utility from improvement in PASI score), the ICER for intermittent etanercept 25 mg vs. BSC further reduced to £15,297 per QALY. In both these scenario analyses, continuous etanercept 25 mg and efalizumab remained dominated by intermittent etanercept 25 mg, while the ICER of intermittent 50 mg etanercept vs. 25 mg decreased but not sufficient to make it cost-effective at commonly accepted cost-effectiveness threshold ranges. In the secondary analysis that compared the full range of systemic therapies (namely, infliximab, methotrexate, cyclosporine and fumaderm) and assumed 21 days of hospitalisation for non-responders, methotrexate dominated all interventions including BSC, with the exception of infliximab. Infliximab was more costly and more effective than methotrexate but the resulting ICER for this comparison exceeded £1 million per QALY gained, with methotrexate emerging as the cost-effective intervention for this analysis.

Appraisals subsequent to TA 103 (TA 134, 146, 180, 350 and 368) all included a cost associated with hospitalisation stay for non-responders (LOS ranging from 10.7 to 26.6 days per annum). This generally resulted in more favourable cost-effectiveness estimates when biologic therapies were compared to BSC. Consistent with the findings of the York model, duration of hospitalisation for non-responders was identified as a key driver of cost-effectiveness for biologic therapies in psoriasis across these appraisals. The base-case analysis of the majority of the appraisals in adults sourced their estimates of utility gains by PASI response on a subgroup of lower baseline HRQoL (TA 134, 146, and 180) leading to higher QALY gains for the most effective drugs in terms of PASI response. This parameter can be considered the second driver of cost-effectiveness in the adult models.

The base-case cost-effectiveness results in the company submissions for infliximab, adalimumab and ustekinumab (TA 134, 146 and 180, respectively) place the ICERs for these drugs at the upper end of the currently accepted NICE cost-effectiveness threshold range, as long as the assumptions for HRQoL and costs of hospitalisation for non-responders referred above hold. The estimates of cost-effectiveness for secukinumab and apremilast presented by the manufacturers in TA 350 and 368 were considered overly optimistic by the NICE appraisal committees, and largely driven by the costs of BSC in non-responders to biologic therapy. These costs were considerably higher than in previous appraisals due to the assumption of a higher consumption of health care resources for non-responders in line with CG 153 (Table 54).

NICE recommended the following biologic treatments in adults with psoriasis: efalizumab, etanercept, infliximab, adalimumab, ustekinumab and secukinumab. With the exception of infliximab the biologic treatments were recommended for severe psoriasis defined as baseline PASI equal or greater than 10 and DLQI greater than 10 for patients who had previously failed or had a contraindication/intolerance to non-biologic systemic therapy. The recommendation for efalizumab further required that patients had failed on etanercept or had a contraindication/intolerance to the drug. Efalizumab is no longer marketed in the UK.

Infliximab was recommended only for very severe psoriasis defined as baseline PASI equal or greater than 20 and DLQI greater than 18 for patients who had previously failed or had a contraindication/intolerance to non-biologic systemic therapy. The recommendation for ustekinumab and secukinumab was conditional on Patient Access Schemes (PAS). The PAS for ustekinumab guarantees a flat price for ustekinumab 45 mg and 90 mg, so that the 90 mg dose is provided at the same price as 45 mg for patients weighing more than 100 kg, while the one for secukinumab consists of a confidential discount over the drug list price.

The NICE recommendations for all these biologic treatments require treatment termination if response is not produced at the end of the 'trial' period (12 weeks for etanercept and secukinumab, 10 weeks for infliximab and 16 weeks for adalimumab and ustekinumab). Treatment response is defined as achieving PASI 75 or PASI 50 accompanied by a five point reduction in DLQI from baseline.

6.5 Summary of the key areas of uncertainty in adult models and motivation for de-novo model in children and young people

There are no studies comparing the cost-effectiveness of biologic therapies for plaque psoriasis in children and young people. Furthermore, none of the companies participating in this appraisal have

submitted an economic evaluation. Our review of previous NICE TAs of plaque psoriasis in adults was conducted to examine existing decision-analytic models, and identified important structural assumptions, highlight key areas of uncertainty and the potential issues associated with generalising evidence from the adult population to a population of children and young people. In this section we summarise the key areas of uncertainty identified in adults in light of potential implications for the *de novo* model in children and young people.

Model structure

Although in clinical practice treatment with biologic therapy is expected to be sequential, i.e. patients are switched to further lines of biologic therapy upon failure of first line biologic; the majority of TAs did not consider treatment sequencing. Lack of evidence to inform treatment sequencing, especially on the efficacy of the treatments conditional on prior therapies received, appears to be the main reason for not formally modelling treatment sequences in all but one appraisal (TA 368). Given that there is very limited evidence to support the cost-effectiveness of sequential use of treatments in adults and that no evidence exists in children and young people (see Section 4), any attempt to model treatment sequences in the population of children and young people will be highly uncertain.

Clinical effectiveness evidence

Due to a lack of head-to-head trials comparing the treatments with each other, network meta-analysis was used to compare the treatments to each other indirectly. There was concern that not all trial populations matched those of the decision problem due to variation in the inclusion criteria, with some trials not explicitly excluding individuals who had not failed non-biologic systemic therapy. Placebo or best supportive care was not defined consistently across trials, which introduced heterogeneity in placebo response rates. Similar issues were identified in the clinical effectiveness evidence for children and young people (see Section 4), where the evidence base is even more sparse with only three RCTs and no common comparator across the trials. Section 5 describes how network meta-analysis was used to expand the evidence base in children and young people by drawing strength from the full network of evidence available for adults, while attempting to account for heterogeneity between trial populations (i.e. children and young people vs. adults) and placebo response rates.

Long-term response and withdrawal rates

To extrapolate data beyond the clinical trials, previous appraisals in adults have assumed that responders to treatment maintain their PASI response rate over time until treatment withdrawal. The same all-cause withdrawal probability of 20% per annum has been assumed for all biological

therapies in the absence of any long-term withdrawal data. Given the paucity of long-term data in children and young people, this parameter will also be uncertain in this population.

Health-related quality of life (HRQoL)

Most of the previous TAs in adults used utility values based on an estimate of the relationship between PASI response rates and changes in DLQI score mapped onto EQ-5D utility values. Although some TAs applied EQ-5D data collected directly in RCTs, this was limited to data collected in the trials sponsored by the company and no evidence synthesis methods were used to synthesise the utility estimates. The estimates of utility gains from treatment were variable across subgroups of patients defined by baseline DLQI, with greater gains achieved for individuals with worse baseline HRQoL. The size of the utility gains in previous appraisals was considered to be largely uncertain and it represented a key driver of the cost-effectiveness results. It is expected that utility gains associated with treatment will also be highly uncertain in the population of children and young people due to an absence of EQ-5D values in this population. In Section 7, a review of HRQoL data in children and young people is reported. Scenario analyses will be used to explore the impact of uncertainty on the cost-effectiveness results.

Resource use and costs

The resource use and costs associated with best supportive care has been one of the key drivers of cost-effectiveness in adult appraisals. In particular, the duration and costs associated with inpatient hospitalisation stay for individuals who do not respond adequately to treatment has been highly uncertain. Until the publication of CG 153, the resource use and costs associated with BSC in adult TAs was largely informed by assumptions and expert opinion. The two TAs which followed the guideline (TA 350 and TA 368) used CG 153 but supplemented it with data from cohort studies that collected resource use data for patients treated for psoriasis with biologic treatments. However, the patient population in which the data was collected was likely to reflect a sicker population than that defined by the NICE scope for these appraisals, and the uncertainty associated with the estimates was not sufficiently explored. The search described in Section 6.2 did not identify any evidence on the resource use and costs of BSC in children and young people. The use of evidence in adults supplemented by clinical expert opinion to inform the costs of BSC in this population is discussed in depth in Section 7. Scenario analyses will be used to explore the implications of uncertainty in the assumptions used for BSC, particularly those in relation to hospitalisation length of stay, on the cost-effectiveness results.

Each of these areas of uncertainty are considered in more detail as part of the decision-analytic model developed to evaluate the cost-effectiveness of adalimumab, etanercept and ustekinumab in children and young people described in the next section.

7 Independent economic assessment

7.1 Introduction

The review of cost-effectiveness evidence in the population of children and young people and the absence of company models highlights the challenges of developing an economic model in this population. The fundamental challenge is the limited clinical evidence base for both short- and long-term outcomes to inform a model. Therefore, any estimation of the cost-effectiveness of biologics in children and young people will be subject to a number of uncertainties. These uncertainties cannot be avoided but a clear and transparent approach, which highlights the assumptions entering the economic model, can be pursued in order to help the decision maker come to an assessment regarding the cost-effectiveness of biologics in this population.

Plaque psoriasis is a chronic non-progressive disease, which manifests in children and young people in a similar manner to adults. The main difference between the younger population and adults is the presence of co-morbidities in adults (such as high blood pressure, liver impairment and renal impairment), which tend to make adults less well with psoriasis compared to a younger population. Currently, there is no treatment pathway specific to psoriasis in children and young people in the UK. The management and approach to care of treatment seems to mirror that used in adults. Our clinical advisor, Dr Ruth Murphy, indicated that where there is an absence of evidence it would be reasonable to extrapolate data from the adult population to children and young people. The company submission for ustekinumab also supports this approach for the development of an economic model given that there are few significant differences in the posology or management of chronic plaque psoriasis in children, young people and adults.

Management and treatment of plaque psoriasis depends on the extent and severity of an individual's disease, local custom and practice. If an individual patient does not respond to or tolerate a particular treatment option, an alternative one is usually tried. This means that treatments are usually 'trialled' on an individual basis until an effective option is found. If an effective treatment is not found, then a patient will receive some form of best supportive care. This approach to treatment appears to be the same for children and young people and adults, but usually more caution is exercised in the younger population due to the limited availability of licensed treatment options.

The trialling of treatments upon treatment failure, or intolerance, suggests that sequences of treatments is a consideration for the cost-effectiveness model, whereby after failure of a first treatment option patients would then be trialled on a second option, and so on, until all options are exhausted. However, this would require additional clinical evidence on the efficacy of the treatments conditional on prior therapies received. There is very limited evidence to support the cost-effectiveness of sequential use of treatments in adults and no evidence exists in children and young people (see Section 4). Therefore, although the model should ideally explore the sequential use of treatments, any attempt in the population of children and young people would be highly uncertain. Furthermore, the optimum treatment sequence may not be suitable for an individual patient with specific characteristics and where treatment in this population is usually tailored to the child or adolescent due to needle phobia or the presence of psoriatic arthritis. Therefore, an alternative approach may be better whereby the optimum ordering of treatments, in terms of their cost-effectiveness, is established. This is achieved by comparing each of the alternative treatment options to BSC and then indicating the most cost-effective order in which to give the therapies based on total expected costs and QALYs associated with each treatment option.

The previous York model appears to be the most widely accepted model of chronic plaque psoriasis. The five NICE TAs which followed TA 103 for the treatment of moderate to severe psoriasis in adults (infliximab TA 134, adalimumab TA 146, ustekinumab TA 180, secukinumab TA 350 and apremilast TA 368) have followed the framework of the York model and these have been accepted by NICE as relevant to plaque psoriasis. The main changes which have followed since the advent of the York model has been the availability of new evidence, the methodology for linking efficacy estimates to health-related quality of life utility values, the parameters used in the model to inform BSC, updated unit costs, time on treatment, and the modelling of treatment sequences in the most recent appraisal of apremilast. It would therefore seem appropriate that the same modelling framework is used for children and young people but with an evidence base informed by outcomes in the younger population. Hence, the structure of the model is very similar to that used in previous TAs in adults and, where evidence is lacking or limited in the population of children and young people, data has been extrapolated from the adult population and supplemented by expert opinion.

7.2 Decision problem and patient population

The decision problem addresses the cost-effectiveness of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people. The population in the model reflects the marketing authorisation of the three interventions. However, the marketing authorisation

for the use of each of the interventions in this population differs by age and severity of psoriasis at baseline, but also in terms of the positioning of the biologic in the pathway of care. A stepwise approach to treatment for the management of plaque psoriasis is usually pursued where topical therapies are offered as first-line treatment following by phototherapies and/or systemic non-biological therapies such as methotrexate as second-line treatment, and then biological treatments are offered as third-line where previous therapies are found to be ineffective. However, adalimumab is licensed in a paediatric population for individuals who have an inadequate response to, or who are inappropriate candidates for, topical therapy and phototherapies, whereas etanercept and ustekinumab are licensed for individuals inadequately controlled by, or intolerant to, other systemic therapies or phototherapies. Therefore, adalimumab is the only biologic treatment indicated in the population of children and young people who have not failed prior systemic therapies.

The biologic interventions also differ in their marketing authorisation by age and severity of psoriasis (see

Figure **9**). Both adalimumab (age ≥4 years) and etanercept (age ≥6 years) are indicated for younger ages and severe psoriasis, whereas ustekinumab is indicated for an adolescent population (age ≥12 years) and moderate to severe psoriasis. The definition of severity also differs in the corresponding trials of the biologics in children and young people (see Table 56). In adults, severe psoriasis is defined by a total PASI score of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10. However, there is not a clear consensus on the definition of moderate or severe psoriasis in children and young people. This is partly due to the fact that PASI has not been validated as a disease severity assessment tool for use in this population and no other tool is available. Mean PASI scores at baseline in the trials were 18.6 for etanercept, 18.3 for adalimumab and 21.1 for ustekinumab. Therefore, although the license for ustekinumab is moderate to severe psoriasis, patients in the CADMUS trial (ustekinumab) had disease severity more comparable to patients in study 20030211 (etanercept) and M04-717 (adalimumab) with severe disease. Hence, the population in the model is chosen to reflect severe psoriasis as defined by the baseline characteristics of the trial populations in children and young people.

Figure 9 Licensed age and severity of biologic therapies in children and young people

Table 56 Definition of disease severity in the trial populations for children and young people

Etanercept	Ustekinumab	Adalimumab
License: Severe chronic plaque psoriasis Trial population: Moderate to severe plaque psoriasis with - Baseline PASI≥12, PGA≥3 and involvement ≥10% of BSA	License: Moderate to severe plaque psoriasis Trial population: Moderate to severe plaque psoriasis with - Baseline PASI≥12, PGA≥3 and involvement ≥10% of BSA for ≥6 months	License: Severe chronic plaque psoriasis Trial population: Severe plaque psoriasis with – Baseline PASI≥20, PGA≥4, involvement ≥20% of BSA or very thick lesions and ≥10% of BSA – or baseline PASI≥10 and one of the following: • Active psoriatic arthritis non-responsive to NSAIDS nonsteroidal • Clinically relevant facial involvement • Clinically relevant genital involvement • Clinically relevant hand or foot involvement • CDLQI>10

In order to reflect the differences in marketing authorisation by age and positioning of treatment in the pathway, the base case cost-effectiveness analysis considers three separate populations:

4. Before systemic therapy – Children and young people **aged 4-17 years** with **adalimumab** as the only licensed intervention for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **topical therapy and phototherapies, i.e. as an alternative to systemic therapies.**
5. After systemic therapy (1) – Children and young people **aged 6-11 years** with **adalimumab** and **etanercept** for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **systemic therapies or phototherapies.**
6. After systemic therapy (2) – Children and young people **aged 12-17 years** with **adalimumab, etanercept** and **ustekinumab** for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to **systemic therapies or phototherapies.**

The population aged 4-5 years with adalimumab as the only licensed intervention for the treatment of severe plaque psoriasis after systemic therapy was not considered as a separate population because no children under 6 years were included in the adalimumab trial (M04-717); therefore efficacy estimates for this age group were assumed to be the same as those for ages 6-11 years, which results in similar cost-effectiveness estimates for adalimumab compared to best supportive care for ages 6-11 years.

The starting age used in the model is 4 years, 6 years and 12 years for the populations above, respectively. The time horizon of the model extends until individuals reach 18 years of age. At this point, the population becomes adults and separate NICE recommendations for the use of the interventions in adults apply. The difference in marketing authorisation of the interventions by age inevitably means that the time horizon of the model will differ according to population. In order to explore the impact of the time horizon, a separate scenario analysis is presented which considers a common time horizon of 14 years for all populations. The time horizon of 14 years (which is greater than the time horizon of 10 years used in previous TAs in adults) is sufficient to capture differences in costs and effects between the interventions under comparison.

7.3 Intervention and comparators

The interventions considered in the cost-effectiveness analysis are adalimumab, etanercept and ustekinumab within their marketing authorisation. The following comparators were considered in the NICE scope:

- Non-biological systemic therapy (including, but not limited to, cyclosporine and methotrexate)
- Topical therapy (for people in whom non-biological systemic therapy is not suitable), i.e. best supportive care
- Biological treatments used outside of their marketing authorisation (such as infliximab, adalimumab, etanercept or ustekinumab if used outside of the constraints of the relevant marketing authorisation in children and young people)
- When appropriate, adalimumab, etanercept and ustekinumab will be compared with each other.

Due to the positioning of adalimumab in the stepwise management of psoriasis, non-biological systemic therapy is only a relevant comparator for adalimumab since it is the only licensed

intervention representing an alternative to systemic therapy; etanercept and ustekinumab are licensed for individuals who are inadequately controlled by, or intolerant to, prior use of systemic therapies. Standard systemic therapies such as methotrexate, cyclosporine and acitretin are not licensed for psoriasis in children and young people. However, it is evident from the UK audit of the assessment and management of psoriasis in children that 19% of children have received systemic drugs (9% methotrexate, 5% acitretin, 4% cyclosporine and 1% dapsone) outside their licensed indication [135,Burden-The,2015]. The non-biologic systemic therapy considered as a comparator in the cost-effectiveness analysis for adalimumab is methotrexate since it is the most widely used systemic in the population of children and young people and was used as a comparator in study M04-717.

If biological treatments are found not to be effective, individuals are usually offered some form of best supportive care (BSC) rather than no treatment. Therefore, BSC is considered a relevant comparator for individuals who have exhausted all treatment options including conventional systemic therapy and phototherapy. BSC tends to include a mix of active non-biologic systemic therapies such as methotrexate and cyclosporine and palliative care, including phototherapy, even though these treatments may have been proven to be largely ineffective.

The interventions of etanercept, adalimumab and ustekinumab are compared with each other as appropriate to the licensed population. The use of these interventions outside of the age constraints of their license (e.g. the use of etanercept in children under 6 years and ustekinumab in children under 12 years) is considered a relevant comparator in a scenario analysis. The use of other off-label biological treatments such as infliximab outside of its licensed indication in adults is not considered. Advice from our clinical expert suggests that it is very unlikely that an unlicensed TNF inhibitor would be used as an alternative to a biological treatment that is licensed and available in this population. Furthermore, there are no RCTs comparing the use of infliximab to any comparator (or placebo) in the population of children and young people. Infliximab also requires the need for intravenous infusion in hospital and clinical opinion suggests that this is not a favourable option in this young population.

The biosimilar of etanercept, namely Benepali 50 mg, is not licensed for use in children and young people. Therefore, the biosimilar is not considered a relevant comparator in the base case analysis. However, a scenario analysis is considered where the drug cost of etanercept is reduced by approximately 10% to match the cost of Benepali in adults (£164.00 per pre-filled syringe). [136,

The drug doses for the intervention and comparators considered in the cost-effectiveness analysis are shown in

Table **57**. These are based on licensed doses for etanercept, adalimumab and ustekinumab and expected doses for methotrexate and BSC. Continuation of treatment is conditioned on response to treatment at the end of the trial period, which corresponds with the time point specified in the SmPC for children and young people. For etanercept and adalimumab, this corresponds to 12 and 16 weeks, respectively. For ustekinumab, the SmPC specifies that consideration should be given to discontinuation if no response up to 28 weeks. In the analysis, the time point for response with ustekinumab was taken to be 16 weeks corresponding to its administration at 12 weeks after the dose given at 4 weeks. This also corresponds to the same time point that was used to assess response with ustekinumab in adults (TA 180). [85] It is assumed that all treatments are used continuously in responders to treatment, until treatment withdrawal. Cyclosporine (used as part of BSC) is assumed to have a maximum treatment duration of 2 years.

Table 57 : Licensed or guideline doses used in the economic analysis

Treatment	Dose	Response assessment
Etanercept	0.8mg/kg up to a maximum of 50 mg weekly for up to 24 weeks	12 weeks
Adalimumab	0.8mg/kg up to a maximum of 40 mg at weeks 0 and 1, then every 2 weeks thereafter	16 weeks
Ustekinumab	0.75mg/kg for bodyweight <60kg; 45mg for bodyweight 60-100kg; 90mg for bodyweight >100kg at weeks 0 and 4 then every 12 weeks thereafter	16 weeks
Methotrexate	0.1-0.4 mg/Kg weekly	16 weeks
Cyclosporine (as part of BSC)	2-5 mg/Kg daily for up to 2 years	Not applicable

7.4 Methods

7.4.1 Overview

A de novo decision analytic model was developed to estimate the cost-effectiveness of adalimumab, etanercept and ustekinumab for the treatment of plaque psoriasis in children and young people. The cost-effectiveness model consists of a Markov cohort transition model developed in Microsoft Excel (2013). The structure of the model is very similar to that used in previous TAs for moderate to severe plaque psoriasis in adults. The model has been developed in accordance with the NICE reference case. The time horizon of the model extends until individuals reach 18 years of age, where they then become adults and current NICE recommendations for the use of the interventions in adults apply. The length of the time horizon varies by the starting age of individuals in the model. As indicated above, three starting ages are considered in the model to reflect the restrictions of the marketing authorisation of the interventions.

Outcomes of the model are expressed using quality adjusted life years (QALYs). The QALY provides a summary measure combining estimates of remaining length of life (life-years) with its associated quality of life. QALYs are derived by multiplying a utility value (quality of life) by the time spent with this utility (length of life). The utility values used in the model are generated via a mapping algorithm from trial collected PedsQL data to EQ-5D. The utilities associated with treatment are based on the proportion of individuals in the different PASI response categories (see Section 7.4.6). All costs are considered from the perspective of the National Health Services and Personal Social Services (NHS & PSS). Healthcare resource use and cost categories include cost of treatment (acquisition, administration, monitoring and adverse event costs) and changes in health service resource utilisation due to loss of response to treatment (see Section 7.4.12).

The parameters of the model were sourced from published literature, information reported in the company submissions and the results of the evidence synthesis described in Section 5. Both costs and QALYs are discounted at 3.5% per annum, in line with current NICE guidance. [137]

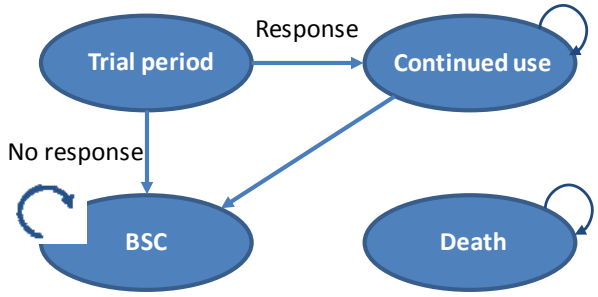
7.4.2 Model structure and assumptions

The model consists of four health states: 'Trial period', 'Continued use', BSC and death (**Figure 10**). Individuals enter the model in the trial period and receive one of the three biologic interventions or a relevant comparator. The length of the trial period is dependent on the intervention and can last from 12 weeks for etanercept to 16 weeks for adalimumab and ustekinumab, corresponding to the time point at which response to treatment is assessed. The cycle length in the model corresponds to 28 days (4 weeks), which takes account of the different lengths of time spent in the trial period.

At the end of the trial period, individuals are assessed as responders or non-responders to treatment based on PASI response rates. PASI response in the base-case analysis is taken to be PASI 75, i.e. response is assessed based on whether an individual achieves a 75% reduction in baseline PASI score. Individuals who do not have an adequate response to treatment at the end of the trial period, move to the health state of BSC. Individuals who are considered responders to treatment transition to the health state of continued use, where they remain in this state until they withdraw from treatment and move to BSC. During the period of continued use, individuals continue to receive the active therapy and are assumed to maintain their level of PASI response until treatment discontinuation due to any cause, such as lack of efficacy, the presence of adverse events or non-compliance to treatment (modelled together as an overall risk of all cause withdrawal).

Upon treatment discontinuation (in either the trial period or continued use state), individuals transition to BSC. BSC consists of non-biologic supportive therapies. The only transition out of the BSC state is death. 'Death' is an all-cause mortality state to which transition is possible from any health state. Mortality is not conditioned on treatment or treatment response. Mortality rates by age were sourced from life tables in England and Wales for the years 2013-15[138] and averaged across gender.

Figure 10 Schematic of model structure



7.4.3 Effectiveness data

The measure of treatment effectiveness used in the model is the proportion of individuals achieving a specific threshold of PASI response relative to baseline. Relative change in PASI response is the most widely reported outcome in clinical trials and has been used as the main outcome in previous models in adults. The PASI response rates used in the model are taken directly from children and young people efficacy estimates of the network meta-analysis which incorporates *all relevant adult evidence* (Section 5.4). Scenario analyses are also conducted where the results from the unadjusted baseline

constrained model with *minimum* adult evidence (Section 5.4) are applied in the model, as well as artial comparisons with direct trial data and the indirect comparison (Section 5.3) are also incorporated in scenario analysis for completeness.

In the base case analysis, PASI 75 response rates are taken as the measure of effectiveness for treatment continuation. Individuals who meet the threshold of PASI 75 are classified as responders at the end of the trial period and assumed to maintain their response for as long as they are in the health state of continued use. In a separate scenario analysis, the threshold of PASI 50 is taken as the measure of effectiveness for treatment continuation.

PASI response rates from the NMA are also used in the model to inform the HRQoL utility values. Gains in utility associated with treatment are conditioned on PASI response rates (see Section 6.4.4), an approach which has been taken in previous models for the treatment of psoriasis in adults. PASI response rates for BSC are assumed to be equivalent to placebo in the NMA.

In the absence of data to model time-varying transition probabilities, response rates are assumed to be constant per cycle in the model. The response rates used to inform the model are presented in Table 70. The uncertainty in the predicted response rates from the NMA is reflected in the model by directly exporting the simulated posterior distributions from the Markov Chain Monte Carlo analysis in WinBUGs to the cost-effectiveness analysis, preserving any correlations in the data.

7.4.4 Treatment withdrawal rates

Responders to treatment are assumed to maintain their response until treatment discontinuation. Discontinuation is modelled as an overall risk of withdrawal due to any cause, such as lack of efficacy, the presence of adverse events or non-compliance to treatment. Previous TAs in adults assumed a constant withdrawal rate of 20% per annum for all treatments.

A literature search described in Section 4 was conducted with the aim of identifying registry data on long-term treatment response to biologics in children and young people with psoriasis. Two registries were identified: the Child-CAPTURE (Netherlands) and DERMBIO (Denmark). However, none of the published studies from these registries allowed the estimation of long-term withdrawal rates in individuals who are responders to treatment and also the DERMBIO registry included only a small number of children. The data indicated that there was no significant predictive relationship between age and treatment continuation, which may suggest that treatment withdrawal rates used in the adult population can be extrapolated to children and young people in the absence of any alternative source

of data. Data from the DERMBIO registry suggests that the withdrawal rate on biological therapies is constant over the treatment period (with no obvious plateau), which supports the use of a constant withdrawal rate over time.[78`]

A recent study on the long-term drug survival rates of four biologics (adalimumab, etanercept, infliximab and ustekinumab) based on data from the UK BADBIR audit of 3,523 biologic naïve adult patients indicates that loss of efficacy is a major reason for treatment discontinuation, decreasing from 77% in the first year to 53% in the third year of use. [80] This is consistent with a withdrawal rate of 20% per annum, which has been used in previous TAs of adults. This study also suggests that there may be differences in the withdrawal rate by treatment, with ustekinumab having a significantly higher survival rate compared to adalimumab and etanercept. However, the study does not distinguish between discontinuation due to a lack of treatment response in the short-term, i.e. during the initial trial period, and the long-term for patients who are responders to treatment. Therefore, the differences in withdrawal rates by treatment may reflect the higher efficacy of ustekinumab compared to adalimumab and etanercept, rather than reflecting differences between the treatments conditional upon response at the initial assessment point.

In the absence of sufficient evidence on the long-term withdrawal rates in children and young people, and given that observational data generally suggests that a constant 20% annual withdrawal rate is a reasonable assumption in adults, the same withdrawal rate was assumed in the model (this rate equates to a 28-day discontinuation rate of 1.70% per cycle).

7.4.5 All-cause mortality

All-cause mortality is incorporated in the model by applying a risk of death during each cycle. The mortality risk is assumed to be independent of response status or treatment received. A common mortality risk is thus assumed for all patients based on the general population mortality risks. The general population mortality risk is obtained from gender specific life tables for England and Wales for the period between 2013 and 2015 and is averaged across males and females assuming equal proportion.[138]

7.4.6 Health-related quality of life

7.4.6.1 Review of utility data in children and young people with psoriasis

A systematic literature review was conducted to identify utility values for plaque psoriasis in children and young people. The aim of the search was to identify any studies that reported utility values or

other measures of HRQoL that could be converted into utility values specifically for the population of children and young people. The search criteria were not restricted to biological treatment or level of disease severity since a dearth of evidence in this population was anticipated. The Health Economics Research Centre (HERC) database of mapping studies from the University of Oxford [139] was also searched to identify any suitable mapping algorithms which would allow conversion of clinical measures routinely collected in studies of psoriasis in children and young people into utility values.

The search did not identify any studies that reported utility values collected in children and young people with psoriasis. The search on the HERC mapping algorithm database identified one study on the development of a mapping algorithm to estimate EQ-5D youth (EQ-5D-Y) utility values from PedsQL general core scales (GSC), Khan et al, 2014. [140]. PedsQL is a generic instrument for measuring HRQoL in children and adolescents and those with acute and chronic health conditions. PedsQL measures core dimensions of health as delineated by the World Health Organisation, as well as role (school) functioning. The four multidimensional scales are physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items).[18] EQ-5D-Y is the youth version of the EQ-5D, which has been specifically adapted in terms of language for children aged 8-11 years and for adolescents aged 12-18 years.

Khan and colleagues [140] assessed different mapping methods for estimating EQ-5D-Y health utilities from PedsQL response scores. The study used data collected in a cross-sectional survey conducted in four secondary schools in England amongst children aged 11–15 years. The sample on which the mapping models were estimated included 559 children and the validation sample comprised 337 children. Children in the full study sample (n=896) were on average 13.3 years old (SD 1.3), 54% were male and approximately 40% were of non-white ethnicity. The authors explored both direct and response mapping approaches to predict EQ-5D-Y utility values, as well as a number of functional forms including ordinary least squares (OLS) regression, generalised linear models, two-part logit-OLS regression, Censored Least Absolute Deviations (CLAD) and Tobit regression. Model performance was assessed on the validation sample and models were re-estimated on the full study sample. Table 58 presents the two best fitting models for the mapping algorithm. These correspond to the models estimated using OLS regression with i) age and gender terms included as regressors; and ii) excluding age and gender terms as regressors.

Table 58 Best fitting mapping algorithms from PedsQL to EQ-5D-Y from Khan et al, 2014[140]

Mapping algorithm	**OLS regression with gender and age terms (1)**		**OLS regression without gender and age terms (2)**	
Variables	**Coefficient**	**SE**	**Coefficient**	**SE**
Age (years)	-0.006136	0.004741	-	-
Gender	-0.009385	0.012292		
PedsQL domain scores				
Physical functioning (PF)	0.009067	0.002571	0.009127	0.002568
Emotional Functioning	0.006807	0.002533	0.006611	0.002530
Social Functioning (SF)	0.00563	0.002831	0.005705	0.002829
School Functioning (SchF)	0.005802	0.002371	0.006011	0.002367
Quadratic terms				
PF squared	0.00002	0.000025	0.00002	0.000025
EF squared	-0.000049	0.000018	-0.000048	0.000018
SF squared	0.000011	0.000016	0.000011	0.000016
SchF squared	-0.000017	0.000015	-0.000017	0.000015
Interaction terms				
PF x EF	-0.000005	0.000027	-0.000004	0.000027
PF x SF	-0.000053	0.000029	-0.000055	0.000029
PF x SchF	-0.000066	0.000030	-0.000066	0.000030
EF x SF	-0.000011	0.000023	-0.000009	0.000023
EF x SchF	0.000061	0.000021	0.000059	0.000021
SF x SchF	-0.000026	0.000022	-0.000027	0.000022
Constant	-0.335861	0.118035	-0.428496	0.094210

The two mapping algorithms were considered to have similar prediction accuracy for the mean EQ-5D-Y. Model 1 which included age and gender as regressors had a better fit across a wider range of EQ-5D-Y values than model 2. Model 2 reported better fit for the EQ-5D-Y utility score range of 0.8–1.0 category. There are a number of potential limitations to the use of these algorithms to predict EQ-5D-Y utilities. The sample on which the algorithms were estimated consisted of healthy children aged 11 to 15 years old, which may limit the predictive accuracy in sicker populations or outside this age range. The authors recognise that there is need for further validation and testing of the algorithm but in the absence of an alternative source it remains a useful tool for estimating EQ-5D-Y utility values in situations where only the PedsQL has been administered.

7.4.6.2 Utility data reported in company submissions

HRQoL assessments were collected in study 20030211 (etanercept), CADMUS (ustekinumab) and M04-717 (adalimumab) using the Children's Dermatologic Life Quality Index (CDLQI) and the PedsQL at selected time points. EQ-5D or EQ-5D-Y values were not collected in any of the trials. Therefore, the only possibility to include EQ-5D utility values in the model is via a mapping from either CDLQI or PedsQL. The literature review described above did not identify any studies that estimated the relationship between CDLQI and EQ-5D, while the study by Khan et al (2014) was the only study that estimated the relationship between PedsQL and EQ-5D. [140] The Assessment Group (AG) requested from the companies access to individual level patient data (IPD) for PedsQL domain scores at baseline and follow-up by category of PASI response, and PedsQL summary scores at the domain level by response category. The AG did not receive access to IPD; however, Janssen (ustekinumab) submitted aggregated summary data (mean and standard deviation) from the CADMUS trial for PedsQL subscale and total scale scores by treatment arm (placebo and ustekinumab standard dose) and PASI response categories at 12 weeks (<50, 50-75, 75-90, ≥90) for baseline,12, 28 and 52 weeks. [141]

7.4.6.3 Utility estimates used in the model

The utility values associated with treatment in previous models in adults have been based on the proportion of individuals in the different PASI response categories (<50, 50-75, 75-90, ≥90) and the change in utility from baseline associated with the PASI response category. Therefore, PASI response rates from the NMA are assumed to be a perfect proxy for change in utility arising from treatment.

The relationship between utility and PASI response was estimated in previous TAs in adults using either DLQI data mapped onto EQ-5D utility values or via direct EQ-5D data collected in the trials. In the population of children and young people, the only possibility of obtaining EQ-5D values is via the mapping algorithm from PedsQL to EQ-5D-Y described above. Without access to the IPD, which would allow full uncertainty to be reflected in the values, the mapping algorithm was applied to the summary scores at the domain level from the CADMUS trial.

Validation of the algorithm was performed by examining data reported in a study by Varni et al (2012), which compared self-reported HRQoL (based on PedsQL scores) among paediatric patients with moderate to severe plaque psoriasis with a healthy sample. [142] The sample used to represent the

psoriasis population corresponded to individuals in the main efficacy trial for etanercept (n=208, age 4 to 17 years) and measurements of PedsQL at baseline were pooled across the two treatment arms (etanercept and placebo). The healthy population sample was taken from a US children's health insurance program evaluation (n=5,079) open to children and young people aged 2 to 16 years old. Table 59 summarises the PedsQL subscale scores reported in Varni et al for the psoriasis and healthy population, alongside the estimates obtained by applying the two best fitting mapping algorithms to obtain EQ-5D-Y utility values (model 1 includes age and gender terms, while model 2 excludes these variables).

Table 59 Application of mapping algorithm to estimate EQ-5D-Y utilities in paediatric populations

	Psoriasis population N=208			**Healthy population N=5,079**		
	Mean	**EQ-5D-Y model 1**	**EQ-5D-Y model 2**	**Mean**	**EQ-5D-Y model 1**	**EQ-5D-Y model 2**
Age (years)	12.71	0.869	0.864	9.72	0.936	0.913
Gender[a]	0.519			0.517		
Physical functioning	82.5			87.8		
Emotional Functioning	67.1			79.2		
Social Functioning	80.7			85		
School Functioning	70.2			70.2		
PedsQoL total score	75.5			83.9		

[a] Assumes that the reference category is female

The EQ-5D utility estimates are higher in the healthy population compared to the population with psoriasis irrespective of the model used to map PedsQL to EQ-5D-Y. The distinction between the models is minimal, especially in the psoriasis population: model 1 provides slightly higher utility values compared to model 2 (0.6% and 2.5% higher in the psoriasis and healthy populations, respectively). Model 2 was subsequently used in the base-case analysis since the reference category for the variable gender was unclear in Khan et al (2014). [140]

The mapping algorithm (model 2 in Table 58) was used to estimate change in EQ-5D-Y utility values from baseline based on PedsQL data from the CADMUS trial (ustekinumab) at baseline and 12 weeks

follow-up (the time point at which response to treatment was assessed in the trial and blinding of randomised subjects in the trial was terminated; after this point cross-over between treatment arms was possible). The mean change in EQ-5D-Y between baseline and week 12 was estimated for individuals with different levels of PASI response. Table 60 reports the EQ-5D-Y utility values estimated for the base-case-analysis, with placebo and treatment arms pooled.

Table 60 Baseline utility and mean change in utility by PASI response estimated based on CADMUS PedsQL data mapped onto EQ-5D-Y

	Utility increment at the end of trial period			
Baseline utility[a] (n=73)	**PASI<50 (n=30)**	**PASI 50-75 (n=10)**	**PASI 75-90 (n=9)**	**PASI ≥90 (n=24)**
0.8596	0.0036	0.0255	0.0340	0.0810

[a]Estimated by pooling the EQ-5D-Y utility values at study baseline of patients in the ustekinumab 0.75 mg/Kg and placebo arms of CADMUS

The baseline utility estimate is similar to that derived from study 20030211 for etanercept (0.864 in Table 59) and is lower than the general healthy population estimate of 0.913 based on Varni et al (2012). [142]. The mean change in EQ-5D utility from baseline by PASI response categories is much smaller than that observed in previous TAs of adults. For example, the EQ-5D changes in utility by PASI response categories in the York model of adults were 0.05 for PASI <50, 0.17 for PASI 50-75, 0.19 for PASI 75-90 and 0.21 for PASI ≥90.

In order to examine whether the magnitude of change in EQ-5D-Y was accompanied by similar changes in other measures of HRQoL in the population of children and young people, the change in EQ-5D-Y was compared with reported CDLQI values by PASI response (Table 61). A comparison of EQ-5D and DLQI values by PASI response in adults is also shown in Table 61 (taken from TA 180 for ustekinumab, which was the only TA in adults which reported both outcomes). [85] The mean change in CDLQI by PASI response in the CADMUS trial is much smaller than the mean change in DLQI in TA 180, which is consistent with the smaller mean change estimated for EQ-5D-Y in the paediatric population compared to EQ-5D in adults. These differences, however, should be interpreted with caution since CDLQI and DLQI scores are not directly comparable and the number of observations is much smaller in the population of children and young people compared to the sample of adults in TA 180.

Table 61 Mean change from baseline in CDLQI/DLQI and EQ-5D/Y by PASI response

	CADMUS trial			TA 180		
	Sample size, n	**Mean change in CDLQI**	**Mean change in EQ-5D-Y**	**Sample size, n**	**Mean change in DLQI**	**Mean change in EQ-5D[a]**
PASI<50	30	[redacted]	0.0036	430	-2.5	0.04
PASI 50-75	10	[redacted]	0.0255	160	-10.3	0.17
PASI 75-90	9	[redacted]	0.0340	207	-13.4	0.22
PASI ≥90	24	[redacted]	0.0810	318	-15.3	0.25

[a]Pooled EQ-5D data collected in the Phoenix trials

The EQ-5D-Y utility estimates suggest that improvements in HRQoL associated with reductions in PASI response rates are of a much smaller magnitude in children and young people compared to adults; however, the evidence is highly uncertain due to the small sample size and the limited data available to validate the findings. In the absence of an alternative source to estimate EQ-5D values for the model, this is used in the base-case analysis. However, it is important to highlight a number of limitations with this approach. Firstly, the use of a mapping algorithm to estimate utilities introduces uncertainty compared to direct EQ-5D measurement. Secondly, the Khan et al (2014) mapping algorithm has not been validated in children younger than 11 years old or in a population with psoriasis. [140] Thirdly, the CADMUS trial from where the PedsQL data mapped to EQ-5D was sourced excluded children younger than 12 years; therefore, it remains uncertain whether the mapped utilities are reflective of children younger than 12 years old. Fourthly, in populations younger than 12 years, there may be issues with lack of agreement or consistency between self-reported and proxy (parent)-reported measurements. [143] Therefore, even if PedsQL data were available for younger children, the mapping algorithm might not consistently perform for self-reported and parent-reported measurements of the instrument. These limitations reduce the robustness of the utility estimates used in the model.

Given the uncertainty surrounding the utility estimates for children and young people, scenario analyses are conducted using utility estimates from previous TAs in adults for etanercept, adalimumab and ustekinumab. Table 62 summarises the utility estimates considered in the scenario analyses.

Table 62 Baseline utility values and mean change in EQ-5D by PASI response used in the base-case and scenario analysis

	Baseline utility	Utility gain by PASI response category			
		PASI<50	PASI 50-75	PASI 75-90	PASI ≥90
Base-case analysis	0.0036	0.0255	0.0340	0.0810	0.0036
TA103 utility values	0.7**	0.050	0.170	0.190	0.210
TA146 utility values*	NR***	0.063	0.178	0.178	0.308
TA180	0.692*	0.04	0.17	0.22	0.25

*DLQI>10; **Based on Revicki et al (2008), [130] as it was not reported in the TAs; ***Constrained to this value, so that the absolute utility valuewould not go above one for patients undergoing the maximum utility increment.

7.4.7 Utility estimates by health state

The HRQoL utility values are applied in the model based on PASI response to treatment. The utility values in the 'trial period' and period of 'continued use' for each treatment is based on the proportion of individuals in the different PASI response categories (<50, 50-75, 75-90, ≥90) and the change in utility from baseline associated with PASI response. During the trial period, individuals are assigned utility values based on treatment response at the end of the trial period:

$$u_{trt}^{TP} = [u_{00} \times (1 - p_{trt}^{PASI50}) + u_{50} \times (p_{trt}^{PASI50} - p_{trt}^{PASI75}) + u_{75} \times (p_{trt}^{PASI75} - p_{trt}^{PASI90}) + u_{90} \times (p_{trt}^{PASI90})]$$

where u_{00}, utility gain for individuals not achieving a PASI 50 response; u_{50}, utility gain for individuals achieving a PASI 50 response but not a PASI 75 response; u_{75}, utility gain for individuals achieving a PASI 75 response but not a PASI 90 response; u_{90}, utility gain for individuals achieving ≥ PASI 90 response; p_{trt}^{PASIxx}, probability of a PASI XX response with treatment.

During the period of continued use, individuals are assigned utility values based on maintaining treatment response at the end of the trial period, which is based on meeting the minimum of a PASI 75 response:

$$u_{trt}^{CU} = [u_{75} \times (p_{trt}^{PASI75} - p_{trt}^{PASI90}) + u_{90} \times (p_{trt}^{PASI90})]/p_{trt}^{PASI75}$$

Individuals who discontinue treatment progress to BSC. The utility associated with BSC is based on the proportion of individuals in the different PASI response categories (<50, 50-75, 75-90, ≥90) for BSC (assumed equal to placebo response from the NMA):

$$u_{BSC} = [u_{00} \times (1 - p_{BSC}^{PASI50}) + u_{50} \times (p_{BSC}^{PASI50} - p_{BSC}^{PASI75}) + u_{75} \times (p_{BSC}^{PASI75} - p_{BSC}^{PASI90}) + u_{90} \times (p_{BSC}^{PASI90})]$$

A scenario analysis is considered where the utility of individuals in BSC is set equal to baseline utility, i.e. there are no health benefits from BSC.

On entering the death state, individuals are assigned a utility value of zero. **Table 63** summarises the utility estimates applied in the base-case analysis by treatment and health state.

Table 63 Utility values by treatment and health state used in the base-case analysis

Treatment	Health state in model		
	Trial period	**Continued use**	**BSC**
Adalimumab	0.9156	0.9261	0.8713
Etanercept	0.8974	0.9177	0.8713
Ustekinumab	0.9186	0.9274	0.8713
Methotrexate	0.8994	0.9164	0.8713
BSC	-	-	0.8713

Given the paucity of evidence on adverse events in children and young people undergoing biological treatment for psoriasis and similarly to the majority of previous TAs in adults, no disutility from treatment was applied in the model.

7.4.8 Resource utilisation and costs

Resource use and costs included in the model correspond to direct NHS costs and include: treatment acquisition costs, administration costs, monitoring costs, costs associated with adverse events, and cost of BSC. Costs were sourced from NHS Reference Costs 2014-15, Monthly Index of Medical Specialities (MIMS), British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and published literature. Where costs were not available for 2015-16, costs are inflated to 2014-2015 based on the Hospital & Community Health Services Index published in the PSSRU (2015). [144] The systematic literature review described in Section 4.1 considered broad search terms in order to capture resource utilisation and costs associated with treatment for psoriasis in the population of children and young people. The search identified five studies [145 , 146, 147, 148 , 149] which estimated resource use and costs of biologic therapies in psoriasis from insurance claim databases, but upon further examination of the population included in the studies it became clear that only adults were considered in the databases. In addition, the studies used data from US insurance databases, which are unlikely to reflect health care resource utilisation in the UK.

Given the lack of data on resource use and costs of treatment for psoriasis in children and young people, previous NICE TAs for adults were hand-searched in order to identify relevant resource use categories and potential sources of resource use estimates and unit costs. These were tabulated and sent to our clinical advisor (see Section 6.4.5), who then worked with us in order to help establish the transferability of adult data and resource use assumptions to the population of children and young people.

Based on clinical opinion, the management of psoriasis in children and young people is very similar to that in adults, according to our clinical advisor. Therefore, it seems reasonable to assume that the resource use associated with the administration of the treatments and monitoring costs would be similar to that used in previous TAs in adults. The assumptions used for resource use and costs for each of the cost categories are described in the sections below.

7.4.9 Drug acquisition costs

Table 64 details the dose and frequency of administration for each treatment and comparator, including cyclosporine which forms part of BSC, and the unit costs associated with each treatment.

Table 64 Drug acquisition costs in children and young people

Treatment	Administration route	Dose / frequency	Presentation /Unit cost	Source

Adalimumab	SC	0.8mg/kg up to a maximum of 40 mg at weeks 0 and 1, then every 2 weeks thereafter	Pre filled syringe 40 mg £352.14	MIMS [150]
Etanercept	SC	0.8mg/kg up to a maximum of 50 mg weekly for up to 24 weeks	Pre filled syringe 25 mg /vial £89.38 Pre filled syringe 50 mg £178.75	MIMS [150]
Ustekinumab	SC	0.75mg/kg for bodyweight <60kg; 45mg for bodyweight 60-100kg; 90mg for bodyweight >100kg at weeks 0 and 4 then every 12 weeks thereafter	Injectable solution , vial 45 mg £2,147.00	MIMS [150]
Methotrexate	Oral (72%), SC (24%), IM (4%)	0.1-0.4 mg/Kg weekly	Oral solution 2 mg/mL 65 mL, £125.00 Injectable solution, Vial 50 mg £2.62	MIMS[150] BNF [151]
Cyclosporine	Oral	2-5 mg/Kg daily for up to 2 years	Oral solution, Neoral®, 100 mg/mL, 50 mL £102.30	BNF [151]

BNF, British National Formulary; SC, subcutaneous; IM, intramuscular.

The dose and posology of the biologic therapies were taken from the summary of product characteristics. For methotrexate and cyclosporine, which are currently not licensed for paediatric use, these were sourced from published literature and confirmed with our clinical advisor to ensure that they reflected UK clinical practice in this population. [152, 153, 154] Methotrexate can be administered orally or injected subcutaneously or intramuscularly. In the model, it is assumed that 72% of individuals are given methotrexate in oral solution and 28% in injectable solution, which reflects the distribution of administration identified in the UK psoriasis audit on the use of systemic treatments in

children and young people. [135] Therefore, the unit cost per mg for methotrexate is a weighted average of the unit cost per mg of the oral and injectable solutions (i.e. £0.71/mg). Unit costs were sourced from MIMS and supplemented by the British National Formulary. [135, 155]

Figure 11 illustrates the number of doses administered in the first five cycles of the model for each treatment based on the licensed dose. Adalimumab is administered at weeks 0 (baseline) and 1, and then every 2 weeks thereafter until response assessment at the end of week 16. If individuals are responders to treatment, they continue to receive adalimumab every two weeks until treatment withdrawal (highlighted in grey). Ustekinumab is administered at weeks 0 and 4, and then every 12 weeks thereafter, with response assessment at week 16. Etanercept and methotrexate are administered weekly, with response assessment at weeks 12 and 16, respectively.

Figure 11 Drug dose distribution during the first five cycles in the model

	Cycle 1				Cycle 2				Cycle 3				Cycle 4				Cycle 5			
ADA	●	●		●		●		●		●		●		●		●		●		●
ETA	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
UST	■				■												■			
MTX	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ
Weeks	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13	13-14	14-15	15-16	16-17	17-18	18-19	19-20

ADA, adalimumab; ETA, etanercept; MTX, methotrexate; UST, ustekinumab; ●, ADA administration; ♦ ETA administration; ■, UST administration; Δ, MTX administration.

The dosage of the interventions are dependent on patient weight. The median weight by age and gender in the population of children and young people was extracted from the Royal College of Paediatrics and Child Health's School age growth charts.[156] Table 65 shows the weight used in the model by age. This was based on an average of girls and boys weight (and where the weight estimate in the growth chart did not correspond to an integer, the next highest integer was used).

Table 65 Median weight by age used in the model

Age	Girls median weight (Kg)	Boys median weight (Kg)	Weight in the model (Kg)
4	17	18	17.5
5	19	19	19
6	21	21	21
7	23	23	23
8	26	26	26
9	29	29	29
10	33	32	32.5
11	36	35	35.5
12	41	39	40
13	46	44	45
14	50	50	50
15	54	56	55
16	56	61	58.5
17	57	66	61.5
18	58	67	62.5

The weight by age was used to estimate the correct dosage of each treatment and the corresponding costs. Table 66 summarises the dosages used in the model for each treatment and the corresponding cost per dose. Following clinical advice, it was assumed that the vial with the lowest dose available would be used to allow administration of a single dose in a paediatric population. This inevitably results in wastage of the remainder of the vial. For example, for individuals less than 60 Kg the full cost of the 45mg vial of ustekinumab is assumed as the remaining product in the vial cannot be stored. Vial splitting across individuals is considered unlikely because in most cases the majority of the vial is used for a single patient and treating patients together is less likely to occur in this population due to low patient numbers. Therefore, the cost per dose is fixed for adalimumab and ustekinumab (£352.14 and £2,147.00, respectively). For etanercept, children younger than 10 years old will receive the 25 mg vial (£89.38), while those 10 years and older will receive the 50 mg vial (£178.75).

Table 66 Drug dosages and cost per dose by age in the model

		Adalimumab **0.8 mg/kg, max 40 mg**		**Etanercept** **0.8 mg/kg, max 50 mg**		**Ustekinumab** **0.75mg/kg weight <60kg; 45mg for weight 60-100kg**		**Methotrexate** **0.4 mg/Kg**		**Cyclosporine** **5 mg/Kg**	
Age	**Weight (Kg)**	**Dosage (mg)**	**Cost per dose**	**Dosage (mg)**	**Cost per dose**	**Dosage (mg)**	**Cost per dose**	**Dosage (mg)**	**Cost per dose (£)**	**Dosage (mg)**	**Cost per dose (£)**
4	17.5	14	£352.14	-	-	-	-	7	£6.73	87.5	£1.79
5	19	15.2	£352.14	-	-	-	-	7.6	£7.31	95	£1.94
6	21	16.8	£352.14	16.8	£89.38	-	-	8.4	£8.08	105	£2.15
7	23	18.4	£352.14	18.4	£89.38	-	-	9.2	£8.85	115	£2.35
8	26	20.8	£352.14	20.8	£89.38	-	-	10.4	£10.00	130	£2.66
9	29	23.2	£352.14	23.2	£89.38	-	-	11.6	£11.15	145	£2.97
10	32.5	26	£352.14	26	£178.75	-	-	13	£12.50	162.5	£3.32
11	35.5	28.4	£352.14	28.4	£178.75	-	-	14.2	£13.65	177.5	£3.63
12	40	32	£352.14	32	£178.75	30.0	£2,147.00	16	£15.38	200	£4.09
13	45	36	£352.14	36	£178.75	33.8	£2,147.00	18	£17.31	225	£4.60
14	50	40	£352.14	40	£178.75	37.5	£2,147.00	20	£19.23	250	£5.12
15	55	40	£352.14	44	£178.75	41.3	£2,147.00	22	£21.15	275	£5.63
16	58.5	40	£352.14	46.8	£178.75	43.9	£2,147.00	23.4	£22.50	292.5	£5.98
17	61.5	40	£352.14	49.2	£178.75	45.0	£2,147.00	24.6	£23.65	307.5	£6.29
18	62.5	40	£352.14	50	£178.75	45.0	£2,147.00	25	£24.04	312.5	£6.39

The absence of values in the grey shaded areas reflect the fact that the intervention is not licensed for this age.

7.4.10 Drug administration costs

Adalimumab, etanercept and ustekinumab are assumed to be self-administered. In the case of younger children, it is assumed that a parent or carer would administer the subcutaneous (SC) injection. SC injections are assumed to incur administration costs only for nurse training for self (or parent/carer) administration in the induction phase. In line with previous TAs in adults, this was assumed to require three hours of nurse time, which was costed based on the cost per working hour of a band 5 hospital nurse with qualifications (£43 per hour). [144] A cost of £129 was applied in the first cycle of the model for the administration of the biologics.

7.4.11 Monitoring costs

Table 67 summarises the resource use assumptions for monitoring and corresponding unit costs applied in the model. In the absence of evidence specifically for the population of children and young people, resource use estimates associated with monitoring and routine laboratory tests for biologics and non-biologic systemic treatments have been taken from the NICE Clinical Guideline 153 (CG 153), [131] [157]which used similar assumptions to those in the original York model (TA 103) [88, 89] and in subsequent NICE appraisals of biologics.[84-87, 128]

Table 67 Monitoring resource use and unit costs

Frequency of testing	Biologic drugs		Methotrexate		Cyclosporine	Unit cost	
Item	**Trial period**	**Continued use (annual)**	**Trial period**	**Continued use/BSC (annual)**	**BSC (annual)**	**Per item**	**Source**
Liver function test (LFT)	2	4	2	4	4	£ 0.77[a]	TA103 [88, 89]
Full blood count (FBC)	2	4	2	4	4	£3.05[a]	TA103[88, 89]
Glomerular filtration rate (GFR)	0	0	0	0	1	£195.07[b]	NHS reference costs, 2014-15
Urea and Electrolytes (U&E)	2	4	2	4	4	£ 1.41[a]	TA103[88, 89]

Outpatient/ physician visits	2	4	2	4	4	£ 119.99[c]	NHS reference costs, 2014-15 [158]

[a]Costs inflated to 2014-15 prices based on the Hospital & Community Health Services Index published in the PSSRU (2015); [b]Activity weighted average of GFR as an outpatient procedure (currency codes RN27B and RN27C for ages below 5 years old and 6 to18 years); [c]Activity weighted average of non-admitted Face to Face Attendance, Follow-up , consultant and non-consultant led visits (service code:257 Paediatric Dermatology; currency code: WF01A).

Individuals on biologic therapy are assumed to undertake a series of tests during the initial trial period, namely a Full Blood Count (FBC), Liver Function Test (LFT), Urea and Electrolytes (U&E). During the trial period, the tests are assumed to be carried out during two routine outpatient visits that occur at treatment initiation and at the end of trial period (treatment response assessment visit). Since methotrexate was not included as a comparator in CG 153 (only as part of BSC), it is assumed that the resource use for the monitoring of methotrexate in the trial period is the same as the biologics. In the maintenance period (corresponding to the health state of 'continued use'), individuals on systemic therapies are assumed to be monitored once every three months. [157]The unit costs for Glomerular filtration rate (GFR) and outpatient visits were taken from NHS reference costs 2014-15, [158] while the costs of the remaining monitoring items were inflated to 2014-15 prices based on estimates presented in TA 103.

The cost of tests undertaken solely to screen individuals for eligibility for treatment are excluded from the analysis, namely chest X-rays, tests for tuberculosis or biopsies of lesions atypical of psoriasis. These costs were also excluded in previous appraisals in adults. The cost of acid folic used in conjunction with methotrexate to prevent side effects was also excluded from previous appraisals as the annual cost of this drug is very low (less than £1). Our clinical advisor indicated that children and young people would be tested for Herpes Zoster before treatment initiation. However, as this test would be performed on every patient not immune to the virus regardless of treatment, it was excluded from the analysis. The costs of liver biopsy and Type III Procollagen Peptide (PIIINP) for the purpose of assessing liver function in individuals treated with methotrexate is also excluded from the analysis based on clinical advice; liver biopsy is seldom conducted in children and young people given its invasiveness, while PIIINP is a marker of growth in this population rather than of hepatic toxicity.

7.4.12 Best supportive care costs

Best supportive care (BSC) corresponds to the management of individuals after failure of conventional systemic therapies. BSC is also considered a relevant comparator to biological treatments. If biologics are found not to be effective, individuals are usually offered some form of BSC rather than no treatment. BSC tends to include a mix of active non-biologic systemic therapies such as methotrexate and cyclosporine and palliative care, including phototherapy, as well as outpatient visits and hospitalisations to manage disease flare-ups.

The resource use and costs associated with BSC have represented a significant area of uncertainty in the cost-effectiveness of biologic treatments for moderate to severe psoriasis in adults. In TAs prior to CG 153, the definition of BSC in terms of resource use and costs was restricted to outpatient visits and hospitalisations to manage symptoms of psoriasis, and these were largely informed by assumptions and clinical opinion (TA 103, 134, 146 and 180). In CG 153, the definition of BSC was expanded to also include non-biologic systemic treatments, phototherapy and attendance at tertiary day centres. As discussed previously in Section 6.4.5, this guideline used estimates of resource use from observational studies in the UK (Fonia et al., 2010) [130] and The Netherlands (Driessen et al., 2010) [133] but also relied heavily on clinical opinion and assumptions. In the absence of evidence for children and young people, the definition of BSC in CG153 was used in the model with input from our clinical advisor on the appropriateness of the assumptions for a younger population.

Table 68 summarises the resource use assumptions for BSC by category of cost in CG 153 and those applied in the model, alongside the associated unit costs. Unit costs were sourced from the BNF 2016, [151] MIMS[150] and NHS reference costs 2014-15. [158] The relative proportion of individuals on active treatment with methotrexate and cyclosporine was modified from that used in CG 153 based on clinical opinion that children and young people are less likely to be managed with cyclosporine compared to adults due to the renal toxicity of the drug. Data from a UK psoriasis audit on the use of systemic treatments in children and young people was used to inform the relative proportion of individuals on methotrexate and cyclosporine. [135] In CG 153, it was assumed that 90% of individuals receiving BSC would be on active treatment with systemic drugs. However, in the audit 53 patients were treated with non-biologic systemic treatments; of these, 25 patients were treated with methotrexate and 12 with cyclosporine. Therefore, instead of assuming that individuals are equally distributed between methotrexate and cyclosporine, a ratio (25/37 and 12/37 for those on methotrexate and cyclosporine, respectively) for each treatment was applied to the overall proportion of 90% in order to reflect the distribution of children and young people receiving these treatments in the audit. The corresponding proportion of individuals assumed to receive methotrexate and cyclosporine as

part of BSC is 61% and 29%, respectively. As in CG 153, treatment with cyclosporine was assumed to be discontinued after a maximum duration of 2 years (due to increased risk of renal toxicity). Monitoring costs associated with the use of these non-biologic systemic therapies were applied in the model as presented in section 7.4.11 above.

In line with CG 153, the cost of 24 sessions of phototherapy per year (narrow band UVB) is assumed for 16% of the population, while 5 outpatient visits per annum are assumed for the 10% of individuals not managed with systemic therapies. All individuals are assumed to incur the costs of 5 visits per annum to a specialist dermatology day centre, in line with CG 153.

The resource use associated with hospitalisations for individuals on BSC was identified as an area of high uncertainty and a key driver of cost-effectiveness in the previous TAs in adults. The number of bed days assumed in CG 153 (26.6 days per year) was based on the average length of stay (LOS) for psoriasis patients with a baseline PASI of 10 to 20 points taken from a UK observational study (Wood et al., 2008) [134] combined with the average number of hospitalisations for individuals at high (1 hospitalisation per year) and very high need (2.55 hospitalisations per year) from a Dutch observational study (Driessen et al., 2010). [133] The total of 26.6 days of hospitalisation per annum was considered by NICE appraisal committees for TA 350 (secukinumab) and TA 368 (apremilast) in adults to be too high. Our clinical advisor suggested that hospitalisations in children and young people are very rare. This is largely because children and young people have not yet developed co-morbidities which often lead to hospitalisation with psoriasis in adults. Therefore, in the base-case analysis it is assumed that children and young people do not incur any inpatient stays. In separate scenario analyses, estimates of 26.6 days of hospitalisation per annum (CG 153) and 6.49 days of hospitalisation per annum from Fonia et al (2010) are considered. [157, #6851]

Table 68 Resource use assumptions and unit costs for BSC in CG 153 and current analysis

	CG 153		Current MTA		
	Resource use	**Unit costs**	**Resource use**	**Unit costs**	**Source**
Drug acquisition costs					
Methotrexate	45% of patients on MTX once weekly	£0.05/mg	**61%** of patients on MTX once weekly	£0.71/mg	MIMS [150] BNF [151]

Cyclosporine	45% of patients on CS daily for a maximum of 2 years	£0.02/mg	**29%** of patients on CS daily for a maximum of 2 years	£0.02/mg	BNF [151]
Health care utilisation costs					
NBUVB	16% of patients have 24 sessions of NBUVB per year	£85.16	16% of patients have 24 sessions of NBUVB per year **(same as CG 153)**	£95.53[a]	NHS reference costs 2014-15 [158]
Monitoring	4 monitoring visits per year for all patients on systemic treatment (including each 1 outpatient visit, 1 FBC, 1 LFT, 1 U&E) + 0.04 liver biopsies and 4 PIIINP per year for patients on MTX +1 GFR per year for patients on CS	£86.85 per monitoring visit £553 per liver biopsy £25.29 per PIIINP £233.00 per GFR	4 monitoring visits per year for all patients on systemic treatment (including each 1 outpatient visit, 1 FBC, 1 LFT, 1 U&E) +1 GFR per year for patients on CS **(same as CG 153 but without liver biopsies and PIIINP)**	£125.22 per monitoring visit for all patients on systemic treatment £195.07 per GFR[b]	Calculated (see section 7.2.9.3) For GFR - NHS reference costs 2014-15 [158]
Day centre care	5 visits per year	£362.60 per visit	5 visits per year **(same as CG 153)**	£472.55 per visit[c]	NHS reference costs 2014-15 [158]
Outpatient visits	5 visits per year for the 10 % patients that are not on systemic treatment	£82	5 visits per year for the 10 % patients that are not on systemic treatment **(same as CG 153)**	£119.99[d]	NHS reference costs 2014-15 [158]
Hospitalisations	26.6 bed days.	£271.17	**0 (base-case)** **Alternative values explored in scenario analysis**	£295.80[e]	NHS reference costs 2014-15 [158]

CS, cyclosporine; FBC, Full Blood Count; GFR, glomerular filtration rate; LFT, Liver Function Test; MTX, methotrexate; NBUVB, narrow band UVB phototherapy; PIIINP, Type III Procollagen Peptide; U&E, Urea and Electrolytes.

[a]Activity weighted average of phototherapy (currency codes JC47A and JC47B for ages below 12 years old and 13 and over) across Total HRGs; [b]Activity weighted average of GFR (currency codes RN27B and RN27C for ages below 5 years old and 6 to18 years) across Total HRGs; [c]Activity weighted average of Skin Disorders Without Interventions (currency codes JD07F-K) for day cases. [d]Activity weighted average of non-admitted Face to Face Attendance, Follow-up , consultant and

non-consultant led outpatient visits (service code:257 Paediatric Dermatology; currency code: WF01A); [e]Non-elective excess bed days across all HRGs.

7.4.13 Adverse event costs

As discussed in Section 6.4.5, only one previous TA in adults (TA 350) considered the costs of hospitalisations due to adverse events in their cost-effectiveness analysis. The adverse events that were assumed to lead to relevant resource use consumption (i.e. those leading to hospitalisations) in this evaluation were a) Non-melanoma skin cancer (NMSC), b) malignancies other than NMSC and c) severe infections. The rates of adverse events as reported in the literature (for adalimumab, etanercept, ustekinumab and infliximab) and from trial data (for secukinumab) were applied to each treatment arm as per the rates of these events occurring.

The safety data from the clinical trials of biologic drugs for the treatment of severe to moderate psoriasis (Sections 4.3.4, 4.4.4 and 4.5.4) suggested that there was little difference in the short- and long-term rates of adverse events between trial arms, with the potential exception of etanercept for which a higher rate of infections (not statistically significant) was observed compared to placebo. However, the trial data included a small number of observations for each treatment and a limited follow-up period (52 weeks for adalimumab to 312 weeks for etanercept). Observational studies in children and young people with psoriasis [75, 76](section 4.6) did not report any increase in infections or serious adverse events (SAEs) associated with the use of biological therapies.

Given the paucity of robust evidence on the incidence of adverse events in children and young people with moderate to severe psoriasis, the costs of these were not included in the base case analysis. However, scenario analyses were conducted to explore the impact on cost-effectiveness results by including the costs associated with hospitalisations due to serious infections serious infections and malignancies (both NMSC and other). The rates of adverse events were sourced from TA 350 and supplemented with data from Dixon et al (2006) [159] for methotrexate, while the unit costs were taken from the NHS reference cost schedule 2014-15. [158] Table 69 summarises the averse event rates applied in the model, alongside the respective unit costs.

Table 69 Adverse event rates applied in the model

Adverse events rates (rate/patient year)	Adalimumab	Etanercept	Ustekinumab	Methotrexate	Unit cost (£)
Non-melanoma skin cancer	0.0097	0.0354	0.0065	-	2,160.37[a]
Non NMSC malignancies	0.006	0.00043	0.0016	-	4,974.76[b]
Severe infections	0.0519	0.0513	0.01	0.0414	2,679.66[c]

[a]Activity weighted average of Intermediate Skin Procedures (currency codes JC42A and JC43B for ages below 12 years old and 13 and over) for non-elective admissions, excess bed days; [b]Activity weighted average of Intermediate Skin Procedures (currency codes JC42A and JC43B for ages below 12 years old and 13 and over) and Malignant Lymphoma (currency codes SA31A-E), for non-elective admissions, excess bed days; [c]Activity weighted average of Pneumonia (currency codes DZ14F-J, DZ23H-N, DZ11K-V), Skin Disorders (JS07A-D), Infections of Bones or Joints(currency code HD25D-H), and Kidney or Urinary Tract Infections (currency codes LA04H-S) for non-elective admissions, excess bed days.

The cost of adverse events associated with biological therapies and methotrexate is applied in the model to individuals while on treatment. Individuals treated with BSC are assumed not to develop adverse events.

7.4.14 Analytic methods

7.4.14.1 Base-case analysis

The expected costs and QALYs of the interventions and comparators are determined for each population, and the relative cost-effectiveness is established using standard decision rules and reported using incremental cost-effectiveness ratios (ICERs) as appropriate. The ICER examines the additional cost that one treatment option incurs over another and compares this with the additional health benefits to give the additional cost of the treatment for each additional QALY gained. When more than two treatment options are being compared, the ICERs are calculated using the following process:

- The treatment options are ranked in terms of mean QALYs (from the least effective to the most effective);
- If a treatment option is more costly and less effective than any other option, then this treatment is said to be dominated and is excluded from the calculation of the ICERs;

- The ICERs are calculated for each successive alternative, from the least effective to the most effective. If the ICER for a given treatment option is higher than that of any more effective option, then this treatment option is ruled out on the basis of extended dominance;
- Finally, the ICERs are recalculated, excluding any treatment options that are ruled out by principles of dominance or extended dominance.

The resulting ICERs provide the basis for establishing which treatment appears optimal based on cost-effectiveness considerations. Guidance from NICE suggests that an incremental cost per additional QALY of around £20,000-£30,000 is considered to represent an appropriate threshold of the health opportunity costs to the NHS.

The ICER comparing all interventions and comparators relates to a situation where the decision maker can only choose one of the treatment options. However, as indicated previously, if an individual patient does not respond to or tolerate one of the biological therapies an alternative one is usually tried. This means that treatments are usually trialled on an individual basis until an effective option is found in children and young people. The ICERs comparing each intervention with BSC (after systemic therapy) or methotrexate (before systemic therapy) is also presented. This is used to indicate the optimum ordering of treatments in terms of their cost-effectiveness. The most cost-effective order in which to give the therapies based on total expected costs and QALYs associated with each treatment option is dependent on the cost-effectiveness threshold.

Probabilistic sensitivity analysis is used to represent uncertainty in the cost-effectiveness results. The effectiveness data are entered as simulated posterior distributions from the Markov Chain Monte Carlo analysis to reflect uncertainty in the mean estimates. Monte Carlo simulation is used to propagate the uncertainty in the input parameters over 10,000 draws, from which mean costs and QALYs are then obtained by averaging over the 10,000 simulations. The probability that a treatment is first in the sequence is also estimated.

Differences in the marketing authorisation of the interventions by age and positioning of adalimumab before non-biological systemic therapy means that the comparative cost-effectiveness of the interventions needs to be evaluated by age and before or after use of systemics. The relevant comparator also depends on the position of the intervention in the pathway. Before systemic therapy, methotrexate is the relevant comparator (as the current standard of care), whereas after systemic therapy BSC represents the most relevant comparator. Three base-case populations are presented:

(i) Children and young people aged 4-17 years with adalimumab compared to methotrexate, i.e. as a second-line therapy in individuals who are inadequately controlled by, or intolerant to, topical therapy and phototherapies;

(ii) Children and young people aged 6-11 years with adalimumab and etanercept compared to BSC, and each other, i.e. as a third-line therapy in individuals who are inadequately controlled by, or intolerant to, systemic therapies or phototherapies;

(iii) Children and young people aged 12-17 years with adalimumab, etanercept and ustekinumab compared to BSC, and each other, i.e. as a third-line therapy in individuals who are inadequately controlled by, or intolerant to, systemic therapies or phototherapies.

Table 70 summarises the input parameters used in the base-case analysis.

Table 70 Summary of parameters in the model

Parameter	Mean	SE	Source
Baseline age (years)	4, 6 or 12	-	According to license for each comparator
Discount rate (per year)	3.5%	-	NICE methods guideline
Time horizon (years)	14, 12 or 6	-	Assumption: Until individuals reach 18 years
Duration of treatment trial period (weeks)			
Adalimumab	16	-	License definition of timing for treatment response assessment
Etanercept	12	-	
Ustekinumab	16	-	
Methotrexate	16	-	Response assessment in study M04-717
Treatment response - adalimumab		Simulated posterior distribution from the Bayesian network meta-analysis	NMA (Section 5.4.3.4)
Probability of PASI 50	91.5%		
Probability of PASI 75	79.0%		
Probability of PASI 90	54.6%		
Treatment response - etanercept			
Probability of PASI 50	75.2%		
Probability of PASI 75	54.4%		
Probability of PASI 90	27.9%		

Parameter	Mean	SE	Source
Treatment response - ustekinumab			
Probability of PASI 50	93.4%		
Probability of PASI 75	82.4%		
Probability of PASI 90	59.4%		
Treatment response - methotrexate			
Probability of PASI 50	70.8%		
Probability of PASI 75	49.2%		
Probability of PASI 90	23.9%		
Treatment response - BSC			
Probability of PASI 50	26.5%		
Probability of PASI 75	11.5%		
Probability of PASI 90	2.9%		
Withdrawal rate (annual)	0.20	SE=mean/4	Assumption based on adult data
Mortality rate	Age varying	-	Life table data for England & Wales 2013-15 [138]
Baseline utility	0.8596	-	CADMUS trial PedsQL data [141] mapped into EQ-5D using the algorithm by Khan et al, 2014 [140]
Utility Increment for PASI<50	0.0036	-	
Utility Increment for PASI50-75	0.0255	-	
Utility Increment for PASI50-90	0.0340	-	
Utility Increment for PASI>=90	0.0810	-	
Drug acquisition resource use and costs			
Adalimumab administrations in 'Trial Period'	9	-	According to license
Etanercept administrations in 'Trial Period'	12	-	
Ustekinumab administrations in 'Trial Period'	2	-	
Methotrexate administrations in 'Trial Period'	16	-	
Adalimumab administrations per cycle in 'Continued use'	2	-	
Etanercept administrations per cycle in 'Continued use'	4	-	

Parameter	Mean	SE	Source
Ustekinumab administrations per cycle in 'Continued use'	0.33	-	
Methotrexate administrations per cycle in 'Continued use' and 'BSC'	4	-	
Ciclosporin administrations per cycle in 'BSC'	28	-	
Proportion of patients on methotrexate in 'BSC'	61%	-	Assumption
Proportion of patients on ciclosporin in 'BSC'	29%	-	
Dosage of methotrexate (per Kg)	0.4 mg	-	Same as in M04-717 trial; de Jager et al (2010) [152]
Dosage of ciclosporin (per Kg)	5 mg	-	Clinical opinion; Mahé et al, (2001) ; Pereira et al (2006). [153, 154]
Adalimumab cost per dose	£352.14	-	MIMS [150]
Etanercept cost per dose (< 10 years old)	£89.38	-	MIMS [150]
Etanercept cost per dose (≥ 10 years old)	£178.75	-	MIMS [150]
Ustekinumab cost per dose	£2,147	-	MIMS [150]
Methotrexate cost per mg	£ 0.71	-	BNF [151]
Ciclosporin cost per mg	£ 0.02	-	BNF [151]
Drug administration costs			
Self-administration instruction (hours)	3	-	Assumption
Cost of hospital nurse Band 5 time (per hour)	£43	-	PSSRU 2015 [144]
Monitoring frequency			
FBC, LFT, U&E and physician visits for adalimumab, etanercept, ustekinumab and methotrexate in 'Trial Period'	2	-	Assumption based on adult data
FBC, LFT, U&E and physician visits for adalimumab, etanercept, ustekinumab and methotrexate per annum in 'Continued Use'	4	-	
FBC, LFT, U&E and physician visits for ciclosporin and methotrexate per annum in 'BSC'	4	-	
GFR for ciclosporin per annum in 'BSC'	1	-	
Monitoring test costs			

Parameter	Mean	SE	Source
FBC	£3.05	-	TA 103 [88, 89]
LFT	£0.77	-	
U&E	£1.41	-	
GFR	£195.07	-	NHS reference costs 2014-15 [158]
Physician monitoring visit	£119.99	-	
Palliative care resource use and costs in BSC		-	
NBUVB sessions per cycle	3.84	-	Assumption based on CG 153 (adults)
Day centre care visits	5	-	
Outpatient visits	0.5	-	
NBUVB cost per sessions	£95.53	-	NHS reference costs 2014/-15 [158]
Day centre care cost per visit	£472.55	-	
Outpatient cost per visit	£119.99	-	

7.4.14.2 Scenario analysis

A number of alternative scenarios are considered in which the assumptions used as part of the base-case analysis are varied. These analyses are undertaken to assess the robustness of the base-case results to variation in the assumptions and sources of the data used to populate the model. Table 71 summarises the alternative scenarios considered. For each element, the position in the base-case analysis is outlined, alongside the alternative assumptions applied. The cost-effectiveness of the interventions is considered under each of the scenarios for each of the licensed populations.

Table 71 Details of the key elements of the base-case analysis and the variation used in the scenario analysis

Scenario	Element	Position in base-case analysis	Variation in scenario analysis
Intervention and comparators			
1	Off-label use of biologics outside of age constraints	Adalimumab licensed for age 4+ years; Etanercept licensed for age 6+ years; Ustekinumab licensed for age 12+ years	Adalimumab, etanercept and ustekinumab for age 4+ years
Model time horizon			
2	Time horizon of model	14 years, 12 years and 6 years for populations 1 to 3, respectively (i.e. until individuals reach 18 years old)	Common time horizon of 14 years
Treatment effectiveness estimates			
3a	Direct trial evidence for treatment effects in children and young people	NMA using full network of evidence in children, young people and adults	M04-717 used to inform ADA vs. MTX; 20030211 used to inform ETA vs. BSC; CADMUS used to inform UST vs. BSC
3b	Indirect treatment comparison in children and young people		Indirect treatment comparison used to inform ETA vs. UST vs. BSC
3c	NMA using minimum evidence from the adult population		NMA using minimum evidence from the adult population (CHAMPION study) to link the trials in children and young people
3d	PASI response assessment	PASI 75	PASI 50
Health-related quality of life utility values			

4a	EQ-5D utility estimates from adults	PedsQL data mapped onto EQ-5D-Y	EQ-5D values from TA 103; TA 146; TA 180
4b	Utility estimates for BSC	Utility gains for BSC weighted by PASI response associated with placebo from NMA	Utility in BSC equal to baseline value (i.e. no utility gain associated with BSC)
Best supportive care costs			
5	Hospitalisations for BSC	No inpatient stay included for children and young people	6.49 days per annum based on Fonia et al (2010) in adults; 26.6 days per annum based on CG 153 in adults
Adverse events costs			
6	Costs associated with adverse events	Not included	Costs of severe infections included; Costs of severe infections and malignancies included
Treatment withdrawal rates			
7	Withdrawal rates from treatment	20% per annum	10% per annum; 30% per annum
Biosimilars			
8	Biosimlar for etanercept	Unit cost of etanercept	Unit cost of Benepali 50 mg (biosimilar)

7.5 Results

7.5.1 Results of the base-case cost-effectiveness analysis

Table 72 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy. Adalimumab is more costly (additional cost of £27,084) but also more effective than methotrexate (incremental gain in QALYs of 0.088). The resulting ICER is £308,329 per QALY gained. The small incremental gain in QALYs for adalimumab compared with methotrexate is a result of the modest utility increments in EQ-5D-Y for the different PASI response categories (<50, 50-75, 75-90, ≥90). The average proportion of individuals achieving PASI 75 response is 79% for adalimumab compared to 49% for methotrexate but the utility gain for individuals achieving a PASI 75–90 and PASI ≥90 response are very small at 0.0340 and 0.0810, respectively. Therefore, the difference in effectiveness translates into a small utility gain while on treatment with adalimumab compared to methotrexate. The difference in total costs for adalimumab compared to methotrexate is driven by the difference in treatment costs of adalimumab of £704.28 per 4-week cycle in the model (i.e. £352.14 per dose every 2 weeks) compared to methotrexate costs of approximately £60 per 4-week cycle. The difference in treatment costs is partly offset by the greater efficacy associated with adalimumab which results in lower costs associated with BSC (i.e. less time spent in BSC) for non-responders compared to higher costs on BSC with methotrexate, but this offset is not sufficient to outweigh the difference in treatment costs. The probability that adalimumab is cost-effective at a threshold of £30,000 per additional QALY is zero.

Table 72 Base-case probabilistic results for adalimumab as an alternative to systemic therapy

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						
MTX	34,914	9.939	-	-	-	MTX
ADA	61,999	10.027	27,084	0.088	308,329	

ADA , adalimumab; MTX, methotrexate.

Table 73 presents the cost-effectiveness results for the interventions after failed systemic therapy by age group. The difference in age group reflects the fact that ustekinumab does not have marketing authorisation for use in children and young people below 12 years of age. For the younger age group of 6-11 years, adalimumab is the most effective treatment (8.890 QALYs), followed by etanercept (8.813 QALYs) and BSC (8.710 QALYs). In terms of costs, adalimumab is the most costly treatment (£57,251), followed by etanercept (£43,808) and BSC (£36,406). Based on a fully incremental analysis, the ICER of etanercept compared to BSC is £71,903 per additional QALY, while the ICER of adalimumab compared to etanercept is £174,519 per additional QALY. The individual pairwise ICERs for etanercept and adalimumab compared to BSC are £71,903 and £115,825 per additional QALY, respectively.

For children and young people aged 12-17 years, ustekinumab is the most effective treatment (4.960 QALYs), followed by adalimumab (4.950 QALYs), etanercept (4.887 QALYs) and BSC (4.804 QALYs). In terms of costs, ustekinumab is the most costly treatment (£39,975), followed by adalimumab (£37,852), etanercept (£33,199) and BSC (£21,749). Based on a fully incremental analysis, etanercept is extendedly dominated by adalimumab (i.e. etanercept produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy of adalimumab, observed by a higher ICER for etanercept than that of adalimumab), the ICER of adalimumab compared to BSC is £110,430 per additional QALY, and the ICER of ustekinumab compared to adalimumab is £201,507 per additional QALY. The individual pairwise ICERs for etanercept, adalimumab and ustekinumab compared to BSC are £137,059, £110,430 and £116,568 per additional QALY, respectively.

Table 73 Base-case probabilistic results for interventions after failed systemic therapy

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	43,808	8.813	7,402	0.103	71,903	71,903	
ADA	57,251	8.890	13,444	0.077	174,519	115,825	
Children and young people aged 12-17 years							

BSC	21,749	4.804	-	-	-	-	BSC
ETA	33,199	4.887	11,450	0.084	ED ADA	137,059	
ADA	37,852	4.950	16,103	0.146	110,430	110,430	
UST	39,975	4.960	2,123	0.011	201,507	116,568	

ADA , adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

There are two important differences to note between the two age populations. Firstly, the reduction in total costs and QALYs for the interventions in the age group of 12-17 years is an artefact of the difference in model time horizon used in each analysis (i.e. 12 years for age group 6-11 years and 6 years for age group 12-17 years). The time horizon of the model extends until individuals reach 18 years of age, at which point it is assumed that separate NICE recommendations for the interventions in adults apply. A separate scenario analysis is presented below which considers a common time horizon of 14 years for both age populations, which is sufficient to capture differences in costs and effects between the interventions. Secondly, the total costs of etanercept are proportionally greater in the age group 12-17 years compared to the costs of etanercept for ages 6-11 years. This is due to the higher drug acquisition costs of etanercept once individuals reach 10 years old, i.e. etanercept costs £715 per 4-week cycle in the model (i.e. £178.75 per 50 mg dose each week) for age 10 years and older, whereas etanercept costs £357.50 per 4-week cycle in the model (i.e. £89.38 per 25 mg dose each week) for children younger than 10 years.

For children and young people aged 6-11 years, adalimumab is the most effective treatment but the incremental gain in QALYs compared to etanercept is relatively small because the utility gains in EQ-5D-Y associated with higher PASI response rates are small. Therefore, the benefits of achieving a greater PASI response do not translate into a large improvement in health outcomes. The benefit of more individuals achieving a higher PASI response rate manifests itself in lower costs associated with less time spent in BSC. The average proportion of individuals achieving PASI 75 response is 79% for adalimumab and 54% for etanercept. The higher efficacy associated with adalimumab compared to etanercept, which results in fewer individuals accumulating the costs associated with BSC (approximately £284 per 4-week cycle), is not sufficient to offset the additional treatment costs for adalimumab, which are £704.28 per 4-week cycle (i.e. £352.14 per dose every 2 weeks) compared to £357.50 per 4-week cycle for etanercept in children under 10 years and £715 per 4-week cycle for age 10 years and older (note that although the costs for etanercept increase at age 10 years, there are fewer

individuals receiving treatment because the starting age in the model is 6 years and the treatment withdrawal rate is assumed to be 20% per annum).

For children and young people aged 12-17 years, ustekinumab is the most effective treatment but again the incremental gain in QALYs compared to the alternative interventions is relatively small due to the small magnitude of utility gains for the different PASI response categories in the population of children and young people compared to adults (see Section 7.4.7). The drug acquisition costs of etanercept in young people aged 12 years and older are greater than those of adalimumab (£715 for etanercept compared to £704.28 for adalimumab per 4-week cycle), while the efficacy for adalimumab is greater than etanercept, which reduces the time on BSC for treatment with adalimumab. As a result, it might be expected that the total costs of adalimumab are lower than etanercept; however, the improved efficacy for adalimumab also extends the time that individuals receive the intervention and therefore the overall costs for adalimumab increase. Despite this, the incremental costs of etanercept relative to BSC are greater for each additional gain in QALYs compared to the incremental costs of adalimumab relative to BSC for each QALY gain. As a result, adalimumab extendedly dominates etanercept, which rules out etanercept as a potential cost-effective treatment option.

Ustekinumab has the highest average proportion of individuals achieving a PASI 75 response rate of 82% compared to 79% for adalimumab and 54% for etanercept, but also has the highest total costs. The higher total costs for ustekinumab compared to adalimumab are due to marginally higher drug acquisition costs associated with ustekinumab of £715.67 per 4-week cycle (i.e. £2,147 per dose with each dose given at 12 weekly intervals) compared to £704.28 per 4-week cycle (i.e. £352.14 per dose at fortnightly intervals) for adalimumab and a greater cost of ustekinumab during the induction period (i.e. a cost of £2,147 per dose given at baseline, 4 weeks and 16 weeks) compared to adalimumab in the induction period (i.e. a cost of £352.14 per dose given at baseline, 1 week and then every 2 weeks up to week 16). The higher efficacy associated with ustekinumab compared to adalimumab with an average of 3% more individuals achieving PASI 75 response results in a reduction in costs associated with individuals remaining off BSC for longer for ustekinumab, but this reduction is not sufficient to offset the additional treatment costs associated with ustekinumab.

The pairwise ICERs for each of the interventions compared to BSC indicate the ICER at which the particular therapy might enter a sequence. Under base-case assumptions, these ICERs are very high, ranging from £110,430 (adalimumab) to £137,059 (etanercept) per additional QALY in children and

young people aged 12-17 years. The optimal treatment option is BSC up until the threshold reaches £111,000 per QALY gained, when adalimumab would then enter as the first treatment in sequence. The fact that BSC is the only form of management listed until the threshold reaches £111,000 per QALY suggests that, under base-case assumptions, none of the biological therapies are sufficiently cost-effective to enter the sequence until this threshold is used. The probability that any of the biologics are cost-effective at a threshold of £30,000 per additional QALY is zero.

7.5.2 Cost-effectiveness results for alternative scenarios

7.5.2.1 Intervention and comparators

Scenario 1: Off-label use of biologics outside of age constraints and position in pathway

As discussed in Section 7.2, the biologic interventions differ in their marketing authorisation by age and positioning of treatment in the pathway. Adalimumab is licensed for the youngest age of 4 years and older and is the only biological treatment positioned as a second-line therapy in individuals who are inadequately controlled by, or intolerant to, topical therapy and phototherapies, i.e. as an alternative to systemic therapy. This makes the comparison of adalimumab with etanercept and ustekinumab more problematic since the latter interventions are licensed as third-line therapies in individuals who are inadequately controlled by, or intolerant to, systemic therapies or phototherapies and for ages 6 years and older in the case of etanercept and 12 years and older for ustekinumab. In this scenario, the off-label use of the biologics outside of their age constraints and positioning in the management pathway is considered.

In the absence of clinical effectiveness evidence in a systemic-naïve population, the same efficacy estimates as the base-case analysis is used in this scenario. Therefore, the only difference between this scenario and the base-case assumptions is the comparator, which is methotrexate in the analysis that considers biologics as an alternative to systemic therapy, and the time horizon of the model, which extends to 14 years because the starting age in the model is now 4 years.

Table 74 presents the cost-effectiveness results for the interventions as an alternative to systemic therapy for all ages (4-17 years). Ustekinumab is the most effective treatment, followed by adalimumab, etanercept and methotrexate, since the efficacy of the treatments follow in this order. In terms of costs, ustekinumab is the most costly treatment, followed by adalimumab, etanercept and

methotrexate. The reason for this ordering is the same as the base-case results where ustekinumab costs £715.67 per 4-week cycle compared to adalimumab at £704.28, etanercept at £357.50 for <10 years and £715 for ≥10 years, and methotrexate at approximately £60 per cycle, but the reduction in costs associated with improved efficacy (i.e. less time spent on BSC) is not sufficient to offset the additional treatment costs. Based on a fully incremental analysis, the incremental costs of etanercept and adalimumab relative to methotrexate are greater for each additional gain in QALYs compared to the incremental costs of ustekinumab relative to methotrexate for each QALY gain. Therefore, etanercept and adalimumab are extendedly dominated by ustekinumab. The ICER of ustekinumab compared to methotrexate is very high at £293,117 per QALY gained. As a result, the optimal treatment option in a systemic-naïve population is methotrexate.

Table 74 Scenario 1 results for interventions as an alternative to systemic therapy: Off-label use of biologics outside of age constraints and position in pathway

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years							
MTX	34,914	9.939	-	-	-	-	MTX
ETA	46,767	9.948	11,853	0.009	ED ADA	1,319,539	
ADA	61,999	10.027	27,084	0.088	ED UST	308,329	
UST	64,426	10.040	29,512	0.101	293,117	293,117	

ADA , adalimumab; BSC, best supportive care; ETA, etanercept; MTX, methotrexate; UST, ustekinumab.

Table 75 presents the cost-effectiveness results for the interventions after failed systemic therapy for all ages (4-17 years). The only difference between this scenario and the base-case analysis is the starting age used in the model of 4 years. The total absolute costs and QALYs are greater compared to the base-case due to a longer model time horizon of 14 years. The ordering of the treatments in terms of costs and QALYs follows that of the base-case with ustekinumab the most effective but more costly treatment, followed by adalimumab, etanercept and BSC. Based on a fully incremental analysis, adalimumab is extendedly dominated by ustekinumab. Compared to the base-case population of ages 12-17 years, etanercept is no longer extendedly dominated because there are more

individuals receiving a lower dose of etanercept at the cost of a 25 mg vial rather than a 50 mg vial. The ICERs are lower than the base-case analysis, but the optimal treatment option remains as BSC. BSC is the optimal option until the threshold reaches £60,000 per QALY gained, when etanercept would then enter as the first treatment in sequence.

Table 75 Scenario 1 results for interventions after failed systemic therapy: Off-label use of biologics outside of age constraints

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years							
BSC	40,478	9.843	-	-	-	-	BSC
ETA	46,767	9.948	6,289	0.105	59,924	59,924	
ADA	61,999	10.027	15,231	0.079	ED UST	117,080	
UST	64,426	10.040	23,948	0.013	121,779	121,779	

ADA , adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.2 Model time horizon

Scenario 2: Time horizon of model

The time horizon of the model was chosen to reflect the fact that once individuals reach 18 years of age separate NICE recommendations for the use of the interventions in adults apply. In order to incorporate these recommendations, evidence on the efficacy of the treatments in biologic experienced patients (i.e. effectiveness estimates conditional on prior biologic therapy) would be required. This would involve modelling the sequential use of therapies, with every possible potential treatment sequence considered based on current recommendations in adults. As well as being outside the scope of this appraisal, this would represent a significant challenge for two reasons; firstly, there is very limited evidence on the efficacy of biologics when used in sequence, i.e. in biologic experienced patients; and secondly, current NICE recommendations for the use of biologic therapies in moderate to severe psoriasis in adults have been informed by a series of STAs rather than an MTA that establishes the optimal sequence of treatments in adults.

Furthermore, the differences in marketing authorisation of the interventions by age inevitably means that the time horizon of the model will differ according to age group. In this scenario, the impact of the time horizon is assessed by considering a common time horizon of 14 years for all age groups, but with the same starting age for each group as used in the base-case analysis. The time horizon of 14 years is sufficient to capture differences in costs and effects between the interventions under comparison because all individuals on each treatment in the model have moved to BSC by 14 years. This time horizon is also greater than 10 years as used in previous TAs in adults.

The base-case results for adalimumab as an alternative to systemic therapy already considers a time horizon of 14 years because the starting age is 4 years. Therefore, Table 76 presents the cost-effectiveness results for the interventions after failed systemic therapy for a common time horizon of 14 years. By extending the time horizon, the total costs and QALYs for the interventions are greater compared to the base-case results, but the relative cost-effectiveness of the interventions remain the same, i.e. the ICERs for each intervention relative to the next best treatment option or BSC are similar to those observed in the base-case. Therefore, the model time horizon used in the base-case analysis is sufficient to capture the differences between the interventions in terms of costs and QALYs.

Table 76 Scenario 2 results for interventions after failed systemic therapy: Common time horizon of 14 years

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	41,413	9.842	-	-	-	-	BSC
ETA	49,109	9.948	7,696	0.105	73,153	73,153	
ADA	62,723	10.027	13,614	0.079	172,000	115,592	
Children and young people aged 12-17 years							
BSC	44,010	9.836	-	-	-	-	BSC
ETA	58,286	9.942	14,275	0.105	ED ADA	135,354	
ADA	64,204	10.021	20,194	0.184	109,531	109,531	
UST	66,503	10.033	2,299	0.012	188,715	114,439	

ADA , adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.3 Treatment effectiveness estimates

Scenario 3a: Direct trial evidence for treatment effects in children and young people

As discussed in Section 5, a NMA was used in the base-case analysis to connect the evidence from the adalimumab trial (M04-717) in children and young people to the evidence from the etanercept (20030211) and ustekinumab (CADMUS) trials by drawing strength from the wider network of evidence in adults. In this scenario, the relative cost-effectiveness of adalimumab compared to methotrexate, and etanercept and ustekinumab compared to BSC, is considered using the direct efficacy estimates derived from their corresponding trials. The limitation of this approach is that it does not allow the relative cost-effectiveness of all three biologics to be assessed in the same analysis. However, it may give an indication of how much influence the wider network of evidence has on the individual pairwise comparisons.

Table 77 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy using the efficacy estimates from the M04-717 trial alone. The incremental costs (£20,256) and QALYs (0.037) for adalimumab compared to methotrexate are lower than the base-case incremental costs (£27,084) and QALYs (0.088). The PASI 75 response rate is 58% for adalimumab and 32% for methotrexate from trial M04-717 compared to 79% and 49%, respectively, from the NMA. The NMA estimates higher absolute values for PASI 75, but the incremental difference between adalimumab and methotrexate is of a similar magnitude in the NMA (30% difference in PASI 75) and M04-717 (26% difference in PASI 75). This smaller difference in relative effectiveness between adalimumab and methotrexate from M04-717 means that the incremental costs for each additional gain in QALYs is greater for adalimumab compared to methotrexate. The resulting ICER increases from £308,329 per additional QALY in the base-case analysis to £549,899 per additional QALY with the direct trial evidence.

Table 77 Scenario 3a results for adalimumab as an alternative to systemic therapy: Direct trial evidence for treatment effects in children and young people

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)

Children and young people aged 4-17 years						
MTX	36,601	9.919	-	-	-	MTX
ADA	56,857	9.956	20,256	0.037	549,899	

ADA , adalimumab; MTX, methotrexate.

Table 78 presents the cost-effectiveness results for the interventions after failed systemic therapy using the efficacy estimates from study 20030211 (etanercept) and CADMUS (ustekinumab). The total costs and QALYs for etanercept and ustekinumab compared with BSC are very similar to the base-case results. This is because the PASI 75 response rates estimated from the NMA for etanercept (54%), ustekinumab (82%) and placebo (11.5%) are very similar to the corresponding response rates from the individual trials (81% ustekinumab vs. 11% placebo, CADMUS; 57% etanercept vs. 11.4% placebo, study 20030211). As a result, the pairwise ICERs for etanercept and ustekinumab compared to BSC are similar to the base-case analysis: ICER for etanercept vs. BSC increases from £71,903 per QALY in base-case analysis to £75,350 per QALY using direct trial evidence, while the ICER for ustekinumab vs. BSC increases marginally from £116,568 per QALY in base-case analysis to £116,982 per QALY using direct trial evidence.

Table 78 Scenario 3a results for interventions after failed systemic therapy: Direct trial evidence for treatment effects in children and young people

	Mean costs (£)	Mean QALYs	Incremental costs vs. BSC (£)	Incremental QALYs vs. BSC	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years						
BSC	36,406	8.720	-	-	-	BSC
ETA	44,108	8.822	7,701	0.102	75,350	
Children and young people aged 12-17 years						
BSC	21,749	4.814	-	-	-	BSC
UST	39,622	4.966	17,873	0.153	116,982	

ADA , adalimumab; BSC, best supportive care; ETA, etanercept; UST, ustekinumab.

Scenario 3b: Indirect treatment comparison estimates in children and young people

In this scenario, the relative cost-effectiveness of etanercept and ustekinumab compared to BSC is considered using the indirect treatment comparison estimates from study 20030211 and CADMUS, with placebo used as a common comparator. The limitation of this approach is that it does not allow the relative cost-effectiveness of etanercept and ustekinumab to be compared with adalimumab due to the absence of a placebo arm in M04-717.

Table 79 presents the cost-effectiveness results for the interventions after failed systemic therapy using efficacy estimates from an indirect treatment comparison of etanercept from study 20030211 and ustekinumab from CADMUS. The total costs and QALYs for etanercept, ustekinumab and BSC are similar to the base-case analysis. This is expected since the efficacy estimates from the individual trials for these interventions are similar to those estimated in the NMA. Etanercept is extendedly dominated by ustekinumab since the incremental costs of etanercept relative to BSC are greater for each additional gain in QALYs compared to the incremental costs of ustekinumab relative to BSC for each QALY gain. This occurs because ustekinumab has better efficacy (78% PASI 75 response) compared to etanercept (57% PASI 75 response), which results in improved health outcomes for ustekinumab. Interestingly, the total costs for ustekinumab are greater than etanercept despite the fact that the drug acquisation costs are similar between the two treatments in children and young people aged 12-17 years. This arises because although the improved efficacy reduces the time spent on BSC, it also means that a greater proportion of time is spent on a cost-ineffective treatment option. The ICER of ustekinumab compared to BSC is £119,092 per QALY gained. As a result, the optimal treatment option is BSC unless the cost-effectiveness threshold reaches £120,000 per additional QALY.

Table 79 Scenario 3b results for interventions after failed systemic therapy: Indirect treatment comparison estimates in children and young people

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 12-17 years							
BSC	21,749	4.809	-	-	-	-	BSC
ETA	33,662	4.901	11,913	0.092	ED UST	128,903	

UST	39,105	4.955	17,356	0.146	119,092	119,092	

ADA , adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

Scenario 3c: Treatment effects from NMA using minimum evidence from adult population

In Section 5 the disconnected network of evidence in children and young people was connected in the first instance by bringing together the minimum amount of evidence required from the adult population in order to link the adalimumab trial with the other paediatric trials. The CHAMPION study in adults, which was a three-arm trial comparing adalimumab, methotrexate and placebo, represented the best way to connect adalimumab to etanercept and ustekinumab using the least amount of evidence borrowed from the adult population. In this scenario, the relative cost-effectiveness of the interventions are considered in the base-case populations using the treatment effects estimated from the minimum network of evidence.

Table 80 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy using the NMA with minimum links to adult evidence. The incremental costs for adalimumab compared to methotrexate of £18,422 are lower than the base-case analysis of £27,084. This is due to a larger difference in PASI 75 response rates between adalimumab and methotrexate in the minimum NMA (approximately 40% difference) compared to the full network of evidence (approximately 30% difference). Although there is a higher efficacy difference between adalimumab and methotrexate in this scenario, the health outcomes also depend on the utility associated with BSC, which is based on the proportion of individuals in the different PASI response categories for the placebo arm in the NMA. In the minimum NMA, the PASI response rates for placebo are greater than the full network. Therefore, the gain in utility associated with better efficacy on adalimumab is offset by a higher gain in utility associated with BSC. As a result, the incremental QALYs for adalimumab compared to methotrexate are very similar to the base-case analysis. The corresponding ICER for adalimumab vs. methotrexate is reduced from the base-case of £308,329 to £211,259 per additional QALY.

Table 80 Scenario 3c results for adalimumab as an alternative to systemic therapy: Treatment effects from NMA using minimum evidence from adult population

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						
MTX	38,177	9.879	-	-	-	MTX
ADA	56,599	9.966	18,422	0.087	211,259	

ADA , adalimumab; MTX, methotrexate.

Table 81 presents the cost-effectiveness results for the interventions after failed systemic therapy using the NMA with minimum links to adult evidence. The incremental costs and QALYs for etanercept and ustekinumab compared to BSC are similar to the base-case analysis, but the incremental costs and QALYs for adalimumab are reduced in both age groups. This is because the difference in PASI 75 response rates between the interventions and BSC in the minimum NMA compared to the full NMA are similar for etanercept (44% vs. 43%) and ustekinumab (66% vs. 71%) but much smaller for adalimumab (44% vs. 68%). As a result, adalimumab is less cost-effective in children and young people aged 6-11 years (ICER vs. BSC increases from base-case of £115,825 to £137,329 per additional QALY) and is extendedly dominated by ustekinumab in the age group of 12-17 years. The ICER for etanercept is reduced by £3,400 in children aged 6-11 years, but etanercept is also extendedly dominated by ustekinumab in ages 12-17 years. The ICER for ustekinumab vs. BSC increases slightly from the base-case value of £116,568 to £118,515 per QALY gained using the minimum NMA.

Table 81 Scenario 3c results for interventions after failed systemic therapy: Treatment effects from NMA using minimum evidence from adult population

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							

BSC	36,406	8.717	-	-	-	-	BSC
ETA	44,063	8.828	7,657	0.112	68,485	68,485	
ADA	52,067	8.831	8,004	0.002	3,587,196	137,329	
Children and young people aged 12-17 years							
BSC	21,749	4.807	-	-	-	-	BSC
ETA	33,598	4.898	11,849	0.091	ED UST	130,389	
ADA	33,977	4.899	380	0.001	ED UST	132,682	
UST	39,264	4.955	17,515	0.148	118,515	118,515	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

Scenario 3d: PASI response assessment

In this scenario, PASI 50 is considered as the primary efficacy endpoint for response assessment at the end of the trial period instead of PASI 75 as used in the base-case analysis.

Table 82 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy using PASI 50. The incremental costs and QALYs for adalimumab compared to methotrexate increase because there is a smaller difference in PASI 50 response rates between the interventions (91.5% ADA vs. 71% MTX) compared to PASI 75 response rates (79% ADA vs. 49% MTX). As a result, the ICER increases from £308,329 to £353,148 per QALY gained.

Table 82 Scenario 3d results for adalimumab as an alternative to systemic therapy: PASI 50 response assessment

	Mean costs (£)	**Mean QALYs**	**Incremental costs vs. MTX (£)**	**Incremental QALYs vs. MTX**	**ICER vs. MTX (£/QALY)**	**Optimal treatment (£30,000 threshold)**
Children and young people aged 4-17 years						
MTX	32,765	9.932	-	-	-	MTX
ADA	65,008	10.023	32,243	0.091	353,148	

ADA, adalimumab; MTX, methotrexate.

Table 83 presents the cost-effectiveness results for the interventions after failed systemic therapy using PASI 50. The incremental cost per additional QALY gained is greater for all interventions compared to the base-case analysis. This is because the total costs have increased (a greater proportion of individuals continue treatment as responders) but total QALYs have decreased across the interventions. The difference in PASI 50 response rates between the interventions and BSC is similar to the difference observed in PASI 75 response rates. The decrease in QALYs is due to a proportionally smaller utility gain associated with PASI 50-75 response category compared to PASI 75-90 and PASI ≥90 response categories. BSC remains the optimal treatment option and the probability that any of the biologics are cost-effective at a threshold of £30,000 per additional QALY is zero.

Table 83 Scenario 3d results for interventions after failed systemic therapy: PASI 50 response assessment

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	46,396	8.807	9,990	0.097	103,388	103,388	
ADA	60,091	8.886	13,695	0.079	172,967	134,724	
Children and young people aged 12-17 years							
BSC	21,749	4.804	-	-	-	-	BSC
ETA	36,930	4.882	15,180	0.078	ED ADA	193,536	
ADA	40,024	4.947	18,275	0.143	127,783	127,783	
UST	41,833	4.957	1,809	0.010	131,128	131,128	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.4 Health-related quality of life utility values

Scenario 4a: EQ-5D utility estimates from adults

The HRQoL utility values in children and young people are subject to considerable uncertainty. EQ-5D-Y values mapped from PedsQL data from the CADMUS trial (ustekinumab) at baseline and 12

weeks follow-up were used to estimate utility gains from baseline associated with different PASI response categories (<50, 50-75, 75-90, ≥90). The utility values associated with treatment were then based on the proportion of individuals in the different PASI response categories from the NMA and the associated utility gain for each PASI category. As discussed in Section 7.4.6.3, the estimated EQ-5D-Y utility gains from the PedsQL data were of a much smaller magnitude compared to the EQ-5D values used in previous TAs in adults. It was also noted that the gains in CDLQI by PASI response category were of a smaller magnitude compared to DLQI values reported in adults. It is not clear whether these smaller utility increments observed in children and young people is a reflection of less impact of severe psoriasis on quality of life in a paediatric population or a result of small sample sizes and limited data in this population.

In this scenario, EQ-5D utility values from the adult population are used to inform the gains in utility associated with PASI response in children and young people. Utility values from TA 103 (etanercept) are used in this scenario; however, the implications of using alternative adult utility values from TA 146 (adalimumab) and TA 180 (ustekinumab) are also considered (see Table 62, Section 7.4.6.3 for comparison of utility values in children and young people and adults).

Table 84 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy using utility estimates from an adult population. The total QALYs for the interventions are lower than those of the base-case analysis, but this is due to the use of a lower baseline utility value in this scenario to prevent the utility values rising above 1.0. Note that changing the baseline utility value used in the model does not significantly affect the cost-effectiveness results because the model is driven by the incremental changes in utility score from baseline. The incremental QALYs for adalimumab compared to methotrexate of 0.150 are significantly higher than those of the base-case of 0.088. As a result, the ICER for adalimumab reduces from £308,329 to £180,773 per additional QALY. The implications of using adult utility values from TA 180 and TA 146 are even more pronounced, where the incremental gain in QALYs for adalimumab compared to methotrexate are 0.204 and 0.260, respectively, resulting in corresponding ICERs of £132,616 and £104,010 per additional QALY (see Appendix 12.13 for results based on utility estimates from TA180).

Table 84 Scenario 4a results for adalimumab as an alternative to systemic therapy: EQ-5D utility estimates from adults

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Utility estimates sourced from TA103						
Children and young people aged 4-17 years						
MTX	34,931	9.116	-	-	-	MTX
ADA	62,043	9.266	27,112	0.150	180,773	
Utility estimates sourced from TA146						
Children and young people aged 4-17 years						
MTX	34,919	9.229	-	-	-	MTX
ADA	62,000	9.489	27,081	0.260	104,010	

ADA, adalimumab; MTX, methotrexate.

Table 85presents the cost-effectiveness results for the interventions after failed systemic therapy using utility estimates from an adult population. The incremental QALYs for the interventions compared to BSC are substantially greater than those of the base-case. Ustekinumab is the most effective intervention, followed by adalimumab, etanercept and BSC, and the incremental gain in QALYs from moving from one intervention to the next is greater than the base-case results. As a result, all the ICERs are substantially lower than the base-case, falling by 55 – 61%. Etanercept has the largest reduction in the ICER, and at a threshold of £30,000 per additional QALY etanercept becomes the optimal treatment in the age group 6-11 years. In the older age group 12-17 years, etanercept is extendedly dominated by adalimumab due to the higher drug acquisition costs associated with young people requiring more than a 25 mg dose. In children and young people aged 12-17 years, the optimal treatment option remains BSC up until a threshold of £51,000 per QALY gained, when adalimumab would then enter as the first treatment in sequence. At a threshold of £60,000 per QALY, adalimumab represents the only cost-effective treatment option based on a fully incremental analysis, whereas all the biologics would be considered cost-effective based on a pairwise comparison with BSC.

The implications of using adult utility values from TA 180 and TA 146 are even more pronounced compared to TA 103 due to greater utility gains in the PASI 75-90 and ≥90 categories. The ICERs for children and young people aged 6-11 years are £22,578 (TA 146) and £21,546 (TA 180) for etanercept vs. BSC and £37,125 (TA 146) and £39,682 (TA 180) for adalimumab vs. BSC. The lowest ICERs for children and young people aged 12-17 years are £33,517 for adalimumab vs. BSC, £35,612 for ustekinumab vs. BSC and £39,247 for etanercept vs. BSC.

Table 85 Scenario 4a results for interventions after failed systemic therapy: EQ-5D utility estimates from adults

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Utility estimates sourced from TA103							
Children and young people aged 6-11 years							
BSC	36,406	7.844	-	-	-	-	ETA
ETA	43,798	8.102	7,392	0.257	28,740	28,740	
ADA	57,257	8.237	13,459	0.135	99,419	53,112	
Utility estimates sourced from TA146							
Children and young people aged 6-11 years							
BSC	36,406	7.890	-	-	-	-	ETA
ETA	43,829	8.219	7,423	0.329	22,578	22,578	
ADA	57,215	8.450	13,386	0.232	57,762	37,125	
Utility estimates sourced from TA103							
Children and young people aged 12-17 years							
BSC	21,749	4.326	-	-	-	-	BSC
ETA	33,181	4.535	11,432	0.209	ED ADA	54,717	
ADA	37,844	4.644	16,095	0.318	50,578	50,578	
UST	39,968	4.661	2,124	0.016	131,702	54,491	
Utility estimates sourced from TA146							
Children and young people aged 12-17 years							
BSC	21,749	4.326	-	-	-	-	BSC

ETA	33,195	4.618	11,446	0.292	ED ADA	39,247	
ADA	37,873	4.807	16,124	0.481	33,517	33,517	
UST	39,928	4.837	2,055	0.029	69,895	35,612	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

Scenario 4b: Utility estimates for best supportive care

The base-case analysis assumes that the utility associated with BSC is based on the proportion of individuals in the different PASI response categories for placebo of the NMA. In this scenario, the utility for BSC is set equal to the baseline value, i.e. there is no utility gain associated with BSC.

Table 86 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy assuming no utility benefit associated with BSC. For the comparison of adalimumab and methotrexate, the assumption of no utility benefit on BSC only affects the utility of non-responders. The total QALYs for both interventions are reduced and the incremental QALYs for adalimumab compared to methotrexate increase from 0.088 (base-case) to 0.102 due to higher efficacy for adalimumab, which reduces the time spent in BSC.

Table 86 Scenario 4b results for interventions as an alternative to systemic therapy: Utility in BSC equal to baseline

	Mean costs (£)	**Mean QALYs**	**Incremental costs vs. MTX (£)**	**Incremental QALYs vs. MTX**	**ICER vs. MTX (£/QALY)**	**Optimal treatment (£30,000 threshold)**
Children and young people aged 4-17 years						
MTX	34,925	9.833	-	-	-	MTX
ADA	62,010	9.935	27,085	0.102	266,161	

ADA, adalimumab; MTX, methotrexate.

Table 87 presents the cost-effectiveness results for the interventions after failed systemic therapy assuming no utility benefit associated with BSC. This assumption reduces the total QALYs for the comparator of BSC and the utility of non-responders. As a result, the incremental QALYs for the

interventions compared to BSC increases, and the incremental gain in QALYs for the interventions relative to the next best option (e.g. ustekinumab is the most effective treatment, followed by adalimumab and etanercept) also increases since less time is spent on BSC. Consequently, the ICERs for the interventions are reduced compared to the base-case values.

Table 87 Scenario 4b results for interventions after failed systemic therapy: Utility in BSC equal to baseline

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	8.593	-	-	-	-	BSC
ETA	43,785	8.724	7,378	0.131	56,430	56,430	
ADA	57,208	8.812	13,423	0.089	151,299	94,780	
Children and young people aged 12-17 years							
BSC	21,749	4.739	-	-	-	-	BSC
ETA	33,193	4.846	11,444	0.106	ED ADA	107,462	
ADA	37,844	4.917	16,095	0.178	90,292	90,292	
UST	39,969	4.929	2,124	0.012	180,232	95,871	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.5 Costs associated with best supportive care

Scenario 5a: Number of hospitalisations per annum for BSC

The resource use associated with BSC, in particular the number of hospitalisations per annum, was identified as an area of high uncertainty and a key driver of cost-effectiveness in previous TAs in adults. Two main sources have been referred to in previous appraisals: (i) resource use estimates used in NICE CG 153, which estimated an average of 26.6 inpatient days per year for individuals whose psoriasis has not responded to treatment; and (ii) resource use estimates based on Fonia et al (2010), which equates to 6.49 days of hospitalisation per annum. During previous NICE appraisals, the clinical experts considered that both sources are likely to overestimate the actual number of hospital

days and resource use associated with BSC. This is in part due to the populations considered in CG 153 and Fonia et al, (2010) where CG 153 considers a high-need population with very severe psoriasis, while Fonia et al describes care in a tertiary care centre known for treating the most severely affected individuals. The clinical experts, in recent appraisals, also noted that the number of individuals hospitalised for severe psoriasis has fallen over time and is continuing to fall. They also indicated that BSC is mostly given to individuals during their outpatient visits. As a result, the resource use associated with BSC is an area of considerable uncertainty and both sources of data have a number of shortcomings, even in the adult population.

In the base-case analysis for children and young people, it is assumed that there are no hospitalisations for psoriasis in this population. This was informed by clinical opinion where our clinical advisor suggested that hospitalisations in children and young people are very rare, partly due to the fact that this population has not yet developed co-morbidities which often complicate more severe cases of psoriasis in adults. In this scenario, the implications of assuming no inpatient stay in children and young people is explored by using an estimate of 6.49 hospitalisations per annum based on Fonia et al, and 26.6 hospitalisations per annum based on CG 153 in adults.

Table 88 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy assuming hospitalisations for BSC. For the comparison of adalimumab and methotrexate, the total costs for both interventions are increased, but the incremental costs for adalimumab compared to methotrexate decrease due to the higher efficacy associated with adalimumab which reduces the time spent in BSC. The resulting ICER decreases from £308,329 to £281,029 for 6.49 inpatient days per annum and £202,571 per additional QALY for 26.6 inpatient days per annum.

Table 88 Scenario 5a results for interventions as an alternative to systemic therapy: Number of hospitalisations per annum for BSC

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
6.49 hospitalisation days per annum for BSC based on Fonia et al (2010) in adults						
Children and young people aged 4-17 years						
MTX	52,280	9.939	-	-	-	MTX
ADA	77,153	10.027	24,873	0.089	281,029	

26.6 hospitalisation days per annum for BSC based on CG 153 in adults						
Children and young people aged 4-17 years						
MTX	106,053	9.939	-	-	-	MTX
ADA	123,929	10.027	17,876	0.088	202,571	

ADA, adalimumab; MTX, methotrexate.

Table 89 presents the cost-effectiveness results for the interventions after failed systemic therapy assuming hospitalisations for BSC. Under this assumption, the costs of BSC increase by £147.67 and £605.25 per 4-week cycle for 6.49 and 26.6 inpatient days per annum, respectively. As a result, the total costs associated with the comparator of BSC increase and the costs for non-responders increase. For children and young people aged 6-11 years, the reduction in incremental costs for etanercept vs. BSC is sufficient to make etanercept the optimal treatment option at a threshold of £30,000 per QALY with 6.49 inpatient days per annum. When the number of hospitalisations per annum are increased to 26.6 days in this age group, etanercept becomes the least costly treatment option and BSC becomes dominated by etanercept (i.e. BSC costs more than etanercept but produces fewer QALYs). In this same age group, adalimumab only enters as a cost-effective option if the threshold increases to £70,000 per QALY gained.

For children and young people aged 12-17 years, etanercept is dominated by adalimumab. The ICER for adalimumab compared to BSC is £74,501 per QALY when 6.49 inpatient days per annum are assumed. When the number of hospitalisations are increased to 26.6 days adalimumab becomes the the least costly treatment option and the most cost-effective option at a threshold of £30,000 per QALY. The ICER for ustekinumab compared to adalimumab is £118,665 per QALY with 26.6 inpatient days per annum.

Table 89 Scenario 4b results for interventions after failed systemic therapy: Utility in BSC equal to baseline

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
6.49 hospitalisation days per annum for BSC based on Fonia et al (2010) in adults							
Children and young people aged 6-11 years							

BSC	55,597	8.710	-	-	-	-	ETA
ETA	58,500	8.813	2,903	0.103	28,286	28,286	
ADA	70,016	8.891	11,516	0.078	148,586	80,046	
Children and young people aged 12-17 years							
BSC	32,333	4.804	-	-	-	-	BSC
ETA	40,099	4.887	7,766	0.083	ED ADA	93,102	
ADA	43,188	4.950	10,855	0.146	74,501	74,501	
UST	45,064	4.960	1,875	0.010	186,634	81,735	
26.6 hospitalisation days per annum for BSC based on CG 153 in adults							
Children and young people aged 6-11 years							
BSC	115,063	8.710	5,550	-0.180	Dominated	-	ETA
ETA	104,113	8.813	-	-	-	Dominant	
ADA	109,512	8.891	5,399	0.077	69,797	Dominant	
Children and young people aged 12-17 years							
BSC	65,129	4.804	4,119	-0.156	Dominated	-	ADA
ETA	61,537	4.887	1,777	-0.062	Dominated	Dominant	
ADA	59,760	4.950	-	-	-	Dominant	
UST	61,010	4.960	1,250	0.011	118,665	Dominant	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.6 Costs associated with adverse events

Scenario 6: Costs of severe infections and malignancies

In the absence of robust evidence on the incidence of adverse events in children and young people, the base-case analysis assumed that there are no adverse events associated with treatment. In this scenario, the costs associated with serious adverse events including non-melanoma skin cancer, malignancies other than non-melanoma skin cancer and severe infections are included. These events are expected to be very rare.

Table 90 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy with costs of adverse events included. The incremental costs for adalimumab have increased by a very small amount of £400. The resulting impact on the ICER is minor, increasing it from £308,329 to £311,067 per QALY gained.

Table 90 Scenario 6 results for interventions as an alternative to systemic therapy: Costs of severe infections and malignancies included

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						
MTX	35,176	9.939	-	-	-	MTX
ADA	62,694	10.027	27,518	0.088	311,067	

ADA, adalimumab; MTX, methotrexate.

Table 91 presents the cost-effectiveness results for the interventions after failed systemic therapy with costs of adverse events included. As expected, the incremental costs for the interventions relative to BSC increase, but the resulting impact on the ICER results for all interventions is very minor.

Table 91 Scenario 6 results for interventions after failed systemic therapy: Costs of severe infections and malignancies included

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	44,310	8.813	7,904	0.103	76,810	76,810	
ADA	57,911	8.891	13,601	0.077	176,012	119,357	
Children and young people aged 12-17 years							
BSC	21,749	4.804	-	-	-	-	BSC
ETA	33,584	4.887	11,835	0.083	ED ADA	142,041	

ADA	38,382	4.950	16,633	0.146	113,974	113,974	
UST	40,063	4.960	1,682	0.010	169,254	117,497	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.7 Treatment withdrawal rates

Scenario 7: Withdrawal rates from treatment

In the base-case analysis discontinuation from treatment is modelled as an all-cause withdrawal probability of 20% per annum, which is applied to all interventions. This withdrawal rate has been used in all previous TAs in adults and is consistent with long-term survival rates of biologics from the BADBIR audit. In the absence of alternative data in children and young people, this scenario considers two separate withdrawal rates of 10% and 30% per annum.

Table 92 presents the cost-effectiveness results for adalimumab as an alternative to systemic therapy for treatment withdrawal rates of 10% and 30% per annum. The lower withdrawal rate implies that individuals spend longer on treatment before moving to BSC, while the higher withdrawal rate means that individuals spend less time on treatment and more time on BSC. The total costs for adalimumab increase for the 10% rate and decrease for the 30% rate, while the total costs for methotrexate decrease for the 10% rate and increase for the 30% rate. This opposite effect between the treatments arises because the drug acquisition costs of adalimumab (£704.28 per 4-week cycle) are proportionally greater than the costs of BSC (approximately £284 per 4-week cycle) compared to the drug acquisition costs of methotrexate (approximately £60 per 4-week cycle) relative to costs of BSC. As a result, the withdrawal rate has less impact on the total costs of methotrexate compared to adalimumab. The incremental costs for adalimumab vs. methotrexate are £40,781 and £19,692 for 10% and 30% annual withdrawal rate, respectively, compared to the base-case incremental costs of £27,084. In terms of health outcomes, the more time spent on treatment the higher the utility gains. Therefore, the QALYs increase with the lower withdrawal rate and decrease with the higher rate. The resulting ICERs for adalimumab are £298,846 and £318,188 per additional QALY for 10% and 30% annual withdrawal rates, respectively, compared to the base-case value of £308,329 per additional QALY.

Table 92 Scenario 7 results for interventions as an alternative to systemic therapy: Treatment withdrawal rates of 10% and 30% per annum

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						
Withdrawal rate of 10% per annum						
MTX	32,274	9.990	-	-	-	MTX
ADA	73,055	10.126	40,781	0.136	298,846	
Withdrawal rate of 30% per annum						
MTX	36,364	9.912	-	-	-	MTX
ADA	56,057	9.974	19,692	0.062	318,188	

ADA, adalimumab; MTX, methotrexate.

Table 93 presents the cost-effectiveness results for the interventions after failed systemic therapy for treatment withdrawal rates of 10% and 30% per annum. The total costs for all the interventions increase for the 10% rate and decrease for the 30% rate due to the accumulation of higher drug acquisition costs while on treatment for longer. This increase in costs is counterbalanced by an increase in utility gains while on treatment. The resulting impact on the ICERs are minimal. BSC remains the optimal treatment option at a threshold of £30,000 per QALY gained.

Table 93 Scenario 7 results for interventions after failed systemic therapy: Treatment withdrawal rate of 10% and 30% per annum

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Withdrawal rate of 10% per annum							
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	49,361	8.864	12,955	0.154	84,138	84,138	
ADA	66,830	8.977	17,469	0.113	154,817	114,029	

Children and young people aged 12-17 years							
BSC	21,749	4.804	-	-	-	-	BSC
ETA	36,194	4.911	14,445	0.107	ED ADA	135,131	
ADA	42,002	4.989	20,253	0.185	109,399	109,399	
UST	44,400	5.002	2,398	0.013	182,511	114,244	
Withdrawal rate of 30% per annum							
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	40,978	8.784	4,572	0.074	61,924	61,924	
ADA	51,745	8.841	10,766	0.056	190,888	117,774	
Children and young people aged 12-17 years							
BSC	21,749	4.804	-	-	-	-	BSC
ETA	30,952	4.870	9,203	0.066	ED ADA	139,568	
ADA	34,732	4.920	3,780	0.050	75,289	111,784	
UST	36,599	4.928	1,867	0.008	230,608	119,527	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.5.2.8 Biosimilars

Scenario 8: Reduction in the cost of etanercept

The biosimilar of etanercept, Benapali 50 mg, does not have marketing authorisation for use in children and young people. In this scenario, the drug acquisition cost of etanercept is reduced by approximately 10% to match the cost of Benapali in adults.

Table 94 presents the cost-effectiveness results for the interventions after failed systemic therapy for a 10% reduction in the acquisition cost of etanercept. For children and young people aged 6-11 years, the incremental cost for etanercept relative to BSC is reduced by £580, which reduces the ICER from £71,903 to £66,240 per additional QALY. For children and young people aged 12-17 years, the incremental cost for etanercept relative to BSC is reduced by £1,480, which is greater than that

observed in the younger age group because it is assumed that the 10% reduction in the drug acquisition cost of etanercept only applies to children ≥10 years who require 50 mg of etanercept. The implications of the cost reduction has a very minor impact on the cost-effectiveness results.

Table 94 Scenario 8 results for interventions after failed systemic therapy: Reduction in the cost of etanercept to match unit cost of Benepali

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	8.710	-	-	-	-	BSC
ETA	43,225	8.813	6,819	0.103	66,240	66,240	
ADA	57,272	8.891	14,047	0.077	181,897	115,815	
Children and young people aged 12-17 years							
BSC	21,749	4.804	-	-	-	-	BSC
ETA	31,719	4.887	9,970	0.083	ED ADA	119,501	
ADA	37,826	4.949	16,077	0.146	110,437	110,437	
UST	39,908	4.960	2,082	0.010	205,422	116,619	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

7.6 Discussion of the cost-effectiveness results and alternative scenarios

The results of the base-case analysis suggest that adalimumab is not a cost-effective treatment option when positioned in the pathway as an alternative to systemic therapy, with an ICER of £308,329 per QALY gained compared to methotrexate. When positioned after systemic therapy, the ICER for adalimumab compared to BSC is £115,825 per QALY for ages 6-11 years and £110,430 per QALY for ages 12-17 years. At a threshold of £30,000 per QALY gained, etanercept is not a cost-effective option for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or intolerant to systemic therapies or phototherapies. The ICER for etanercept compared to BSC is £71,903 per QALY for ages 6-11 years and is extendedly dominated by adalimumab for ages 12-17

years. Ustekinumab is the most effective treatment in children and young people aged 12-17 years but it is also the most costly treatment. Based on a fully incremental analysis, the ICER for ustekinumab compared to adalimumab is £201,507 per QALY, while the ICER for ustekinumab compared to BSC is £116,568 per QALY. The base-case results suggest that BSC is the only cost-effective form of management for the treatment of severe plaque psoriasis unless the threshold reaches at least £111,000 per additional QALY. The probability that any of the biologics are cost-effective at a threshold of £30,000 per QALY is zero.

The lack of cost-effectiveness appears to result from very modest QALY gains associated with treatment. The small incremental difference in health benefits between the treatments is a result of relatively small utility gains in EQ-5D-Y associated with higher PASI response rates. As a consequence, the benefits of achieving a greater PASI response do not translate into large improvements in health outcomes. The acquisition costs of the treatments are also not substantially different: ustekinumab costs £715.67 per 4-week cycle (i.e. £2,147 per dose with each dose given at 12 weekly intervals) compared to £704.28 per 4-week cycle (i.e. £352.14 per dose given every 2 weeks) for adalimumab and £715.00/£357.50 per 4-week cycle (i.e. £178.75 per 50 mg / £89.38 per 25 mg dose given each week) for etanercept depending on patient weight.

A number of scenarios were used to explore the impact of alternative assumptions on the cost-effectiveness of the biological treatments. Table 95 and Table 96 summarise the cost-effectiveness results for the scenario analyses as an alternative to systemic therapy and after failed systemic therapy, respectively.

Table 95 Summary of the cost-effectiveness results for adalimumab as an alternative to systemic therapy: base-case results and alternative scenarios

	Analysis	ICER ADA vs. MTX (£/QALY)
Children and young people aged 4-17 years	**Base-case**	**308,329**
	Scenario 1: Off-label use of biologics outside age constraints	-
	Scenario 2: Common time horizon of 14 years	-
	Scenario 3a: Direct trial evidence estimates of effect	549,899
	Scenario 3b: Indirect treatment comparison estimates	-
	Scenario 3c: NMA using minimum evidence from adult population	211,259

	Scenario 3d: PASI 50 response assessment	353,148
	Scenario 4a: EQ-5D utility estimates from adults TA 103	180,773
	EQ-5D utility estimates from adults TA 146	104,010
	Scenario 4b: Utility in BSC equal to baseline value	266,161
	Scenario 5: Hospitalisations of 6.49 days per annum	281,029
	Hospitalisations of 26.6 days per annum	202,571
	Scenario 6: Costs associated with adverse events	311,067
	Scenario 7: Treatment withdrawal rate of 10% per annum	298,846
	Treatment withdrawal rate of 30% per annum	318,188
	Scenario 8: Unit cost of biosimilar for etanercept	-

-, scenario is not applicable; ADA, adalimumab; MTX, methotrexate.

Table 96 Summary of the pairwise cost-effectiveness results for interventions after failed systemic therapy: base-case results and alternative scenarios

	Analysis	**ICER (£/QALY)**		
		ADA vs. BSC	**ETA vs. BSC**	**UST vs. BSC**
	Base-case	**117,080**	**-**	**-**
	Scenario 1: Off-label use of biologics outside age constraints	117,080	59,924	121,779
Children and young people aged 6-11 years	**Base-case**	**115,825**	**71,903**	-
	Scenario 1: Off-label use of biologics outside age constraints	-	-	-
	Scenario 2: Common time horizon of 14 years	115,592	73,153	-
	Scenario 3a: Direct trial evidence estimates of effect	-	75,350	-
	Scenario 3b: Indirect treatment comparison estimates	-	-	-
	Scenario 3c: NMA using minimum evidence from adult population	137,329	68,485	-
	Scenario 3d: PASI 50 response assessment	134,724	103,388	-
	Scenario 4a: EQ-5D utility estimates from adults TA 103	53,112	28,740	-
	EQ-5D utility estimates from adults TA 146	37,125	22,578	
	Scenario 4b: Utility in BSC equal to baseline value	94,780	56,430	-
	Scenario 5: Hospitalisations of 6.49 days per annum	80,046	28,286	-
	Hospitalisations of 26.6 days per annum	Dominant	Dominant	
	Scenario 6: Costs associated with adverse events	119,357	76,810	-

	Scenario 7: Treatment withdrawal rate of 10% per annum	114,029	84,138	-
	Treatment withdrawal rate of 30% per annum	117,774	61,924	
	Scenario 8: Unit cost of biosimilar for etanercept	115,815	66,240	-
Children and young people aged 12-17 years	**Base-case**	**110,430**	**137,059**	**116,568**
	Scenario 1: Off-label use of biologics outside age constraints	-	-	-
	Scenario 2: Common time horizon of 14 years	109,531	135,354	114,439
	Scenario 3a: Direct trial evidence estimates of effect	-	-	116,982
	Scenario 3b: Indirect treatment comparison estimates	-	128,903	119,092
	Scenario 3c: NMA using minimum evidence from adult population	132,682	130,389	118,515
	Scenario 3d: PASI 50 response assessment	127,783	193,536	131,128
	Scenario 4a: EQ-5D utility estimates from adults TA 103	50,578	54,717	54,491
	EQ-5D utility estimates from adults TA 146	33,517	39,247	35,612
	Scenario 4b: Utility in BSC equal to baseline value	90,292	107,462	95,871
	Scenario 5: Hospitalisations of 6.49 days per annum	74,501	93,102	81,735
	Hospitalisations of 26.6 days per annum	Dominant	Dominant	Dominant
	Scenario 6: Costs associated with adverse events	113,974	142,041	117,497
	Scenario 7: Treatment withdrawal rate of 10% per annum	109,399	135,131	114,244
	Treatment withdrawal rate of 30% per annum	111,784	139,568	119,527
	Scenario 8: Unit cost of biosimilar for etanercept	110,437	119,501	116,619

-, scenario is not applicable; ADA, adalimumab; MTX, methotrexate; ETA, etanercept; UST, ustekinumab.

The scenarios which have the most impact on the cost-effectiveness results are: (i) utility estimates from an adult population (scenario 4a); (ii) no health benefits associated with BSC (scenario 4b); and (iii) hospitalisations associated with BSC (scenario 5).

The gains in utility in the adult population for the different PASI response categories are of an order of magnitude up to 6.6 times greater than the utility gains estimated in children and young people. It is unclear whether this difference reflects a lower impact of severe psoriasis on health-related quality of life in children and young people or simply reflects the limited data available in this population and the significant uncertainty surrounding quality of life estimates for a paediatric psoriasis population. The use of utility values from an adult population brings the ICER of etanercept compared to BSC under a threshold of £30,000 per QALY gained in children and young people aged 6-11 years. The

ICERs for ustekinumab and adalimumab with adult utility data are reduced significantly but remain above £30,000 per QALY threshold, even with the most favourable estimates from TA 146. Under the assumption of no health benefits associated with treatment on BSC, the ICERs are reduced by up to £30,000 from the base-case value but remain quite high with the lowest ICER of £56,430 per QALY gained for etanercept compared to BSC.

The number of hospitalisations associated with BSC is a key driver of the cost-effectiveness of the biological interventions. This was also identified as a key consideration in previous TAs of adults. Based on clinical opinion, the base-case analysis assumed that hospitalisations for severe psoriasis are very rare in children and young people. If the average number of hospitalisations per annum is considered to be as much as 6.49 days based on Fonia et al (2010), the ICERs for the interventions reduce significantly; however, the only ICER which falls below £30,000 is for the use of etanercept compared to BSC in children and young people aged 6-11 years. If the average number of hospitalisations per annum is increased significantly to 26.6 days per annum based on the very high need population described in CG 153, the biological treatments compared to BSC are all considered cost-effective in individuals who have failed systemic therapy. However, recent appraisals in adults have considered the estimate of 26.6 days per annum to be too high.

The combined impact of the most optimistic utility estimates in adults (TA 146), 6.49 inpatient days per annum and no health benefits for BSC are presented in Table 97 and Table 98 for the use of the interventions before and after systemic therapy. The combined impact of the utility gains from an adult population and an assumption of 6.49 hospitalisations per annum is sufficient to reduce the pairwise ICERs for the interventions compared to BSC to below a threshold of £30,000 per additional QALY, while the additional assumption of no health benefits on BSC reduces the ICERs further to below a threshold of £20,000 per additional QALY. Based on a fully incremental analysis, etanercept is the optimal treatment for children and young people aged 6-11 years, while adalimumab is the optimal treatment for ages 12-17 years.

Table 97 Combined impact of alternative assumptions on the cost-effectiveness of adalimumab as an alternative to systemic therapy

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						

Adult utility data (TA 146) + 6.49 hospitalisations per annum						
MTX	52,273	9.229	-	-	-	MTX
ADA	77,106	9.489	24,834	0.260	95,527	
Adult utility data (TA 146) + 6.49 hospitalisations per annum + no health benefits for BSC						
MTX	52,291	8.351	-	-	-	MTX
ADA	77,136	8.727	24,845	0.376	66,126	

ADA, adalimumab; MTX, methotrexate.

Table 98 Combined impact of alternative assumptions on the cost-effectiveness of the interventions after failed systemic therapy

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
Adult utility data (TA 146) + 6.49 hospitalisations per annum							
BSC	55,597	7.890	-	-	-	-	ETA
ETA	58,515	8.218	2,917	0.328	8,897	8,897	
ADA	69,982	8.451	11,467	0.233	49,274	25,657	
Adult utility data (TA 146) + 6.49 hospitalisations per annum + no health benefits for BSC							
BSC	55,597	6.918	-	-	-	-	ETA
ETA	58,506	7.474	2,909	0.557	5,227	5,227	
ADA	70,021	7.809	11,515	0.334	34,438	16,190	
Children and young people aged 12-17 years							
Adult utility data (TA 146) + 6.49 hospitalisations per annum							
BSC	32,333	4.351	-	-	-	-	ADA
ETA	40,102	4.618	7,769	0.266	ED ADA	29,177	
ADA	43,193	4.807	10,860	0.455	23,861	23,861	
UST	45,087	4.837	1,894	0.031	61,722	26,253	
Adult utility data (TA 146) + 6.49 hospitalisations per annum + no health benefits for BSC							

BSC	32,333	3.815	-	-	-		ADA
ETA	40,100	4.269	7,767	0.454	ED ADA	17,108	
ADA	43,194	4.537	10,861	0.722	15,040	15,040	
UST	45,099	4.579	1,905	0.042	45,818	16,716	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

8 Assessment of factors relevant to the NHS and other parties

The potential extra cost to the NHS of providing adalimumab, etanercept or ustekinumab to children and young people with moderate to severe plaque psoriasis is largely uncertain, given the paucity of evidence on the health care resource use specific to this population and the uncertainties on the effectiveness evidence base. The resource use associated with BSC in terms of the expected number of hospitalisations per annum was identified as a key area of uncertainty, similarly to previous TAs of psoriasis in adults. Reducing uncertainty at this level, would allow a more accurate assessment of the the potential impact on the consumption of NHS resources of providing biologic treatment to children and young people with moderate to severe plaque psoriasis.

9 Discussion

9.1 Statement of principal findings

One multicentre RCT (M04-717) found that adalimumab at the licenced dose of 0.8mg/kg (up to 40mg) lead to significantly greater responses than methotrexate for the outcomes of PASI 50 and PASI 75, but not PASI 90 at 16 weeks. PGA 0/1 response rates were non-significantly higher for adalimumab 0.8mg/kg than methotrexate. The benefits of half-dose adalimumab were not statistically greater than those for methotrexate. Evidence on quality of life was inconsistent across different measures, possibly due to baseline imbalance on PedsQL. In children and young people, adalimumab did not appear to be associated with an increase in adverse effects relative to methotrexate over 16 weeks, though the possibility of rare adverse events cannot be entirely excluded. The trial did not provide evidence for children aged 4 to 6 years of age. [redacted]

One multicentre RCT (20030211) found etanercept to be significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50, 75 and 90, and PGA 0/1 response rates at 12 weeks. Improvements in health-related quality of life were larger for etanercept than placebo, but only reached statistical significance when measured by CDLQI. Adverse events rates were mostly similar in etanercept and placebo groups at 12 weeks with no serious adverse events observed for either treatment. However, a higher observed rate of infections among participants receiving etanercept was of borderline statistical significance. Relatively few young children (9% aged under 8 years; 4.3% aged under 6 years) were included in study. Up to six years open-label follow-up (20050111) found that the proportion of PASI and PGA responders were stable over time, though only 36% of participants were available at the latest follow-up point. The proportion of participant withdrawing due to lack of efficacy is unknown. Through 264 weeks of follow-up, withdrawals due to adverse events were infrequent, and no deaths or malignancies were observed.

One multicentre trial (CADMUS) in children 12 to 17 years of age found both the standard dosage and half dosage of ustekinumab were significantly more effective than placebo in improving the severity of plaque psoriasis based on PASI 50, 75 and 90 and PGA 0/1 responses at 12 weeks. Both ustekinumab dosages also lead to significantly greater improvements in health-related quality of life

(CDLQI and PedsQL). Among participants originally allocated to ustekinumab, PASI and PGA effects observed at 12 weeks appeared to be largely sustained at 52 weeks, with few withdrawals due to lack of efficacy. There were no notable adverse effects associated with ustekinumab, though the number of observations was small and longest the follow-up time was just 60 weeks. Few participants withdrew due to adverse effects.

No statistically significant differences were identified in PASI response outcomes across different age groups within the trials. Therefore, in order to establish the relative efficacy of the interventions the analyses assumed that treatment effects were exchangeable across ages in the population of children and young people. Based on an indirect treatment comparison of PASI response outcomes at 12 weeks from study 20030211 and CADMUS, using the placebo arms of the trials as a common comparator, ustekinumab is a more effective treatment option compared to etanercept. The lack of a common comparator arm between the adalimumab trial (M04-717) and study 20030211 and CADMUS meant that it was not possible to draw conclusions about the relative efficacy of adalimumab, etanercept and ustekinumab based on the three trials in children and young people alone. In order to fill this evidence gap for the economic analysis it was necessary to draw strength from a wider evidence base of trials examining the efficacy of the interventions in adults. This wider network of evidence was used to facilitate an indirect comparison of adalimumab with etanercept and ustekinumab by examining the relationships that exist between the different interventions and study populations (i.e. children and young people and adults) and drawing conclusions for each population based on the full network of evidence. Adjustments were also made for differences in placebo response rates across the trials. The network meta-analysis results – adjusted for differences in population and placebo response rates – demonstrated that ustekinumab is the most effective intervention, followed by adalimumab, etanercept and methotrexate in children and young people. These rankings also matched those of the adult population. The absolute PASI response outcomes were estimated to be higher in children and young people compared to adults, due to higher placebo response rates in study 20030211 and CADMUS, but the relative effectiveness of the interventions were similar across the two populations.

The cost-effectiveness of adalimumab, etanercept and ustekinumab was evaluated by comparing the additional costs of the interventions to each other and to either, methotrexate or BSC depending on the position of the intervention in the pathway, with the additional health benefits, over a time horizon sufficient to capture differences in costs and effects. Health outcomes were expressed in QALYs and all costs were considered from the perspective of the NHS & PSS. Due to differences in the

marketing authorisation of the interventions by age and positioning of adalimumab before non-biologic systemic therapy, cost-effectiveness estimates were presented for three base-case populations: (i) children and young people aged 4-17 years with adalimumab compared to methotrexate; (ii) children and young people aged 6-11 years with adalimumab and etanercept compared to BSC; and (iii) children and young people aged 12-17 years with adalimumab, etanercept and ustekinumab compared to BSC.

The paucity of clinical and economic evidence to inform the evaluation of cost-effectiveness in children and young people resulted in a number of strong assumptions and uncertainties in the analysis. These assumptions arose from the need to extrapolate data from the adult population to inform the population of children and young people. A number of alternative scenarios were considered in order to examine the impact of these assumptions on the cost-effectiveness results. The base-case cost-effectiveness results indicated that adalimumab was not a cost-effective treatment option when positioned in the treatment pathway as an alternative to systemic therapy. When positioned after systemic therapy, the ICER for adalimumab compared to BSC was more favourable, but it still remained well above conventional NICE thresholds of cost-effectiveness. Etanercept was also not considered a cost-effective option after systemic therapy for ages 6-11 years and was extendedly dominated by adalimumab for ages 12-17 years. Ustekinumab was the most effective treatment in children and young people aged 12-17 years but it was also the most costly treatment. The ICERs for ustekinumab compared to adalimumab and BSC were above £100,000 per QALY gained. Based on base-case assumptions, the probability that any of the biological treatments would be considered cost-effective at the higher end of the NICE threshold of £30,000 per QALY was zero.

The lack of cost-effectiveness of the biologics compared to BSC was due to very modest QALY gains associated with improvements in PASI response outcomes. The difference in total costs between the interventions was driven by the time spent on BSC (non-responders). The acquisition costs of the biologics were not significantly different. The key drivers of cost-effectiveness were the utility estimates, the health benefits associated with BSC, and the number of hospitalisations on BSC. Extrapolating utility estimates from the adult population to the population of children and young people reduced the ICERs by over 50% because the gains in utility associated with different PASI response outcomes were up to 6.6 times greater than the estimated utility gains from mapping PedsQL data from CADMUS onto EQ-5D-Y. The choice of EQ-5D utility values from other previous TAs in adults also had a significant impact. The base-case analysis included the possibility that psoriasis can improve with BSC and used the response rates for placebo from the NMA to inform this. When this

assumption was altered to assume that there were no health benefits from BSC, the ICERs were reduced by £20,000 - £30,000 per additional QALY. The resource use associated with BSC in terms of the expected number of hospitalisations per annum had a major impact on the cost-effectiveness results, reducing the ICERs compared to BSC considerably with the more days of hospitalisations assumed. This was also identified as a key area of uncertainty in previous TAs of psoriasis in adults.

9.2 Strengths and limitations of the assessment

Strengths

The reviews of clinical and cost-effectiveness were based on comprehensive searches of the literature, which were supplemented by data from multiple additional sources, including EMEA and FDA documents and clinical study reports, allowing the inclusion of unpublished studies and data.

The clinical effectiveness review presented here focused directly on evidence relating to children and young people with plaque psoriasis, resulting in just four relevant studies for the three biologics of interest. Consequently, the total number of included participants and average length of follow-up (for adalimumab and ustekinumab) was limited. However, this provides the best evidence of efficacy and short- to medium-term safety of adalimumab, etanercept and ustekinumab directly relevant to the decision problem.

A key strength of this evaluation was the fact that it went beyond the scope of the appraisal by bringing together evidence from the adult population in order to support an economic evaluation in children and young people. The review of cost-effectiveness evidence in this population, and the absence of economic models from the companies, highlighted the challenges involved in evaluating the cost-effectiveness of biological interventions in children and young people with plaque psoriasis. The fundamental challenge was the limited clinical evidence base for short- and long-term outcomes. Therefore, any estimation was going to be subject to a number of uncertainties. Clinical opinion suggests that the management and approach to care of treatment appears to mirror that used in adults. Therefore, in the absence of evidence, it seemed reasonable to extrapolate data from the adult population to inform the economic model in children and young people. This approach was also supported by the companies.

A major strength of the network meta-analysis was the fact that it brought together clinical evidence from the adult population in order to allow the evidence from the M04-717 trial to be connected with the other paediatric trials, while making an adjustment for any differences in PASI outcomes by population. This enabled the relative effectiveness of adalimumab, etanercept and ustekinumab to be estimated in children and young people by using what is already known about the relative effectiveness of the interventions in adults.

The economic model represents the first attempt at evaluating the cost-effectiveness of biological treatments in children and young people. This model used the same approach as the most widely accepted York model, which has been used in previous TAs in adults. This ensures consistency in the approaches undertaken for both populations. The main changes have been the availability of new evidence, including evidence in a paediatric population, health-related quality of life outcomes specific to a paediatric population, and resource use and cost estimates. The analysis also attempted to reflect differences between the interventions in terms of their marketing authorisation by age and positioning of treatment before and after systemic therapy.

Limitations

The flow of participants through the etanercept studies was complex, with data spread across a number of publications and regulatory data sources. No CSR data were available to investigate this in further detail. Similarly, the lack of a CSR meant that some details of study conduct required for a complete risk of bias assessment were unavailable. Wherever possible, we avoided making assumptions and presented the most complete data as reported.

In the absence of sufficient clinical evidence and economic data in children and young people, a simplified modelling approach was undertaken. This simplified approach involved modelling a single line of therapy before receiving BSC. However, plaque psoriasis is a lifelong chronic condition where if the condition no longer responds to a biological treatment, individuals are usually offered another biological treatment; a pattern which is likely to be repeated over an individual's lifetime. This means that treatments are usually trialled on an individual basis until an effective option is found. If individuals do not respond to multiple biological interventions, then the only remaining option is BSC. This approach to treatment is expected to be similar for children and young people and adults. However, much more caution is usually exercised in the younger population due to the limited availability of licensed treatment options. Therefore, the modelling approach undertaken is likely to be a simplification of reality. This simplification was necessary due to an absence of evidence on the

sequential use of biologics in children and young people, where treatment response would need to be conditioned on prior biological treatments received. The modelling of sequential treatments also requires every potential treatment permutation to be considered. This has already presented a significant issue in the most recent TAs for adults which did consider more than one line of therapy (TA 368 for apremilast and the appraisal of ixekizumab which is currently out for consultation), where the modelled sequences did not reflect current clinical practice. Any attempt at treatment sequencing in the population of children and young people would be highly uncertain; this is not only because of the lack of data but also due to the further complication of differences between the biological treatments in terms of marketing authorisation by age, severity and positioning in the treatment pathway. Furthermore, if a cost-effectiveness analysis identifies the optimal treatment sequence in children and young people, this is less likely to be helpful to clinical practice as that particular sequence may not be suitable for all (or any) individuals. For example, treatment in this population is usually tailored to the child or young person due to needle phobia or the presence of psoriatic arthritis.

9.3 Uncertainties

Evidence on the efficacy and safety of adalimumab, etanercept and ustekinumab in younger children is mostly absent from the included RCTs. The ustekinumab trial (CADMUS) restricted inclusion to participants aged over 12 years. No subjects below the age of 6 received the licenced dose of adalimumab (0.8 mg/kg), with the majority of participants in the adalimumab trial being 9-18 years of age. Similarly, only 19 children (9%) included in the trial evaluating etanercept were under the age of 8 years.

It has not been possible to define moderate or severe psoriasis in children and young people. The definition varies across the three trials in this population, with ustekinumab licensed for moderate to severe psoriasis, while etanercept and adalimumab are licensed for severe psoriasis. Previous TAs in adults has defined severe psoriasis as a PASI score of 10 or more and a DLQI of more than 10. The trial populations for etanercept and ustekinumab included children or young people with a baseline PASI score of 12 or more (mean score was around 18-21), a 10% or greater of body surface area affected (for at least 6 months in the case of ustekinumab), and a Physician Global Assessment score of at least 3. The trial population for adalimumab included a baseline PASI score of 20 or more, involvement of 20% or greater of body surface area affected or very thick lesions and 10% or greater

body surface area affected, a Physician Global Assessment score of at least 4, or a baseline PASI score of 10 or more (mean score was 18.3 in trial) and a number of other characteristics such as active psoriatic arthritis or CDLQI of more than 10. There does not appear to be a standard routine assessment because the tools of PASI and CDLQI have not been validated in this population.

The paucity of clinical and economic evidence to inform the cost-effectiveness of biological treatments in a population of children and young people has led to a number of uncertainties. The most significant of these is the health-related quality of life gains associated with treatment. The incremental health benefits between the biological treatments are very sensitive to the utility gains associated with PASI response outcomes. In the base-case analysis these gains were estimated based on a mapping of PedsQL data from the ustekinumab trial onto EQ-5D-Y values. The PedsQL data were based on a very small sample size. In the absence of any other data, this represented the only method available to estimate EQ-5D values in this population. However, the PedsQL or CDLQI instruments have not been validated for the assessment of disease severity in a population of children and young people with psoriasis and PedsQL does not appear to be used routinely in clinical practice. Furthermore, these instruments are not specific to psoriasis and therefore may not capture all the important impacts of the condition, such as anxiety, depression, schooling and social interactions with friends. The PedsQL data from the ustekinumab trial is also based on a population aged 12-17 years; therefore it is unlikely to reflect the same quality of life outcomes in younger children. For example, very young children may not have developed a certain level of self-awareness, which means that any quality of life instrument in young children is unlikely to be accurate. Quality of life outcomes in children and young people can be lower due to the fear of subcutaneous injections rather than the severity of the condition itself.

The cost-effectiveness results are also very sensitive to the benefits and resource use associated with BSC. The number of hospitalisations per annum in children and young people is an area of considerable uncertainty. Extrapolating the data on hospitalisations from adults to this population is also subject to uncertainty due to a number of shortcomings that exist among all sources of data on resource use for BSC. Given these uncertainties the results from the base-case cost-effectiveness analysis should be considered alongside the results of the separate scenarios.

10 Conclusions

Etanercept and ustekinumab, within their licenced indications, lead to significantly greater improvements in psoriasis symptoms than placebo at 12 weeks' follow-up. Quality of life benefits were also observed. While these effects appear to persist beyond 12 weeks, their magnitude and persistence is less certain.

Adalimumab at the licenced dose of 0.8mg/kg (up to 40mg) leads to significantly greater improvements in psoriasis symptoms than methotrexate for some, but not all measures at 16 weeks. Observed quality of life benefits were inconsistent across different measures.

With the exception of a non-significantly higher observed rate of infections among participants receiving etanercept, there was little evidence of short-term adverse events. However, the relatively small number of observations and limited length of follow-up across trials cannot exclude the possibility of rare events being undetected.

The absence of head-to-head comparisons of the three drugs meant that these treatments would have to be compared indirectly. In addition, the lack of a common comparator meant that a wider network of data from adults with psoriasis needed to be used to connect the network. This further increased uncertainty about the relative effects of these treatments and further diminished the relative contribution of data from children to the analysis.

Based on the economic assessment, the majority of ICERs for the use of biologics in children and young people are in excess of NICE's usual range of cost-effectiveness and are reduced significantly only when combined assumptions that align with those for the management of psoriasis in adults are adopted.

10.1 Implications for service provision

- While two biologics are licenced for younger children with plaque psoriasis (adalimumab from age four years, etanercept from six years) the existing randomised trials include very few young children, with just four children under the age of six having received biologic treatment (etanercept in all cases). Consequently, evidence of the effectiveness and safety of these treatments in younger children has been generalised from observations in older children and young people.

10.2 Suggested research priorities

- Adequately powered randomised trials are needed to inform the effectiveness of biological treatments in biologic-experienced populations of children and young people, i.e. treatment response rates conditional on prior treatment are required.
- In particular, further evidence is needed to inform the clinical effectiveness and safety of adalimumab and etanercept in younger children
- Further research is needed to establish the impact of biological therapies on improving the health-related quality of life of children and young people. Future trials should consider collecting direct estimates of EQ-5D-Y.
- There is a need for PASI and other tools such as CDLQI to be validated for disease severity assessment in a population of children and young people.
- With the introduction of biological treatments in the population of children and young people continued collection of data through biologic registries for < 18 years is warranted in order to investigate safety, patterns of treatment switching, and long-term withdrawal rates.
- Resource use and costs associated with best supportive care is an area of further research.

11 References

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12 Appendices

12.1 Search strategy for clinical effectiveness searches

The following searches were carried out to identify:

- RCTs of adalimumab, etanercept and ustekinumab for children and young people with plaque psoriasis

Database search strategies

MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R))

via Ovid http://ovidsp.ovid.com/

1946 to present

Searched on: 24th May 2016

Records retrieved: 334

The search was updated on 30th September 2016 and retrieved 347 records.

1 Psoriasis/ (29080)

2 (psorias$ or psoriat$).ti,ab. (36767)

3 parapsoriasis.ti,ab. (525)

4 (pustul$ adj2 palm$).ti,ab. (785)

5 1 or 2 or 3 or 4 (42607)

6 Adalimumab/ (3349)

7 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (5219)

8 (adfrar or exemptia or MSB11022 or MSB 11022 or GP2017 or GP 2017 or GP2015 or GP 2015 or M923 or "M 923" or ABP501 or ABP 501).af. (19)

9 Etanercept/ (4651)

10 (etanercept or enbrel or 185243-69-0).af. (6612)

11 (benepali or brenzys or SB4 or CHS-0214 or CHS0214).af. (107)

12 Ustekinumab/ (414)

13 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (796)

14 or/6-13 (10289)

15 5 and 14 (2651)

16 exp Child/ (1665584)

17 exp Infant/ (1007205)

18 Adolescent/ (1731066)

19 (adolescen$ or baby or babies or child or children or boy or boys or girl or girls or infant$ or infanc$ or juvenile$ or paediatric or pediatric or preschooler$ or schoolboy$ or schoolgirl$ or schoolchild$ or teens or teenage$ or toddler$ or youth or youths or young people or young person$).ti,ab. (1671736)

20 16 or 17 or 18 or 19 (3484944)

21 15 and 20 (334)

Key:

/ = indexing term (MeSH heading)

exp = exploded indexing term (MeSH heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = terms in any field

adj = terms next to each other (order specified)

adj2 = terms within two words of each other (any order)

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Issue 4 of 12, April 2016

Searched on: 24th May 2016

Records retrieved: 32

The strategy below was used to search CENTRAL and CDSR.

The search was updated on 30th September 2016 and retrieved 39 records from CENTRAL.

#1 MeSH descriptor: [Psoriasis] this term only 1891

#2 (psorias* or psoriat*):ti,ab,kw 4321

#3 parapsoriasis:ti,ab,kw 3

#4 (pustul* near/2 palm*):ti,ab,kw 72

#5 #1 or #2 or #3 or #4 4353

#6 MeSH descriptor: [Adalimumab] this term only 239

#7 (adalimumab or humira or D2E7 or (D2 next E7) or "331731-18-1") 1088

#8 (adfrar or exemptia or MSB11022 or "MSB 11022" or GP2017 or "GP 2017" or GP2015 or "GP 2015" or M923 or "M 923" or ABP501 or "ABP 501") 2

#9 MeSH descriptor: [Etanercept] this term only 383

#10 (etanercept or enbrel or "185243-69-0") 1162

#11 (benepali or brenzys or SB4 or CHS-0214 or CHS0214) 2

#12 MeSH descriptor: [Ustekinumab] this term only 49

#13 (ustekinumab or stelara or "CNTO1275" or "CNTO-1275" or "815610-63-0") 194

#14 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 2054

#15 #5 and #14 614

#16 MeSH descriptor: [Child] explode all trees 173

#17 MeSH descriptor: [Infant] explode all trees 14329

#18 MeSH descriptor: [Adolescent] this term only 85135

#19 (adolescen* or baby or babies or child or children or boy or boys or girl or girls or infant* or infanc* or juvenile* or paediatric or pediatric or preschooler* or schoolboy* or schoolgirl* or schoolchild* or teens or teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") 193089

#20 #16 or #17 or #18 or #19 193089

#21 #15 and #20 50

NB: Results at line #21 are the total results for all databases within the Cochrane Library.

Key:

MeSH descriptor = indexing term (MeSH heading)

* = truncation

ti,ab,kw = terms in either title or abstract or keyword fields

near/2 = terms within two words of each other (any order)

next = terms are next to each other

" " = phrase search

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Issue 5 of 12, May 2016

Searched on: 24th May 2016

Records retrieved: 10

See above under CENTRAL for search strategy used.

The search was updated on 30th September 2016 and retrieved 10 records.

Cumulative Index to Nursing & Allied Health (CINAHL Plus)

via EBSCO https://www.ebscohost.com/

Inception to 23rd May 2016

Searched on: 24th May 2016

Records retrieved: 69

The search was updated on 30th September 2016 and retrieved 77 records.

S19	S14 AND S18	69
S18	S15 OR S16 OR S17	815,757
S17	TX adolescen* or baby or babies or child or children or boy or boys or girl or girls or infant* or infanc* or juvenile* or paediatric or pediatric or preschooler* or schoolboy* or schoolgirl* or schoolchild* or teens or teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons"	815,757
S16	(MH "Adolescence+")	355,038
S15	(MH "Child+")	459,154
S14	S5 AND S13	532
S13	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	2,252
S12	TX ustekinumab or stelara or CNTO1275 or "CNTO-1275" or "815610-63-0"	157
S11	TX benepali or brenzys or SB4 or "CHS-0214" or CHS0214	3
S10	TX etanercept or enbrel or "185243-69-0"	1,528
S9	(MH "Etanercept")	701
S8	TX adfrar or exemptia or MSB11022 or "MSB 11022" or GP2017 or "GP 2017" or GP2015 or "GP 2015" or M923 or "M 923" or ABP501 or "ABP 501"	4
S7	TX (adalimumab or humira or D2E7 or "D2-E7" or "D2 E7" or "331731-18-1")	933
S6	(MH "Adalimumab")	124
S5	S1 OR S2 OR S3 OR S4	5,573
S4	TI (pustul* N2 palm*) OR AB (pustul* N2 palm*)	50

S3	TI parapsoriasis OR AB parapsoriasis	11
S2	TI (psorias* or psoriat*) OR AB (psorias* or psoriat*)	4,364
S1	(MH "Psoriasis")	3,589

Key:

MH = indexing term (CINAHL heading)

* = truncation

TI = terms in the title

AB = terms in the abstract

TX = all text - search of all the database's searchable fields

" " = phrase search

N2 = terms within two words of each other (any order)

Database of Abstracts of Reviews of Effects (DARE)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 24th May 2016

Records retrieved: 4

This search strategy was not updated as DARE closed at the end of March 2015.

1	MeSH DESCRIPTOR Psoriasis	202
2	(psorias* or psoriat*)	311
3	(parapsoriasis)	1
4	(pustul* NEAR2 palm*)	2
5	(palm* NEAR2 pustul*)	3
6	#1 OR #2 OR #3 OR #4 OR #5	311
7	MeSH DESCRIPTOR Adalimumab	112
8	(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1")	240
9	MeSH DESCRIPTOR Etanercept	99
10	(etanercept or enbrel or "185243-69-0")	246
11	MeSH DESCRIPTOR Ustekinumab	16
12	(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0")	32

13	(adfrar or exemptia or MSB11022 or "MSB 11022" or GP2017 or "MSB-11022" or "GP 2017" or "GP-2017" or GP2015 or "GP 2015" or "GP-2015" or M923 or "M 923" or "M-923" OR ABP501 or "ABP 501" or "ABP-501")	0
14	(benepali or brenzys or SB4 or CHS-0214 or CHS0214)	0
15	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	355
16	MeSH DESCRIPTOR child EXPLODE ALL TREES	4890
17	MeSH DESCRIPTOR infant EXPLODE ALL TREES	2947
18	MeSH DESCRIPTOR adolescent	4584
19	(adolescen* or baby or babies or child or children or boy or boys or girl or girls or infant* or infanc* or juvenile* or paediatric or pediatric or preschooler* or schoolboy* or schoolgirl* or schoolchild* or teens or teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons")	13284
20	#16 OR #17 OR #18 OR #19	13284
21	#6 AND #15 AND #20	11
22	(#6 AND #15 AND #20) IN DARE	4
23	(#6 AND #15 AND #20) IN HTA	7
24	(#6 AND #15 AND #20) IN NHSEED	0

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

" " = phrase search

NEAR2 = terms within two words of each other (order specified)

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2016 May 20

Searched on: 23rd May 2016

Records retrieved: 771

The search was updated on 30th September 2016 and retrieved 826 records.

1 exp psoriasis/ (57775)

2 (psorias$ or psoriat$).ti,ab. (53835)

3 parapsoriasis.ti,ab. (571)

4 (pustul$ adj2 palm$).ti,ab. (1042)

5 1 or 2 or 3 or 4 (70014)

6 adalimumab/ (20228)

7 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (20663)

8 (adfrar or exemptia or MSB11022 or MSB 11022 or GP2017 or GP 2017 or GP2015 or GP 2015 or M923 or "M 923" or ABP501 or ABP 501).af. (49)

9 etanercept/ (22718)

10 (etanercept or enbrel or 185243-69-0).af. (23579)

11 (benepali or brenzys or SB4 or CHS-0214 or CHS0214).af. (85)

12 ustekinumab/ (2696)

13 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (2813)

14 or/6-13 (34307)

15 5 and 14 (8172)

16 exp child/ (2315907)

17 exp adolescent/ (1350949)

18 juvenile/ (26103)

19 (adolescen$ or baby or babies or child or children or boy or boys or girl or girls or infant$ or infanc$ or juvenile$ or paediatric or pediatric or preschooler$ or schoolboy$ or schoolgirl$ or schoolchild$ or teens or teenage$ or toddler$ or youth or youths or young people or young person$).ti,ab. (2067003)

20 16 or 17 or 18 or 19 (3558532)

21 15 and 20 (771)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = all fields

adj2 = terms within two words of each other (any order)

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 24th May 2016

Searched on: 24th May 2016

Records retrieved: 7

See above under DARE for search strategy used.

The search was updated on 30th September 2016 and retrieved 7 records.

PubMed

http://www.ncbi.nlm.nih.gov/pubmed/

Searched on: 24th May 2016

Records retrieved: 333

The search was updated on 30th September 2016 and retrieved 347 records.

((((((((((((((("Adalimumab"[Mesh:noexp]) OR ((adalimumab OR humira OR D2E7 OR "D2 E7" OR "D2-E7" OR "331731-18-1"))) OR ((adfrar OR exemptia))) OR (("MSB11022" OR "MSB 11022" OR "MSB 11022"))) OR "Etanercept"[Mesh:noexp]) OR ((etanercept OR enbrel OR "185243-69-0"))) OR ((benepali OR brenzys))) OR (("SB4" OR "CHS-0214" OR "CHS0214"))) OR "Ustekinumab"[Mesh:noexp]) OR ((ustekinumab OR stelara OR CNTO1275 OR "CNTO-1275" OR "815610-63-0"))) OR ("M923"[All Fields] OR "M 923"[All Fields] OR "M-923"[All Fields])) OR (("ABP501") OR "ABP 501") OR "ABP-501")) OR (("GP2017") OR "GP-2017") OR "GP 2017")) OR (("GP2015"[All Fields] OR "GP-2015"[All Fields] OR "GP 2015"[All Fields]))))) AND ((((("Psoriasis"[Mesh:noexp]) OR ((psorias*[Title/Abstract] OR psoriat*[Title/Abstract]))) OR parapsoriasis[Title/Abstract]) OR ((pustul*[Title/Abstract] AND palm*[Title/Abstract])))))) AND ((((("Child"[Mesh]) OR "Infant"[Mesh]) OR "Adolescent"[Mesh]) OR ((adolescen*[Title/Abstract] OR baby[Title/Abstract] OR babies[Title/Abstract] OR child[Title/Abstract] OR children[Title/Abstract] OR boy[Title/Abstract] OR boys[Title/Abstract] OR girl[Title/Abstract] OR girls[Title/Abstract] OR infant*[Title/Abstract] OR infanc*[Title/Abstract] OR juvenile*[Title/Abstract] OR paediatric[Title/Abstract] OR pediatric[Title/Abstract] OR preschooler*[Title/Abstract] OR schoolboy*[Title/Abstract] OR schoolgirl*[Title/Abstract] OR schoolchild*[Title/Abstract] OR teens[Title/Abstract] OR teenage*[Title/Abstract] OR toddler*[Title/Abstract] OR youth[Title/Abstract] OR youths[Title/Abstract] OR "young people"[Title/Abstract] OR "young person"[Title/Abstract] OR "young persons"[Title/Abstract])))

Key:

[Mesh] = exploded indexing term (MeSH heading)

[Mesh:noexp] = indexing term (MeSH heading) not exploded

* = truncation

" " = phrase search

[Title/Abstract]) = terms in either title or abstract fields

Science Citation Index

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1900 – 20th May 2016

Searched on: 23rd May 2016

Records retrieved: 256

The search was updated on 30th September 2016 and retrieved 272 records.

# 13	256	#12 AND #11 *Indexes=SCI-EXPANDED Timespan=All years*
# 12	1,516,336	TS=(adolescen* or baby or babies or child or children or boy or boys or girl or girls or infant* or infanc* or juvenile* or paediatric or pediatric or preschooler* or schoolboy* or schoolgirl* or schoolchild* or teens or teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") *Indexes=SCI-EXPANDED Timespan=All years*
# 11	3,490	#10 AND #4 *Indexes=SCI-EXPANDED Timespan=All years*
# 10	13,549	#9 OR #8 OR #7 OR #6 OR #5 *Indexes=SCI-EXPANDED Timespan=All years*
# 9	1,006	TS=(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0") *Indexes=SCI-EXPANDED Timespan=All years*
# 8	145	TS=(benepali or brenzys or SB4 or CHS-0214 or CHS0214) *Indexes=SCI-EXPANDED Timespan=All years*
# 7	8,405	TS=(etanercept or enbrel or "185243-69-0") *Indexes=SCI-EXPANDED Timespan=All years*
# 6	12	TS=(adfrar or exemptia or MSB11022 or "MSB 11022" or GP2017 or "GP 2017" or GP2015 or "GP 2015" or M923 or "M 923" or ABP501 or "ABP 501") *Indexes=SCI-EXPANDED Timespan=All years*
# 5	6,376	TS=(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1") *Indexes=SCI-EXPANDED Timespan=All years*

# 4	46,577	#3 OR #2 OR #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 3	806	TS=(pustul* NEAR/2 palm*) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	480	TS=parapsoriasis *Indexes=SCI-EXPANDED Timespan=All years*
# 1	45,734	TS=(psorias* or psoriat*) *Indexes=SCI-EXPANDED Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

On-going, unpublished or grey literature search strategies

ClinicalTrials.gov

https://clinicaltrials.gov/

Searched on: 24th May 2016

Records retrieved: 23

Searches were carried out as per the search strings below. A total of 28 studies were found, which came down to 23 after deduplication of results.

The search was updated on 15th September 2016 – see under network meta-analysis Search 2. Update searches for the biosimilar drugs (lines 2, 3, 4, 6) was carried out on 30th September 2016 but did not identify any further studies.

1. **6 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1)

2. **no studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (adfrar OR exemptia)

3. **no studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (MSB11022 OR "MSB 11022" OR MSB-11022 OR GP2017 OR "GP 2017" OR GP-2017 OR GP2015 OR "GP 2015" OR GP-2015)

4. **no studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (M923 OR "M 923" OR M-923 OR ABP501 OR "ABP 501" OR ABP-501)

5. **15 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (etanercept OR enbrel OR 185243-69-0)

6. **no studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (benepali OR brenzys OR SB4 OR CHS-0214 OR CHS0214)

7. **7 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0)

Conference Proceedings Citation Index: Science

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1990 – 20th May 2016

Searched on: 23rd May 2016

Records retrieved: 21

The search was updated on 30th September 2016 and retrieved 21 records.

# 13	21	#12 AND #11 *Indexes=CPCI-S Timespan=All years*
# 12	148,800	TS=(adolescen* or baby or babies or child or children or boy or boys or girl or girls or infant* or infanc* or juvenile* or paediatric or pediatric or preschooler* or schoolboy* or schoolgirl* or schoolchild* or teens or teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") *Indexes=CPCI-S Timespan=All years*

# 11	633	#10 AND #4 *Indexes=CPCI-S Timespan=All years*
# 10	2,726	#9 OR #8 OR #7 OR #6 OR #5 *Indexes=CPCI-S Timespan=All years*
# 9	179	TS=(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0") *Indexes=CPCI-S Timespan=All years*
# 8	30	TS=(benepali or brenzys or SB4 or CHS-0214 or CHS0214) *Indexes=CPCI-S Timespan=All years*
# 7	1,341	TS=(etanercept or enbrel or "185243-69-0") *Indexes=CPCI-S Timespan=All years*
# 6	6	TS=(adfrar or exemptia or MSB11022 or "MSB 11022" or GP2017 or "GP 2017" or GP2015 or "GP 2015" or M923 or "M 923" or ABP501 or "ABP 501") *Indexes=CPCI-S Timespan=All years*
# 5	1,351	TS=(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1") *Indexes=CPCI-S Timespan=All years*
# 4	6,375	#3 OR #2 OR #1 *Indexes=CPCI-S Timespan=All years*
# 3	68	TS=(pustul* NEAR/2 palm*) *Indexes=CPCI-S Timespan=All years*
# 2	18	TS=parapsoriasis *Indexes=CPCI-S Timespan=All years*
# 1	6,317	TS=(psorias* or psoriat*) *Indexes=CPCI-S Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/ctr-search/search

Searched on: 24th May 2016

Records retrieved: 10

The search was updated on 19th September 2016 – see under network meta-analysis Search 2. Update searches for the biosimilar drugs (lines 2, 3, 4, 6) was carried out on 30th September 2016 but did not identify any further studies.

1. 2 result(s) found for: (Psoriasis OR psoriatic) AND (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

2. 0 result(s) found for: (Psoriasis OR psoriatic) AND (adfrar OR exemptia). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

3. 1 result(s) found for: (Psoriasis OR psoriatic) AND (MSB11022 OR "MSB 11022" OR MSB-11022 OR GP2017 OR "GP 2017" OR GP-2017 OR GP2015 OR "GP 2015" OR GP-2015) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

4. 0 result(s) found for: (Psoriasis OR psoriatic) AND (M923 OR "M 923" OR M-923 OR ABP501 OR "ABP 501" OR ABP-501). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

5. 5 result(s) found for: (Psoriasis OR psoriatic) AND (etanercept OR enbrel OR 185243-69-0) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

6. 0 result(s) found for: (Psoriasis OR psoriatic) AND (benepali OR brenzys OR SB4 OR CHS-0214 OR CHS0214). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

7. 2 result(s) found for: (Psoriasis OR psoriatic) AND (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

PROSPERO

http://www.crd.york.ac.uk/PROSPERO/

Searched on: 24th May 2016

Records retrieved: 32

Search: Psoriasis in all fields.

The search was updated on 30th September 2016 and retrieved 13 new records, added since the previous search on 24th May 2016.

WHO International Clinical Trials Registry Platform

http://www.who.int/ictrp/search/en/

Searched on: 24th May 2016

Records retrieved: 32

The search was updated on 19th September 2016 – see under network meta-analysis Search 2. Update searches for the biosimilar drugs (lines 2, 3, 4, 6) was carried out on 30th September 2016 but did not identify any further studies.

1. Condition: (psoriasis OR psoriatic) AND Intervention: (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1) limited to clinical trials in children (birth to 18 years)

8 trials found.

2. Condition: (psoriasis OR psoriatic) AND Intervention: (adfrar OR exemptia) limited to clinical trials in children (birth to 18 years)

0 trials

3. Condition: (psoriasis OR psoriatic) AND Intervention: (MSB11022 OR “MSB 11022” OR MSB-11022 OR GP2017 OR “GP 2017” OR GP-2017 OR GP2015 OR “GP 2015” OR GP-2015) limited to clinical trials in children (birth to 18 years)

0 trials

4. Condition: (psoriasis OR psoriatic) AND Intervention: (M923 OR "M 923" OR M-923 OR ABP501 OR “ABP 501” OR ABP-501) limited to clinical trials in children (birth to 18 years)

0 trials

5. Condition: (psoriasis OR psoriatic) AND Intervention: (etanercept OR enbrel OR 185243-69-0) limited to clinical trials in children (birth to 18 years)

15 trials found

6. Condition: (psoriasis OR psoriatic) AND Intervention: (benepali OR brenzys OR SB4 OR CHS-0214 OR CHS0214) limited to clinical trials in children (birth to 18 years)

2 trials found

7. Condition: (psoriasis OR psoriatic) AND Intervention: (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0) limited to clinical trials in children (birth to 18 years)

7 trials found

Guideline searches

The following resources were searched for relevant guidelines on 25th May 2016. The same searches were repeated on 30th September 2016 with 1 further guideline identified from NHS Evidence.

National Guideline Clearinghouse

http://www.guideline.gov/

Searched on: 25th May 2016 (update search on 30th September 2016)

Records retrieved: 4

Keyword: psorias* or psoriat*
Age of Target Population: Infant, Newborn (to 1 month), Infant (1 to 23 months), Child (2 to 12 years), Adolescent (13 to 18 years)

10 results were browsed and 4 were identified as potentially relevant.

NICE Clinical Knowledge Summaries (CKS)

http://cks.nice.org.uk/

Searched on: 25th May 2016 (update search on 30th September 2016)

Records retrieved: 1

The topics section was browsed and 1 CKS for psoriasis identified.

NHS Evidence

https://www.evidence.nhs.uk/

Searched on: 25th May 2016 (update search on 30th September 2016)

Records retrieved: 22

((intitle:psorias* OR intags: psorias* OR inurl:psorias*) AND (child* or infant* or adolescen*))

Results filtered by type of information = guidance. Results scanned for relevance, 22 documents identified.

NICE Evidence summaries: new medicines

https://www.nice.org.uk/about/what-we-do/our-programmes/nice-advice/evidence-summaries-new-medicines

Searched on: 24th May 2016 (update search on 30th September 2016)

Records retrieved: 0

Browsed 63 titles of published evidence summaries – no relevant summaries found.

NICE website

https://www.nice.org.uk/

Searched on: 25th May 2016 (update search on 30th September 2016)

Records retrieved: 4

Browsed psoriasis topic page https://www.nice.org.uk/guidance/conditions-and-diseases/skin-conditions/psoriasis – 4 relevant documents identified.

Network meta-analysis searches

The following searches were carried out to identify:

1. RCTs of systemic non-biological (acitretin, methotrexate, cyclosporine) and biological therapies (infliximab, secukinumab) in children and young people with plaque psoriasis

2. RCTs of adalimumab, etanercept, ustekinumab, acitretin, methotrexate, cyclosporine, infliximab or secukinumab in adults with plaque psoriasis

Search 1

RCTs of systemic non-biological (acitretin, methotrexate, cyclosporine) and biological therapies (infliximab, secukinumab) in children and young people with plaque psoriasis

Database search strategies

MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R))

via Ovid http://ovidsp.ovid.com/

1946 to present

Searched on: 31st May 2016

Records retrieved: 760

The search was updated on 30th September 2016 and retrieved 784 records.

1 Psoriasis/ (29106)

2 (psorias$ or psoriat$).ti,ab. (36848)

3 parapsoriasis.ti,ab. (525)

4 (pustul$ adj2 palm$).ti,ab. (787)

5 or/1-4 (42692)

6 Acitretin/ (922)

7 (acitretin$ or etretin or neotigason or soriatane or 55079-83-9).af. (2571)

8 Methotrexate/ (33972)

9 (methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or 15475-56-6 or 59-05-2 or 7413-34-5).af. (48192)

10 exp Cyclosporins/ (37382)

11 (cyclosporin$ or ciclosporin$ or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or 59865-13-3 or 63798-73-2).af. (55065)

12 Infliximab/ (7830)

13 (infliximab or remicade or 170277-31-3).af. (11015)

14 (inflectra or remsima or CT-P13).af. (63)

15 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (193)

16 or/6-15 (111288)

17 5 and 16 (5655)

18 exp Child/ (1666387)

19 exp Infant/ (1007661)

20 Adolescent/ (1732216)

21 (adolescen$ or baby or babies or child or children or boy or boys or girl or girls or infant$ or infanc$ or juvenile$ or paediatric or pediatric or preschooler$ or schoolboy$ or schoolgirl$ or schoolchild$ or teens or teenage$ or toddler$ or youth or youths or young people or young person$).ti,ab. (1674732)

22 or/18-21 (3488828)

23 17 and 22 (761)

24 exp animals/ not humans/ (4247320)

25 23 not 24 (760)

Key:

/ = indexing term (MeSH heading)

exp = exploded indexing term (MeSH heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = terms in any field

adj2 = terms within two words of each other (any order)

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Issue 5 of 12, May 2016

Searched on: 31st May 2016

Records retrieved: 70

The strategy below was used to search CENTRAL and CDSR.

The search was updated on 30th September 2016 and retrieved 79 records from CENTRAL.

#1 MeSH descriptor: [Psoriasis] this term only 1891

#2 (psorias* or psoriat*):ti,ab,kw 4328

#3 parapsoriasis:ti,ab,kw 3

#4 (pustul* near/2 palm*):ti,ab,kw 73

#5 #1 or #2 or #3 or #4 4360

#6 MeSH descriptor: [Acitretin] this term only 66

#7 (acitretin* or etretin or neotigason or soriatane or "55079-83-9") 162

#8 MeSH descriptor: [Methotrexate] this term only 3050

#9 (methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5") 7671

#10 MeSH descriptor: [Cyclosporins] explode all trees 2699

#11 (cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2") 6059

#12 MeSH descriptor: [Infliximab] this term only 433

#13 (infliximab or remicade or "170277-31-3") 1347

#14 (inflectra or remsima or "CT-P13") 17

#15 (secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6") 153

#16 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 14174

#17 #5 and #16 822

#18 MeSH descriptor: [Child] explode all trees 178

#19 MeSH descriptor: [Infant] explode all trees 14343

#20 MeSH descriptor: [Adolescent] this term only 85203

#21 (adolescen* or baby or babies or child or children or boy or boys or girl or girls or infant* or infanc* or juvenile* or paediatric or pediatric or preschooler* or schoolboy* or schoolgirl* or schoolchild* or teens or teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") 193591

#22 #18 or #19 or #20 or #21 193591

#23 #17 and #22 89

#24 #17 and #22 in Cochrane Reviews (Reviews and Protocols) 15

#25 #17 and #22 in Trials 70

Key:

MeSH descriptor = indexing term (MeSH heading)

* = truncation

ti,ab,kw = terms in either title or abstract or keyword fields

near/2 = terms within two words of each other (any order)

" " = phrase search

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Issue 5 of 12, May 2016

Searched on: 31st May 2016

Records retrieved: 15

See above under CENTRAL for search strategy used.

The search was updated on 30th September 2016 and retrieved 15 records from CDSR.

Cumulative Index to Nursing & Allied Health (CINAHL Plus)

via EBSCO https://www.ebscohost.com/

Inception to 30th May 2016

Searched on: 31st May 2016

Records retrieved: 68

The search was updated on 30th September 2016 and retrieved 74 records.

S22	S17 AND S21	68
S21	S18 OR S19 OR S20	816,943
S20	TX adolescen* or baby or babies or child or children or boy or boys or girl or girls or infant* or infanc* or juvenile* or paediatric or pediatric or preschooler* or schoolboy* or schoolgirl* or schoolchild* or teens or teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons"	816,943
S19	(MH "Adolescence+")	355,343
S18	(MH "Child+")	459,529
S17	S5 AND S16	718
S16	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	9,936
S15	TX (secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6")	73
S14	TX (inflectra or remsima or "CT-P13")	34
S13	TX (infliximab or remicade or "170277-31-3")	2,106
S12	(MH "Infliximab")	1,001

S11	TX (cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2")	2,710
S10	(MH "Cyclosporins") OR (MH "Cyclosporine")	1,875
S9	TX methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5")	5,106
S8	(MH "Methotrexate")	3,692
S7	TX acitretin* or etretin or neotigason or soriatane or "55079-83-9"	90
S6	(MH "Retinoids")	662
S5	S1 OR S2 OR S3 OR S4	5,585
S4	TI (pustul* N2 palm*) OR AB (pustul* N2 palm*)	50
S3	TI parapsoriasis OR AB parapsoriasis	11
S2	TI (psorias* or psoriat*) OR AB (psorias* or psoriat*)	4,375
S1	(MH "Psoriasis")	3,599

Key:

MH = indexing term (CINAHL heading)

* = truncation

TI = terms in the title

AB = terms in the abstract

TX = all text - search of all the database's searchable fields

" " = phrase search

N2 = terms within two words of each other (any order)

Database of Abstracts of Reviews of Effects (DARE)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 31st May 2016

Records retrieved: 6

This search strategy was not updated as DARE closed at the end of March 2015.

1	MeSH DESCRIPTOR Psoriasis	202
2	(psorias* or psoriat*)	311

3	(parapsoriasis)	1
4	(pustul* NEAR2 palm*)	2
5	(palm* NEAR2 pustul*)	3
6	#1 OR #2 OR #3 OR #4 OR #5	311
7	MeSH DESCRIPTOR Acitretin	7
8	(acitretin* or etretin or neotigason or soriatane or "55079-83-9")	25
9	MeSH DESCRIPTOR Methotrexate	176
10	(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5")	452
11	MeSH DESCRIPTOR Cyclosporins EXPLODE ALL TREES	109
12	(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2")	279
13	MeSH DESCRIPTOR Infliximab	163
14	(infliximab or remicade or "170277-31-3")	349
15	(inflectra or remsima or "CT-P13")	5
16	(secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6")	11
17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	921
18	#6 AND #17	118
19	MeSH DESCRIPTOR child EXPLODE ALL TREES	4890
20	MeSH DESCRIPTOR infant EXPLODE ALL TREES	2947
21	MeSH DESCRIPTOR adolescent	4585
22	(adolescen* or baby or babies or child or children or boy or boys or girl or girls or infant* or infanc* or juvenile* or paediatric or pediatric or preschooler*)	13225
23	(schoolboy* or schoolgirl* or schoolchild* or teens or teenage*)	148
24	(toddler* or youth or youths or "young people" or "young person" or "young persons")	614
25	#19 OR #20 OR #21 OR #22 OR #23 OR #24	13340
26	#18 AND #25	7
27	(#18 AND #25) IN DARE	6
28	(#18 AND #25) IN HTA	1
29	(#18 AND #25) IN NHSEED	0

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

" " = phrase search

NEAR2 = terms within two words of each other (order specified)

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2016 May 27

Searched on: 31st May 2016

Records retrieved: 1467

The search was updated on 30th September 2016 and retrieved 1564 records.

1 exp psoriasis/ (57814)

2 (psorias$ or psoriat$).ti,ab. (53874)

3 parapsoriasis.ti,ab. (571)

4 (pustul$ adj2 palm$).ti,ab. (1043)

5 1 or 2 or 3 or 4 (70062)

6 etretin/ (4892)

7 (acitretin$ or etretin or neotigason or soriatane or 55079-83-9).af. (5033)

8 methotrexate/ (146811)

9 (methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or 15475-56-6 or 59-05-2 or 7413-34-5).af. (152425)

10 cyclosporin derivative/ (1950)

11 cyclosporin/ (70557)

12 cyclosporin A/ (65595)

13 (cyclosporin$ or ciclosporin$ or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or 59865-13-3 or 63798-73-2).af. (139555)

14 infliximab/ (35519)

15 (infliximab or remicade or 170277-31-3).af. (36260)

16 (inflectra or remsima or CT-P13).af. (157)

17 secukinumab/ (768)

18 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (849)

19 or/6-18 (289812)

20 5 and 19 (15485)

21 exp child/ (2317206)

22 exp adolescent/ (1351704)

23 juvenile/ (26120)

24 (adolescen$ or baby or babies or child or children or boy or boys or girl or girls or infant$ or infanc$ or juvenile$ or paediatric or pediatric or preschooler$ or schoolboy$ or schoolgirl$ or schoolchild$ or teens or teenage$ or toddler$ or youth or youths or young people or young person$).ti,ab. (2068480)

25 or/21-24 (3560620)

26 20 and 25 (1468)

27 (animal/ or nonhuman/) not exp human/ (5037476)

28 26 not 27 (1467)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = all fields

adj2 = terms within two words of each other (any order)

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st May 2016

Searched on: 31st May 2016

Records retrieved: 1

See above under DARE for search strategy used.

The search was updated on 30th September 2016 and retrieved 1 record.

PubMed

http://www.ncbi.nlm.nih.gov/pubmed/

Searched on: 31st May 2016

Records retrieved: 698

The search was updated on 30th September 2016 and retrieved 715 records.

Search ((((((((((("Acitretin"[Mesh:NoExp]) OR ((acitretin* OR etretin OR neotigason OR soriatane OR "55079-83-9"))) OR "Methotrexate"[Mesh:NoExp]) OR ((methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR "15475-56-6" OR "59-05-2" OR "7413-34-5"))) OR "Cyclosporins"[Mesh]) OR ((cyclosporin$ OR ciclosporin$ OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR "59865-13-3" OR "63798-73-2"))) OR "Infliximab"[Mesh:NoExp]) OR ((infliximab OR remicade OR "170277-31-3"))) OR ((inflectra OR remsima OR CT-P13))) OR ((secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR "1229022-83-6")))) AND ((((("Psoriasis"[Mesh:NoExp]) OR ((psorias*[Title/Abstract] OR psoriat*[Title/Abstract]))) OR parapsoriasis[Title/Abstract]) OR ((pustul*[Title/Abstract] AND palm*[Title/Abstract])))))) AND ((((("Child"[Mesh]) OR "Infant"[Mesh]) OR "Adolescent"[Mesh:NoExp]) OR ((adolescen*[Title/Abstract] OR baby[Title/Abstract] OR babies[Title/Abstract] OR child[Title/Abstract] OR children[Title/Abstract] OR boy[Title/Abstract] OR boys[Title/Abstract] OR girl[Title/Abstract] OR girls[Title/Abstract] OR infant*[Title/Abstract] OR infanc*[Title/Abstract] OR juvenile*[Title/Abstract] OR paediatric[Title/Abstract] OR pediatric[Title/Abstract] OR preschooler*[Title/Abstract] OR schoolboy*[Title/Abstract] OR schoolgirl*[Title/Abstract] OR schoolchild*[Title/Abstract] OR teens[Title/Abstract] OR teenage*[Title/Abstract] OR toddler*[Title/Abstract] OR youth[Title/Abstract] OR youths[Title/Abstract] OR “young people”[Title/Abstract] OR “young person”[Title/Abstract] OR “young persons”[Title/Abstract])))

Key:

[Mesh] = exploded indexing term (MeSH heading)

[Mesh:NoExp] = indexing term (MeSH heading) not exploded

* = truncation

" " = phrase search

[Title/Abstract]) = terms in either title or abstract fields

Science Citation Index

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1900 – 30th May 2016

Searched on: 31st May 2016

Records retrieved: 402

The search was updated on 30th September 2016 and retrieved 420 records.

# 14	402	#13 AND #12 *Indexes=SCI-EXPANDED Timespan=All years*
# 13	1,529,440	TS=(adolescen* or baby or babies or child or children or boy or boys or girl or girls or infant* or infanc* or juvenile* or paediatric or pediatric or preschooler* or schoolboy* or schoolgirl* or schoolchild* or teens or teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") *Indexes=SCI-EXPANDED Timespan=All years*
# 12	6,098	#11 AND #4 *Indexes=SCI-EXPANDED Timespan=All years*
# 11	122,506	#10 OR #9 OR #8 OR #7 OR #6 OR #5 *Indexes=SCI-EXPANDED Timespan=All years*
# 10	329	TS=(secukinumab or Cosentyx or AIN457 or AIN-457 or "1229022-83-6") *Indexes=SCI-EXPANDED Timespan=All years*
# 9	78	TS=(inflectra or remsima or CT-P13) *Indexes=SCI-EXPANDED Timespan=All years*
# 8	16,040	TS=(infliximab or remicade or "170277-31-3") *Indexes=SCI-EXPANDED Timespan=All years*
# 7	67,052	TS=(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2") *Indexes=SCI-EXPANDED Timespan=All years*
# 6	44,388	TS=(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5") *Indexes=SCI-EXPANDED Timespan=All years*
# 5	1,259	TS=(acitretin* or etretin or neotigason or soriatane or "55079-83-9") *Indexes=SCI-EXPANDED Timespan=All years*
# 4	46,956	#3 OR #2 OR #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 3	808	TS=(pustul* NEAR/2 palm*) *Indexes=SCI-EXPANDED Timespan=All years*

# 2	480	TS=parapsoriasis *Indexes=SCI-EXPANDED Timespan=All years*
# 1	46,113	TS=(psorias* or psoriat*) *Indexes=SCI-EXPANDED Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

On-going, unpublished or grey literature search strategies

ClinicalTrials.gov

https://clinicaltrials.gov/

Searched on: 31st May 2016

Records retrieved: 20

Searches were carried out as per the search strings below. A total of 47 studies were found, which came down to 20 after deduplication of results.

The search was updated on 15th September 2016 – see under network meta-analysis Search 2.

1. **3 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (acitretin OR etretin OR neotigason OR soriatane OR 55079-83-9)

2. **9 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal)

3. **9 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5)

4. **7 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (cyclosporin OR ciclosporin OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin)

5. **7 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2)

6. **9 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (infliximab OR remicade OR 170277-31-3)

7. **no studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (inflectra OR remsima OR CT-P13)

8. **3 studies found for**: (Psoriasis OR psoriatic) AND (adolescent OR adolescence OR adolescents OR child OR children OR infant OR infancy OR infants) AND (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6)

Conference Proceedings Citation Index: Science

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1990 – 30th May 2016

Searched on: 31st May 2016

Records retrieved: 16

The search was updated on 30th September 2016 and retrieved 16 records.

# 14	16	#13 AND #12 *Indexes=CPCI-S Timespan=All years*
# 13	149,897	TS=(adolescen* or baby or babies or child or children or boy or boys or girl or girls or infant* or infanc* or juvenile* or paediatric or pediatric or preschooler* or schoolboy* or schoolgirl* or schoolchild* or teens or teenage* or toddler* or youth or youths or "young people" or "young person" or "young persons") *Indexes=CPCI-S Timespan=All years*

# 12	592	#11 AND #4 *Indexes=CPCI-S Timespan=All years*
# 11	15,410	#10 OR #9 OR #8 OR #7 OR #6 OR #5 *Indexes=CPCI-S Timespan=All years*
# 10	76	TS=(secukinumab or Cosentyx or AIN457 or AIN-457 or "1229022-83-6") *Indexes=CPCI-S Timespan=All years*
# 9	8	TS=(inflectra or remsima or CT-P13) *Indexes=CPCI-S Timespan=All years*
# 8	2,781	TS=(infliximab or remicade or "170277-31-3") *Indexes=CPCI-S Timespan=All years*
# 7	8,929	TS=(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2") *Indexes=CPCI-S Timespan=All years*
# 6	4,027	TS=(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5") *Indexes=CPCI-S Timespan=All years*
# 5	129	TS=(acitretin* or etretin or neotigason or soriatane or "55079-83-9") *Indexes=CPCI-S Timespan=All years*
# 4	6,417	#3 OR #2 OR #1 *Indexes=CPCI-S Timespan=All years*
# 3	68	TS=(pustul* NEAR/2 palm*) *Indexes=CPCI-S Timespan=All years*
# 2	18	TS=parapsoriasis *Indexes=CPCI-S Timespan=All years*
# 1	6,359	TS=(psorias* or psoriat*) *Indexes=CPCI-S Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/ctr-search/search

Searched on: 31st May 2016

Records retrieved: 7

The search was updated on 19th September 2016 – see under network meta-analysis Search 2.

1. 0 result(s) found for: (Psoriasis OR psoriatic) AND (acitretin* OR etretin OR neotigason OR soriatane OR 55079-83-9). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

2. 5 result(s) found for: (Psoriasis OR psoriatic) AND (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5)). Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

3. 0 trials found for: (Psoriasis OR psoriatic) AND (cyclosporin* OR ciclosporin* OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

4. 1 result(s) found for: (Psoriasis OR psoriatic) AND (infliximab OR remicade OR 170277-31-3) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

5. 0 results(s) found for: (Psoriasis OR psoriatic) AND (inflectra OR remsima OR CT-P13) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

6. 1 result(s) found for: (Psoriasis OR psoriatic) AND (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6) Limited by age range to adolescent, children, infant and toddler, newborn, preterm, under 18

Key:

* = truncation

WHO International Clinical Trials Registry Platform

http://www.who.int/ictrp/search/en/

Searched on: 30th May 2016

Records retrieved: 25

The search was updated on 19th September 2016 – see network meta-analysis Search 2.

1. Condition: (psoriasis OR psoriatic) AND Intervention: (acitretin* OR etretin OR neotigason OR soriatane OR 55079-83-9) limited to clinical trials in children (birth to 18 years)

0 trials found.

2. Condition: (psoriasis OR psoriatic) AND Intervention: (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5) limited to clinical trials in children (birth to 18 years)

5 trials found.

3. Condition: (psoriasis OR psoriatic) AND Intervention: (cyclosporin* OR ciclosporin* OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2) limited to clinical trials in children (birth to 18 years)

2 trials found.

4. Condition: (psoriasis OR psoriatic) AND Intervention: (infliximab OR remicade OR 170277-31-3) limited to clinical trials in children (birth to 18 years)

5 trials found

5. Condition: (psoriasis OR psoriatic) AND Intervention: (inflectra OR remsima OR CT-P13) limited to clinical trials in children (birth to 18 years)

1 trial found

6. Condition: (psoriasis OR psoriatic) AND Intervention: (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6) limited to clinical trials in children (birth to 18 years)

12 trials found

Search 2

RCTs of adalimumab, etanercept, ustekinumab, acitretin, methotrexate, cyclosporine, infliximab or secukinumab in adults with plaque psoriasis

Database search strategies

MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R))

via Ovid http://ovidsp.ovid.com/

1946 to present

Searched on: 14th September 2016

Records retrieved: 274

The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in Ovid MEDLINE: sensitivity-maximizing version was used to limit retrieval to RCTs (lines 26-35).[1]

1 Psoriasis/ (29604)

2 (psorias$ or psoriat$).ti,ab. (37897)

3 parapsoriasis.ti,ab. (529)

4 (pustul$ adj2 palm$).ti,ab. (804)

5 1 or 2 or 3 or 4 (43797)

6 Adalimumab/ (3560)

7 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (5547)

8 Etanercept/ (4829)

9 (etanercept or enbrel or 185243-69-0).af. (6906)

10 Ustekinumab/ (449)

11 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (859)

12 or/6-11 (10712)

13 Acitretin/ (944)

14 (acitretin$ or etretin or neotigason or soriatane or 55079-83-9).af. (2610)

15 Methotrexate/ (34625)

16 (methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or 15475-56-6 or 59-05-2 or 7413-34-5).af. (49306)

17 exp Cyclosporins/ (37792)

18 (cyclosporin$ or ciclosporin$ or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or 59865-13-3 or 63798-73-2).af. (55843)

19 Infliximab/ (8112)

20 (infliximab or remicade or 170277-31-3).af. (11419)

21 (inflectra or remsima or CT-P13).af. (78)

22 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (236)

23 or/13-22 (113486)

24 5 and 12 (2777)

25 5 and 23 (5831)

26 randomized controlled trial.pt. (430970)

27 controlled clinical trial.pt. (91709)

28 randomized.ab. (370512)

29 placebo.ab. (179018)

30 clinical trials as topic.sh. (179518)

31 randomly.ab. (263747)

32 trial.ti. (162078)

33 26 or 27 or 28 or 29 or 30 or 31 or 32 (1067990)

34 exp animals/ not humans.sh. (4316367)

35 33 not 34 (984770)

36 24 and 35 (611)

37 25 and 35 (851)

38 36 or 37 (1163)

39 (2014$ or 2015$ or 2016$).ed,dc. (3860024)

40 38 and 39 (274)

Key:

/ = indexing term (MeSH heading)

exp = exploded indexing term (MeSH heading)

$ = truncation

ti,ab = terms in either title or abstract fields

adj2 = terms within two words of each other (any order)

af = terms in any field

sh = subject heading

ed = entry date field

dc = date record created field

pt = publication type

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Issue 8 of 12, August 2016

Searched on: 14th September 2016

Records retrieved: 280

The strategy below was used to search CENTRAL and CDSR.

#1	MeSH descriptor: [Psoriasis] this term only	1903
#2	(psorias* or psoriat*):ti,ab,kw	4457
#3	parapsoriasis:ti,ab,kw	3
#4	(pustul* near/2 palm*):ti,ab,kw	75
#5	#1 or #2 or #3 or #4	4489
#6	MeSH descriptor: [Adalimumab] this term only	253
#7	(adalimumab or humira or D2E7 or (D2 next E7) or "331731-18-1")	1167
#8	MeSH descriptor: [Etanercept] this term only	391
#9	(etanercept or enbrel or "185243-69-0")	1216
#10	MeSH descriptor: [Ustekinumab] this term only	50
#11	(ustekinumab or stelara or "CNTO1275" or "CNTO-1275" or "815610-63-0")	207
#12	#6 or #7 or #8 or #9 or #10 or #11	2186

#13 MeSH descriptor: [Acitretin] this term only 66

#14 acitretin* or etretin or neotigason or soriatane or "55079-83-9" 167

#15 MeSH descriptor: [Methotrexate] this term only 3087

#16 methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5" 7891

#17 MeSH descriptor: [Cyclosporins] explode all trees 2708

#18 cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2" 6124

#19 MeSH descriptor: [Infliximab] this term only 445

#20 infliximab or remicade or "170277-31-3" 1404

#21 inflectra or remsima or "CT-P13" 19

#22 secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6" 187

#23 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 14517

#24 #5 and #12 651

#25 #5 and #23 869

#26 #24 or #25 1271

#27 #24 or #25 Publication Year from 2014 to 2016 305

NB: Results at line #27 are the total results for this search including all databases within the Cochrane Library.

Key:

MeSH descriptor = indexing term (MeSH heading)

* = truncation

ti,ab,kw = terms in either title or abstract or keyword fields

near/2 = terms within two words of each other (any order)

" " = phrase search

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Issue 9 of 12, September 2016

Searched on: 14th September 2016

Records retrieved: 10

See above under CENTRAL for search strategy used.

Cumulative Index to Nursing & Allied Health (CINAHL Plus)

via EBSCO https://www.ebscohost.com/

Inception to 14th September 2016

Searched on: 14th September 2016

Records retrieved: 108

S43	S40 OR S42	108
S42	S38 AND S41	28
S41	(ZD "in process")	225,905
S40	S38 AND S39	80
S39	EM 2014-	914,196
S38	S25 AND S37	378
S37	S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36	1,073,032
S36	TX allocat* random*	5,244
S35	(MH "Quantitative Studies")	14,844
S34	(MH "Placebos")	9,797
S33	TX placebo*	39,440
S32	TX random* allocat*	5,244
S31	(MH "Random Assignment")	41,555
S30	TX randomi* control* trial*	109,672
S29	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	850,155

S28	TX clinic* n1 trial*	189,284
S27	PT Clinical trial	79,715
S26	(MH "Clinical Trials+")	202,495
S25	S12 OR S24	1,104
S24	S5 AND S23	746
S23	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22	10,196
S22	TX (secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6")	83
S21	TX (inflectra or remsima or "CT-P13")	37
S20	TX (infliximab or remicade or "170277-31-3")	2,163
S19	(MH "Infliximab")	1,013
S18	TX (cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2")	2,766
S17	(MH "Cyclosporins") OR (MH "Cyclosporine")	1,909
S16	TX methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5")	5,246
S15	(MH "Methotrexate")	3,761
S14	TX acitretin* or etretin or neotigason or soriatane or "55079-83-9"	95
S13	(MH "Retinoids")	672
S12	S5 AND S11	567
S11	S6 OR S7 OR S8 OR S9 OR S10	2,369
S10	TX ustekinumab or stelara or CNTO1275 or "CNTO-1275" or "815610-63-0"	176
S9	TX etanercept or enbrel or "185243-69-0"	1,590

S8	(MH "Etanercept")	708
S7	TX (adalimumab or humira or D2E7 or "D2-E7" or "D2 E7" or "331731-18-1")	1,003
S6	(MH "Adalimumab")	135
S5	S1 OR S2 OR S3 OR S4	5,815
S4	TI (pustul* N2 palm*) OR AB (pustul* N2 palm*)	52
S3	TI parapsoriasis OR AB parapsoriasis	11
S2	TI (psorias* or psoriat*) OR AB (psorias* or psoriat*)	4,590
S1	(MH "Psoriasis")	3,656

Key:

MH = indexing term (CINAHL heading)

* = truncation

TI = terms in the title

AB = terms in the abstract

TX = all text - search of all the database's searchable fields

" " = phrase search

N2 = terms within two words of each other (any order)

Database of Abstracts of Reviews of Effects (DARE)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 14th September 2016

Records retrieved: 15

1	MeSH DESCRIPTOR Psoriasis	203
2	(psorias* or psoriat*)	312
3	(parapsoriasis)	1
4	(pustul* NEAR2 palm*)	2
5	(palm* NEAR2 pustul*)	3

6	#1 OR #2 OR #3 OR #4 OR #5	312
7	MeSH DESCRIPTOR Adalimumab	113
8	(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1")	241
9	MeSH DESCRIPTOR Etanercept	99
10	(etanercept or enbrel or "185243-69-0")	246
11	MeSH DESCRIPTOR Ustekinumab	17
12	(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0")	33
13	#7 OR #8 OR #9 OR #10 OR #11 OR #12	357
14	#6 AND #13	111
15	MeSH DESCRIPTOR Acitretin	7
16	(acitretin* or etretin or neotigason or soriatane or "55079-83-9")	25
17	MeSH DESCRIPTOR Methotrexate	176
18	(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5")	453
19	MeSH DESCRIPTOR Cyclosporins EXPLODE ALL TREES	109
20	(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2")	279
21	MeSH DESCRIPTOR Infliximab	164
22	(infliximab or remicade or "170277-31-3")	350
23	(inflectra or remsima or "CT-P13")	5
24	(secukinumab or Cosentyx or "AIN457" or "AIN-457" or "1229022-83-6")	11
25	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	923
26	#6 AND #25	119
27	#14 OR #26	155
28	(#14 OR #26) IN DARE, HTA FROM 2014 TO 2016	26

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

" " = phrase search

NEAR2 = terms within two words of each other (order specified)

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2016 September 13

Searched on: 14th September 2016

Records retrieved: 832

A search strategy developed by Lefebvre et al. to limit retrieval of studies to RCTs was used (see lines 29-45).[2]

1 exp psoriasis/ (59685)

2 (psorias$ or psoriat$).ti,ab. (55841)

3 parapsoriasis.ti,ab. (576)

4 (pustul$ adj2 palm$).ti,ab. (1072)

5 1 or 2 or 3 or 4 (72314)

6 adalimumab/ (21367)

7 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (21859)

8 etanercept/ (23491)

9 (etanercept or enbrel or 185243-69-0).af. (24393)

10 ustekinumab/ (2986)

11 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (3119)

12 or/6-11 (35874)

13 etretin/ (5060)

14 (acitretin$ or etretin or neotigason or soriatane or 55079-83-9).af. (5207)

15 methotrexate/ (149388)

16 (methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or 15475-56-6 or 59-05-2 or 7413-34-5).af. (155196)

17 cyclosporin derivative/ (1951)

18 cyclosporin/ (71661)

19 cyclosporin A/ (66255)

20 (cyclosporin$ or ciclosporin$ or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or 59865-13-3 or 63798-73-2).af. (141395)

21 infliximab/ (36969)

22 (infliximab or remicade or 170277-31-3).af. (37773)

23 (inflectra or remsima or CT-P13).af. (227)

24 secukinumab/ (909)

25 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (994)
26 or/13-25 (295191)
27 5 and 12 (8698)
28 5 and 26 (16051)
29 random$.ti,ab. (1123629)
30 factorial$.ti,ab. (28599)
31 crossover$.ti,ab. (59028)
32 cross-over$.ti,ab. (26272)
33 placebo$.ti,ab. (244396)
34 (doubl$ adj blind$).ti,ab. (172319)
35 (singl$ adj blind$).ti,ab. (18249)
36 assign$.ti,ab. (296256)
37 allocat$.ti,ab. (107971)
38 volunteer$.ti,ab. (211580)
39 Crossover Procedure/ (48681)
40 double blind procedure/ (134149)
41 Randomized Controlled Trial/ (420204)
42 single blind procedure/ (23202)
43 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (1760154)
44 (animal/ or nonhuman/) not exp human/ (5111869)
45 43 not 44 (1564985)
46 27 and 45 (1443)
47 28 and 45 (1756)
48 46 or 47 (2351)
49 (2014$ or 2015$ or 2016$).em. (4971904)
50 48 and 49 (832)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = all fields

adj2 = terms within two words of each other (any order)

em = entry date

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 14th September 2016

Searched on: 14th September 2016

Records retrieved: 11

See above under DARE for search strategy used.

PubMed

http://www.ncbi.nlm.nih.gov/pubmed/

Searched on: 14th September 2016

Records retrieved: 225

The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in PubMed sensitivity-maximizing version was used to limit retrieval to clinical trials.[1]

Search ((((((("Psoriasis"[Mesh:NoExp]) OR ((psorias*[Title/Abstract] OR psoriat*[Title/Abstract] OR parapsoriasis[Title/Abstract]))) OR ((pustul*[Title/Abstract] AND palm*[Title/Abstract])))) AND ((((((("Adalimumab"[Mesh:NoExp]) OR ((adalimumab OR humira OR D2E7 OR "D2 E7" OR "331731-18-1"))) OR "Etanercept"[Mesh:NoExp]) OR ((etanercept OR enbrel OR "185243-69-0"))) OR "Ustekinumab"[Mesh:NoExp]) OR ((ustekinumab OR stelara OR CNTO1275 OR "CNTO-1275" OR "815610-63-0")))) OR ((((((((((acitretin* OR etretin OR neotigason OR soriatane OR "55079-83-9"))) OR "Acitretin"[Mesh:NoExp]) OR "Methotrexate"[Mesh:NoExp]) OR ((methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR "15475-56-6" OR "59-05-2" OR "7413-34-5"))) OR "Cyclosporins"[Mesh]) OR ((cyclosporin$ OR ciclosporin$ OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR "59865-13-3" OR "63798-73-2"))) OR "Infliximab"[Mesh:NoExp]) OR ((infliximab OR remicade OR "170277-31-3"))) OR ((inflectra OR remsima OR CT-P13))) OR ((secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR "1229022-83-6")))))) AND (((((((((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR clinical trials as topic [mesh: noexp]) OR randomly [tiab]) OR trial [ti])) NOT ((animals [mh] NOT humans [mh]))) Filters: Publication date from 2014/01/01 to 2016/12/31

Key:

[Mesh] = exploded indexing term (MeSH heading)

[Mesh:NoExp] = indexing term (MeSH heading) not exploded

* = truncation

" " = phrase search

[Title/Abstract]) = terms in either title or abstract fields

[tiab] = terms in either title or abstract fields

[pt] = publication type

[mh] = exploded indexing term (MeSH heading)

Science Citation Index

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1900 – 13th September 2016

Searched on: 14th September 2016

Records retrieved: 820

# 28	820	#26 not #27 *Indexes=SCI-EXPANDED Timespan=2014-2016*
# 27	3,866,779	TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*) *Indexes=SCI-EXPANDED Timespan=All years*
# 26	3,492	#24 AND #18 *Indexes=SCI-EXPANDED Timespan=All years*
# 25	3,492	#24 AND #18 *Indexes=SCI-EXPANDED Timespan=All years*
# 24	5,910,291	#23 OR #22 OR #21 OR #20 OR #19 *Indexes=SCI-EXPANDED Timespan=All years*
# 23	5,038,629	TS=(placebo* or random* or control* or prospectiv* or volunteer*) *Indexes=SCI-EXPANDED Timespan=All years*
# 22	518,826	TS=(clinic* SAME trial*) *Indexes=SCI-EXPANDED Timespan=All years*
# 21	15,215	TS=(singl* SAME mask*) or TS=(doubl* SAME mask*) or TS=(trebl* SAME mask*) or TS=(tripl* SAME mask*)

		Indexes=SCI-EXPANDED Timespan=All years
# 20	218,910	TS=(singl* SAME blind*) or TS=(doubl* SAME blind*) or TS=(trebl* SAME blind*) or TS=(tripl* SAME blind*) *Indexes=SCI-EXPANDED Timespan=All years*
# 19	1,076,694	TS=(stud* SAME design*) *Indexes=SCI-EXPANDED Timespan=All years*
# 18	8,309	#17 OR #9 *Indexes=SCI-EXPANDED Timespan=All years*
# 17	6,234	#16 AND #4 *Indexes=SCI-EXPANDED Timespan=All years*
# 16	123,797	#15 OR #14 OR #13 OR #12 OR #11 OR #10 *Indexes=SCI-EXPANDED Timespan=All years*
# 15	374	TS=(secukinumab or Cosentyx or AIN457 or AIN-457 or "1229022-83-6") *Indexes=SCI-EXPANDED Timespan=All years*
# 14	99	TS=(inflectra or remsima or CT-P13) *Indexes=SCI-EXPANDED Timespan=All years*
# 13	16,441	TS=(infliximab or remicade or "170277-31-3") *Indexes=SCI-EXPANDED Timespan=All years*
# 12	67,409	TS=(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2") *Indexes=SCI-EXPANDED Timespan=All years*
# 11	44,932	TS=(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5") *Indexes=SCI-EXPANDED Timespan=All years*
# 10	1,288	TS=(acitretin* or etretin or neotigason or soriatane or "55079-83-9") *Indexes=SCI-EXPANDED Timespan=All years*
# 9	3,641	#8 AND #4 *Indexes=SCI-EXPANDED Timespan=All years*
# 8	13,940	#7 OR #6 OR #5

		Indexes=SCI-EXPANDED Timespan=All years
# 7	1,098	TS=(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0") *Indexes=SCI-EXPANDED Timespan=All years*
# 6	8,642	TS=(etanercept or enbrel or "185243-69-0") *Indexes=SCI-EXPANDED Timespan=All years*
# 5	6,703	TS=(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1") *Indexes=SCI-EXPANDED Timespan=All years*
# 4	47,963	#3 OR #2 OR #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 3	819	TS=(pustul* NEAR/2 palm*) *Indexes=SCI-EXPANDED Timespan=All years*
# 2	482	TS=parapsoriasis *Indexes=SCI-EXPANDED Timespan=All years*
# 1	47,116	TS=(psorias* or psoriat*) *Indexes=SCI-EXPANDED Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

SAME = terms in the same record

On-going, unpublished or grey literature search strategies

ClinicalTrials.gov

https://clinicaltrials.gov/

Searched on: 15th September 2016

Records retrieved: 105

Searches were carried out as per the search strings below. A total of 171 studies were found, which came down to 105 after deduplication of results.

1. **26 studies found for**: (Psoriasis OR psoriatic) AND (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1) | Studies received from 01/01/2014 to 09/15/2016

2. **22 studies found for**: (Psoriasis OR psoriatic) AND (etanercept OR enbrel OR 185243-69-0) | Studies received from 01/01/2014 to 09/15/2016

3. **23 studies found for**: (Psoriasis OR psoriatic) AND (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0) | Studies received from 01/01/2014 to 09/15/2016

4. **5 studies found for**: (Psoriasis OR psoriatic) AND (acitretin OR etretin OR neotigason OR soriatane OR 55079-83-9) | Studies received from 01/01/2014 to 09/15/2016

5. **24 studies found for**: (Psoriasis OR psoriatic) AND (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal) | Studies received from 01/01/2014 to 09/15/2016

6. **24 studies found for**: (Psoriasis OR psoriatic) AND (trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5) | Studies received from 01/01/2014 to 09/15/2016

7. **4 studies found for**: (Psoriasis OR psoriatic) AND (cyclosporin OR ciclosporin OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin) | Studies received from 01/01/2014 to 09/15/2016

8. **4 studies found for**: (Psoriasis OR psoriatic) AND (sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2) | Studies received from 01/01/2014 to 09/15/2016

9. **6 studies found for**: (Psoriasis OR psoriatic) AND (infliximab OR remicade OR 170277-31-3) | Studies received from 01/01/2014 to 09/15/2016

10. **3 studies found for**: (Psoriasis OR psoriatic) AND (inflectra OR remsima OR CT-P13) | Studies received from 01/01/2014 to 09/15/2016

11. **30 studies found for**: (Psoriasis OR psoriatic) AND (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6) | Studies received from 01/01/2014 to 09/15/2016

Conference Proceedings Citation Index: Science

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1990 – 13th September 2016

Searched on: 14th September 2016

Records retrieved: 33

# 28	33	#26 not #27 *Indexes=CPCI-S Timespan=2014-2016*
# 27	306,516	TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*) *Indexes=CPCI-S Timespan=All years*
# 26	235	#24 AND #18 *Indexes=CPCI-S Timespan=All years*
# 25	235	#24 AND #18 *Indexes=CPCI-S Timespan=All years*
# 24	1,276,541	#23 OR #22 OR #21 OR #20 OR #19 *Indexes=CPCI-S Timespan=All years*
# 23	1,060,361	TS=(placebo* or random* or control* or prospectiv* or volunteer*) *Indexes=CPCI-S Timespan=All years*
# 22	41,861	TS=(clinic* SAME trial*) *Indexes=CPCI-S Timespan=All years*
# 21	5,279	TS=(singl* SAME mask*) or TS=(doubl* SAME mask*) or TS=(trebl* SAME mask*) or TS=(tripl* SAME mask*) *Indexes=CPCI-S Timespan=All years*
# 20	19,759	TS=(singl* SAME blind*) or TS=(doubl* SAME blind*) or TS=(trebl* SAME blind*) or TS=(tripl* SAME blind*) *Indexes=CPCI-S Timespan=All years*
# 19	257,226	TS=(stud* SAME design*) *Indexes=CPCI-S Timespan=All years*
# 18	1,159	#17 OR #9

		Indexes=CPCI-S Timespan=All years
# 17	599	#16 AND #4 *Indexes=CPCI-S Timespan=All years*
# 16	15,543	#15 OR #14 OR #13 OR #12 OR #11 OR #10 *Indexes=CPCI-S Timespan=All years*
# 15	83	TS=(secukinumab or Cosentyx or AIN457 or AIN-457 or "1229022-83-6") *Indexes=CPCI-S Timespan=All years*
# 14	10	TS=(inflectra or remsima or CT-P13) *Indexes=CPCI-S Timespan=All years*
# 13	2,799	TS=(infliximab or remicade or "170277-31-3") *Indexes=CPCI-S Timespan=All years*
# 12	8,983	TS=(cyclosporin* or ciclosporin* or capimune or capsorin or deximune or emulsoforal or neoral or neciclopin or sandimmun or syncloral or vanquoral or gengraf or "59865-13-3" or "63798-73-2") *Indexes=CPCI-S Timespan=All years*
# 11	4,083	TS=(methotrexate or amethopterin or MTX or ebetrex or maxtrex or metoject or methofill or namaxir or zlatal or trexall or otrexup or rasuvo or "15475-56-6" or "59-05-2" or "7413-34-5") *Indexes=CPCI-S Timespan=All years*
# 10	133	TS=(acitretin* or etretin or neotigason or soriatane or "55079-83-9") *Indexes=CPCI-S Timespan=All years*
# 9	645	#8 AND #4 *Indexes=CPCI-S Timespan=All years*
# 8	2,720	#7 OR #6 OR #5 *Indexes=CPCI-S Timespan=All years*
# 7	185	TS=(ustekinumab or stelara or CNTO1275 or CNTO-1275 or "815610-63-0") *Indexes=CPCI-S Timespan=All years*
# 6	1,356	TS=(etanercept or enbrel or "185243-69-0") *Indexes=CPCI-S Timespan=All years*
# 5	1,361	TS=(adalimumab or humira or D2E7 or D2-E7 or "D2 E7" or "331731-18-1")

		Indexes=CPCI-S Timespan=All years
# 4	6,587	#3 OR #2 OR #1 *Indexes=CPCI-S Timespan=All years*
# 3	69	TS=(pustul* NEAR/2 palm*) *Indexes=CPCI-S Timespan=All years*
# 2	18	TS=parapsoriasis *Indexes=CPCI-S Timespan=All years*
# 1	6,529	TS=(psorias* or psoriat*) *Indexes=CPCI-S Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

" " = phrase search

NEAR/2 = terms within 2 words of each other (any order)

SAME = terms in the same record

EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/ctr-search/search

Searched on: 19th September 2016

Records retrieved: 85

Date limits: 2014-01-01 to 2016-09-19

1. 17 result(s) found for: (Psoriasis OR psoriatic) AND (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1

2. 9 result(s) found for: (Psoriasis OR psoriatic) AND (etanercept OR enbrel OR 185243-69-0)

3. 11 result(s) found for: (Psoriasis OR psoriatic) AND (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0)

4. 1 result(s) found for: (Psoriasis OR psoriatic) AND (acitretin* OR etretin OR neotigason OR soriatane OR 55079-83-9)

5. 20 result(s) found for: (Psoriasis OR psoriatic) AND (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5)

6. 5 result(s) found for (Psoriasis OR psoriatic) AND (cyclosporin* OR ciclosporin* OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2)

7. 3 result(s) found for: (Psoriasis OR psoriatic) AND (infliximab OR remicade OR 170277-31-3)

8. 1 result(s) found for (Psoriasis OR psoriatic) AND (inflectra OR remsima OR CT-P13)

9. 18 result(s) found for: (Psoriasis OR psoriatic) AND (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6)

Key:

* = truncation

WHO International Clinical Trials Registry Platform

http://www.who.int/ictrp/search/en/

Searched on: 19th September 2016

Records retrieved: 188

Date limits: 01/01/2014 to 19/09/2016

1. Condition: (psoriasis OR psoriatic) AND Intervention: (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1)

41 trials found.

2. Condition: (psoriasis OR psoriatic) AND Intervention: (etanercept OR enbrel OR 185243-69-0)

26 trials found

3. Condition: (psoriasis OR psoriatic) AND Intervention: (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0)

25 trials found

4. Condition: (psoriasis OR psoriatic) AND Intervention: (acitretin* OR etretin OR neotigason OR soriatane OR 55079-83-9)

6 trials found

5. Condition: (psoriasis OR psoriatic) AND Intervention: (methotrexate OR amethopterin OR MTX OR ebetrex OR maxtrex OR metoject OR methofill OR namaxir OR zlatal OR trexall OR otrexup OR rasuvo OR 15475-56-6 OR 59-05-2 OR 7413-34-5)

30 trials found

6. Condition: (psoriasis OR psoriatic) AND Intervention: (cyclosporin* OR ciclosporin* OR capimune OR capsorin OR deximune OR emulsoforal OR neoral OR neciclopin OR sandimmun OR syncloral OR vanquoral OR gengraf OR 59865-13-3 OR 63798-73-2)

4 trials found

7. Condition: (psoriasis OR psoriatic) AND Intervention: (infliximab OR remicade OR 170277-31-3)

7 trials found

8. Condition: (psoriasis OR psoriatic) AND Intervention: (inflectra OR remsima OR CT-P13)

2 trials found

9. Condition: (psoriasis OR psoriatic) AND Intervention: (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6)

47 trials found

12.2 Summary of included records

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
ADALIMUMAB				
M04-717 (NCT01251614)	RCT / Open-label extension	AbbVie, 2010	A Double Blind Study in Pediatric Participants With Chronic Plaque Psoriasis, Studying Adalimumab vs. Methotrexate[42]	Protocol
		Papp et al, 2013	Study design and baseline characteristics from a phase 3, randomized, double-blind study of adalimumab versus methotrexate treatment in pediatric patients with chronic plaque psoriasis[37]	Meeting abstract
		Papp et al, 2014	Baseline characteristics in pediatric patients with chronic plaque psoriasis from a phase 3, randomized, double-blind study of adalimumab versus methotrexate treatment[36]	Meeting abstract

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
		Papp et al, 2014	Study design and baseline characteristics from a phase 3, randomized, double-blind study of adalimumab versus methotrexate treatment in pediatric patients with chronic plaque psoriasis[41]	Meeting abstract
		Papp et al, 2015	Efficacy and safety of adalimumab versus methotrexate treatment in pediatric patients with severe chronic plaque psoriasis: Results from the 16-Week randomized, double-blind period of a phase 3 study[39]	Meeting abstract
		Phillip et al, 2015	Efficacy, safety of adalimumab versus methotrexate in pediatric patients with severe chronic plaque psoriasis: Results from the treatment withdrawal and double-blind retreatment periods of a phase 3 study[40]	Meeting abstract
		EMEA, 2015	Extension of indication variation assessment report. Procedure No. EMEA/H/C/000481/II/0134[43]	Regulatory documentation
		EMEA, 2015	Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006[44]	Regulatory documentation

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
		Papp et al 2016	Adalimumab long-term safety/efficacy results for pediatric patients with chronic plaque psoriasis from a phase 3, randomized study[38]	Meeting abstract
ETANERCEPT				
20030211 (NCT00078819)	RCT / open-label	Amgen, 2004	Etanercept (Enbrel®) in Psoriasis - Pediatrics[160]	Protocol
		Levy et al, 2005	Etanercept in children and adolescents with psoriasis[53]	Meeting abstract
		Siegfried et al, 2006	Etanercept in children and adolescents with psoriasis[54]	Meeting abstract
		Paller et al, 2007	A 12-week phase 3 study of efficacy and safety of etanercept therapy in children and adolescents with moderate to severe plaque psoriasis[55]	Meeting abstract
		Paller et al, 2008	Etanercept treatment for children and adolescents with plaque psoriasis[48]	Journal article

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
		Paller et al, 2008	Etanercept treatment in children and adolescents with plaque psoriasis[56]	Meeting abstract
		Langley et al, 2010	Patient-reported outcomes in pediatric patients with psoriasis undergoing etanercept treatment: 12-week results from a phase III randomized controlled trial[46]	Journal article
		Siegfried et al, 2010	Intermittent etanercept therapy in pediatric patients with psoriasis[161]	Journal article
		Paller et al, 2010	Subgroup analyses of etanercept in pediatric patients with psoriasis[49]	Research letter
		Landells et al, 2010	Efficacy and safety of etanercept in children and adolescents aged > or = 8 years with severe plaque psoriasis[50]	Journal article

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
		Paller et al, 2010	Interim results of a long-term safety and tolerability study of etanercept treatment in children and adolescents age 8 to 17 years with plaque psoriasis[57]	Meeting abstract
		FDA, 2008	Enbrel (etanercept) for the Treatment of Pediatric Plaque Psoriasis[60]	Regulatory documentation
		Amgen (via FDA), 2008	Background information for the dermatologic and ophthalmologic drugs advisory committee (DODAC) meeting, 18 June 2008[61]	Regulatory documentation
		EMEA, 2008	ASSESSMENT REPORT FOR ENBREL. International Nonproprietary Name: INN- etanercept. Procedure No. EMEA/H/C/262/II/94[62]	Regulatory documentation
		EMEA, 2011	ASSESSMENT REPORT FOR ENBREL. International Nonproprietary Name: Etanercept. Procedure No. Type II variation EMEA/H/C/262/II/134[63]	Regulatory documentation

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
20050111 (NCT00141921)	Observational study (long term extension of 20030211)	Amgen, 2005	An Open-Label Extension Study to Evaluate the Safety of Etanercept in Pediatric Participants With Plaque Psoriasis[65]	Protocol
		Amgen, 2012	An Open-Label Extension Study to Evaluate the Safety of Etanercept in Pediatric Participants With Plaque Psoriasis[64]	Protocol
		Paller et al, 2010	Long-term etanercept in pediatric patients with plaque psoriasis[51]	Journal article
		Paller et al, 2010	Safety and efficacy of etanercept treatment in children and adolescents with plaque psoriasis: 96-week results of open-label extension study[58]	Meeting abstract
		Paller et al, 2015	Long-term safety and efficacy of etanercept in children and adolescents with plaque psoriasis[52]	Journal article

Study ID (clinicaltrials.gov ID)	**Design**	**Author / Source, year**	**Title**	**Record type**
		Paller et al, 2016	Five-year open-label extension study of safety and efficacy of etanercept in children and adolescents with moderate to severe plaque psoriasis[59]	Meeting abstract
		EMEA, 2013	Enbrel: etanercept. Procedure No. EMEA/H/C/000262/A46/134. CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006[66]	Regulatory documentation
NCT01100034	Observational study	Pfizer, 2010	A Long-term, Prospective, Observational Cohort Study Of The Safety And Effectiveness Of Etanercept In The Treatment Of Paediatric Psoriasis Patients In A Naturalistic Setting: A Post-authorization Safety Study (Pass)[67]	Protocol
NCT01432249	Observational study	Pfizer, 2011	Post Marketing Surveillance To Observe Safety And Efficacy Of Enbrel In Pediatric Patients With Psoriasis[68]	Protocol

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
CAIN457A2310 (NCT02471144)	RCT	Novartis Pharmaceuticals, 2015	A Randomized, Double-blind, Placebo- and Active Controlled Multicenter Trial to Demonstrate Efficacy of Subcutaneous Secukinumab Compared to Placebo and Etanercept (in a Single-blinded Arm) After Twelve Weeks of Treatment, and to Assess the Safety, Tolerability, and Long-term Efficacy in Participants From 6 to Less Than 18 Years of Age With Severe Chronic Plaque Psoriasis[69]	Protocol
		Novartis Pharma Services AG, 2015	A randomized, double-blind, placebo- and active controlled multicenter trial to demonstrate efficacy of subcutaneous secukinumab compared to placebo and etanercept (in a single blinded arm) after twelve weeks of treatment, and to assess the safety, tolerability, and long-term efficacy in participants from 6 to less than 18 years of age with severe chronic plaque psoriasis[70]	Protocol
USTEKINUMAB				

Study ID (clinicaltrials.gov ID)	**Design**	**Author / Source, year**	**Title**	**Record type**
CNTO1275PSO3006/CADMUS (NCT01090427)	RCT / Open-label extension	Janssen Research & Development, 2010	A Study of the Safety and Efficacy of Ustekinumab in Adolescent Patients With Psoriasis (CADMUS)[73]	Protocol
		Landells et al 2015	Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study[71]	Journal article
		Landells et al 2015	Safety and efficacy of ustekinumab in adolescent patients with moderate to severe plaque psoriasis: Results through 1 year of the phase 3 CADMUS trial[72]	Meeting abstract
		EMEA, 2015	Assessment report: Stelara. International non-proprietary name: USTEKINUMAB. Procedure No. EMEA/H/C/000958/II/0042[74]	Regulatory documentation

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
CR108129 / CNTO1275PSO3013 / CADMUS Jr (NCT02698475)	Observational study	Janssen Research & Development, 2016	An Efficacy, Safety, and Pharmacokinetics Study of Subcutaneously Administered Ustekinumab in the Treatment of Moderate to Severe Chronic Plaque Psoriasis in Pediatric Participants Greater Than 6 to Less Than 12 Years of Age (CADMUS Jr)[162]	Protocol
	Observational study	Janssen-Cilag International, 2016	A phase 3 open-label study to assess the efficacy, safety, and pharmacokinetics of subcutaneously administered ustekinumab in the treatment of moderate to severe chronic plaque psoriasis in pediatric participants greater than 6 to less than 12 years of age[163]	Protocol
MULTIPLE BIOLOGIC/SYSTEMIC TREATMENTS				
Garber et al, 2015	Observational study	Garber et al, 2015	Systemic Treatment of Recalcitrant Pediatric Psoriasis: A Case Series and Literature Review[75]	Journal article
Klufas et al, 2016	Observational study	Klufas et al, 2016	Treatment of moderate to severe pediatric psoriasis: A retrospective case series[76]	Journal article

Study ID (clinicaltrials.gov ID)	Design	Author / Source, year	Title	Record type
SYSTEMATIC REVIEWS				
PROSPERO2015:CRD42015025262	Systematic review	Chingcuanco, 2015	TNF-inhibitors: comparing the safety, efficacy and physicochemical profiles of biosimilars and innovators: PROSPERO2015:CRD42015025262[164]	Systematic review protocol
PROSPERO2015:CRD42015017538	Systematic review	Smith et al, 2015	In people with psoriasis (all types), what are the clinical effectiveness/efficacy, safety and tolerability of systemic biologics (adalimumab, etanercept, infliximab, secukinumab or ustekinumab) compared with each other, with methotrexate or with placebo?: PROSPERO2015:CRD42015017538[165]	Systematic review protocol
Sanclemente et al, 2015	Systematic review	Sanclemente et al, 2015	Anti-TNF agents for paediatric psoriasis[166]	Systematic review
de Jager et al, 2010	Systematic review	de Jager et al, 2010	Efficacy and safety of treatments for childhood psoriasis: a systematic literature review[152, 167]	Systematic review

12.3 List of excluded studies with reasons for exclusion

Author & Year	Record title	Reason for exclusion
Vencovsky et al, 2015	A phase III randomised, double-blind clinical study comparing SB4, an etanercept biosimilar, with etanercept reference product (Enbrel) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy (24-week results) [168]	1
Tarp et al, 2015	Comparative effectiveness associated with the use of biologics and small-molecules for psoriasis: protocol for a systematic review and meta-analysis [169]	1
Soliman et al, 2015	Combination therapy of methotrexate plus NBUVB phototherapy is more effective than methotrexate monotherapy in the treatment of chronic plaque psoriasis [170]	2
Ruano et al, 2015	Short-term effectiveness and safety of new biologic agents targeting IL-23/Th17 pathway for moderate to severe plaque psoriasis: a systematic review and network meta-analysis [171]	1
Puig et al, 2015	Long-term efficacy, safety and drug survival of ustekinumab in a Spanish cohort of patients with moderate to severe plaque psoriasis [172]	1
Lebwohl et at,2015	Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis [173]	1
Langley et al, 2015	Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up [174]	1
Kimball et al, 2015	OBSERVE-5: observational postmarketing safety surveillance registry of etanercept for the treatment of psoriasis final 5-year results [175]	1
Branisteanu et al, 2015	Adverse reactions of biological therapy for psoriasis [176]	2
Ali et al, 2015	A systematic review of the impact on quality of life of topical, systemic and biologic therapies for psoriasis [177]	1

Author & Year	Record title	Reason for exclusion
NIHR Horizon Scanning Centre, 2014	Adalimumab (Humira) for severe chronic plaque psoriasis in children and adolescents – second line [178]	4
Umezawa et al, 2013	Drug survival rates in patients with psoriasis after treatment with biologics [179]	2
Strohal et al, 2013	Etanercept provides an effective, safe and flexible short- and long-term treatment regimen for moderate-to-severe psoriasis: a systematic review of current evidence [180]	1
Park et al, 2013	A randomized, 'head-to-head' pilot study comparing the effects of etanercept monotherapy vs. etanercept and narrowband ultraviolet B (NB-UVB) phototherapy in obese psoriasis patients.	1
NIHR Horizon Scanning Centre, 2013	Ustekinumab (Stelara) for plaque psoriasis in adolescents [181]	4
Lopez-Ferrer et al, 2014	Adalimumab for the treatment of psoriasis in real life: a retrospective cohort of 119 patients at a single Spanish centre [182]	1
Lebwohl et al, 2013	A randomized study to evaluate the efficacy and safety of adding topical therapy to etanercept in patients with moderate to severe plaque psoriasis [183]	1
Janagond etal, 2013	Efficacy and safety of systemic methotrexate vs. acitretin in psoriasis patients with significant palmoplantar involvement: a prospective, randomized study [184]	2
Gisondi et al, 2013	Metabolic abnormalities associated with initiation of systemic treatment for psoriasis: evidence from the Italian Psocare Registry [185]	1
Da silva et al, 2013	Methotrexate for psoriasis [186]	5
Chen et al, 2013	Narrow-band ultraviolet B phototherapy versus broad-band ultraviolet B or psoralen-ultraviolet A photochemotherapy for psoriasis [187]	3
Burmester et al, 2013	Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease	1

Author & Year	Record title	Reason for exclusion
Balzola et al, 2013	Adalimumab: Long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease [188]	1
All Wales Medicines Strategy Group, 2013	Etanercept (Enbrel®) [189]	4
Strand et al, 2012	Comparison of health-related quality of life in rheumatoid arthritis, psoriatic arthritis and psoriasis and effects of etanercept treatment [190]	1
Lynde et al, 2012	A randomized study comparing the combination of nbUVB and etanercept to etanercept monotherapy in patients with psoriasis who do not exhibit an excellent response after 12 weeks of etanercept [191]	1
Kim et al, 2012	Comparative efficacy of biologics in psoriasis: a review [192]	1
Famenini et al, 2012	The Safety of Ustekinumab in Psoriasis [193]	1
Chiu et al, 2012	The effectiveness and safety of adalimumab in the treatment of non-reimbursed patients with mild-to-moderate psoriasis [194]	1
Burmester et al, 2012	Long-term safety of adalimumab in patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, and crohn's disease [195]	1
Young et al, 2011	The ACCEPT study: ustekinumab versus etanercept in moderate-to-severe psoriasis patients [196]	1
Ryan et al, 2011	Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials [197]	1
Lara-Corrales et al, 2011	Childhood psoriasis treatment: Evidence published over the last 5 years [198]	5
Brunasso et al, 2011	Tolerability and safety of biological therapies for psoriasis in daily clinical practice: a study of 103 Italian patients [199]	1

Author & Year	Record title	Reason for exclusion
Menter et al, 2010	Efficacy and safety of adalimumab across subgroups of patients with moderate to severe psoriasis [200]	1
Esposito et al, 2010	Continuous treatment of plaque-type psoriasis with etanercept: an observational long-term experience [201]	1
All Wales Medicines Strategy Group, 2010	Final appraisal report Etanercept (Enbrel®) [127]	5
National Horizon Scanning Centre, 2008	Etanercept (Enbrel) for moderate-to-severe plaque psoriasis in children and adolescents [202]	4
Flytstrom et al, 2008	Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial [110]	1
Romero-Mate et al, 2007	Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review [203]	1
Ranjan et al, 2007	Methotrexate versus hydroxycarbamide (hydroxyurea) as a weekly dose to treat moderate-to-severe chronic plaque psoriasis: a comparative study [204]	1
Krueger et al, 2006	Patients with psoriasis respond to continuous open-label etanercept treatment after initial incomplete response in a randomized, placebo-controlled trial [205]	1
Gordon et al, 2006	Efficacy of etanercept in an integrated multistudy database of patients with psoriasis [206]	1
Amornpinyokeit et al, 2006	8-Methoxypsoralen cream plus targeted narrowband ultraviolet B for psoriasis [207]	3
Bigby, 2004	A randomized controlled trial of methotrexate and cyclosporine in the treatment of psoriasis [208]	1
Heydendael et al, 2002	Cyclosporin trough levels: Is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels [209]	1
Faerber et al, 2001	Cyclosporine in severe psoriasis. Results of a meta-analysis in 579 patients [210]	1

Author & Year	Record title	Reason for exclusion
Ho et al, 1999	Intermittent short courses of cyclosporin (Neoral(R)) for psoriasis unresponsive to topical therapy: a 1-year multicentre, randomized study. The PISCES Study Group [211]	2
Zachariae et al, 1998	Conversion of psoriasis patients from the conventional formulation of cyclosporin A to a new microemulsion formulation: a randomized, open, multicentre assessment of safety and tolerability [212]	1
Koo, 1998	A randomized, double-blind study comparing the efficacy, safety and optimal dose of two formulations of cyclosporin, Neoral and Sandimmun, in patients with severe psoriasis. OLP302 Study Group [213]	1
Laburte et al, 1994	Efficacy and safety of oral cyclosporin A (CyA; Sandimmun) for long-term treatment of chronic severe plaque psoriasis [214]	1
_____1993	Cyclosporin versus etretinate: Italian multicenter comparative trial in severe plaque-form psoriasis. Italian Multicenter Study Group on Cyclosporin in Psoriasis [215]	1
Christophers et al, 1992	Cyclosporine in psoriasis: a multicenter dose-finding study in severe plaque psoriasis. The German Multicenter Study [216]	1
Tanew et al, 1991	Photochemotherapy for severe psoriasis without or in combination with acitretin: a randomized, double-blind comparison study [217]	1
Ruzicka et al, 1990	Efficiency of acitretin in combination with UV-B in the treatment of severe psoriasis [218]	1
Kragballe et al, 1989	A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis. Results of a Nordic multicentre study [219]	1
Takashima et al, 1988	Comparison of therapeutic efficacy of topical PUVA, oral etretinate, and combined PUVA and etretinate for the treatment of psoriasis and development of PUVA lentigines and antinuclear antibodies [220]	1
Geiger and Czarnetzki, 1988	Acitretin (Ro 10-1670, etretin): overall evaluation of clinical studies [221]	1

Author & Year	Record title	Reason for exclusion
Melis, 1984	[Treatment of plaque psoriasis with an aromatic retinoid (etretinate)] [222]	2
Christiansen et al, 1982	Etretinate (Tigason) and betamethasone valerate (Celeston valerate) in the treatment of psoriasis. A double-blind, randomized, multicenter trial [223]	2
	Ustekinumab Safety and Surveillance Program Using the Ingenix NHI Database [224]	1
	Study Evaluating the Safety of Enbrel (Etanercept) [225]	1

Key: 1= Not children and/or young people who have moderate to severe plaque psoriasis; 2= Mixed adults and children - unable to separate into subgroups; 3= Does not include data on adalimumab, etanercept, ustekinumab, methotrexate, cyclosporine, or acitretin; 4= Does not measure a clinical outcome (e.g. only pharmacokinetics); 5= Not an RCT, open label extension, or observational study (e.g. reject if a single case report).

12.4 Adalimumab risk of bias assessment for trial extension periods

	Period B		Period C		Period D	
	Judgement	**Justification**	**Judgement**	**Justification**	**Judgement**	**Justification**
Is the population based on a representative sample selected from a relevant population?	Unclear	Only responders in period A (RCT) entered the stage of the study	No	Not representative of patients receiving first biologic or switching biologic treatments: All participants had received adalimumab or methotrexate and experienced loss of disease control before being retreated	Yes	Participants from periods A, B, and C were included
Are the criteria for inclusion explicit?	Yes	Participants with a PASI 75 and PGA 0/1 response at the end of Period A	Yes	Participants from period B who had 16 weeks adalimumab of methotrexate and experienced loss of disease control were included	Yes	Participants from A,B and C who met entry criteria in period A were included
Were groups similar at baseline in terms of important confounding variables? If not, was the analysis adjusted to account for the imbalance?	N/A		Unclear	Insufficient demographic information. PASI 50 rates differ (p=0.06)	N/A	Non-comparative observational period.

Was knowledge of the allocated intervention to outcome assessors adequately prevented during the study?	Unclear	No information provided	Yes	Blinded re-treatment	N/A	Non-comparative observational period. Adalimumab dose was blinded for some participants, open-label for others.
Were losses to follow-up <20%?	Yes	53 of 54 patients entering group B completed follow-up	Yes	34 of 38 participants completed follow-up	Yes	90 of 108 participants completed follow-up
Were all patients accounted for at the end of study follow-up?	Yes		Yes		Yes	
Were reliable methods used to measure outcomes?	Yes	PGA worsening by at least two grades	Yes	Outcomes and methods were reported	Yes	Outcomes and methods were reported
Was the study sufficiently powered to detect treatment effect?	Unclear	No information was provided	Unclear	No information was provided	Unclear	No information was provided
Was study follow-up duration sufficient to detect long-term treatment effect?	Yes	Patients were followed-up for 36 weeks	Yes	As in Period A, participants were followed-up for 16 weeks	Yes	Participants were followed-up for 52 weeks in period D.

N/A= not applicable

12.5 Etanercept risk of bias assessment for trial extension periods

	Open-label treatment (24 weeks)		Withdrawal-retreatment period (12 weeks)		Long-term follow-up (264 weeks)	
	Judgement	**Justification**	**Judgement**	**Justification**	**Judgement**	**Justification**
Is the population based on a representative sample selected from a relevant population?	Yes	All patients entered to the randomisation stage were included	No	Only those who achieved PASI 50 at week 24 or PASI 75 at week 36 entered the study	Yes	182 of the 211 participants from the blinded period and completing the withdrawal-retreatment period entered this study
Are the criteria for inclusion explicit?	Yes	With the exception of 3 withdrawals, all patients entered the randomisation stage were included	Yes	Those who achieved PASI 50 at week 24 or PASI 75 at week 36 entered the study	Yes	All participants who completed the withdrawal-retreatment period were included
Were groups similar at baseline in terms of important confounding variables? If not, was the analysis adjusted to account for the imbalance?	N/A	All patients received the same treatment (etanercept), that is, no comparative efficacy analyses were planned.	Yes	Participants were similar in terms of age, sex, weight, height, PASI scores and BSA affected %.	N/A	The follow-up study did not aim for comparative analyses.

Was knowledge of the allocated intervention to outcome assessors adequately prevented during the study?	Unclear	Every patient was receiving etanercept	Unclear	Although the participants, caregiver, investigator and outcomes assessor were blinded during the blinding period, no information was available for this phase of the study.	Unclear	Although the participants, caregiver, investigator and outcomes assessor were blinded during the blinding period, no information was available for this phase of the study.
Were losses to follow-up <20%?	Yes	94.7% (197/208) of patients entered this stage were present at the end of this period	Yes	137/138 of participants completed the study.	No	115/182 of participants withdrew by the end of the study (week 264)
Were all patients accounted for at the end of study follow-up?	Yes	11 patients withdrew and 197 patients were present at the end of the study	Yes	137 completed and 1 lost to follow-up	Yes	Withdrawals and reasons (e.g. adverse events, lost to follow-up, withdrawal consent and protocol deviations) reported
Were reliable methods used to measure outcomes?	Yes	PASI scores and adverse events were recorded	Yes	PASI scores were reported	Yes	PASI scores and adverse events reported
Was the study sufficiently powered to detect treatment effect?	N/A	Power analysis was not done or needed for the study	Unclear	No power calculation was done or reported for this phase of the study.	Unclear	No power calculations were done or evidenced in the study reports.

Was study follow-up duration sufficient to detect long-term treatment effect?	Yes	Patients were followed up for 24 weeks	Unclear	The follow-up period was 12 weeks	Yes	The followed-up period was 5 years.

12.6 Ustekinumab risk of bias assessment for trial extension periods

	Placebo crossover and active treatment period (12-52 weeks)		**Follow-up period (52-60 weeks)**	
	Judgement	**Justification**	**Judgement**	**Justification**
Is the population based on a representative sample selected from a relevant population?	Yes	All participants from the initial blinded period were eligible to enter the crossover phase of the study	Yes	All participants who from previous phases were eligible for follow-up
Are the criteria for inclusion explicit?	Yes	All participants from the initial blinded period were eligible to enter the crossover phase of the study	Yes	All participants who from previous phases were eligible for follow-up
Were groups similar at baseline in terms of important confounding variables? If not, was the analysis adjusted to account for the imbalance?	N/A	This phase of the study did aim for comparative analysis.	N/A	This phase of the study did aim for comparative analysis.
Was knowledge of the allocated intervention to outcome assessors adequately prevented during the study?	Yes	The Sponsor, investigative study sites, and participants remained blinded to treatment assignment until the last participant enrolled completed the study	Yes	The Sponsor, investigative study sites, and participants remained blinded to treatment assignment until the last participant enrolled completed the Week 60 evaluations and the database was locked

Were losses to follow-up <20%?	Yes	Only 7/110 of the participants withdrew by the end of this phase.	Unclear	The total loss to follow-up or withdrawals at this phase of the study was not reported
Were all patients accounted for at the end of study follow-up?	Yes	Withdrawals and reasons (e.g. adverse events, death and lack of efficacy) were reported.	Unclear	The total loss to follow-up for this phase of the study was not reported
Were reliable methods used to measure outcomes?	Yes	PASI scores were reported	N/A	The follow-up only aimed at safety reports
Was the study sufficiently powered to detect treatment effect?	N/A	The follow-up period did not aim for comparative analyses	N/A	The follow-up period did not aim for comparative analyses
Was study follow-up duration sufficient to detect long-term treatment effect?	Yes	Participants were followed-up for 40 weeks.	No	Participants were followed-up for only 8 weeks.

12.7 Risk of bias assessment for observational multiple biologics studies

	Garber et al 2015		Klufas et al 2016	
	Judgement	**Justification**	**Judgement**	**Justification**
Is the population based on a representative sample selected from a relevant population?	Yes	All patients with the disease code ICD-9-CM 696.1 were considered in the study	Yes	All patients with the disease code ICD-9-CM 696.1 were considered in the study
Are the criteria for inclusion explicit?	Yes	Patients with S-MAPA ≥ 15 or otherwise documented moderate-to-severe psoriasis were included	Yes	Patients with moderate-to-severe psoriasis were included
Were groups similar at baseline in terms of important confounding variables? If not, was the analysis adjusted to account for the imbalance?	N/A	Not a comparative study	N/A	Not a comparative study
Was knowledge of the allocated intervention to outcome assessors adequately prevented during the study?	Unclear	No information provided	Unclear	No information provided
Were losses to follow-up <20%?	N/A	Retrospective analysis of health records	N/A	Retrospective analysis of health records
Were all patients accounted for at the end of study follow-up?	N/A	Retrospective analysis of health records	N/A	Retrospective analysis of health records

Were reliable methods used to measure outcomes?	Unclear	No information was provided	Unclear	No information was provided
Was the study sufficiently powered to detect treatment effect?	N/A	Not a comparative analysis	N/A	Not a comparative analysis
Was study follow-up duration sufficient to detect long-term treatment effect?	No	Mean duration of treatment was as short as 11 weeks in etanercept+MTX group.	No	Mean duration of treatment was as short as 3 weeks in Adalimumab+MTX group.

12.8 Evidence synthesis modelling, software and WinBUGS code

Bayesian NMA was conducted to pool trial results. NMA models were programmed in WinBUGS software (version 1.4.3) using a Bayesian statistical framework. WinBUGS is a Bayesian analysis software tool that, through the use of Gibbs sampling (a Markov Chain Monte Carlo method), evaluates posterior distributions for the parameters of interest given likelihood functions derived from data and prior probabilities. Fixed- and random-effects models were evaluated. Model selection was determined by model fit statistics (i.e., deviance information criterion and total residual deviance) to identify the best model choice. Treatment effects were expressed in relation to placebo. Uninformative priors were used throughout.

The Bayesian NMA for PASI utilised a framework of analysis that evaluated the probability of PASI responses in different categories of PASI thresholds 50/75/90 within a single model. The analyses followed the principles outlined in the NICE DSU. [81] This single synthesis multinomial model with a probit link is recommended by the NICE DSU [81] and assumes that there is an underlying continuous variable which has been categorised by specifying the cut-offs. It assumes also that the treatment effect is the same regardless of the different cut-offs in each trial. All PASI response models were run for 10,000 iterations after a burn-in of 20,000 on 2 chains. Synthesis model results provide pooled probabilities of achieving PASI 50, 75 and 90 for each treatment of interest, alongside a measure of uncertainty, i.e. 95% credibility intervals.

In brief, trials report r_{ikj}, the number of patients in arm k of trial i belonging to different, mutually exclusive categories j = 1, 2, 3, where these categories represent the different thresholds of PASI score (e.g., 50%, 75%, or 90% improvement). The responses for each arm k of trial i in category j follows a multinomial distribution as $r_{i,k,j=1,\ldots,J} \sim Multinomial\left(p_{i,k,j=1,\ldots,J}, n_{i,k}\right) with\ \sum_{j=1}^{J} p_{i,k,j} = 1$,which has been parameterised as a series of conditional binomial distributions, with parameters of interest the probabilities, p_{ikj}, that a patient in arm k (k = 1, 2,3) of trial i (i = 1,….., I) belongs to category j (j = 1,2,3). A probit link function was used, the inverse of the normal cumulative distribution function Φ, to define the p_{ikj} as a function of a set of threshold values, z_j. The threshold values (estimated within the model) are such that the probability that the standard normal (the probit score) will take a value less than or equal to z_1 will reflect the probability of obtaining a PASI response lower than 50%, that is, 1-PASI50. The probability that the standard normal will take a value less than or equal to z_2

will reflect the probability of obtaining a PASI response lower than 75%, that is, 1-PASI75, and analogously, evaluating Φ at z_3 will approximate 1- PASI90. Placebo and treatments are assumed to shift the mean of the distribution. This means that the pooled effect of taking the experimental treatment instead of the control is to change the probit score (or *Z* score) of the control arm, by $d_{i,1}$ standard deviations. Therefore, the model is written as $p_{ikj} = \Phi(\mu_i + z_j + \delta_{i,1k} I_{\{k \neq 1\}})$. The terms z_j as the differences on the standard normal scale between the response to category *j* and the response to category *j-1* in all the arms of trial *i*. Correlation structure induced by 3-arm trials was accounted for as a substantial proportion of the studies forming the evidence base had such characteristics.

We assumed that the baselines, μ_i, were trial-specific (i.e. unconstrained – except for model 1b) and were given non-informative prior. A non-informative prior was assign to the treatment effects parameter (δ_t). A uniform prior was assign to the parameter z_j.

Alternative assumptions were tested in two analyses. The first assumed a meta-regression for placebo effects (Model 2a). In a second analysis, we explored the impact on treatment effects of adjusting for age i.e. explicitly modelling children and young people and adult subgroups (Model 2b). Key assumptions for the models implemented for PASI responses and detailed coding of the models are presented in the table below. The preferred model was used to evaluate estimated probability of achieving PASI 50/75/90 responses on treatment *t* , using $T_{ajt} = 1 - \Phi(A + \delta_t + z_j)$ for adults, and $T_{cjt} = 1 - \Phi(A + \delta_t + z_j + B)$ for children and young people. Where A is the pooled baseline effect. The baseline effect, *A*, was estimated as, $A = \frac{\sum \mu_{i1}}{NS}$, where μ_{i1} is the baseline effects, where *i* is the studies and 1 = placebo; NS is the number of studies. And *B* is the common regression (slope) coefficient relating to the treatment by age interaction that is assumed identical for all treatments. This is a strong assumption but, due to only increasing the number of parameters in the model by one, is the least data demanding. Other interaction assumptions were tested (i.e. independent and exchangeable) [125] but the model was unable to appropriately estimate all parameters.

We adopted the WinBUG code presented in the DSU2 [226] for the analysis. Although, we identified that the model was not specifying the *z* score correctly in the liner predictor specification when the first category of the response data (in this case PASI50) was missing. A correction was made to incorporate the correct specification for the *z* score in the linear predictor specification.

Description of models and underlying assumptions for PASI response

Model 2	Model 2a	Model 2b
Likelihood $r_{ikj} \sim Binomial(p_{ikj}, n_{ikj})$ *Model* $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ $\delta_t \sim dnorm(d_t, \sigma^2)$ *Priors* $\sigma \sim dunif(0,2)$ $\mu_i \sim dnorm(0,0.000001)$ $z_j \sim dunif(0,5)$	*Likelihood* $r_{ikj} \sim Binomial(p_{ikj} n_{ikj})$ *Model* $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j + \beta(\mu_i - \overline{\mu})$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ $\delta_t \sim dnorm(d_t, \sigma^2)$ *Priors* $\sigma \sim dunif(0,2)$ $\mu_i \sim dnorm(0,0.0001)$ $\beta \sim dnorm(0,0.0001)$ $z_j \sim dunif(0,5)$	*Likelihood* $r_{ikj} \sim Binomial(p_{ikj} n_{ikj})$ *Model* $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j + \beta(\mu_i - \overline{\mu}) + \gamma \cdot x_i$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ $\delta_t \sim dnorm(d_t, \sigma^2)$ *Priors* $\sigma \sim dunif(0,2)$ $\mu_i \sim dnorm(0,0.0001)$ $\beta \sim dnorm(0,0.0001)$ $\gamma \sim dnorm(0,0.0001)$ $z_j \sim dunif(0,5)$
Assumptions • Unconstrained baselines • Independent treatment effects • Random effects between studies • Fixed effect for each of the *j-1* categories over all trials.	Assumptions • Unconstrained baselines • Independent treatment effects • Random effects between studies • Fixed effect for each of the *j-1* categories over all trials • Common interaction term between studies (placebo effect adjustment, β)	Assumptions • Unconstrained baselines • Independent treatment effects • Random effects between studies • Fixed effect for each of the *j-1* categories over all trials • Common interaction term between studies (placebo effect adjustment, β) • Common interaction term between studies (population adjustment, γ)

WinBUGS code of preferred model:

```
model {

   sw[1]<- 0
   for(i in 1:N) {
      p[i,1] <- 1
      for (j in 1:nc[i]-1) {
         r[i,j] ~ dbin(q[i,j],n[i,j])
         q[i,j] <- 1-(p[i,C[i,j+1]]/p[i,C[i,j]])
         z.index[i,j]<- C[i,j+1]-1
         theta[i,j] <- mu[s[i]] + delta[i]*(1-equals(t[i],b[i])) + z[z.index[i,j]] +
                       betaplac*(mu[s[i]]-mu_m)*(1-equals(t[i],1)) +
                       (beta[t[i]]-beta[t[1]]) * (1-equals(t[i],1)) * pop[i]
         rhat[i,j] <- q[i,j] * n[i,j]
         dv[i,j] <- 2 * (r[i,j]*(log(r[i,j])-log(rhat[i,j])) + (n[i,j]-r[i,j])*(log(n[i,j]-r[i,j]) - log(n[i,j]-rhat[i,j])))
         }
   dev[i] <- sum(dv[i,1:nc[i]-1])
```

```
   delta[i] ~ dnorm(md[i], prec)
   md[i] <- d[t[i]] - d[b[i]] + equals(m[i],3) * sw[i]

   for (j in 2:nc[i]) {
      p[i,C[i,j]] <- 1 - phi.adj[i,j]
      phi.adj[i,j] <- phi(theta[i,j-1])
      }
   }

   for(k in 2:N) {
      sw[k]<- (delta[k-1] - d[t[k-1]] + d[b[k-1]]) / 2
      }
   totresdev <- sum(dev[])
   z[1] <- 0
   for (j in 2:Cmax-1) {
      z.aux[j] ~ dunif(0,5)
      z[j] <- z[j-1] + z.aux[j]
      }

   for(i in 1:ns){ mu[i] ~ dnorm(0,0.0001) }

   d[1] <- 0
   beta[1] <- 0
   for (k in 2:nt){
      d[k] ~ dnorm(0,0.00001)
      beta[k] <- B
      }

   betaplac ~ dnorm(0,0.00001)
   tau~dunif(0,2)
   tau.sq<-tau*tau
   prec<-1/(tau.sq)

#baseline mu - based on average of the 31 trials including it.
   for (i in 1:31) { mu1[i]<-mu[i]*equals(b[i*2-1],1) }
   for (i in 1:6) { mu1[31+i]<-mu[31+i]*equals(b[60+i*3],1) }
```

```
   A<-sum(mu1[])/31
   B ~ dnorm(0,0.0001)

# calculate prob of achieving PASI50/75/90 on treat k for adults (Ta) and children (Tc)
   for (k in 1:nt) {
      for (j in 1: Cmax-1) {
         Ta[j,k] <- 1 - phi(A + d[k] + z[j])
         Tc[j,k] <- 1 - phi(A + d[k] + z[j] + B)
         }
      }

# calculate RR PASI50,75,90 on treat k
   for (c in 1:(nt-1)) {
      for (k in (c+1):nt) {
         for (j in 1: Cmax-1) {
            RRa[j,c,k] <- Ta[j,k]/Ta[j,c]
            RRc[j,c,k] <- Tc[j,k]/Tc[j,c]
            }
         }
      }

}
```

12.9 Studies excluded from the NMA analyses

No treatment arm of interest (12 studies)

Lebwohl 2003

Lebwohl M, Tyring SK, Hamilton TK, Toth D, Glazer S, Tawfik NH, et al. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003;349:2004-13

Gordon 2003

Gordon KB, Papp KA, Hamilton TK, Walicke PA, Dummer W, Li N, et al. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. JAMA 2003;290:3073-80

ACD2058g

ACD2058g. Phase III, randomised double blind placebo-controlled study evaluating 12 weeks of therapy with XOMA1 efalizumab administered subcutaneously (SC), followed by either continued treatment for an additional 12

weeks or re-treatment for 12 weeks following relapse. In: Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]. Feltham: Serono Ltd., 2004.

ACD2600g

ACD2600g. Phase IIIb, randomised, double-blind, parallel group, placebocontrolled, multicentre study evaluating 12 weeks therapy with subcutaneously administered Genentech efalizumab in adults with moderate to severe psoriasis who

are candidates for systemic therapy. In: Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]. Feltham: Serono Ltd., 2004.

IMP24011

IMP24011. Phase III, randomised, double blind, placebo-controlled, multicentre study evaluating 12 weeks subcutaneous therapy with Genentech efalizumab in patients with moderate to severe psoriasis who are candidates for systemic therapy. In: Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]. Feltham: Serono Ltd., 2004.

Rich 2013

Rich P, Sigurgeirsson B, Thaci D, et al. Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study. The British Journal of Dermatology. Feb 2013;168(2):402–411.

Papp 2013

Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebocontrolled phase II dose-ranging study. The British Journal of Dermatology. Feb 2013;168(2):412–421.

SCULPTURE 2013

Novartis. Study Comparing secukinumab Use in Long-term Psoriasis maintenance therapy: fixed regimens vs reTreatment Upon start of Relapse SCULPTURE. 2013.

Mroweitz U, et al., editors. Secukinumab retreatment-as-needed maintenance regimen: efficacy and safety outcomes from the SCULPTURE Study2014 2014/03//.

ERASURE 2014

Rich P, et al., editors. Secukinumab efficacy stratified by body weight: A subanalysis from the ERASURE phase 3 study in psoriasis2014 2014/03//.

Papp K, et al., editors. Efficacy in relationship with response to previous biologic psoriasis therapy: A subanalysis from the ERASURE phase 3 study in psoriasis2014 2014/03//.

Lebwohl M, Vender R, Menter A, Karpov A, Papavassilis C. ERASURE: Sekinumab shows sustained efficacy in subjects regardless of previous biologic exposure. European Association of Dermatology and Venereology (EADV) Conference. 2014.

Gottlieb A, et al., editors. Secukinumab time to posriasis response on patient-reported symptoms (ERASURE Study)2014 2014/03//.

Novartis. Efficacy of Response And Safety of 2 Fixed Secukinumab Regimens in Psoriasis (ERASURE). 2013.

FEATURE 2014

Blauvelt A GAPJPRCS. Secukinumab efficacy and safety: Results from the First study of sEcukinumAb in prefilled syringes in subjecTs with chronic plaqUe-type psoriasis REsponse at 12 weeks (FEATURE). Journal of the American Academy of Dermatology. 2014.

Blauvelt A, et al. Secukinumab adminstration by pre-filled syringe: Efficacy, safety and usability results from a randomised controlled trial in psoriasis (FEATURE). BJD. 2014.

Novartis. First study of SEcukinumAb in pre-filled syringes in subjects with chronic plaqUe-type psoriasis: REsponse at 12 weeks (FEATURE). 2014.

JUNCTURE 2015

Paul C LJPYRCS. Secukinumab efficacy and safety in subjects with moderate to severe plaque psoriasis: Results from the Judging the efficacy of secUkinumab in patients with psoriasis using autoiNjector: A Clinical Trial evalUating treatment REsults trial (JUNCTURE). Journal of the American Academy of Dermatology. 2014.

Paul C, Lacour JP, Tedremets L, Jazayeri S, Adams S, Guidon C, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). JEADV. 2014.

Novartis. Judging the Efficacy of SecUkinumab in Patients With Psoriasis using Autoinjector: a Clinical Trial EvalUating Treatment Results (JUNCTURE). 2014.

Rivas E, Griffiths C, Rich P, Gong Y, Papavassilis C. FIXTURE: Secukinumab shows sustained efficacy in subjects regardless of previous biologic exposure. European Association of Dermatology and Venereology (EADV) Conference. 2014.

FIXTURE 2014

Novartis. FIXTURE (Full year Investigative eXamination of secukinumab vs. eTanercept Using 2 dosing Regimens to determine Efficacy in psoriasis). 2013.

Novartis. FIXTURE (Full year Investigative eXamination of secukinumab vs. eTanercept Using 2 dosing Regimens to determine Efficacy in psoriasis). 2013.

Reich K, et al., editors. Sustainability of response with secukinumab to 52 weeks in moderate-to-severe plaque psoriasis: Data from the full year investigative examination of secukinumab vs etanercept using 2 dosing regimens to determine efficacy in psoriasis (FIXTURE) study2014 2014/03//.

PASI outcome reported at irrelevant time points (2 studies)

Van Joost 1988

van Joost T, Bos JD, Heule F, Meinardi MM. Low-dose cyclosporin A in severe psoriasis. A double-blind study. Br J Dermatol 1988;118:183-90.

Ellis 1991

Ellis CN, Fradin MS, Messana JM, Brown MD, Siegel MT, Hartley AH, et al. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. N Engl J Med 1991;324:277-84.

With treatment arm of interest but not recommended dose (4 studies)

Tyring 2006

Tyring S, Gordon KB, Poulin Y et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. Arch Dermatol 2007; 143:719–26.

Bagel 2012

Bagel J, Lynde C, Tyring S, Kricorian G, Shi Y, Klekotka P. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebo-controlled study of etanercept. Journal of the American Academy of Dermatology. Jul 2012;67(1):86–92.

Tyring S, Bagel J, Lynde C, et al. Patient-reported outcomes in moderate-to-severe plaque psoriasis with scalp involvement: results from a randomized, double-blind, placebo-controlled study of etanercept. Journal of the European Academy of Dermatology and Venereology: Jan 2013;27(1):125–128.

Gottlieb 2011

Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. The British Journal of Dermatology. Sep 2011;165(3):652–660.

Strober 2011

Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. The British Journal of Dermatology. Sep 2011;165(3):661-668.

12.10 Evidence synthesis – fixed-effect models' results

NMA results of PASI response for analysis 2 assuming a fixed-effects approach: probability of achieving PASI 50/75/90

Analysis	2 - Fixed-effects approach			
	PASI 50 Mean (95% CrI)	**PASI 75 Mean (95% CrI)**	**PASI 90 Mean (95% CrI)**	**r**
Placebo	0.212 (0.20 to 0.23)	0.087 (0.08 to 0.10)	0.020 (0.02 to 0.02)	5
Etanercept	0.726 (0.68 to 0.77)	0.517 (0.47 to 0.57)	0.259 (0.22 to 0.30)	3
Ustekinumab	0.863 (0.84 to 0.89)	0.704 (0.67 to 0.74)	0.439 (0.40 to 0.48)	2
Adalimumab	0.868 (0.84 to 0.90)	0.711 (0.67 to 0.76)	0.447 (0.40 to 0.50)	1
Methotrexate	0.369 (0.28 to 0.47)	0.187 (0.13 to 0.26)	0.099 (0.03 to 0.09)	4
Residual deviance	938.5*	921.2	959.8	
DIC		1790.3		

r-– ranking of treatments according to point estimates; *Compared with 209 data points.

NMA results of PASI response for analyses 2a (placebo adjusted) assuming a fixed-effects approach: probability of achieving PASI 50/75/90

Analysis	2a - Fixed-effects approach			
	PASI 50 Mean (95% CrI)	**PASI 75 Mean (95% CrI)**	**PASI 90 Mean (95% CrI)**	**r**

Placebo	0.147 (0.13 to 0.17)	0.051 (0.04 to 0.06)	0.010 (0.01 to 0.01)	5
Etanercept	0.595 (0.55 to 0.65)	0.367 (0.32 to 0.42)	0.148 (0.12 to 0.18)	3
Ustekinumab	0.862 (0.83 to 0.89)	0.695 (0.65 to 0.74)	0.422 (0.37 to 0.47)	1
Adalimumab	0.821 (0.79 to 0.85)	0.632 (0.59 to 0.68)	0.356 (0.31 to 0.40)	2
Methotrexate	0.552 (0.49 to 0.62)	0.326 (0.27 to 0.39)	0.124 (0.09 to 0.16)	4
Residual deviance	406.3*	385.7	431.4	
DIC		1259.5		

r-– ranking of treatments according to point estimates; *Compared with 209 data points.

12.12 Consistency assessment

The validity of a NMA depends upon an assumption of homogeneity/exchangeability between all the trials included in the network, i.e. that there are no essential differences between the methods, populations and interventions being studied, and that any differences are due to chance (as in a standard meta-analysis). The lack of homogeneity/exchangeability between studies involving one of the treatments of interest and studies involving the other treatments of interest may generate inconsistency. The main potential threat to consistency of the evidence network is the pooling of evidence across trials in children and young people with those in adult populations.

The main network evidence loops that require close examination are PLB *vs* MTX *vs* ADA, PLB *vs* ETA *vs* APRE and PLB *vs* UST *45vs* UST 90 (Figure 5), as these involve the main agents of interest. As illustrated in Figure 5, these evidence loops contain 1, 1 and 4 three-arm trials, respectively (Figure 5 – discontinued line boxes). Within a three-arm trial no inconsistency exists, and no inconsistency is brought from these multi-arm trials to the evidence network, potentially only between-trial heterogeneity [227]. These 3 evidence loops of interest have a mixture of two- and three-arm trial evidence. In these circumstances defining and assessing inconsistency create inherent technical difficulties. Solutions to this problem are labelled by the NICE DSU TSD4 [227] document on inconsistency of evidence as "not entirely satisfactory" and are "predicated on the assumption that the majority of trials are two-arm trials and there is unlikely to be any material impact on detection of inconsistency".

To overcome these potential inconsistency assessment issues, a scenario analysis was performed which consisted of excluding the evidence from trials in children and young people from the analysis, and only synthesising the evidence from adult populations. Therefore, analysis 2a above (i.e. a baseline risk adjusted random-effects model) was replicated only using the evidence from the 34 adult trials and the results of this scenario analysis was compared to the results from using the full evidence base.

The following table presents PASI response outcomes for the trials in the adult population only. Overall, the results are similar to the ones observed in analyses 2a. Overall, these results bring some reassurance that consistency exists between the two subpopulations.

NMA results of PASI response for analysis 2a restricted to adult evidence: probability of achieving PASI 50/75/90 in adults' subpopulation

Consistency assessment	2a restricted to adult evidence			
Adults subpopulation only	**PASI 50 Mean (95% CrI)**	**PASI 75 Mean (95% CrI)**	**PASI 90 Mean (95% CrI)**	**r**
Placebo	0.144 (0.12 to 0.17)	0.050 (0.04 to 0.06)	0.010 (0.01 to 0.01)	5
Etanercept	0.619 (0.55 to 0.69)	0.389 (0.32 to 0.46)	0.161 (0.12 to 0.21)	3
Ustekinumab 45	0.875 (0.83 to 0.91)	0.714 (0.65 to 0.78)	0.442 (0.37 to 0.52)	1
Adalimumab	0.84 (0.78 to 0.89)	0.654 (0.57 to 0.73)	0.377 (0.30 to 0.46)	2
Methotrexate	0.548 (0.44 to 0.65)	0.322 (0.23 to 0.42)	0.121 (0.07 to 0.18)	4
Residual deviance	360.3	337.2	387.0	
DIC		45.02		

r-– ranking of treatments according to point estimates; *Compared with 191 data points;

12.13 Additional cost-effectiveness results

Scenario results for interventions as an alternative to systemic therapy: EQ-5D utility estimates from adults (TA180)

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children aged 4-17 years						
MTX	34,910	9.156	-	-	-	MTX
ADA	62,019	9.361	27,109	0.204	132,616	

ADA, adalimumab; MTX, methotrexate.

Scenario results for interventions after failed systemic therapy: EQ-5D utility estimates from adults (TA180)

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	36,406	7.808	-	-	-	-	
ETA	43,779	8.150	7,373	0.342	21,546	21,546	ETA
ADA	57,230	8.333	13,451	0.183	73,670	39,682	
Children and young people aged 12-17 years							
BSC	21,749	4.306	-	-	-	-	
ETA	33,186	4.585	11,437	0.278	ED ADA	41,085	BSC
ADA	37,848	4.732	16,099	0.426	37,802	37,802	
UST	39,924	4.753	2,075	0.021	100,423	40,700	

ADA, adalimumab; BSC, best supportive care; ED, extendedly dominated by; ETA, etanercept; UST, ustekinumab.

National Institute for Health and Care Excellence

Multiple Technology Appraisal

Psoriasis (plaque, chronic, severe, children, young people) - adalimumab, etanercept and ustekinumab [ID854]

AbbVie's Response to the Assessment Group's Report (no ACIC)

Dear Meindert,

AbbVie welcomes the opportunity to comment on the report produced by the Assessment Group for the ongoing multiple technology appraisal of adalimumab, etanercept and ustekinumab in psoriasis (plaque, chronic, severe, children, young people).

We have identified four key issues of concern in the handling of the cost utility assessment, together with a number of clarifications and corrections.

Please find our comments summarised below.

With kind regards

[redacted]

[redacted]

Key issues in relation to the cost-utility analysis

Issue 1.

Selection of appropriate source for utilities estimates in the economic model

The Assessment Group have developed an economic model using efficacy estimates from a mixed treatment comparison incorporating data from studies involving both adults and children. This decision reflects both the incompleteness of the network consisting purely of childhood-specific studies and an acknowledgement that treatment benefits are not likely to be age-specific. In order to map these clinical benefits to utilities in their base-case, , the Assessment Group have used data derived from a single study in adolescents. The utility estimates from this study are considerably at variance with results derived from adult studies, which have been used in previous NICE technology appraisals in psoriasis, and we believe they are unlikely to represent a true assessment of the impact of successful treatment on quality of life.

Utility estimates for adults previously used in this clinical area have typically demonstrated that treatment success is associated with an incremental utility in the range 0.17-0.22 for PASI 50-75, 0.18-0.22 for PASI 75-90 and 0.21-0.31 for PASI >90 [table 62; p180 in Assessment Group report). The corresponding baseline values used by the Assessment Group for the current model are 0.0255, 0.0340 and 0.0810 respectively.

This implies that adult utility gains are 6.7-8.6 times greater than values estimated for adolescents for PASI 50-75, 5.3-6.5 times greater for PASI 75-90 and 2.6-3.8 times greater for PASI>90. Whilst some degree of quality of life difference between adolescents and adults is possible, incremental differences of this magnitude are not clinically plausible.

There are a number of methodological problems with the approach adopted by the Assessment Group that may reduce the validity of their utility modelling:

1. The quality of life data were drawn from a single study recruiting children aged 12-17 with moderate-severe psoriasis (CADMUS study)[1]. The relevance of these results to patients aged <12, who are relevant to two of the three comparisons modelled is unknown.
2. The adolescents in this study completed the PedsQL questionnaire but only summary results were available to the Assessment Group. A previously published algorithm mapping PedsQL scores to EQ-5D-Y was then used [2]. This algorithm was derived using data from healthy adolescents aged 11-15. Its validity outside this age range or in populations with impaired health has not been established. Additionally, in the absence of individual patient scores from the CADMUS study, the Assessment Group had to adapt the algorithm to provide estimates of EQ-5D-Y scores based on domain-level summary results, introducing further uncertainty.
3. Although it is not clear from the report, it appears that the Assessment Group calculated an EQ-5D-Y index score from the mapped data and seems to have directly equated these scores to utilities. Current EuroQol guidance on the EQ-5D-Y states:

> *"…At present, it is not possible to calculate a single index value for the EQ-5DY. A value set for the EQ-5D-Y is not yet available. It is not recommended to use the 3L value set as proxy value set for the EQ-5D-Y…" [3]*

The utility estimates chosen have a major impact on the ultimate ICER (see table 92, Scenario analysis 4a; p230 Assessment Group Report). Given the methodological uncertainties associated with the mapping model used by the Assessment Group and clinically implausible results, we suggest that the base case model should use an adult utility sets, with the PedsQL-mapped utilities used within a scenario analysis.

The use of adult efficacy and utility data in the absence of specific information for children and adolescents is well established within the context of NICE Technology Appraisals, where there is no reason to expect treatment efficacy to be age-dependent (please see for instance NICE TA300: Peginterferon alpha and ribavirin for treating chronic hepatitis C in children and young people November 2013) [4]. Adopting this approach will not only ensure that the best estimate of the true ICER is obtained, but will also allow more meaningful cross-comparison with the results of other technology assessments in psoriasis already published by NICE.

Proposed amendment: The base case economic assessment should use direct adult estimates of utility, as currently modelled in Scenario analysis 4a, rather than the indirect adolescent estimates currently used.

Issue 2

Underestimation of utility values in economic model.

The NICE reference case states that the perspective to adopt when incorporating health outcomes in a cost-effectiveness analysis ought to ensure that "all direct health effects, whether for patients or, when relevant, carers" are taken into account.

Given the age of the patient population considered for the purpose of this MTA, the impact of both the disease and the treatment given would be expected to impact on the quality of life of parents and other carers. Unfortunately, AbbVie recognises that there are no quantitative estimates of the impact on the health related quality of life of carers for children and young people with psoriasis receiving any of the interventions considered by this MTA. However, the committee should recognise that the utility values currently used in the base case analysis, and also those used in scenario 4a which would represent our preferred base case (see Issue 1), present a very conservative estimate of the global impact on health related quality of life of the technologies under consideration.

Issue 3

Hospital admissions during BSC phase of economic model

The base case economic model assumes that once therapy with biologic treatment has failed, Best Standard Care (BSC) will incur an additional two consultant outpatient appointments but no hospital admissions. Previous technology appraisals in psoriasis (TA153, TA 350, TA 368) have considered that hospital admission is an integral part of BSC and estimated a mean annual length of stay (LOS) of 26.6 days for all patients in this health state. It should be noted that this has been criticised as an overestimate and a published UK analysis of resource utilisation for patients with moderate-severe psoriasis prior to and after initiation of biologic therapy (Fonia et al) identified a mean LOS of 6.49 days in the year prior to treatment initiation, declining to 1.55 days in the year following treatment initiation[5]. Although this patient group is not analogous to those who have failed biological therapy, and is limited to adult patients, it is probably the best estimate currently available to inform this model.

The average length of hospitalisation is a key driver of the ICER in the Assessment Group model (see table 92, Scenario analysis 5; p230 Assessment Group Report). Indeed, using the 26.6 day estimate, BSC is dominated by biologic therapy for those patients who have failed methotrexate. Whilst we share the opinion that 26.6 days is probably an overestimate of the mean resource utilisation, it is equally difficult to justify the assumption of no admissions at all, as used by the Assessment Group in the current model.

In the absence of any clear estimates from routinely gathered NHS activity data, we believe that the 6.49 day estimate from Fonia et al represents our current best understanding of the pattern of care in the UK and should therefore be used in the base case analysis. The estimates of zero admissions and 26.6 days mean duration of hospitalisation could then reasonably be used as scenario analyses.

Proposed amendment: The base case economic assessment should use a mean annual estimate of 6.49 days hospitalisation for patients in the BSC state, as currently modelled in Scenario analysis 5, rather than the current estimate of zero hospitalisations.

NICE policy context for this amendment

In the Assessment Group report, the figure of 26.6 days mean admission in the BSC group is discussed, based on the figure used in the NICE costing template for CG153 (Psoriasis: assessment and management). The Assessment Group commented that "The total of 26.6 days of hospitalisation per annum was considered by NICE appraisal committees for TA 350 (secukinumab) and TA 368 (apremilast) in adults to be too high" [AG report; p190].

For CG153, the estimate of 26.6 days was drawn from the following assumptions, as described in appendix P of the guidelines development documentation:

"...Fonia and colleagues estimated inpatient length of stay to be 6.49 days per year before biologics [5]; Driessen and colleagues estimated it to be 14.9 days per year for 82% of patients and 53.0 days per year for 18% of patients [6]. Combining the subgroups in Driessen and colleagues would give a weighted mean of 21.8 days per year

*(0.82*14.9+0.18*53=21.8). The observed length of stay from Fonia and colleagues seems low compared to HES data, length of stay listed in the relevant NHS reference costs (between 9 and 15 days per admission) and GDG opinion. It is difficult to know how applicable the observations from Driessen and colleagues are because they are from a Dutch health system perspective and there may be important differences in terms of service configuration and delivery of care.*

For the NCGC model, we took the breakdown in high-need versus very high-need as observed in the Driessen cohort study (82% vs 18%) to inform a weighted average length of stay. In the base case, we assumed that high-need patients (82%) will require one hospital admission per year, which was assumed to correspond to a mean length of stay of 20.8 days (from Woods and colleagues [6]…). This is much longer than the 6.5 days observed in Fonia and colleagues, but as this is likely to be a higher-need population than their cohort, the GDG considered this to be a reasonable assumption.

In the base case, we assumed that very high-need patients (18%) will require 2.55 hospital admissions per year, each also 20.8 days in length, which equals out to 53 inpatient days per year, the figure reported for this population in Driessen and colleagues..."

We have reviewed how this issue was handled in TA350 (see below). Unfortunately, because TA368 has now been superseded by TA419, the relevant detailed documentation for this appraisal is no longer available on the NICE website

TA350: Secukinumab for treating moderate to severe plaque psoriasis (July 2015)

The economic model submitted by the manufacturer used an analysis of HES data to estimate a mean of 10.7 days hospital admission per year in the standard care arm.

The AG reviewed the literature:

- Woods et al [7] looked at four centres in England and arrived at a mean estimate of 19.7 days (range 13.1-23.4)
- Conway & Curry [8] looked at 15 years data for an urban area in South Wales and estimated a mean admission duration of 16.8 days
- Fonia et al [5] reported on admissions to a single centre in London and reported a mean of 6.49 days
- Driessen et al [6] reported on admissions in a single centre in the Netherlands and estimated a mean admission of 14.9 days.

The AG modified the company model to exclude hospitalisation costs in BSC patients achieving PASI 75 response, while retaining the 10.7 days for other patients. In a scenario analysis they modelled the results using their "preferred base case" using the Fonia data (6.49 days).

As part of this response, AbbVie also re-assessed current NHS length of stay, based on the latest Hospital Episode Statistics for England [9]. In 2015-16, there were 324 episodes of hospital admission in England for treatment of psoriasis in people aged 18 or under, out of a total of 11,786 for all ages. The mean duration of admission for all ages was 6.7 days, which is consistent with Fonia et al, but it was not possible to separate out specifically paediatric

LOS data from the published information. Additionally, we cannot identify what proportion of these patients represents those who have failed therapy with biologics. However, we can reasonably assert that:

- Admissions for psoriasis are not common for children but do occur
- The mean length of stay for all psoriasis admissions (6.7 days) is consistent with our proposed baseline assumption of 6.49 days

Issue 4

Definition of BSC in the economic assessment of adalimumab as an alternative to systemic therapy

Patients who fail treatment with adalimumab or methotrexate in this part of the economic model revert to BSC, which is defined in the same way as for the analyses of patients who have failed prior systemic therapy. We believe that the BSC category for this part of the analysis needs to be separately defined. Within BSC, 61% of patients are treated with methotrexate, 29% with cyclosporine and the remainder with topical therapies.

- For patients who fail methotrexate, continuation of methotrexate is clearly inappropriate. Our advice from a UK clinician is that if MTX at an appropriate dose for an adequate duration had failed, a patient would be switched to other systemic therapy (ciclosporin or acitretin) or a biologic therapy
- For patients who fail adalimumab, our advice from a UK clinician is that they will either be switched to another biologic, or possibly back to conventional systemic therapy - methotrexate/ cyclosporine - as they will not have previously been treated with systemic therapy.

This arm of the model as it stands does not reflect reasonable clinical practice, nor does it represent the likely cost effectiveness of the treatment strategies in this patient group. Altering the treatment pathways to reflect clinical practice will influence both costs and utilities and consequently affect the estimated ICERs. Whilst it is not possible to estimate the direction or magnitude of this influence without detailed remodelling, there is sufficient uncertainty around the current estimates that it casts doubt on their value.

Proposed amendment: The base case economic assessment for adalimumab in patients who have not failed systemic therapy should be re-modelled to reflect a more relevant and meaningful BSC state.

Clarifications and corrections

AbbVie has identified a number of occasions within the AG report where further clarification can be provided or factual inaccuracies corrected, as detailed in the Table 1. AbbVie requests that any inaccuracies in reporting within the AG report be amended, as suggested in the final column of the table.

Table 1: Minor clarifications and corrections

Section of the report	Description of the issue	Suggested change and justification of the amendment
Table 62; Page 180	The top row of the table (base-case utilities) is incorrect and does not reflect the values listed in the previous table and used in the economic model.	Substitute the correct values, as shown in table 61
Table 89, page 222	The heading used for the table is incorrect as it reads as "Table 89 Scenario 4b results for interventions after failed systemic therapy: Utility in BSC equal to baseline"	The heading should read: "Table 89 Scenario 4b: cost-effectiveness results for the interventions after failed systemic therapy assuming hospitalisations for BSC"
Section 5.4.1 (NMA using minimum evidence from the adult population); Page 116, Paragraph 3; Line 6	Spelling mistake to adalimumab trial; "CHAMPTION"	This should be spelt and written as 'CHAMPION'
Section 1.4.1.1 Adalimumab; page 29	The trial did not provide evidence for children aged 4 to 6 years of age.	**Suggested change:** This wording should be deleted from the report because it is misleading. **Justification:** Due to privacy laws and rules surrounding collection of personal information for clinical studies, birthdates for all subjects were normalised to January 1 of their birth year. In the adalimumab 0.4 mg/kg arm, one subject was 4 years old when enrolled, but was recorded as 5 years old when normalised by birth year. Additionally, in the 0.8 mg/kg

Section of the report	Description of the issue	Suggested change and justification of the amendment
		adalimumab arm, one subject was 6 years old when enrolled, but was recorded as 7 years old when normalised by birth year [See Table 13, Page 185 of the of CSR for the M04-717 trial for further details] Also, on 26 February 2015, Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Adalimimab. The CHMP adopted a new indication as follows: *Treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.* Therefore, evidence for children between the ages of 4 to 6 was put in to consideration to inform the full adalimimab marketing authorisation for 4 years and older with severe chronic plaque psoriasis; thus the decision should be upheld by the Assessment Group. AbbVie request that the AG delete this wording throughout the entire report to ensure consistency with regulatory approval for adalimimab for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age and above.
Section 1.8, page 33	Evidence for the clinical effectiveness and safety of adalimumab [..] in younger children in particular is currently lacking	**Suggested change:** This sentence should be deleted from the report because it is misleading, as far as adalimumab is concerned. **Justification:** Due to privacy laws and rules surrounding collection of personal information for clinical studies, birthdates for all subjects were normalised to January 1 of their birth year. In the adalimumab 0.4 mg/kg arm, one subject was 4 years old when enrolled, but was recorded as 5 years old when normalised by birth year. Additionally, in the 0.8 mg/kg adalimumab arm, one subject was 6 years old when enrolled, but was recorded as 7 years old when normalised by birth year [See Table 13, Page 185 of the of CSR for the M04-717 trial for further details]

Section of the report	Description of the issue	Suggested change and justification of the amendment
		Also, on 26 February 2015, Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Adalimimab. The CHMP adopted a new indication as follows: *Treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.* Therefore, evidence for children between the ages of 4 to 6 was put in to consideration to inform the full adalimimab marketing authorisation for 4 years and older with severe chronic plaque psoriasis; thus the decision should be upheld by the Assessment Group. AbbVie request that the AG delete the wording throughout the entire report to ensure consistency with regulatory approval for adalimimab for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age and above.
Section 9.1, page 236	One multicentre RCT (M04-717) found that adalimumab at the licenced dose of 0.8 mg/kg (up to 40 mg) lead to significantly greater responses than methotrexate for the outcomes of PASI 50 and PASI 75, but not PASI 90 at 16 weeks.	**Suggested change:** One multicentre RCT (M04-717) found that adalimumab at the licenced dose of 0.8 mg/kg (up to 40 mg) lead to significantly greater responses than methotrexate for the outcomes of PASI 50 and PASI 75, but not PASI 90 at 16 weeks; however, a numerically higher proportion of subjects randomised to adalimumab 0.8 mg/kg achieved a PASI 90 or PASI 100 response at Week 16 than subjects randomised to methotrexate [See Table 28, Page 218 of the M04-717 CSR] **Justification:** As indicated above, evidence shows a numerical difference in response rates between the two trial arms. Therefore, only reporting the 'statistically significant' results doesn't capture the full concept of the response rates between adalimumab 0.8 mg/kg and methotrexate trial arms, during the planned treatment period (16 week time point).

Section of the report	Description of the issue	Suggested change and justification of the amendment
Section 4.2.1 (Quantity of identified evidence); page 47, Line 2.	In addition, **eight** relevant regulatory documents were retrieved.	**Suggested change:** In addition, **nine** relevant regulatory documents were retrieved. **Justification:** Text in Section 4.2.1 and numbers reported in Figure 1 'PRISMA flow diagram' (Page 48) are inconsistently reported.
Section 4.2.1 (Quantity of identified evidence); page 47, Line 4.	Thus, a total of 111 records were read in full, resulting in 62 records being excluded and a total of **48 records** being included in the review.	**Suggested change:** Thus, a total of 111 records were read in full, resulting in 62 records being excluded and a total of **49 records** being included in the review. **Justification:** Text in Section 4.2.1 and numbers reported in Figure 1 'PRISMA flow diagram' (Page 48) are inconsistently reported.
Table 2, pages 51-58	Use of the word "participants" while in the CSR for M04-717 patients are referred to as "subjects"	**Suggested change:** for consistency reasons, AbbVie requests that rather than "participants" the word "subjects" is used when reporting adalimuamb data from M04-717, to be in line with the wording used in the CSR.
Section 4.3.1 (Risk of bias assessment); Page 60, Paragraph 1, Line 6.	This means that, despite adalimumab having marketing authorisation in children aged 4 years and older, this particular trial does not provide any efficacy data on the licenced standard dose of adalimumab in children aged 4-6 years.	**Suggested change:** This wording should be deleted because it is incorrect and misleading. **Justification:** All efficacy analyses for the adalimumab trial were based on the ITT set, which included all subjects who were randomised (N = 114); hence included patients aged between 4-6 years of age [See Table 11, Page 178 of the adalimumab CSR, for further details] Also, due to privacy laws and rules surrounding collection of personal information for clinical studies, birthdates for all subjects were normalised to January 1 of their birth year [See Table 13, Page 185 of the of CSR for the M04-717 trial for further details].

Section of the report	Description of the issue	Suggested change and justification of the amendment
Section 4.3.2.2, page 63	"The proportion of participants achieving a sPGA"	**Suggested change:** delete "sPGA" and replace it with "PGA", as per CSR records.
Section 4.3.2.3 (quality of life), Page 64, Paragraph 3, Lines 3-4	"…….see **Table 4 Error! Reference source not found.**	Correct referencing required
Section 4.3.4.1 (Adverse events at 16 weeks), Page 67, Paragraph 1, Lines 1-2	**"…..Error! Reference source not found…"**	Correct referencing required
Section 4.3.5 (Summary of efficacy and safety of adalimumab)	The trial does not provide evidence for children aged 4 to 6 years of age.	**Suggested change:** This wording should be deleted because it is incorrect and misleading. **Justification:** All efficacy analyses for the adalimumab trial were based on the ITT set, which included all subjects who were randomised (N = 114); hence included patients aged between 4-6 years of age [See Table 11, Page 178 of the adalimumab CSR, for further details] Also, due to privacy laws and rules surrounding collection of personal information for clinical studies, birthdates for all subjects were normalised to January 1 of their birth year [See Table 13, Page 185 of the of CSR for the M04-717 trial for further details].
Section 4.3.5 (Summary of efficacy and safety	Adalimumab at the licenced dose of 0.8 mg/kg (up to 40 mg) leads to significantly greater responses than	**Suggested change:** Adalimumab at the licenced dose of 0.8mg/kg (up to 40mg) leads to significantly greater responses than methotrexate for the outcomes of PASI 50, PASI 75, but not PASI 90; however, a numerically higher proportion of subjects randomised to adalimumab 0.8 mg/kg

Section of the report	Description of the issue	Suggested change and justification of the amendment
of adalimumab)	methotrexate for the outcomes of PASI 50, PASI 75, but not PASI 90.	achieved a PASI 90 or PASI 100 response at Week 16 than subjects randomised to methotrexate [See Table 28, Page 218 of the M04-717 CSR] **Justification:** As indicated above, evidence shows a numerical difference in response rates between the two trial arms. Therefore, only reporting the 'statistically significant' results doesn't capture the full concept of the response rates between adalimumab 0.8 mg/kg and methotrexate trial arms.
Section 9.1 (Statement of principal findings); paragraph Line 8-9	The trial does not provide evidence for children aged 4 to 6 years of age.	**Suggested change:** This wording should be deleted because it is incorrect and misleading. **Justification:** Due to privacy laws and rules surrounding collection of personal information for clinical studies, birthdates for all subjects were normalised to January 1 of their birth year. In the adalimumab 0.4 mg/kg arm, one subject was 4 years old when enrolled, but was recorded as 5 years old when normalised by birth year. Additionally, in the 0.8 mg/kg adalimumab arm, one subject was 6 years old when enrolled, but was recorded as 7 years old when normalised by birth year [See Table 13, Page 185 of the of CSR for the M04-717 trial for further details].
Section 5.4.4 (Summary of findings of relative efficacy from NMA); Page 230, paragraph 4, Lines 2-3	PASI response results were generally consistent across the different models, adjusted and unadjusted. **Ustekinumab was identified as the most efficacious treatment followed by adalimumab and etanercept.**	**Suggested change:** PASI response results were generally consistent across the different models, adjusted and unadjusted. The relative efficacy of ustekinumab and adalimumab is similar based on relative effectiveness estimates for PASI 75 (adalimumab vs. ustekinumab 45, RR: 0.96, 95% CrI: 0.85 to 1.05). **Justification:** This statement is conclusive, but not reflected in the estimates presented from analysis 2b. The Assessment Group indicates that NMA analysis 2b was most appropriate in informing the clinical and cost analyses; therefore results from this analysis should be used to draw final conclusions of efficacy of adalimumab relative to etanercept and ustekinumab.

Section of the report	Description of the issue	Suggested change and justification of the amendment
		From page 126-7 of the report it is reported that: "*The results from analysis 2b (section 5.4.3.4, page 126, paragraph 4) indicate that the relative efficacy of ustekinumab and adalimumab is similar based on relative effectiveness estimates for PASI 75 (adalimumab vs. ustekinumab 45, RR: 0.96, 95% CrI 0.85 to 1.05). In children and young people, ustekinumab (RR 1.47, 95% CrI 1.28 to 1.92) and adalimumab (RR 1.47, 95% CrI 1.23 to 1.79) are statistically significantly more effective than etanercept*." Also, where results of the mean probability of PASI response for ustekinumab (PASI 75: 82%, 95% CrI: 71% to 90%) and adalimumab (PASI 75: 79%, 95% CrI: 31% to 68%) are assessed, these are relatively comparable; 3% different in point estimates relative to the CrIs for adalimumab and ustekinumab was not deemed statistically or clinically significant. Therefore, the data is not conclusively demonstrate that ustekinumab is more efficacious then adalimumab. AbbVie request that the AG capture these messages consistently between the two sections (Section 5.4.4; Summary of findings of relative efficacy from NMA and Section 5.4.3.4, page 126, paragraph 4).
Section 6.3.5	AbbVie submission for ustekinumab	Delete "ustekinumab" and replace with "adalimumab"
Section 7.4.9 Drug acquisition costs (table 64)	Adalimumab SC 0.8mg/kg up to a maximum of 40 mg at weeks 0 and 1, then every 2 weeks thereafter Pre filled syringe 40 mg, £352.14	Please replace with the following statement: Adalimumab 40 mg solution for injection in pre-filled syringe Adalimumab 40 mg solution for injection in pre-filled pen Adalimumab 40 mg/0.8 ml solution for injection for paediatric use £352.14

Section of the report	Description of the issue	Suggested change and justification of the amendment
	MIMS 150	MIMS 150

References

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Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people – review [ID854]

Janssen Cilag Ltd. response to Technology Assessment Report [TAR]
27th January 2017

Janssen Cilag Ltd. welcomes the opportunity to comment on the NICE technology assessment report (TAR) from the Centre for Reviews and Dissemination/Centre for Health Economics Assessment Group for the review of plaque psoriasis in children and young people – adalimumab, etanercept and ustekinumab [ID854].

Overall, we have serious concerns with regards to the conclusions reached by the Assessment Group (AG). We understand that difficulties associated with economic modelling in plaque psoriasis given the limited clinical and economic data in children and young people. However, we believe that the AG have been overly conservative in their assumptions used in the economic model. We do not agree with the conclusions on cost effectiveness as being a reasonable interpretation of the available evidence and we feel that the cost effectiveness of biologics is being significantly underestimated when compared to best supportive care (BSC) and methotrexate by the Assessment Group (AG). We have major concerns with how the overall cost effectiveness conclusions were reached for the following reasons:

- **The AG have not modelled the continuation of biologics into adulthood and, as a result, has caused significant equity concerns with regards to children and young people with plaque psoriasis having access to biologics.**
- **Utility data used in the model does not reflect the quality of life benefits that children and young people with plaque psoriasis receive from biologic treatment.**
- **Assumptions around BSC, including no inpatient hospitalisation for patients on BSC, are significantly underestimating the cost BSC in children and young people with plaque psoriasis.**

We believe that these issues have caused the results and conclusions of the AG's economic evaluation to conflict with previous NICE appraisals of biologics in adults with plaque psoriasis [TA103, TA134, TA146, TA180, TA350]. This raises a number of potential equity concerns around children and young people not being able to get access to treatment until 18 years of age. Given the similarities in the treatment of plaque psoriasis in adults and children and young people, we feel that the AG's choice of assumptions are driving the difference between the cost effectiveness of biologics in adults and children. However, we acknowledge and welcome that the AG have tried to fully explore the uncertainty in the data available to them. We note that when the data and assumptions used in an adult population are applied to children and young people, then, biologics are a cost effective option for the treatment of moderate to severe psoriasis in children and young people. We would therefore request that AG reconsider their basecase assumptions and to incorporate data from an adult population.

We believe that the following key points need to be further addressed in the TAR and during the NICE Appraisal Committee meeting and should be the focus of the Committee's discussion:

1. **The AG have not modelled the continuation of biologics into adulthood and, as a result, has caused significant equity concerns with regards to children and young people with plaque psoriasis having access to biologics.**
    1.1 The AG have not modelled the continuation of biologic treatment into adults. The current analysis does not take into account the benefits of biologics seen in adults,

which has been explored in other NICE appraisals in paediatric populations and underestimates the cost effectiveness of biologics in children and young people.

1.2 There are significant equity considerations around biologics not being cost effective in children and young people, but being cost effective in adults. As currently, the QALY benefits in children and adult population in the model are not equally valued depending of the age of the patients.

2. **Utility data used in the economic model does not reflect the quality of life benefit that children and young people with plaque psoriasis receive from biologic treatment.**
   2.1 Utility data used in the base case of the model does not reflect significant quality of life benefits from biologic treatment that children and young adults with plaque psoriasis experience and accordingly underestimates the benefit that biologics offer in treatment.
   2.2 The AG have not taken into account any potential benefits to biologics that fall outside the QALY calculation, for example, carer disutility. Again we believe this is underestimating the benefits of biologics and should be incorporated by the AG and considered by the NICE Appraisal Committee.
3. **Assumptions around BSC, including no inpatient hospitalisation for patients on BSC, are underestimating the cost of BSC in children and young people with plaque psoriasis**
   3.1 The assumption that children will have no inpatient hospitalisation on BSC is too conservative and does not reflect the serious psychological and social isolation problems related to psoriasis which can lead to further illness, co-morbidities and hospitalisations, especially in an adolescent population.
   3.2 The AG don't appear to have taken account of the transition between paediatric and adult clinical services within the model and the NHS reference costs used in the model appear to have been used inconsistently.
   3.3 Assumptions around the proportion of children and young people receiving systematic therapies and phototherapy are likely to underestimate the cost of BSC in the model.

In addition, we have a number of other comments on the assumptions and approached taken by the AG, which are outlined in more detail below.

In conclusion, we acknowledge the uncertainty associated with evaluating the clinical and cost effectiveness of biologics in children and young people with psoriasis. However, the basecase economic assumptions in the TAR are not appropriate and lead to a significant underestimation of biologics' cost effectiveness. Overall, we believe that ustekinumab is a cost effective option for the treatment of people aged 12 years and older with plaque psoriasis and offers an important option to young people who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

The following sections provide further details on these key points for consideration

Janssen Cilag Ltd. review of the Technology Appraisal Report (TAR)

1. The AG have not modelled the continuation of biologics into adulthood and, as a result, has caused significant equity concerns with regards to children and young people with plaque psoriasis having access to biologics

1.1. The AG have not modelled the continuation of biologic treatment into adults with plaque psoriasis. The current analysis does not take into account the benefits of biologics seen in adults, which has been explored in other NICE appraisals in children and young people and accordingly underestimates the cost effectiveness of biologics.

We believe that the time horizon chosen by the AG is inappropriate and does not reflect the lifetime nature of psoriasis in children and young people that have early onset psoriasis and is inconsistent with previous NICE appraisals in children and young people. The AG have made the decision to limit the time horizon on the basis that there is already existing guidance in an adult population and that there is limited evidence regarding the sequencing of biologics and there is no MTA that establishes the optimal sequence of treatments in adults [TAR, pg.207].

We believe the AG's current approach does not explore the benefits of treating children and young people with psoriasis and therefore underestimates cost effectiveness of biologics. Evidence suggests that the clearance of psoriasis may have long term benefits, which may extend into adulthood. Adolescents with psoriasis may be at increased risk of mental illness, especially depression and anxiety. This is particularly important since depressive episodes at a young age increase the risk of subsequent recurrences and long-term psychiatric disorders [Gonzalez et al]. In particular, psoriasis negatively impacts physical activities. This is especially detrimental to an adolescent with psoriasis since they are already at a twofold risk for comorbidities including obesity, diabetes mellitus, hypertension and psychiatric disorders. [Augustin et al] Most of these effects tend to originate from the cutaneous nature of the disease which leads to decreased exercise both to avoid lesions being visible to peers and due to increased pruritus with diaphoresis [Gonzalez et al]. Overtime these comorbidities could have an impact in terms of mortality and long term health related quality of life (HRQoL). We understand that there is limited evidence to explore these impacts, but we suggest that further sensitivity analyses are undertaken to look a possible mortality and quality of life impacts differences into adulthood.

We also note that this assumption is also inconsistent with other previous NICE technology appraisal that have looked at health technologies in children and young people. Most notably the recent appraisal of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (JIA) (TA373), which took a lifetime perspective. This is also inconsistent compared to a number of other disease areas where there are previous recommendations in both children and adults and where the appraisal in children has taken a lifetime horizon, such as NICE TA188 (growth failure) and TA300 (hepatitis C). This raises inconsistencies with previous NICE appraisals in terms of decision making for health technologies in children and young people. We note that the AG have undertaken scenario analyses where they have extended the time horizon into adulthood [TAR, pg.207-208], but have not adjusted the model for an adult population and therefore we do not believe this reflects an accurate estimate of the cost effectiveness of extending biologics into adulthood and the considerable benefit gains seen in an adult population [TA103, TA134, TA146, TA180, TA350].

- We suggest that the economic model is extended to appropriately explore the impact and benefits of biologics in childhood that may extend into adulthood. The model should also appropriately take into account the benefit gains seen in adults from biologic therapy, as seen in previous adult appraisals of biologics in moderate to severe plaque psoriasis.

1.2. There are significant equity considerations around biologics not being cost effective in children and young people, but being cost effective in adults. As currently, the QALY benefits in children and adult population in the model are not equally valued depending of the age of the patients.

The AG decision not to model patients into adulthood has, in effect, separated out patients with moderate to severe psoriasis into distinct populations: an adult (18 years and over), and children or young people population. This has created significant equity concerns regarding the conclusions in the analysis. We note that the NICE reference case states that an additional QALY should receive the same weight regardless of any other characteristics of the people receiving the health benefit, including age [NICE methods guide,2013]. By splitting the populations and applying different assumptions and most notably different utilities, we believe that children and young people with moderate and severe psoriasis do not have an QALY estimation equal to adults, as stipulated in the reference case [NICE methods guide,2013]. This means that patients that are 17 years and younger will not have access to biologics, but patients 18 years or older will have access to biologics. This is an arbitrary decision based on the age of the patient and does not reflect the QALY benefit for these patients.

- We urge AG to consider modelling the benefits of biologics treatment into an adult population and reconcile differences between children, adolescents and adults in terms of the quality of life benefit from biologics in the current economic model to remove the current equity concern within the appraisal.

2. <u>Utility data used in the model does not reflect the quality of life benefits that children and young people with plaque psoriasis receive from biologic treatment.</u>

2.1. Utility data used in the base case of the model does not reflect significant quality of life benefits from biologic treatment that children and young adults with plaque psoriasis experience and accordingly underestimates the benefit that biologics offer in treatment.

There are significant uncertainties and limitations, which the AG acknowledge, with the utilities used in the basecase of the model. We believe that the current utilities are significantly underestimating the responses, especially for PASI 70 and 90, which represent very good responses for a disease that has a significant impact on quality of life. Patients with moderate to severe psoriasis experience considerable physical discomfort linked with their skin lesions. Symptoms and manifestations include severe itching (pruritis), burning sensations, skin discomfort, skin sensitivity, irritation and pain. Both the physical symptoms, in particular severe pruritis, and the psychological and social impact of symptoms mean that psoriasis can have a substantial impact on HRQol. The underestimation of utilities is especially stark when compared to equivalent utility responses for PASI 70 and 90 responses in adults from NICE TA180. See Table 2 below.

Table 2 Comparison of the mean change in utility used in AG's model and TA180

	CADMUS trial			TA 180		
	Sample size, n	Mean change in CDLQI	Mean change in EQ-5D-Y	Sample size, n	Mean change in DLQI	Mean change in EQ-5D[a]
PASI<50	30	[redacted]	0.0036	430	-2.5	0.04
PASI 50-75	10	[redacted]	0.0255	160	-10.3	0.17
PASI 75-90	9	[redacted]	0.0340	207	-13.4	0.22
PASI ≥90	24	[redacted]	0.0810	318	-15.3	0.25

[a]Pooled EQ-5D data collected in the Phoenix trials

Table taken from the TAR: Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people. Table 61, pg. 179.

We note the limitations and uncertainties that the AG have identified with the current approach of health utility estimation and agree with the AG that they reduce the robustness of the utility values used in the model [TAR, PG.179]. However, we would like to point out further limitations with the current mapping approach that should be considered and accordingly should justify the use of adult utilities in the model.

In summary the AG have noted the following limitations with utility estimation [TAR, pg.179], including:

- Small sample size and limited data to validate the relationship;
- Reliance on a mapping relationship compared to direct EQ-5D measurement;
- Khan et al mapping algorithm has not been validated in children younger than 11 years old or in a population with psoriasis;
- CADMUS trial from where the PedsQL data mapped to EQ-5D was sourced excluded children younger than 12 years; therefore, it remains uncertain whether the mapped utilities are reflective of children younger than 12 years old;
- In populations younger than 12 years, there may be issues with lack of agreement or consistency between self-reported and proxy (parent)-reported measurements

We acknowledge that the AG have used the most generalisable evidence available to them in the population of interest. However, we contest its validity, particularly in adolescents whose utility gains are likely to be closer to adults than children. Indeed, our clinical expert has suggested that, in an adolescent population at least, he would expect a quality of life benefits from the clearance of psoriasis to be in line with or greater than that of adults. Our clinical expert stated, that this is because adults have better coping mechanisms and strategies to cope with their skin care problems. Adolescents on the other hand are more likely to be prone to significant psychosocial issues. Therefore, the benefit that they gain from having skin clear of psoriasis would be greater than an adult. Gonzalez et al have noted that due to the visibility of skin lesions, psoriasis patients risk feeling

stigmatised and bullied, especially since bullying during adolescence is commonly related to physical appearance. Unfortunately, there has been little research on its relationship to skin disease, and there are no validated bullying or victimisation scales in this population. One study interviewed 15 paediatric psoriasis patients (mean age 12.8 ± 4.25 years), 65% of whom felt stigmatised due to bullying or name calling [De Jager et al]. The stigmatisation and bullying can lead to a decreased perception of social connectivity that impacts family and social relationships [Gonzalez et al]. Furthermore, it has been noted that adolescents are often grouped in with paediatric populations or adult populations and thus are given measurement tools that may not address developmentally appropriate physical and psychosocial challenges that this group encounters. Even the modification of adult scales often fails to recognise the unique aspects of adolescent development and function [Gonzalez et al].

The generality of the PedsQL may also be a disadvantage compared to the disease specific instruments such as CDLQI (or DLQI) and this may explain the difference in sensitivity between the utilities in children and adults seen in the TAR. Gonzalez et al argue that the PedsQL may not be specific enough to adequately address the concerns of psoriasis patients. For example, the unique characteristics of psoriasis, such as the physical activities that patients do not participate in due to psychosocial factors or the pruritus associated with psoriasis, are not addressed by the PedsQL [Gonzalez et al].

- We believe that the current estimation of utilities significantly underestimates the benefits of biologics seen in these patients and that the current mapping relationship between PedsQL and EQ-5D is not appropriate and lacks face validity. Response rates from biologics in children and young people with moderate to severe psoriasis are equivalent to or better than adults and accordingly it would be expected that utility improvements from response to biologics would also be similar or greater than those seen in adults. We strongly believe that adult mapping relationship between DLQI and EQ-5D may be more appropriate than the current relationship used by the AG for children and young people, especially in an adolescent population.

2.2. **The AG have not taken into account any potential benefits to treatment that fall outside the QALY calculation, for example, carer disutility. Again we believe this is underestimating the benefits of biologics and should be incorporated by the AG and considered by the NICE Appraisal Committee.**

The AG in TA373 abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (JIA) noted additional consequences of a long term condition like JIA (and psoriasis) can have on children and young people's education. Children and young people may miss school days to attend health care appointments and may be absent for longer periods from school whilst experiencing symptoms. This can have a negative impact on their education and, in future, their ability to gain employment. It may also affect their social and psychological health through the reduced ability to participate in social and leisure activities and sport, and the general burden of a serious health condition during the sensitive period of adolescence [TAR, pg. 147, TA373].

It was noted by the AG, in TA373, that biologics led to a statistical significant higher increase in school days than placebo patients. The AG suggested that this 'indicates the potential for [biologics] to improve education as well as health outcomes, though further evidence is required particularly in a UK context.' [TAR, pg.147, TA373] We see no reason to believe that similar benefits would not be seen in children with psoriasis receiving biologic therapy and this benefit is unlikely to be captured by the QALY and we urge the NICE appraisal committee to take this into consideration.

The AG, in TA373, suggested further there would be a significant impact on parents and carers of children and young people with JIA. We believe that a similar impact may be seen in parents and carers of children and young people with moderate to severe psoriasis given the severity of the disease and the likelihood that parents and carers will have a similar burden of care to JIA. The AG wrote in TA373, that "[parents and carers] may have to pay for child care, take time away from work or even cease employment to provide their own care. This will negatively affect their income and may increase dependency on welfare benefits (where available). Again this is likely to increase socio-economic inequalities. The inability of parents and caregivers to work may have a negative impact on society and the economy, through reduced productivity, less income tax collection, and in some profession a shortage of skilled workforce capacity" [TAR, pg.147, TA373]. One RCT was identified to support this assertion which showed improvements in the number of normal activities per month missed by parents, including work and no work activities, for a biologics compared to placebo. We note that AG, in TA373, assessed this potential impact through adding in carer disutility into their economic analyses and we believe that it is also appropriate to explore in this current appraisal. We note that the Appraisal Committee in TA373 agreed that 'JIA not only affects the quality of life of the child or young person with the disease but can also affect the quality of life of their carers and family.' The Appraisal Committee concluded that caregiver utility should be taken into account when appraising the cost effectiveness of the biological treatment for JIA [NICE TA373]. We believe that a similar approach should be used in this children and young people with moderate to severe psoriasis.

- We suggest that the AG should explore the impact on carers disutility in the economic analysis and the impact of carers/families of children and young people with moderate to severe plaque psoriasis, as was done in TA373. These benefits of biologics treatment are not currently being captured in the AG economic analysis or the current QALY estimation and these should be considered by the NICE appraisal committee.

3. <u>Assumptions around BSC, including no inpatient hospitalisation for patients on BSC, are significantly underestimating the cost BSC in children and young people with plaque psoriasis.</u>

    3.1. **The assumption that children will have no inpatient hospitalisation on BSC is too conservative and does not reflect the serious psychological and social isolation problems related to psoriasis which can lead to further illness, co-morbidities and hospitalisations, especially in an adolescent population**.

We believe that the AG's assumption, based on expert opinion, that children and young people with moderate to severe psoriasis receiving BSC require no hospitalisations is too conservative, especially when compared to previous assumptions in adults. Previous NICE adult appraisals for ustekinumab (TA180), adalimumab (TA146) and etanercept (TA103) have assumed that people on BSC will spend 21 days in hospital. Therefore, to assume no hospitalisations in children and adolescents in contrast to 21 days in adults is unrealistic. It does not take into account the clinical practice of transitioning children to adult clinical pathways between the ages of 13 to 16 and the increasingly complex psychological and social problems that will likely lead to hospitalisations, especially for adolescents. We suggest that the AG revise the economic modelling to reflect the increasing number of hospitalisations, as patients move from childhood, into adolescence and, then, into adulthood.

We disagree with the AG's assumption, based on expert opinion, that children and young people will not have developed comorbidities that complicate severe plaque psoriasis which will lead to hospitalisations [AG report, pg. 190]. A number of studies have identified significant comorbidities in children with plaque psoriasis compared to population norms including and increased rate of metabolic syndrome, hyperlipidaemia, obesity, hypertension, diabetes, depression, anxiety and bi-polar disorder [Augustin 2015, Augustin 2010, Puig 2010]. We accept that these comorbidities are

unlikely to be as developed as in adults, however, to assume that these comorbidities, especially mental health comorbidities, will result in no hospitalisations is unlikely to be a realistic scenario.

We acknowledge that there is limited published evidence to support the number of hospitalisation in children and young people and therefore understand the reliance on clinical expert opinion by the AG. Our clinical expert for the appraisal felt that assuming no inpatient hospitalisations, especially for adolescents with complex psychosocial problems was not reflective of his clinical experience. His belief was that an appropriate figure, at least, for an adolescent population likely to be closer to 21 days based on the Fonia et al study. However, our clinical expert did acknowledge that hospitalisation length of stay will vary across the population of interest and may be much lower for younger children. We also note a British Association of Dermatologist Audit from 2008, which does suggest a need for inpatient hospital care in children and young people, the 'need for dermatology admissions appears to have reduced, but some adults and children with chronic diseases such as psoriasis… may still require inpatient care under the supervision of the dermatologist.' This audit performed before the widespread use of biologics is likely to reflect a population receiving BSC in the absence of biologics. Our clinical expert also believed that there are further costs associated with BSC that have not been captured currently within the AG economic analysis, specifically around the significant amount of resource used to treat the complex psychosocial issues in children and young people by child and adolescent Mental Health services (CAMHS). Again there is no published evidence around the use of these services by children and young people on BSC with moderate to severe psoriasis, but we suggest that the AG explore this through sensitivity analyses for these potentially resource intensive services.

3.2. **The AG don't appear to have taken account of the transition between paediatric and adult clinical services within the model and NHS reference costs used in the model appear to have been used inconsistently.**

A mixture of adult or paediatric reference costs have been used within the model, which is likely to further underestimate the cost of BSC. Furthermore, the AG have not taken into account the transition that takes place from paediatric to adult clinical services starting from the age of 13 years onwards in the model. Therefore, the cost of BSC across the whole population being appraised should be revised by the AG to take account of adolescents moving to the adult clinical pathway.

For inpatient hospitalisations in the model, the AG have used an 'adult skin disorders non-elective excess bed day cost' from the latest NHS reference costs which has been weighted across all codes and gives a weighted average cost of £295.80. We would argue that for a majority of the population in the appraisal, it would be more appropriate to use a 'paediatric skin disorders non-elective excess bed day cost', which gives a weighted average cost of £496.83. This is likely to represent the specialist nursing costs that children require with plaque psoriasis.

The AG appear to have used a paediatric cost for physician visits in an outpatient setting, but for the day centre costs they have used an adult services costs. We are unclear why the AG have switched between adult and paediatric costs in the model for health care visits, as this is not explained in the TAR. The difference between an adult and paediatric costs for selected health care visits are presented in Table 1 below. Overall, we believe this inconsistency in the references costs chosen by the AG underestimates the cost of BSC. This will be accentuated further if any inpatient hospitalisation were to be included in the basecase analysis, as suggested above, given the AG's used of adult costs which are lower than the paediatric costs identified in Table 1.

Table 1: Reference costs used in the Assessment Group model for health care visits

Health care utilisation	Adults reference costs (2014-2015)	Reference	Paediatric reference costs	Reference
Inpatient hospitalisations	**£295.80** ***Cost used in the AG economic model.***	Activity weighted across adult skin disorders non-elective excess bed days. N.B. unclear which costs reference codes used in AG model	£496.83	Activity weighted across Paediatric skin disorders non-elective excess bed day cost] NHS reference cost 2014-2015; Service code:257 Paediatric Dermatology; Currency code: WF01A.
Outpatient visits	£97.03	Activity weighted average of non-admitted Face to Face Attendance, Follow-up, consultant and non-consultant led outpatient visits (service code:330 Dermatology; currency code: WF01A);	**£119.99** ***Cost used in the AG economic model.***	Activity weighted average of non-admitted Face to Face Attendance, Follow-up, consultant and non-consultant led outpatient visits (service code:257 Paediatric Dermatology; currency code: WF01A);
Day centre costs	**£472.55** **Cost used in the AG economic model.**	Activity weighted average of Skin Disorders Without Interventions (currency codes JD07F-K) for day cases.	£622.29	Activity weighted average of Paediatric Skin Disorders (currency codes PJ35A-D) for day cases.

- The current cost estimations for hospitalisation are not reflective of the transition of care from childhood to adolescents and into adulthood or the significant comorbidities and psychosocial issues seen, particularly in adolescents. The AG should consider updating the model with the appropriate costs dependent on the child's age and re-calculate the cost effectiveness with inpatients hospitalisation used in the base case analysis. We also suggest that a sensitivity analysis is conducted around the use of CAMHs services in children receiving BSC for the treatment of their moderate to severe psoriasis.

3.3. **Assumptions around the proportion of children and young people receiving systematic therapies and phototherapy are likely to underestimate the cost of best supportive care in the model.**

We believe that the proportion of BSC patients on systemic therapies like methotrexate and cyclosporine is too high in the model. We feel that this underestimates the cost of BSC because of the low cost of these generic medicines compared to patients receiving active management of their psoriasis in an outpatient setting. The AG have assumed that 90% of children and young people on BSC are likely to be receiving systemic therapies based on the estimates used in NICE CG153 for an

adult population [NICE CG153]. We think that this is likely to be an overestimation of the use of systematic therapies for a number of reasons:

- Methotrexate and cyclosporine are not licensed for use in children.
- Drug survival rates for systematic therapies in children and young people are much lower than that seen in biologics in adults [Ergun et al].
- Methotrexate has been associated with fertility concerns in paediatric patients and as the AG noted 'patients on cyclosporine will only receive treatment for a maximum of two years, because of increased risk of renal toxicity.'

Given these issues, we believe that the use of systemic therapies should be much lower than 90% in the model. If a higher proportion of patients receive active management in an outpatient setting in the model, then this should be reflected in the cost of BSC in the model.

In addition, from a review of the model we note that patients on cyclosporine have no further cost attached to them after they discontinue at 2 years. This further underestimates the cost of BSC in the model, as this is unrealistic assumption for these patients. We believe these patients should be assumed to have active management in an outpatient setting, as was assumed for the 10% of patients not receiving systemic therapy in the model. This would be more reflective of costs seen in these patients after discontinuing cyclosporine in a clinical setting.

We also believe that number of patients receiving phototherapy has been significantly underestimated currently (16%). Our clinical expert, from his experience, has suggested a much higher percentage of patients receiving phototherapy in clinical practice, suggesting closer to 100% of patients. The current low level of phototherapy used in the model further underestimates the cost of BSC in the model.

- The current values in the AG model should be revised to better reflect the burden and cost of BSC for children and young people with moderate to severe plaque psoriasis.

In the section below, we outline further comments that we believe should be considered by the NICE Appraisal Committee:

- **There are a number of additional concerns that we have with the AG's modelling approach, assumptions, data inputs and reporting that are highlighted in Table 3 below.**

Table 3. Other concerns with the technology appraisal report (TAR)

Other concerns with the TAR/model/ modelling approach	Janssen Cilag Ltd. comment and request for action
Combination of paediatric and adult trials in the NMA	• The inclusion of adult clinical trials for the purpose of undertaking a network meta-analysis with the three biologics increases the uncertainty in the AG's basecase results. We would suggest that for etanercept and ustekinumab the results from the MTC analysis would be more appropriate and should be used in the basecase analysis. We believe this is the most appropriate evidence available and free from any biases introduced by including adult trials in the NMA.
Exploration of higher doses of MTX seen in clinical practice	• There is variation in the doses used for MTX in clinical practice and studies [Paller et al]. Higher doses are used and these should be explored in the AG's sensitivity analyses.
Off label use of ustekinumab	• We understand that NICE scope asks to look at off label use of treatments, however, we would like to reiterate that ustekinumab is only licensed in Children and young people aged 12-17 years for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or are intolerant to systemic therapies or phototherapies. There is limited evidence outside the licensed indication with regards to the clinical efficacy and safety of ustekinumab.
Differences in withdrawal rates between treatment does not represent evidence to suggest differences between treatments	• There is significant variation in the withdrawal rates between biologics and systemic therapies, which should be explored by the AG. There is evidence from the UK BADBIR registry to suggest that patient remain on treatment significantly longer with ustekinumab compared to other biologics [Warren et al]. Furthermore, there is evidence that patients stay on systematic therapies for a shorter duration than biologics [Ergun et al]. Currently in the model, ustekinumab, as the most effective treatment is disadvantaged for maintaining response over time, as costs accrue faster than benefits over time compared to BSC. However, after amending assumptions regarding the utilities and the cost of BSC, as suggested in our response, then, it is likely that ustekinumab would be the most cost effective treatment due to its effectiveness and data concerning time on treatment.

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27th January 2017

Psoriasis (plaque, chronic, severe, children, young people) - adalimumab, etanercept and ustekinumab

To whom it may concern,

Many of our members and supporters describe having difficult, lonely childhoods with psoriasis. They feel that having psoriasis from a young age affected their educational performance, which in turn had an impact on future careers. Issues in relating to peers, bullying, feeling unable to pursue intimate or romantic relationships in their teens, all have a cumulative impact on mental wellbeing and their life's direction. Many people who have had psoriasis since childhood have told us they feel their life and mental health would have been significantly better had they been able to access effective treatment and gain control of their skin at a young age.

The children who would be candidates for the treatments being appraised here are likely to have particularly severe psoriasis, and will have tried, and 'failed' most if not all of the other treatments available to them. We know that the biologic treatments being appraised have proven effectiveness in adult psoriasis. Whilst we appreciate there is a lack of data regarding effectiveness of biologics in children – and that the number of children requiring these treatments is likely to be relatively low - we do urge further consideration towards making these treatments available.

To withhold these treatments from children with few other options until adulthood will surely prolong suffering, and have immeasurable impacts on mental wellbeing and quality of life – not only for the child themselves, but for their parents and other family members also.

Yours faithfully,

[redacted]

[redacted]

British Association of Dermatologists Response to NICE Appraisal Consultation Document On the Multiple Technology Appraisal (MTA) Adalimumab, etanercept and ustekinumab for treating severe, chronic plaque psoriasis in children and young people [ID854]

British Association of Dermatologists Therapy & Guidelines and BADBIR sub-committees

On behalf of the British Association of Dermatologists, thank you for the opportunity to comment on the Appraisal Consultation Document. The British Association of Dermatologists have no comments.

[redacted]

Response to AbbVie's Response and Factual Inaccuracies

AbbVie's Comments			York's Response
Page	Location	Comment	
Main Comments on the Assessment Report			
	Issue 1: Selection of appropriate source for utilities estimates in the economic model	The Assessment Group have developed an economic model using efficacy estimates from a mixed treatment comparison incorporating data from studies involving both adults and children. This decision reflects both the incompleteness of the network consisting purely of childhood-specific studies and an acknowledgement that treatment benefits are not likely to be age-specific. In order to map these clinical benefits to utilities in their base-case, , the Assessment Group have used data derived from a single study in adolescents. The utility estimates from this study are considerably at variance with results derived from adult studies, which have been used in previous NICE technology appraisals in psoriasis, and we believe they are unlikely to represent a true assessment of the impact of successful treatment on quality of life. Utility estimates for adults previously used in this clinical area have typically demonstrated that treatment success is associated with an incremental utility in the range 0.17-0.22 for PASI 50-75, 0.18-0.22 for PASI 75-90 and 0.21-0.31 for PASI >90 [table 62; p180 in Assessment Group report). The corresponding baseline values used by the Assessment Group for the current model are 0.0255, 0.0340 and 0.0810 respectively. This implies that adult utility gains are 6.7-8.6 times greater than values estimated for adolescents for PASI 50-75, 5.3-6.5 times greater for PASI 75-90 and 2.6-3.8 times greater for PASI>90. Whilst some degree of quality of life difference between adolescents and adults is possible, incremental differences of this magnitude are not clinically plausible. There are a number of methodological problems with the approach adopted by the Assessment Group that may reduce the validity of their utility modelling: 1. The quality of life data were drawn from a single study	The AG acknowledges the concerns expressed regarding the most appropriate source of utility estimates for the model. This was identified as a key area of uncertainty. The AG did undertake a systematic literature review to identify appropriate utility values for the population of children and young people. Unfortunately, no utility values were identified in this population. In addition, none of the three trials in children and young people collected EQ-5D or EQ-5D-Y utility values. Health-related quality of life was assessed in the trials using CDLQI and PedsQL at selected time points. Therefore, the AG's only possibility to include EQ-5D utility values in the model was via a mapping from either CDLQI or PedsQL. The literature review did not identify any studies that estimated the relationship between CDLQI and EQ-5D/Y, while one study by Khan et al (2014) estimated the relationship between PedsQL and EQ-5D-Y. Therefore, the study by Khan et al represented the only possible route to include generic preference-based utility values in the model for children and young people. Despite a request to the companies for access to patient-level PedsQL data, Janssen Cilag Ltd was the only company to submit aggregated summary data for PedsQL from the CADMUS trial (ustekinumab) within the timescale of the report. Therefore, the AG was limited to data from this single study in adolescents. The AG acknowledged in the report that the utility gains (EQ-

		recruiting children aged 12-17 with moderate-severe psoriasis (CADMUS study)[1]. The relevance of these results to patients aged <12, who are relevant to two of the three comparisons modelled is unknown. 2. The adolescents in this study completed the PedsQL questionnaire but only summary results were available to the Assessment Group. A previously published algorithm mapping PedsQL scores to EQ-5D-Y was then used [2]. This algorithm was derived using data from healthy adolescents aged 11-15. Its validity outside this age range or in populations with impaired health has not been established. Additionally, in the absence of individual patient scores from the CADMUS study, the Assessment Group had to adapt the algorithm to provide estimates of EQ-5D-Y scores based on domain-level summary results, introducing further uncertainty. 3. Although it is not clear from the report, it appears that the Assessment Group calculated an EQ-5D-Y index score from the mapped data and seems to have directly equated these scores to utilities. Current EuroQol guidance on the EQ-5D-Y states: *"…At present, it is not possible to calculate a single index value for the EQ-5DY. A value set for the EQ-5D-Y is not yet available. It is not recommended to use the 3L value set as proxy value set for the EQ-5D-Y…" [3]* The utility estimates chosen have a major impact on the ultimate ICER (see table 92, Scenario analysis 4a; p230 Assessment Group Report). Given the methodological uncertainties associated with the mapping model used by the Assessment Group and clinically implausible results, we suggest that the base case model should use an adult utility sets, with the PedsQL-mapped utilities used within a scenario analysis. The use of adult efficacy and utility data in the absence of specific information for children and adolescents is well established within the context of NICE Technology Appraisals, where there is no reason to expect treatment efficacy to be age-dependent (please see for instance NICE TA300: Peginterferon alpha and ribavirin for treating chronic hepatitis C in children and young people November 2013) [4]. Adopting this approach will not only ensure that the best estimate of the true ICER is obtained, but will also allow more meaningful cross-comparison with	5D-Y) from baseline by PASI response category in children and young people are much smaller than those observed in adults from previous NICE TAs (Table 60, p177). In response to the methodological problems identified with the approach: 1. The AG has acknowledged the limitations of using a single study (Section 7.4.6.3). 2. The AG has acknowledged the limitations of the CADMUS data (Section 7.4.6.3). Although the AG did not have access to individual-patient level data (IPD) from CADMUS, the aggregate summary data for each of the dimensions of PedsQL was made available to the AG. The mapping algorithm of Khan et al (2014) was applied to the summary data for each of the dimensions of PedsQL – this did not require the algorithm to be adapted - a mean estimate of EQ-5D-Y was derived based on domain-level summary scores. The AG acknowledged in the report that this does not allow full uncertainty to be incorporated into the estimates. 3. This is a limitation of the Khan et al study. In the Khan et al study, a cross-sectional survey of young people aged 11-15 years in four secondary schools in England was conducted by completing both PedsQL and EQ-5D-Y. The data from this survey was used to derive the mapping algorithm from PedsQL to EQ-5D-Y utility values in Khan et al. Therefore the values from the mapping algorithm equate directly to EQ-5D-Y utility scores. However, the company have correctly noted that Khan et al have used the 3L value set as a proxy for EQ-5D-Y in the absence of an alternative tariff set. The AG have presented base-case results for the cost-effectiveness of the biologic interventions for treating plaque psoriasis in children and young people using the only available source of utility estimates in this population. The

		the results of other technology assessments in psoriasis already published by NICE. **Proposed amendment:** The base case economic assessment should use direct adult estimates of utility, as currently modelled in Scenario analysis 4a, rather than the indirect adolescent estimates currently used.	AG have acknowledged the limitations of these utility estimates and have identified them as a key source of uncertainty for the cost-effectiveness of the interventions. Due to the limitations and uncertainties of the utility estimates in children and young people, the AG have presented a scenario analysis (Scenario 4a, p214) using utility estimates from adults based on those presented in previous NICE TAs. This is a key strength of the evaluation since it goes beyond the scope of the appraisal.
	Issue 2: Underestimation of utility values in economic model.	The NICE reference case states that the perspective to adopt when incorporating health outcomes in a cost-effectiveness analysis ought to ensure that "all direct health effects, whether for patients or, when relevant, carers" are taken into account. Given the age of the patient population considered for the purpose of this MTA, the impact of both the disease and the treatment given would be expected to impact on the quality of life of parents and other carers. Unfortunately, AbbVie recognises that there are no quantitative estimates of the impact on the health related quality of life of carers for children and young people with psoriasis receiving any of the interventions considered by this MTA. However, the committee should recognise that the utility values currently used in the base case analysis, and also those used in scenario 4a which would represent our preferred base case (see Issue 1), present a very conservative estimate of the global impact on health related quality of life of the technologies under consideration.	No response necessary. This will be an important discussion point for the NICE Appraisal Committee.
	Issue 3: Hospital admissions during BSC phase of economic model	The base case economic model assumes that once therapy with biologic treatment has failed, Best Standard Care (BSC) will incur an additional two consultant outpatient appointments but no hospital admissions. Previous technology appraisals in psoriasis (TA153, TA 350, TA 368) have considered that hospital admission is an integral part of BSC and estimated a mean annual length of stay (LOS) of 26.6 days for all patients in this health state. It should be noted that this has been criticised as an overestimate and a published UK analysis of resource utilisation for patients with moderate-severe psoriasis prior to and after initiation of biologic therapy (Fonia et al) identified a mean LOS of 6.49	The resource use associated with hospitalisations for individuals on BSC was identified as an area of uncertainty and a key driver of the cost-effectiveness results. The base-case analysis assumes no hospitalisations based on clinical opinion that hospitalisations in children and young people for plaque psoriasis are very rare. The AG have presented scenario analysis (Scenario 5, Section 7.5.2.5, p219) using the higher estimates of 6.49

		days in the year prior to treatment initiation, declining to 1.55 days in the year following treatment initiation[5]. Although this patient group is not analogous to those who have failed biological therapy, and is limited to adult patients, it is probably the best estimate currently available to inform this model. The average length of hospitalisation is a key driver of the ICER in the Assessment Group model (see table 92, Scenario analysis 5; p230 Assessment Group Report). Indeed, using the 26.6 day estimate, BSC is dominated by biologic therapy for those patients who have failed methotrexate. Whilst we share the opinion that 26.6 days is probably an overestimate of the mean resource utilisation, it is equally difficult to justify the assumption of no admissions at all, as used by the Assessment Group in the current model. In the absence of any clear estimates from routinely gathered NHS activity data, we believe that the 6.49 day estimate from Fonia et al represents our current best understanding of the pattern of care in the UK and should therefore be used in the base case analysis. The estimates of zero admissions and 26.6 days mean duration of hospitalisation could then reasonably be used as scenario analyses. **Proposed amendment:** The base case economic assessment should use a mean annual estimate of 6.49 days hospitalisation for patients in the BSC state, as currently modelled in Scenario analysis 5, rather than the current estimate of zero hospitalisations.	days per annum based on Fonia et al and 26.6 days per annum based on CG 153. In previous NICE TAs in adults, both sources were considered to represent overestimates of the actual number of hospital days associated with BSC. This is in part due to the populations considered in CG 153 and Fonia et al, where CG 153 considers a high-need population with severe psoriasis, while Fonia describes care in a tertiary care centre known for treating the most severely affected individuals. In recent adult appraisals, the clinical experts also indicated that the number of individuals hospitalized for severe psoriasis has fallen over time and continues to fall. The AG have also presented an analysis of the combined impact of increasing the number of hospitalisations per annum and using adult utility values (see Table 97, p232)
	Issue 4: Definition of BSC in the economic assessment of adalimumab as an alternative to systemic therapy	Patients who fail treatment with adalimumab or methotrexate in this part of the economic model revert to BSC, which is defined in the same way as for the analyses of patients who have failed prior systemic therapy. We believe that the BSC category for this part of the analysis needs to be separately defined. Within BSC, 61% of patients are treated with methotrexate, 29% with cyclosporine and the remainder with topical therapies. • For patients who fail methotrexate, continuation of methotrexate is clearly inappropriate. Our advice from a UK clinician is that if MTX at an appropriate dose for an adequate duration had failed, a patient would be switched to other systemic therapy (ciclosporin or acitretin) or a biologic therapy • For patients who fail adalimumab, our advice from a UK clinician is that they will either be switched to another biologic,	The AG acknowledges these concerns. This is a limitation of the analysis, which has been highlighted in the report. There is no data available on the sequential use of therapies. In clinical practice, we would expect patients who have failed adalimumab to be switched to another biologic, or to conventional systemic therapy. Unfortunately, there is no data to explore the sequential use of treatments in the population of children and young people and very limited evidence in adults. There is no clear definition of BSC in the literature. It is not clear how BSC would change depending on prior therapy received. Removing the costs of methotrexate from BSC for patients who have previously failed methotrexate is likely to

		or possibly back to conventional systemic therapy - methotrexate/ cyclosporine - as they will not have previously been treated with systemic therapy. This arm of the model as it stands does not reflect reasonable clinical practice, nor does it represent the likely cost effectiveness of the treatment strategies in this patient group. Altering the treatment pathways to reflect clinical practice will influence both costs and utilities and consequently affect the estimated ICERs. Whilst it is not possible to estimate the direction or magnitude of this influence without detailed remodelling, there is sufficient uncertainty around the current estimates that it casts doubt on their value. **Proposed amendment:** The base case economic assessment for adalimumab in patients who have not failed systemic therapy should be re-modelled to reflect a more relevant and meaningful BSC state.	make adalimumab look less cost-effectiveness, unless methotrexate is replaced with a more expensive alternative biologic. In the absence of clinical efficacy data on the sequential use of treatments and the absence of a clear definition of BSC based on prior therapies received, the AG is unable to make the proposed amendments.
Minor Comments and Factual Inaccuracies			
180	Table 62.	The top row of the table (base-case utilities) is incorrect and does not reflect the values listed in the previous table and used in the economic model. Substitute the correct values, as shown in table 61	The values in Table 62 are correct and do correspond with Table 61.
222	Table 89.	The heading used for the table is incorrect as it reads as “Table 89 Scenario 4b results for interventions after failed systemic therapy: Utility in BSC equal to baseline” The heading should read: “Table 89 Scenario 4b: cost-effectiveness results for the interventions after failed systemic therapy assuming hospitalisations for BSC”	We acknowledge the inaccuracy in the table caption. This will be updated in the final report to HTA.
116	Section 5.4.1 (NMA using minimum evidence from the adult population); Page 116, Paragraph 3; Line 6	Spelling mistake to adalimumab trial; “CHAMPTION” This should be spelt and written as ‘CHAMPION’	We acknowledge the spelling mistake and this will be updated in the final report to HTA.
29	Section 1.4.1.1	The trial did not provide evidence for children aged 4 to 6 years of age. **Suggested change:** This wording should be deleted from the report because it is misleading. **Justification:** Due to privacy laws and rules surrounding collection of	The table noted in the comment (table 13, p.252 of M04-717 CSR) shows that seven children in total (6% of all participants) were aged 4-6 years at recruitment, six of whom were in the half-dose treatment arm.

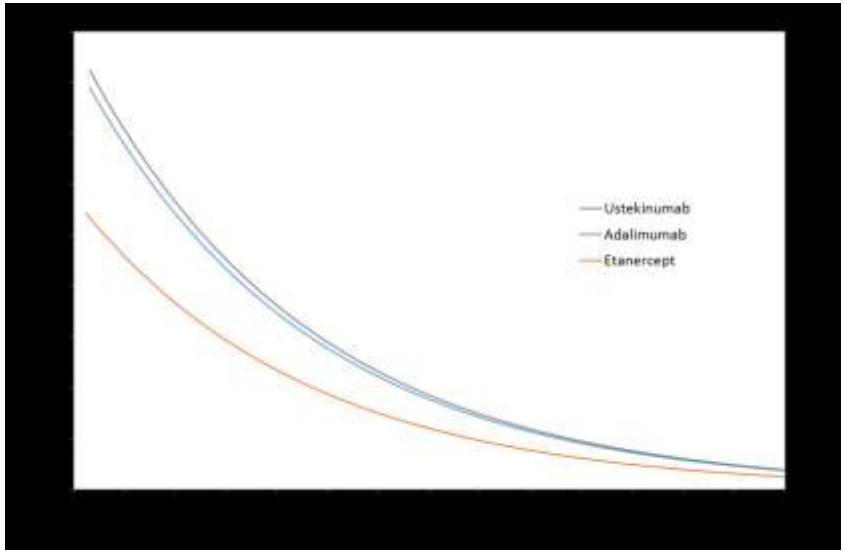
		personal information for clinical studies, birthdates for all subjects were normalised to January 1 of their birth year. In the adalimumab 0.4 mg/kg arm, one subject was 4 years old when enrolled, but was recorded as 5 years old when normalised by birth year. Additionally, in the 0.8 mg/kg adalimumab arm, one subject was 6 years old when enrolled, but was recorded as 7 years old when normalised by birth year [See Table 13, Page 185 of the of CSR for the M04-717 trial for further details] Also, on 26 February 2015, Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Adalimimab. The CHMP adopted a new indication as follows: *Treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.* Therefore, evidence for children between the ages of 4 to 6 was put in to consideration to inform the full adalimimab marketing authorisation for 4 years and older with severe chronic plaque psoriasis; thus the decision should be upheld by the Assessment Group. AbbVie request that the AG delete this wording throughout the entire report to ensure consistency with regulatory approval for adalimimab for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age and above.	Just one child received adalimumab at the approved dose of 0.8mg/kg, and zero children received methotrexate. A single participant cannot provide meaningful evidence of the efficacy or safety of standard dose adalimumab. The absence of any participants in the methotrexate arm means there cannot be comparative evidence for this age group for either dose of adalimumab. To avoid ambiguity, the phrase will be reworded as: “The trial did not provide any comparative evidence for children aged 4 to 6 years of age.” The report repeatedly notes that adalimumab has regulatory approval for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age and above. However, the AG is required to assess the evidence of effectiveness and safety, something which was insufficient for the 4-6 year age group
33	Section 1.8.	Evidence for the clinical effectiveness and safety of adalimumab [..] in younger children in particular is currently lacking. **Suggested change:** This sentence should be deleted from the report because it is misleading, as far as adalimumab is concerned.	Please see previous response. To avoid ambiguity, the phrase will be reworded as: “Evidence for the comparative clinical effectiveness and safety of adalimumab [..] in younger children in particular is currently lacking” in the final report to HTA.
236	Section 9.1	One multicentre RCT (M04-717) found that adalimumab at the licenced dose of 0.8 mg/kg (up to 40 mg) lead to significantly greater responses than methotrexate for the outcomes of PASI 50 and PASI 75, but not PASI 90 at 16 weeks. **Suggested change:** One multicentre RCT (M04-717) found that adalimumab at the licenced dose of 0.8 mg/kg (up to 40 mg) lead to	‘Numerical differences’ for all available treatment comparisons are presented in tables throughout the report, and the discussion of these results is not limited to those reaching formal statistical significance. However, it would not be appropriate to specifically comment on non-statistically significant differences as being nevertheless “numerically higher” where these differences may be attributable to

		significantly greater responses than methotrexate for the outcomes of PASI 50 and PASI 75, but not PASI 90 at 16 weeks; however, a numerically higher proportion of subjects randomised to adalimumab 0.8 mg/kg achieved a PASI 90 or PASI 100 response at Week 16 than subjects randomised to methotrexate [See Table 28, Page 218 of the M04-717 CSR] **Justification:** As indicated above, evidence shows a numerical difference in response rates between the two trial arms. Therefore, only reporting the 'statistically significant' results doesn't capture the full concept of the response rates between adalimumab 0.8 mg/kg and methotrexate trial arms, during the planned treatment period (16 week time point).	chance. In relation to the specific suggested change, the numerical difference between methotrexate and standard dose adalimumab is 8/37 participants vs 11/38 participants.
47	Section 4.2.1	In addition, **eight** relevant regulatory documents were retrieved. **Suggested change:** In addition, **nine** relevant regulatory documents were retrieved. **Justification:** Text in Section 4.2.1 and numbers reported in Figure 1 'PRISMA flow diagram' (Page 48) are inconsistently reported.	We acknowledge the inaccuracy. This will be corrected in the final report to HTA.
47	Section 4.2.1	Thus, a total of 111 records were read in full, resulting in 62 records being excluded and a total of **48 records** being included in the review. **Suggested change:** Thus, a total of 111 records were read in full, resulting in 62 records being excluded and a total of **49 records** being included in the review. **Justification:** Text in Section 4.2.1 and numbers reported in Figure 1 'PRISMA flow diagram' (Page 48) are inconsistently reported.	We acknowledge the inaccuracy. This will be corrected in the final report to HTA.
51-58	Table 2	Use of the word "participants" while in the CSR for M04-717 patients are referred to as "subjects". **Suggested change:** for consistency reasons, AbbVie requests that rather than "participants" the word "subjects" is used when reporting adalimuamb data from M04-717, to be in line with the wording used in the CSR.	This is a minor suggestion that does not affect the conclusions of the report. No change made.
60	Section 4.3.1	This means that, despite adalimumab having marketing authorisation in children aged 4 years and older, this particular trial does not provide any efficacy data on the licenced standard dose of adalimumab in children aged 4-6 years.	Just one child received the standard dose of adalimumab and none received the comparator drug (methotrexate). On this basis, there is no way to establish the relative efficacy of standard dose adalimumab.

		Suggested change: This wording should be deleted because it is incorrect and misleading.	To avoid ambiguity, the phrase will be reworded as: "This means that, despite adalimumab having marketing authorisation in children aged 4 years and older, this particular trial does not provide any comparative efficacy data on the licenced standard dose of adalimumab in children aged 4-6 years" in the final report to HTA.
63	Section 4.3.2.2	"The proportion of participants achieving a sPGA" **Suggested change:** delete "sPGA" and replace it with "PGA", as per CSR records.	This will be corrected in the final report to HTA.
64	Section 4.3.2.3	"…….see Table 4 Error! Reference source not found. Correct referencing required	This will be corrected in the final report to HTA.
67	Section 4.3.4.1	"…..Error! Reference source not found…" Correct referencing required	This will be corrected in the final report to HTA.
	Section 4.3.5	The trial does not provide evidence for children aged 4 to 6 years of age. **Suggested change:** This wording should be deleted because it is incorrect and misleading.	Please see previous response on this comment.
	Section 4.3.5	Adalimumab at the licenced dose of 0.8 mg/kg (up to 40 mg) leads to significantly greater responses than methotrexate for the outcomes of PASI 50, PASI 75, but not PASI 90. **Suggested change:** Adalimumab at the licenced dose of 0.8mg/kg (up to 40mg) leads to significantly greater responses than methotrexate for the outcomes of PASI 50, PASI 75, but not PASI 90; however, a numerically higher proportion of subjects randomised to adalimumab 0.8 mg/kg achieved a PASI 90 or PASI 100 response at Week 16 than subjects randomised to methotrexate [See Table 28, Page 218 of the M04-717 CSR]	Please see previous response on this comment.
	Section 9.1	The trial does not provide evidence for children aged 4 to 6 years of age. **Suggested change:** This wording should be deleted because it is incorrect and misleading.	Please see previous response on this comment.
	Section 5.4.4	PASI response results were generally consistent across the different models, adjusted and unadjusted. **Ustekinumab was identified as the most efficacious treatment followed by adalimumab and etanercept.**	We acknowledge the inaccuracy. This will be updated in the final report to HTA.

		Suggested change: PASI response results were generally consistent across the different models, adjusted and unadjusted. The relative efficacy of ustekinumab and adalimumab is similar based on relative effectiveness estimates for PASI 75 (adalimumab vs. ustekinumab 45, RR: 0.96, 95% CrI: 0.85 to 1.05).	
	Section 6.3.5	AbbVie submission for ustekinumab. Delete “ustekinumab” and replace with “adalimumab”	We acknowledge the inaccuracy. This will be updated in the final report to HTA.
	Section 7.4.9	Adalimumab SC 0.8mg/kg up to a maximum of 40 mg at weeks 0 and 1, then every 2 weeks thereafter Pre filled syringe 40 mg, £352.14. Please replace with the following statement: Adalimumab 40 mg solution for injection in pre-filled syringe Adalimumab 40 mg solution for injection in pre-filled pen Adalimumab 40 mg/0.8 ml solution for injection for paediatric use £352.14	This is not a factual inaccuracy.

Response to Janssen Cilag Ltd. Response and Factual Inaccuracies

Janssen Cilag Ltd. Comments		York's Response
Issue	Comment	
Main Comments on the Assessment Report		
Issue 1.1: The AG have not modelled the continuation of biologic treatment into adults with plaque psoriasis. The current analysis does not take into account the benefits of biologics seen in adults, which has been explored in other NICE appraisals in children and young people and accordingly underestimates the cost effectiveness of biologics.	We believe that the time horizon chosen by the AG is inappropriate and does not reflect the lifetime nature of psoriasis in children and young people that have early onset psoriasis and is inconsistent with previous NICE appraisals in children and young people. The AG have made the decision to limit the time horizon on the basis that there is already existing guidance in an adult population and that there is limited evidence regarding the sequencing of biologics and there is no MTA that establishes the optimal sequence of treatments in adults [TAR, pg.207]. We believe the AG's current approach does not explore the benefits of treating children and young people with psoriasis and therefore underestimates cost effectiveness of biologics. Evidence suggests that the clearance of psoriasis may have long term benefits, which may extend into adulthood. Adolescents with psoriasis may be at increased risk of mental illness, especially depression and anxiety. This is particularly important since depressive episodes at a young age increase the risk of subsequent recurrences and long-term psychiatric disorders [Gonzalez et al]. In particular, psoriasis negatively impacts physical activities. This is especially detrimental to an adolescent with psoriasis since they are already at a twofold risk for comorbidities including obesity, diabetes mellitus, hypertension and psychiatric disorders. [Augustin et al] Most of these effects tend to originate from the cutaneous nature of the disease which leads to decreased exercise both to avoid lesions being visible to peers and due to	The AG acknowledges the concerns expressed by the company regarding the most appropriate time horizon of the model. The alternative time horizon of 14 years, which was used in scenario 2 (p206) extends the use of the interventions into adulthood. The time horizon of 14 years was chosen in this scenario because it is sufficient to capture all the differences in costs and effects between the interventions under comparison, since all individuals in the model have moved to BSC within 14 years of starting treatment (see Figure 1 below). **Figure 1: Proportion of the cohort on biological therapy over time for children and young people aged 12-17 years after failed systemic therapy (starting age 12 years)** 

	increased pruritus with diaphoresis [Gonzalez et al]. Overtime these comorbidities could have an impact in terms of mortality and long term health related quality of life (HRQoL). We understand that there is limited evidence to explore these impacts, but we suggest that further sensitivity analyses are undertaken to look a possible mortality and quality of life impacts differences into adulthood. We also note that this assumption is also inconsistent with other previous NICE technology appraisal that have looked at health technologies in children and young people. Most notably the recent appraisal of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (JIA) (TA373), which took a lifetime perspective. This is also inconsistent compared to a number of other disease areas where there are previous recommendations in both children and adults and where the appraisal in children has taken a lifetime horizon, such as NICE TA188 (growth failure) and TA300 (hepatitis C). This raises inconsistencies with previous NICE appraisals in terms of decision making for health technologies in children and young people. We note that the AG have undertaken scenario analyses where they have extended the time horizon into adulthood [TAR, pg.207-208], but have not adjusted the model for an adult population and therefore we do not believe this reflects an accurate estimate of the cost effectiveness of extending biologics into adulthood and the considerable benefit gains seen in an adult population [TA103, TA134, TA146, TA180, TA350]. We suggest that the economic model is extended to appropriately explore the impact and benefits of biologics in childhood that may extend into adulthood. The model should also appropriately take into account the benefit gains seen in adults from biologic therapy, as seen in previous adult appraisals of biologics in moderate to severe plaque psoriasis.	Scenario 2 (p206) does not include the quality of life benefits associated with an adult population from 18 years onwards. If we were to use the utility values from previous TAs in adults at 18 years onwards, this would result in a sudden 'jump' (increase) in health-related quality of life benefits at 18 years old. Therefore, the AG considered a separate scenario (scenario 4a, p214) that incorporated the utility values from previous TAs in adults for all ages, i.e. for ages less than 18 years. For completeness, Table 1 below presents the cost-effectiveness results using utility estimates from adults (sourced from TA146, which had the highest utility gains) for all ages and a time horizon of 14 years (sufficient to capture all differences between the interventions in terms of costs and QALYs). The resulting ICERs are higher than those presented in scenario 4a (p217) because the relative difference in QALYs between the interventions decrease after 18 years old (see Figure 1 above). Table 1: Cost-effectiveness results using utility estimates from adults and a time horizon of 14 years.

	Mean costs (£)	Mean QALYs	Increm. costs vs. next best option (£)	Increm. QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	41,413	8.800	-	-	-	-	BSC
ETN	49,085	9.031	7,672	0.230	33,310	33,310	
ADL	62,626	9.188	13,541	0.157	86,046	54,717	
Children and young people aged 12-17 years							
BSC	44,010	8.795	-	-	-	-	BSC
ETN	58,268	9.026	14,257	0.231	ED ADL	61,697	
ADL	64,124	9.183	20,113	0.388	51,845	51,845	
UST	66,447	9.207	2,323	0.024	96,326	54,448	

Issue 1.2: There are significant equity considerations around biologics not being cost effective in children and young people, but being cost effective in adults. As currently, the QALY benefits in children and adult population in the model are not equally valued depending of the age of the patients.	The AG decision not to model patients into adulthood has, in effect, separated out patients with moderate to severe psoriasis into distinct populations: an adult (18 years and over), and children or young people population. This has created significant equity concerns regarding the conclusions in the analysis. We note that the NICE reference case states that an additional QALY should receive the same weight regardless of any other characteristics of the people receiving the health benefit, including age [NICE methods guide,2013]. By splitting the populations and applying different assumptions and most notably different utilities, we believe that children and young people with moderate and severe psoriasis do not have an QALY estimation equal to adults, as stipulated in the reference case [NICE methods guide,2013]. This means that patients that are 17 years and younger will not have access to biologics, but patients 18 years or older will have access to biologics. This is an arbitrary decision based on the age of the patient and does not reflect the QALY benefit for these patients. We urge AG to consider modelling the benefits of biologics treatment into an adult population and reconcile differences between children, adolescents and adults in terms of the quality of life benefit from biologics in the current economic model to remove the current equity concern within the appraisal.	Please see response to comment above. This will be an important discussion point for the NICE Appraisal Committee.
Issue 2.1: Utility data used in the base case of the model does not reflect significant quality of life benefits	There are significant uncertainties and limitations, which the AG acknowledge, with the utilities used in the basecase of the model. We believe that the current utilities are significantly underestimating the responses, especially for PASI 70 and 90, which represent very good responses for a disease that has a significant impact on quality of life. Patients with moderate to severe psoriasis experience	The AG acknowledges the concerns expressed regarding the quality of life benefits used in the model. This was identified as a key area of uncertainty. The AG undertook a systematic literature review to identify appropriate quality of life utility values for the population of children and young people. Unfortunately, no utility values were identified in this population. In addition, none of the three trials in children and young people collected EQ-5D or EQ-5D-Y utility values. Health-related quality of life was assessed in the

from biologic treatment that children and young adults with plaque psoriasis experience and accordingly underestimates the benefit that biologics offer in treatment.	considerable physical discomfort linked with their skin lesions. Symptoms and manifestations include severe itching (pruritis), burning sensations, skin discomfort, skin sensitivity, irritation and pain. Both the physical symptoms, in particular severe pruritis, and the psychological and social impact of symptoms mean that psoriasis can have a substantial impact on HRQol. The underestimation of utilities is especially stark when compared to equivalent utility responses for PASI 70 and 90 responses in adults from NICE TA180. We note the limitations and uncertainties that the AG have identified with the current approach of health utility estimation and agree with the AG that they reduce the robustness of the utility values used in the model [TAR, PG.179]. However, we would like to point out further limitations with the current mapping approach that should be considered and accordingly should justify the use of adult utilities in the model. In summary the AG have noted the following limitations with utility estimation [TAR, pg.179], including: • Small sample size and limited data to validate the relationship; • Reliance on a mapping relationship compared to direct EQ-5D measurement; • Khan et al mapping algorithm has not been validated in children younger than 11 years old or in a population with psoriasis; • CADMUS trial from where the PedsQL data mapped to EQ-5D was sourced excluded children younger than 12 years; therefore, it remains uncertain whether the mapped utilities are reflective of children younger than 12 years old; • In populations younger than 12 years, there may be issues with lack of agreement or consistency between self-reported and proxy (parent)-reported measurements	trials using CDLQI and PedsQL at selected time points. Therefore, the only possibility to include EQ-5D utility values in the model was via a mapping from either CDLQI or PedsQL. The literature review did not identify any studies that estimated the relationship between CDLQI and EQ-5D/Y, while one study by Khan et al (2014) estimated the relationship between PedsQL and EQ-5D-Y. Therefore, the study by Khan et al represented the only possible route to include generic preference-based utility values in the model for children and young people; the AG recognises the limitations associated with the estimation (Section 7.4.6.3). The AG have presented base-case results for the cost-effectiveness of the biologic interventions for treating plaque psoriasis in children and young people using the only available source of utility estimates in this population. The AG have acknowledged the limitations of these utility estimates and have identified them as a key source of uncertainty for the cost-effectiveness of the interventions. Due to the limitations and uncertainties of the utility estimates in children and young people, the AG have presented a scenario analysis (Scenario 4a, p214) using utility estimates from adults based on those presented in previous NICE TAs. This is a key strength of the evaluation since it goes beyond the scope of the appraisal. The most appropriate utility estimates for the population of children and young people will be an important discussion point for the NICE Appraisal Committee.

	We acknowledge that the AG have used the most generalisable evidence available to them in the population of interest. However, we contest its validity, particularly in adolescents whose utility gains are likely to be closer to adults than children. Indeed, our clinical expert has suggested that, in an adolescent population at least, he would expect a quality of life benefits from the clearance of psoriasis to be in line with or greater than that of adults. Our clinical expert stated, that this is because adults have better coping mechanisms and strategies to cope with their skin care problems. Adolescents on the other hand are more likely to be prone to significant psychosocial issues. Therefore, the benefit that they gain from having skin clear of psoriasis would be greater than an adult. Gonzalez et al have noted that due to the visibility of skin lesions, psoriasis patients risk feeling stigmatised and bullied, especially since bullying during adolescence is commonly related to physical appearance. Unfortunately, there has been little research on its relationship to skin disease, and there are no validated bullying or victimisation scales in this population. One study interviewed 15 paediatric psoriasis patients (mean age 12.8 ± 4.25 years), 65% of whom felt stigmatised due to bullying or name calling [De Jager et al]. The stigmatisation and bullying can lead to a decreased perception of social connectivity that impacts family and social relationships [Gonzalez et al]. Furthermore, it has been noted that adolescents are often grouped in with paediatric populations or adult populations and thus are given measurement tools that may not address developmentally appropriate physical and psychosocial challenges that this group encounters. Even the modification of adult scales often fails to recognise the unique aspects of adolescent development and function [Gonzalez et al]. The generality of the PedsQL may also be a disadvantage compared to the disease specific instruments such as	

	CDLQI (or DLQI) and this may explain the difference in sensitivity between the utilities in children and adults seen in the TAR. Gonzalez et al argue that the PedsQL may not be specific enough to adequately address the concerns of psoriasis patients. For example, the unique characteristics of psoriasis, such as the physical activities that patients do not participate in due to psychosocial factors or the pruritus associated with psoriasis, are not addressed by the PedsQL [Gonzalez et al]. We believe that the current estimation of utilities significantly underestimates the benefits of biologics seen in these patients and that the current mapping relationship between PedsQL and EQ-5D is not appropriate and lacks face validity. Response rates from biologics in children and young people with moderate to severe psoriasis are equivalent to or better than adults and accordingly it would be expected that utility improvements from response to biologics would also be similar or greater than those seen in adults. We strongly believe that adult mapping relationship between DLQI and EQ-5D may be more appropriate than the current relationship used by the AG for children and young people, especially in an adolescent population.	
Issue 2.2: The AG have not taken into account any potential benefits to treatment that fall outside the QALY calculation, for example, carer disutility. Again we believe this is underestimating the benefits of	The AG in TA373 abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (JIA) noted additional consequences of a long term condition like JIA (and psoriasis) can have on children and young people's education. Children and young people may miss school days to attend health care appointments and may be absent for longer periods from school whilst experiencing symptoms. This can have a negative impact on their education and, in future, their ability to gain employment. It may also affect their social and psychological health through the reduced ability to participate in social and leisure activities and sport, and the general burden of a serious health condition during the sensitive period of adolescence [TAR, pg. 147, TA373].	The AG acknowledges that there may be potential benefits to treatment that fall outside the QALY calculation. Unfortunately, there are no quantitative estimates of the impact on the health related quality of life of carers for children and young people with psoriasis receiving any of the interventions considered by this MTA. In the absence of quantitative estimates of these potential benefits, the AG is unable to incorporate these into the economic analysis. Any attempt to add arbitrary values to the utility estimates that are already highly uncertain will introduce further uncertainty. These potential additional benefits to treatment represent an important discussion point for the NICE Appraisal Committee.

biologics and should be incorporated by the AG and considered by the NICE Appraisal Committee.	It was noted by the AG, in TA373, that biologics led to a statistical significant higher increase in school days than placebo patients. The AG suggested that this 'indicates the potential for [biologics] to improve education as well as health outcomes, though further evidence is required particularly in a UK context.' [TAR, pg.147, TA373] We see no reason to believe that similar benefits would not be seen in children with psoriasis receiving biologic therapy and this benefit is unlikely to be captured by the QALY and we urge the NICE appraisal committee to take this into consideration. The AG, in TA373, suggested further there would be a significant impact on parents and carers of children and young people with JIA. We believe that a similar impact may be seen in parents and carers of children and young people with moderate to severe psoriasis given the severity of the disease and the likelihood that parents and carers will have a similar burden of care to JIA. The AG wrote in TA373, that "[parents and carers] may have to pay for child care, take time away from work or even cease employment to provide their own care. This will negatively affect their income and may increase dependency on welfare benefits (where available). Again this is likely to increase socio-economic inequalities. The inability of parents and caregivers to work may have a negative impact on society and the economy, through reduced productivity, less income tax collection, and in some profession a shortage of skilled workforce capacity" [TAR, pg.147, TA373]. One RCT was identified to support this assertion which showed improvements in the number of normal activities per month missed by parents, including work and no work activities, for a biologics compared to placebo. We note that AG, in TA373, assessed this potential impact through adding in carer disutility into their economic analyses and we believe that it is also appropriate to explore in this current appraisal. We note that the Appraisal Committee in TA373 agreed that	

	'JIA not only affects the quality of life of the child or young person with the disease but can also affect the quality of life of their carers and family.' The Appraisal Committee concluded that caregiver utility should be taken into account when appraising the cost effectiveness of the biological treatment for JIA [NICE TA373]. We believe that a similar approach should be used in this children and young people with moderate to severe psoriasis. We suggest that the AG should explore the impact on carers disutility in the economic analysis and the impact of carers/families of children and young people with moderate to severe plaque psoriasis, as was done in TA373. These benefits of biologics treatment are not currently being captured in the AG economic analysis or the current QALY estimation and these should be considered by the NICE appraisal committee.	
Issue 3.1: The assumption that children will have no inpatient hospitalisation on BSC is too conservative and does not reflect the serious psychological and social isolation problems related to psoriasis which can lead to further illness, co-morbidities and hospitalisations, especially in an adolescent population.	We believe that the AG's assumption, based on expert opinion, that children and young people with moderate to severe psoriasis receiving BSC require no hospitalisations is too conservative, especially when compared to previous assumptions in adults. Previous NICE adult appraisals for ustekinumab (TA180), adalimumab (TA146) and etanercept (TA103) have assumed that people on BSC will spend 21 days in hospital. Therefore, to assume no hospitalisations in children and adolescents in contrast to 21 days in adults is unrealistic. It does not take into account the clinical practice of transitioning children to adult clinical pathways between the ages of 13 to 16 and the increasingly complex psychological and social problems that will likely lead to hospitalisations, especially for adolescents. We suggest that the AG revise the economic modelling to reflect the increasing number of hospitalisations, as patients move from childhood, into adolescence and, then, into adulthood. We disagree with the AG's assumption, based on expert opinion, that children and young people will not have developed comorbidities that complicate severe plaque	The resource use associated with hospitalisations for individuals on BSC was identified as an area of uncertainty and a key driver of the cost-effectiveness results. The base-case analysis assumes no hospitalisations based on clinical opinion that hospitalisations in children and young people for plaque psoriasis are very rare. The AG have presented scenario analysis (Scenario 5, Section 7.5.2.5, p219) using the higher estimates of 6.49 days per annum based on Fonia et al and 26.6 days per annum based on CG 153. In previous NICE TAs in adults, both sources were considered to represent overestimates of the actual number of hospital days associated with BSC. This is in part due to the populations considered in CG 153 and Fonia et al, where CG 153 considers a high-need population with severe psoriasis, while Fonia describes care in a tertiary care centre known for treating the most severely affected individuals. In recent adult appraisals, the clinical experts also indicated that the number of individuals hospitalized for severe psoriasis has fallen over time and continues to fall. The AG have also presented an analysis of the combined impact of increasing the number of hospitalisations per annum and using adult utility values (see Table 97, p232) Inpatient hospitalisation stay and resource use associated with BSC for the population of children and young people will be an important discussion point for the NICE Appraisal

	psoriasis which will lead to hospitalisations [AG report, pg. 190]. A number of studies have identified significant comorbidities in children with plaque psoriasis compared to population norms including and increased rate of metabolic syndrome, hyperlipidaemia, obesity, hypertension, diabetes, depression, anxiety and bi-polar disorder [Augustin 2015, Augustin 2010, Puig 2010]. We accept that these comorbidities are unlikely to be as developed as in adults, however, to assume that these comorbidities, especially mental health comorbidities, will result in no hospitalisations is unlikely to be a realistic scenario. We acknowledge that there is limited published evidence to support the number of hospitalisation in children and young people and therefore understand the reliance on clinical expert opinion by the AG. Our clinical expert for the appraisal felt that assuming no inpatient hospitalisations, especially for adolescents with complex psychosocial problems was not reflective of his clinical experience. His belief was that an appropriate figure, at least, for an adolescent population likely to be closer to 21 days based on the Fonia et al study. However, our clinical expert did acknowledge that hospitalisation length of stay will vary across the population of interest and may be much lower for younger children. We also note a British Association of Dermatologist Audit from 2008, which does suggest a need for inpatient hospital care in children and young people, the 'need for dermatology admissions appears to have reduced, but some adults and children with chronic diseases such as psoriasis… may still require inpatient care under the supervision of the dermatologist.' This audit performed before the widespread use of biologics is likely to reflect a population receiving BSC in the absence of biologics. Our clinical expert also believed that there are further costs associated with BSC that have not been captured currently within the AG economic analysis, specifically around the significant amount of resource used to treat the complex psychosocial issues in children and young people by child	Committee.

	and adolescent Mental Health services (CAMHS). Again there is no published evidence around the use of these services by children and young people on BSC with moderate to severe psoriasis, but we suggest that the AG explore this through sensitivity analyses for these potentially resource intensive services.	
Issue 3.2: The AG don't appear to have taken account of the transition between paediatric and adult clinical services within the model and NHS reference costs used in the model appear to have been used inconsistently.	A mixture of adult or paediatric reference costs have been used within the model, which is likely to further underestimate the cost of BSC. Furthermore, the AG have not taken into account the transition that takes place from paediatric to adult clinical services starting from the age of 13 years onwards in the model. Therefore, the cost of BSC across the whole population being appraised should be revised by the AG to take account of adolescents moving to the adult clinical pathway. For inpatient hospitalisations in the model, the AG have used an 'adult skin disorders non-elective excess bed day cost' from the latest NHS reference costs which has been weighted across all codes and gives a weighted average cost of £295.80. We would argue that for a majority of the population in the appraisal, it would be more appropriate to use a 'paediatric skin disorders non-elective excess bed day cost', which gives a weighted average cost of £496.83. This is likely to represent the specialist nursing costs that children require with plaque psoriasis. The AG appear to have used a paediatric cost for physician visits in an outpatient setting, but for the day centre costs they have used an adult services costs. We are unclear why the AG have switched between adult and paediatric costs in the model for health care visits, as this is not explained in the TAR. The difference between an adult and paediatric costs for selected health care visits are presented in Table 1 below. Overall, we believe this inconsistency in the references costs chosen by the AG underestimates the cost of BSC. This will be accentuated further if any inpatient hospitalisation were to be included in the basecase	The unit cost selected for inpatient bed day (£295.80) corresponds to the average unit cost of a non-elective excess bed day in the NHS across all HRG codes (see Index sheet on the NHS reference costs 2014-15). This unit cost is not specific to adults or skin conditions, as it is estimated from the totality of HRGs. The AG chose not to use a paediatric specific skin disorder unit cost for inpatient stay since it is unclear whether this unit cost also includes costs related to treatment. Treatment costs are included separately in the cost of BSC via its other components (drugs, monitoring, and phototherapy costs). The unit cost estimate for inpatient stay used in the AG scenario is very similar to that used in CG153 (£271.17), which appears to be an average unit cost of a non-elective excess bed day in the NHS. We have been unable to identify the cost suggested by Janssen Cilag Ltd. for an activity weighted average across the Paediatric skin disorders HRG codes for non-elective excess bed day (£496.83). The paediatric inpatient stay unit cost based on an activity weighted average for Paediatric Skin disorders (currency codes PJ35A-D) is £520.68 per bed day. This value is almost twice as high as the average unit cost of a non-elective excess bed day in the NHS across all HRG codes. Tables 2a and 2b below present the cost-effectiveness results using the higher unit cost of £520.68 per bed day for paediatric skin disorders. The ICERs fall compared to the base-case due to the increased costs of BSC. The increase in the costs of BSC is proportionally greater for the interventions where transition to BSC occurs earlier in the model (etanercept, followed by adalimumab, followed by ustekinumab). This has no impact on the optimal decision for adalimumab as an alternative to methotrexate as the ICER is well in excess of a £30,000 per QALY cost-effectiveness threshold. For the interventions after failed systemic therapy, adalimumab becomes the less costly treatment instead of etanercept (scenario 5, p222) and dominates the other comparators when 26.6 hospitalisations days per annum are considered.

analysis, as suggested above, given the AG's used of adult costs which are lower than the paediatric costs identified in Table 1.

Table 1: Reference costs used in the Assessment Group model for health care visits

Health care utilisation	Adults reference costs (2014-2015)	Reference
Inpatient hospitalisations	**£295.80** ***Cost used in the AG economic model.***	Activity weighted ad adult skin disorders elective excess bed days. N.B. unclear v costs reference coc used in AG model
Outpatient visits	£97.03	Activity weighted average of non-adm Face to Face Attendance, Follow consultant and non- consultant led outpa visits (service code: Dermatology; curre code: WF01A);
Day centre costs	**£472.55** **Cost used in the AG economic model.**	Activity weighted average of Skin Disorders Without Interventions (curre codes JD07F-K) for cases.

The current cost estimations for hospitalisation are not reflective of the transition of care from childhood to adolescents and into adulthood or the significant comorbidities and psychosocial issues seen, particularly in adolescents. The AG should consider updating the model with the appropriate costs dependent on the child's age and re-calculate the cost effectiveness with inpatients hospitalisation used in the base case analysis. We also suggest that a sensitivity analysis is conducted around the use of CAMHs services in children receiving BSC for the

Table 2a: Cost-effectiveness results for interventions as an alternative to systemic therapy using the higher unit cost of £520.68 per bed day for paediatric skin disorders.

	Mean costs (£)	Mean QALYs	Increm. costs vs. MTX (£)	Increm. QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
6.49 hospitalisation days per annum for BSC based on Fonia et al (2010) in adults						
Children and young people aged 4-17 years						
MTX	65,482	9.939	-	-	-	MTX
ADA	88,620	10.027	23,138	0.088	261,837	
26.6 hospitalisation days per annum for BSC based on CG 153 in adults						
Children and young people aged 4-17 years						
MTX	160,215	9.939	-	-	-	MTX
ADA	170,933	10.028	10,718	0.089	120,686	

Table 2b: Cost-effectiveness results for interventions after failed systemic therapy using the higher unit cost of £520.68 per bed day for paediatric skin disorders.

	Mean costs (£)	Mean QALYs	Increm. costs vs. next best option (£)	Increm. QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
6.49 hospitalisation days per annum for BSC based on Fonia et al (2010) in adults							
Children and young people aged 6-11 years							
BSC	70,187	8.710	481	-0.103	Dominated	-	ETA
ETA	69,706	8.814	-	-	-	Dominant	

	treatment of their moderate to severe psoriasis.	ADA	79,668	8.890	9,962	0.076	130,740	Dominant	
		Children and young people aged 12-17 years							
		BSC	40,379	4.804	-	-	-	-	BSC
		ETA	45,363	4.887	4,984	0.084	ED ADA	59,661	
		ADA	47,251	4.950	6,872	0.146	47,186	47,186	
		UST	48,988	4.960	1,737	0.010	168,819	55,212	
		26.6 hospitalisation days per annum for BSC based on CG 153 in adults							
		Children and young people aged 6-11 years							
		BSC	174,861	8.710	25,573	-0.180	Dominated	-	ADA
		ETA	149,946	8.813	658	-0.077	Dominated	Dominant	
		ADA	149,287	8.890	-	-	Dominant	Dominant	
		Children and young people aged 12-17 years							
		BSC	98,108	4.804	21,079	-0.156	Dominated	-	ADA
		ETA	83,052	4.887	6,024	-0.073	Dominated	Dominant	
		ADA	76,407	4.950	-	-	-	Dominant	
		UST	77,028	4.960	621	0.010	62,100	Dominant	

The day centre cost included in the AG model refers to skin disorders without interventions (£472.55). The cost of treatment (e.g. phototherapy sessions) is considered separately in the cost of BSC. In the currency codes specific to children there is no separation between skin disorders with and without interventions and, therefore, the possibility of double counting cannot be excluded from the company's suggested value of £622.29.

Tables 3a and 3b below present the cost-effectiveness results using the higher day centre cost of £622.29. The ICERs fall due to the increased costs of BSC, but the optimal treatment remains the same as the base-case analysis.

Table 3a: Cost-effectiveness results for interventions as an alternative to systemic therapy using the higher day centre cost of £622.29.

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						
MTX	41,673	9.939	-	-	-	MTX
ADL	67,899	10.027	18,963	0.088	216,034	

Table 3b: Cost-effectiveness results for interventions after failed systemic therapy using the higher day centre cost of £622.29.

	Mean costs (£)	Mean QALYs	Incremental costs vs. next best option (£)	Incremental QALYs vs. next best option	ICER vs. next best option (£/QALY)	ICER vs. BSC (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 6-11 years							
BSC	43,891	8.710	-	-	-	-	BSC
ETN	49,556	8.814	5,665	0.103	54,963	54,963	
ADL	62,172	8.890	12,616	0.076	165,268	101,896	
Children and young people aged 12-17 years							
BSC	25,877	4.804	-	-	-	-	BSC
ETN	35,879	4.887	10,002	0.083	ED ADL	119,924	
ADL	39,943	4.950	14,066	0.146	96,418	96,418	
UST	41,931	4.960	1,988	0.010	199,378	103,005	

Issue 3.3: Assumptions around the proportion of children and young people receiving systematic therapies and phototherapy are likely to underestimate the cost of best supportive care in the model.	We believe that the proportion of BSC patients on systemic therapies like methotrexate and cyclosporine is too high in the model. We feel that this underestimates the cost of BSC because of the low cost of these generic medicines compared to patients receiving active management of their psoriasis in an outpatient setting. The AG have assumed that 90% of children and young people on BSC are likely to be receiving systemic therapies based on the estimates used in NICE CG153 for an adult population [NICE CG153]. We think that this is likely to be an overestimation of the use of systematic therapies for a number of reasons: • Methotrexate and cyclosporine are not licensed for use in children. • Drug survival rates for systematic therapies in children and young people are much lower than that seen in biologics in adults [Ergun et al]. • Methotrexate has been associated with fertility concerns in paediatric patients and as the AG noted 'patients on cyclosporine will only receive treatment for a maximum of two years, because of increased risk of renal toxicity.' Given these issues, we believe that the use of systemic therapies should be much lower than 90% in the model. If a higher proportion of patients receive active management in an outpatient setting in the model, then this should be reflected in the cost of BSC in the model. In addition, from a review of the model we note that patients on cyclosporine have no further cost attached to them after they discontinue at 2 years. This further underestimates the cost of BSC in the model, as this is unrealistic assumption for these patients. We believe these patients should be assumed to have active management in an outpatient setting, as was assumed for the 10% of patients not receiving systemic therapy in the model. This would be more reflective of costs seen in these patients after	The proportion of patients on systemic therapies (Table 68, p189) was informed by our clinical advisor. Although methotrexate and ciclosporin are not licensed in children and young people they are currently used in this population, as recorded in BADBIR and confirmed by our clinical advisor – see Burden-Teh E, Lam ML, Taibjee SM, Taylor A, Webster S, Dolman S, et al. How are we using systemic drugs to treat psoriasis in children? An insight into current clinical UK practice. British Journal of Dermatology. 2015;173(2):614-8. The proportion of patients on phototherapy was also verified by our clinical advisor. She stated that clinicians are more reluctant to deliver phototherapy to children and young people compared to adults due to the associated risks with lifetime exposure to radiation. Tables 4a and 4b below present the cost-effectiveness results for an increase in the proportion of patients receiving 24 sessions of NBUVB per annum from 16% to 100% in BSC. This increase in the proportion of individuals receiving phototherapy as part of BSC increases the cost per cycle of palliative care from £214.58 to £362.73 and reduces the ICERs, due to the increased cost of BSC. This has no impact on the optimal decision for adalimumab as an alternative to methotrexate as the ICER is well in excess of a £30,000 per QALY threshold. For the interventions after failed systemic therapy, etanercept has an ICER of £28,236 per QALY compared to BSC in the population of children and young people aged 6-11 years. Table 4a: Cost-effectiveness results for interventions as an alternative to systemic therapy for 100% of patients receiving 24 sessions of NBUVB per annum in BSC.

	Mean costs (£)	Mean QALYs	Incremental costs vs. MTX (£)	Incremental QALYs vs. MTX	ICER vs. MTX (£/QALY)	Optimal treatment (£30,000 threshold)
Children and young people aged 4-17 years						
MTX	52,365	9.939	-	-	-	MTX
ADL	77,164	10.027	24,799	0.088	280,738	

<table>
<tr>
<td></td>
<td>discontinuing cyclosporine in a clinical setting.

We also believe that number of patients receiving phototherapy has been significantly underestimated currently (16%). Our clinical expert, from his experience, has suggested a much higher percentage of patients receiving phototherapy in clinical practice, suggesting closer to 100% of patients. The current low level of phototherapy used in the model further underestimates the cost of BSC in the model.

The current values in the AG model should be revised to better reflect the burden and cost of BSC for children and young people with moderate to severe plaque psoriasis.</td>
<td>Table 4b: Cost-effectiveness results for interventions after failed systemic therapy for 100% of patients receiving 24 sessions of NBUVB per annum in BSC.
<table>
<tr><th></th><th>Mean costs (£)</th><th>Mean QALYs</th><th>Increm. costs vs. next best option (£)</th><th>Increm. QALYs vs. next best option</th><th>ICER vs. next best option (£/QALY)</th><th>ICER vs. BSC (£/QALY)</th><th>Optimal treatment (£30,000 threshold)</th></tr>
<tr><td colspan="8">Children and young people aged 6-11 years</td></tr>
<tr><td>BSC</td><td>55,659</td><td>8.710</td><td>-</td><td>-</td><td>-</td><td>-</td><td rowspan="3">ETA</td></tr>
<tr><td>ETN</td><td>58,566</td><td>8.813</td><td>2,907</td><td>0.103</td><td>28,236</td><td>28,236</td></tr>
<tr><td>ADL</td><td>70,042</td><td>8.890</td><td>11,476</td><td>0.077</td><td>79,937</td><td>79,937</td></tr>
<tr><td colspan="8">Children and young people aged 12-17 years</td></tr>
<tr><td>BSC</td><td>32,367</td><td>4.804</td><td>-</td><td>-</td><td>-</td><td>-</td><td rowspan="4">BSC</td></tr>
<tr><td>ETN</td><td>40,119</td><td>4.887</td><td>7,753</td><td>0.083</td><td>ED ADL</td><td>92,960</td></tr>
<tr><td>ADL</td><td>43,224</td><td>4.950</td><td>10,857</td><td>0.146</td><td>74,378</td><td>74,378</td></tr>
<tr><td>UST</td><td>45,087</td><td>4.960</td><td>1,863</td><td>0.010</td><td>188,841</td><td>81,623</td></tr>
</table>
</td>
</tr>
<tr><td colspan="3">Other Comments and Factual Inaccuracies</td></tr>
<tr><td>Combination of paediatric and adult trials in the NMA</td><td>The inclusion of adult clinical trials for the purpose of undertaking a network meta-analysis with the three biologics increases the uncertainty in the AG's basecase results. We would suggest that for etanercept and ustekinumab the results from the MTC analysis would be more appropriate and should be used in the basecase analysis. We believe this is the most appropriate evidence available and free from any biases introduced by including adult trials in the NMA.</td><td>Section 7.5.2.3 details the results of the cost-effectiveness analysis for alternative scenarios regarding the source of treatment effect estimates used in the model.

Scenarios 3a and 3b present the cost-effectiveness results based on the direct trial evidence in children and young people alone. Therefore, these scenarios are free from any potential biases introduced by including evidence in adults.</td></tr>
<tr><td>Exploration of higher doses of MTX seen in clinical practice</td><td>There is variation in the doses used for MTX in clinical practice and studies [Paller et al]. Higher doses are used and these should be explored in the AG's sensitivity analyses.</td><td>Use of higher doses of methotrexate would have minimal impact on the cost-effectiveness results.</td></tr>
<tr><td>Off label use of ustekinumab</td><td>We understand that NICE scope asks to look at off label use of treatments, however, we would like to reiterate that</td><td>Off-label use of the treatments was not included in the AG's base-case analysis.</td></tr>
</table>

	ustekinumab is only licensed in Children and young people aged 12-17 years for the treatment of severe plaque psoriasis in individuals who are inadequately controlled by, or are intolerant to systemic therapies or phototherapies. There is limited evidence outside the licensed indication with regards to the clinical efficacy and safety of ustekinumab.	Off-label use of biologics outside of age constraints and position in pathway was considered as a separate scenario analysis (Section 7.5.2.1) to reflect the NICE scope for the appraisal.
Differences in withdrawal rates between treatment does not represent evidence to suggest differences between treatments	There is significant variation in the withdrawal rates between biologics and systemic therapies, which should be explored by the AG. There is evidence from the UK BADBIR registry to suggest that patient remain on treatment significantly longer with ustekinumab compared to other biologics [Warren et al]. Furthermore, there is evidence that patients stay on systematic therapies for a shorter duration than biologics [Ergun et al]. Currently in the model, ustekinumab, as the most effective treatment is disadvantaged for maintaining response over time, as costs accrue faster than benefits over time compared to BSC. However, after amending assumptions regarding the utilities and the cost of BSC, as suggested in our response, then, it is likely that ustekinumab would be the most cost effective treatment due to its effectiveness and data concerning time on treatment.	The AG considered this issue in Section 7.4.4 of the report. Unfortunately, none of the studies identified distinguish between discontinuation due to a lack of treatment response in the short term (trial period) and long-term for individuals who are responders to treatment. Ustekinumab costs more than adalimumab and etanercept per 4-week cycle. Ustekinumab also has a greater cost in the induction period (£2,147 per dose at baseline, 4 weeks and 16 weeks) compared to the costs of adalimumab and etanercept in this period. The greater efficacy associated with ustekinumab results in less time spent on BSC, but also extends the time on treatment. The additional costs of ustekinumab accrue faster than the benefits over time compared to BSC. The cost-effectiveness results for the additional scenarios suggested by the company are presented above.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people [ID854]

Company evidence submission

Submitted by

AbbVie UK Ltd.

6th September 2016

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List of abbreviations

6-MP	6-mercaptopurine
ADA	Adalimumab
AE	Adverse events
AS	Ankylosing spondylitis
AWMSG	All Wales Medicine Strategy Group
AZA	Azathioprine
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CBI	Cutaneous Body Image Scale
cDLQI	Children's Dermatology Quality of Life Index
cDMQI	Children Dermatology Life Quality Index
CLCI	Cumulative life course impairment
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
DMARDs	Disease modifying anti-rheumatic drugs
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Assessment Report
EQ-5D	EuroQol five dimensions questionnaire
EU	European Union
FDA	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
HADS	Hospital Anxiety and Depression Scale
HBV	Hepatitis B virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HRQoL	Health related quality of life
HRU	Healthcare resource use
HS	Hidradenitis suppurativa
HTA	Health Technology Assessment
IGA	Investigator's Global Assessment
IRR	Incidence rate ratio
ITT	Intention to treat
JIA	Juvenile idiopathic arthritis
LOCF	Last Observation Carried Forward
MA	Marketing Authorisation
MTX	Methotrexate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NYHA	New York Heart Association
OCT	Ocular coherence tomography
PASI	Psoriasis Area and Severity Index
PBO	Placebo
PedsQL™	Pediatric Quality of Life Inventory
PGA	Physician's Global Assessment
PICOS	Population, Intervention, Comparator, Outcome, Study framework
PIL	Patient Information Leaflet
PPD	Purified protein derivative skin test
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PRO	Patient reported outcomes
PUVA	Psoralen ultraviolet light A
PUVA	Psolaren Plus UVA Light
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
SAE	Serious adverse events
SAPASI	Self-administered Psoriasis Area and Severity Index
SC	Subcutaneous
SD	Standard deviation
SF-12	Short Form–12 dimensions
SF-6D	Short Form–6 dimensions
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	Standard of Care
TNF	Tumour necrosis factor
UK	United Kingdom
UVB	Ultraviolet B
VAT	Value Added Tax
WHO	World Health Organization

1 Executive Summary

Plaque psoriasis is an inflammatory skin condition associated with exacerbations, pain; symptoms leading to morbidity and reduced quality of life.

The disease is characterised by an unpredictable course, due to the intermittent exacerbations/flare-ups or remissions. Plaque psoriasis at some 'difficult-to-treat sites' such as the face, flexures, genitalia, scalp, palms and soles may result in functional impairment, and can be resistant to treatment. Due to the nature of the disease and the heightened burden for it occurring in children and young people (due to cumulative life course impairment), it is important to treat patients as early as possible from onset of the disease. The main aim of treatment is to reduce symptoms and improve quality of life for patients/families. A step-wise approach for treatment is recommended; topical therapies are offered as first line therapy followed by phototherapies and/or systemic non-biological therapies such as methotrexate. Where such therapies are ineffective, biological treatments such as adalimumab can be used. Adalimumab is licensed as a 1st line systemic treatment for use after topical and phototherapy failure/contra-indication.

Adalimumab is an innovative and well established technology for a range of conditions, including plaque psoriasis, within the paediatric population.

Adalimumab (Humira®) was granted a broad license for paediatric plaque psoriasis by the EMA (ages 4 – 18 years) following a robust head to head comparison with MTX (which is the current standard of care), demonstrating superiority of efficacy over MTX. Therefore, adalimumab fulfils the un-met need for the treatment of patients with plaque psoriasis as young as 4 years of age, contrary to etanercept and ustekinumab.

Adalimumab is also the only biologic treatment indicated in paediatric plaque psoriasis patients who have not failed prior systemic therapies. As such, adalimumab can be prescribed as a first choice for biologics in patients who inadequately respond or are contraindicated to topical treatments, and have no prior exposure to systemic treatments.

Adalimumab has demonstrated sustained PASI responses both in the short and long term.

Patients in the M04-717 trial treated with 0.8mg/kg ADA achieved PASI75 responses earlier than patients treated with MTX; at week 4, PASI75 response rates were 23.7% and 0%, respectively. Furthermore, a statistically significantly higher proportion of patients receiving 0.8 mg/kg ADA achieved PASI75 response at week

16 vs. patients receiving MTX (57.9% vs. 32.4%; *P* = 0.027). The 25.5% treatment difference between 0.8 mg/kg ADA and MTX is clinically relevant. Also, a numerically higher proportion of patients receiving 0.8mg /kg ADA achieved a PASI90 or PASI100 response at week 16 than patients receiving MTX.

Adalimumab has a long-term safety and tolerability profile established in at least 10 years of real-world use within the paediatric population.

The safety profile of adalimumab in the paediatric population across all licensed indications has been extensively studied in both randomised controlled trials, as well as observational studies; low rates of serious adverse events are reported across the studies. In the head to head trial with MTX (standard of care), adalimumab was generally well tolerated and had a similar safety profile to MTX, with no new safety risks identified relative to drug administration and treatment. These results are in line with existing peer reviewed literature by Seyger et al. (2016) indicating that adalimumab is a well-tolerated drug in the paediatric population based on the similarity in rates of treatment-emergent adverse events detected across various chronic immune diseases, including plaque psoriasis. [redacted].[1]

Treatment with adalimumab improves HRQoL in a patient population with painful and debilitating symptoms.

Adalimumab use is associated with a substantial positive impact on health-related benefits that are unlikely to be included in the QALY calculation such as productivity and caregiver burden. In the M04-717 trial, patients treated with adalimumab achieved important long term outcomes such CDLQI and PedsQL responses at various time-points.

[redacted]

[redacted]

Adalimumab is clinically effective and represents good value for money to the NHS.

AbbVie is confident that the efficacy of adalimumab in the head to head M04-717 trial with MTX (standard of care) has been validated by its use in the real-world setting following recommendations by the SMC and AWMSG HTA bodies.

In the absence of head to head trials of adalimumab and other biologics, AbbVie considered undertaking an indirect comparison. However, this was not considered feasible due to the substantial differences in respective marketing authorisations as well as heterogeneity in study designs and patient demographics. A similar feasibility assessment was undertaken regarding the development of a cost effectiveness model. Following a targeted literature review, it was ascertained that there were limitations in identifying data for key model attributes such as utilities and natural history required for modelling a life-time horizon, as per the NICE Reference Case. For these reasons, any cost-effectiveness evidence submitted would continue to be associated with considerable and unresolvable uncertainty. Therefore, AbbVie has not submitted a cost-effectiveness model for this appraisal**.**

Adalimumab is administered subcutaneously, which means that the treatment can be undertaken by the carer and/or patient at home. This offers flexibility to patients and their families, and has no cost impact to the NHS.

In conclusion, AbbVie believe that the clinical evidence base demonstrates that adalimumab provides rapid and sustained improvements in disease activity, function and health-related quality of life in a paediatric population with plaque psoriasis. Furthermore, adalimumab has a well-defined safety and tolerability profile, which is confirmed by its use in the real-world setting spanning over 10 years. Equally, adalimumab has demonstrated a similar safety profile as methotrexate (MTX), within the M404-717 trial, which is the current standard of care for patients with psoriasis in the UK.

AbbVie believe that adalimumab is a cost saving treatment, offers value to patients and the NHS, and should therefore continue to be recommended as an effective technology for the treatment of plaque psoriasis in a paediatric population.

1.1 Statement of decision problem

The decision problem for this appraisal, in line with the NICE final scope is presented in Table 1 below. Where differences between the final scope and the decision problem of the submission are evidenced, justifications and/or rationales have been provided.

Table 1: The decision problem

Domain	Final scope issued by NICE	Decision problem addressed by company submission	Rationale if different from the final NICE scope
Population	Children and young people with plaque psoriasis	Paediatric patients with severe chronic plaque psoriasis. *Patients with severe disease as defined by a total Psoriasis Area Severity Index (PASI) score of ≥10 and a Dermatology Life Quality Index (DLQI) of >10.*	In line with MA, the evidence base for adalimumab was studied in paediatric patients with severe chronic plaque psoriasis.
Intervention	• Adalimumab • Etanercept • Ustekinumab	Adalimumab within its licensed indication	Substantial differences in the respective marketing authorisations of the biologics may lead to inappropriate comparisons outside of licence. Therefore, only evidence on adalimumab (in line with its MA) as an intervention is considered for this appraisal.

Domain	Final scope issued by NICE	Decision problem addressed by company submission	Rationale if different from the final NICE scope
Comparator(s)	Non-biological systemic therapy (including, but not limited to, ciclosporin and methotrexate) • Topical therapy (for people in whom non-biological systemic therapy is not suitable) • Biological treatments used outside of their marketing authorisation (such as infliximab, adalimumab, etanercept or ustekinumab if used outside of the constraints of the relevant marketing authorisation in children and young people) • When appropriate, adalimumab, etanercept and ustekinumab will be compared with each other.	Evidence is presented from all relevant adalimumab studies identified regardless of comparator.	Differences in study populations (e.g. age, disease severity, treatment history), trial design, evolution of licenses and scarcity of trials, limit comparability. Therefore, meta-analyses, mixed treatment and indirect comparisons were neither appropriate nor feasible to conduct.
Outcomes	The outcome measures to be considered include: • severity of psoriasis • response and remission rate • relapse rate • adverse effects of treatment • Health-related quality of life.	As scope	Not applicable
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.	A cost-effectiveness analysis is not presented. Nevertheless, where cost analysis based on distribution of patients' weight is deemed feasible, this has been presented. Also, where available, HRQoL data have been presented.	A cost-utility analysis will be associated with uncertainty due to data limitations, as well as challenges in ascertaining valid utility estimates in young children from existing literature. On this basis, a cost effectiveness analysis was deemed neither feasible nor appropriate to

Domain	Final scope issued by NICE	Decision problem addressed by company submission	Rationale if different from the final NICE scope
	The availability and cost of biosimilars should be taken into account. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.		conduct.
Other considerations	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. If evidence allows, the appraisal should consider the sequential use of the interventions. If evidence allows, the clinical and cost effectiveness of adalimumab, etanercept and ustekinumab should be considered separately for people receiving these treatments following an inadequate response, intolerance or contraindication to: • topical therapies • phototherapies • non-biological systemic therapies • biological therapies The 3 interventions have marketing authorisations covering different age ranges, therefore if evidence allows, the clinical and cost effectiveness of adalimumab, etanercept and ustekinumab should be considered separately for different age groups.	Due to the scarcity of data relevant to the sub-groups of interest, no evidence will be presented.	Not applicable

2 The technology

2.1 Description of the technology

The brand name, UK approved name, therapeutic class and mechanism of action is presented in Table 2 below.

Table 2: Description of the technology

Brand name	Humira®
UK approved name	Adalimumab
Therapeutic class	Adalimumab is a recombinant human monoclonal antibody
Mechanism of action	Adalimumab is a fully human antibody that binds specifically to tumour necrosis factor alpha (TNF-α) and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.

2.2 Marketing authorisation/CE marking and health technology assessment

A summary of the marketing authorisation of adalimumab (Humira®) is presented in Table 3 below

Table 3: A summary of the marketing authorisation for adalimumab (Humira®)

UK approved name and brand	**Approved name:** Adalimumab **Brand name:** (Humira®)
Marketing authorisation/CE mark status	Date of first authorisation: 8th September 2003. Authorisation for the updated licensed indication (severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to, or are inappropriate candidates for, topical therapies and phototherapy) was received on: 26 March 2015
Indications as described in the summary of product characteristics	Adalimumab is approved in paediatric use for the[4] • Treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies. • Treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

	• Adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). • Treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy
Any restrictions as described in the summary of product characteristics	**Contraindications** • Hypersensitivity to the active substance or to any of the excipients such as mannitol, sodium citrate • Active tuberculosis or other severe infections such as sepsis, and opportunistic infections such as neurological events • Moderate to severe heart failure (NYHA class III/IV) **Special warnings and precautions for use** It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy. Patients on Humira may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. There is no relevant use of Humira in children aged less than 4 years for this indication.
Method of administration and dosage	Humira is administered by subcutaneous injection The recommended humira dose in paediatric use is 0.8 milligram (mg) per kilogram (kg) body weight (up to a maximum of 40 mg per dose) weekly (SC), for the first two doses and every other week thereafter. The volume for injection is selected based on the patients' weight.

2.2.1 Regulatory approval outside the United Kingdom

Adalimumab (Humira®) was granted the paediatric psoriasis licence through the European Medicines Agency (EMA) centralised procedure, and is therefore licenced for use in all European Union (EU) member states. The technology is approved for use in the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have an inadequate response to, or are inappropriate candidates for topical therapy and phototherapies.

2.2.2 Ongoing HTAs in the UK

With the exception of this appraisal [1D854], there are no other on-going health technology assessments in the UK for adalimumab in treatment of severe chronic plaque psoriasis in children and young people.

At present, adalimumab (Humira®) holds positive recommendations from UK HTA bodies, for use in the paediatric population for the treatment of severe chronic plaque psoriasis namely;

Scottish Medicines Consortium (SMC) [2]

SMC No. 1068/15

ADVICE: following an abbreviated submission [advice drafted on 5th June 2015]

Adalimumab (Humira®) is accepted for restricted use within NHS Scotland.

Indication under review: Treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

SMC restriction: Patients with severe disease as defined by a total Psoriasis Area Severity Index (PASI) score of ≥10 and a Dermatology Life Quality Index (DLQI) of >10.

Treatment with adalimumab in a paediatric population improves both signs and symptoms of psoriasis and quality of life.

All Wales Medicines Strategy Group (AWMSG).[3]

Advice No: 3615

Ministerial ratification: 09/12/2015

ADVICE: Adalimumab (Humira®) is recommended as an option for restricted use within NHS Wales for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to, or are inappropriate candidates for, topical therapy and phototherapies.

Prescribing should be restricted to clinical situations as specified within the National Institute for Health and Care Excellence (NICE) guidance for adults.

2.3 Administration and costs of the technology

2.3.1 Administration of the adalimumab (Humira®)

Humira is 40 mg/0.8 ml solution injection for paediatric use.[4] Each 0.8 ml single dose vial contains 40 mg of adalimumab. Dosing is administered via body surface area (BSA). A 40 mg pen and a 40 mg prefilled syringe are also available for patients to administer a full 40 mg dose. The volume for injection (paediatric psoriasis dose) is selected based on the patients' body weight as indicated in the SmPC.[4] For example, for patients weighing between 13 and 16kg a corresponding dose of 0.2mL (10mg) would be recommended.

Generally, the majority of patients with psoriasis are managed in primary care, though up to 60% of patients will require referral to a specialist at some point during the course of the disease.[5] Humira treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of paediatric plaque psoriasis. Following proper training in injection technique, patients may self-inject with Humira at home, if their physician determines that it is appropriate and with medical follow-up as necessary.

Adalimumab (Humira®) should always be used in line with its SmPC. [4]

2.3.2 Cost of adalimumab (Humira®)

A summary of the costs associated with the use of adalimumab in paediatric patients with severe chronic plaque psoriasis is presented in Table 4 below.

Table 4: Adalimumab related costs

Domain	Information	Source
Pharmaceutical formulation	40 mg/0.8 ml solution for paediatric injection; clear and colourless solution.	Humira SmPC[4]
Acquisition cost (excluding VAT) *	1 vial/pen/syringe (40 mg/0.8 ml): **£352.14**	BNF[40]
Method of administration	Subcutaneous injection	Humira SmPC[4]
Doses	The recommended dose is 0.8 mg per kg body weight (up to a maximum of 40 mg per dose) administered weekly for the first two doses and every two weeks thereafter.	Humira SmPC[4]
Dosing frequency	See above	Humira SmPC[4]
Average length of a course of treatment	Initial length of treatment is 16 weeks.	Humira SmPC[4]
Maximum cost of a course of treatment**	**Year 1:** £9,507.8 [£352.14 per vial @ 27 vials / year] **Year 2 and subsequent years:** £9155.64 [£352.14 per vial @ 26 vials / year] ***Note: Drug acquisition costs are exclusive of value added tax (VAT)***	BNF[40]
Anticipated average interval between courses of treatments	Not applicable	
Anticipated no. of repeat courses of treatments	Not applicable	
Dose adjustments	**Dose is calculated based on the patients' body weight:** 13–16 0.2 mL (10 mg) 17–22 0.3 mL (15 mg) 23–28 0.4 mL (20 mg) 29–34 0.5 mL (25 mg) 35–40 0.6 mL (30 mg) 41–46 0.7 mL (35 mg) 47+ 0.8 mL (40 mg)	Humira SmPC[4]
Anticipated care setting	The setting for the initiation and supervision of humira treatment should be undertaken by specialist physicians experienced in the diagnosis and treatment of conditions for which Humira is indicated; the majority of patients are anticipated to receive humira treatment in a secondary care setting.	Humira SmPC[4]
* List price ** This is maximum cost of treatment as the calculations assume that all patients stay on treatment.		

BNF=British National Formulary; SmPC=Summary of Product Characteristics

2.4 Changes in service provision and management

Since its approved licence extension in March 2015, adalimumab has become an established technology for use in the paediatric population within England, Wales and Scotland.

No change in current service provision and management is anticipated, where adalimumab receives positive recommendation from the National Institute for Health and Care Excellence (NICE). Additionally, there are no further additional tests and/or investigations above and beyond routine clinical practice for the use of adalimumab in the paediatric population.

2.5 Innovation

Adalimumab may be considered an innovative technology with the potential to make substantial impact on health-related benefits that are unlikely to be included in the QALY calculation including, but not limited to, productivity and caregiver burden. A summary of the adalimumab-related innovation in children and young people with chronic plaque psoriasis is presented below.

Furthermore, due to the paucity of data in children and young people with severe chronic plaque psoriasis, the evidence base for adalimumab-related innovation depicted across the respective humira licensed paediatric indications, as well as in adult patients with plaque psoriasis has been presented.

2.5.1 Evidence base for plaque psoriasis in the paediatric population

Innovation: Impact on the management of severe chronic plaque psoriasis

Adalimumab created a 'step-change' in the management of severe chronic plaque psoriasis.

Adalimumab is the only biologic comparing its clinical effectiveness rates against those of the usual standard of care (MTX) in a paediatric population with severe chronic plaque psoriasis. Furthermore, adalimumab has demonstrated to be superior in efficacy (based on PASI 75 response) to methotrexate (MTX), in a head to head, multi centre, double-dummy randomised controlled trial.[6]

Adalimumab is also the only biologic treatment indicated in paediatric plaque psoriasis for patients who have not failed prior systemic therapies.[4] As such, adalimumab can be prescribed as a first choice for biologics in patients who inadequately respond or are contraindicated to topical treatments and have no prior exposure to systemic treatments. Therefore, adalimumab offers an additional treatment option for paediatric patients with severe chronic plaque psoriasis.

In comparison to other biologics such as etanercept and ustekinumab, adalimumab is the only licensed treatment for paediatric plaque psoriasis for patients from the age of 4, thus taking in to consideration a vital subgroup of patients (4 to 6 years of age) with plaque psoriasis suitable for treatment with adalimumab.

Therefore, adalimumab fulfils the un-met need for the treatment of patients with plaque psoriasis as young as 4 years, with an adequate response to or inappropriate candidates for topical therapy and phototherapies, contrary to the etanercept and ustekinumab.

Benefits unlikely to be included in the quality adjusted life year (QALY) calculation

The QALY calculation is unlikely to capture psychosocial or wider societal benefits such as impact on educational attainment. If not adequately managed, plaque psoriasis can be a painful condition which impacts on many aspects of the child's life; health-related anxiety, disability related stigma.[7] This impact may carry through to the caregivers (parents) in terms of the potential impact on quality of life and workforce participation of meeting the child's extra physical and mobility needs and the time needed to attend appointments. Given that the QALY calculation does not put in to considerations such domains, AbbVie undertook a targeted review to identify articles relating to wider societal benefits of adalimumab in plaque psoriasis, beyond clinical efficacy. However very few studies were identified; with most studies in this field relating to the adult patients with plaque psoriasis.

Health related quality of life

Severe plaque psoriasis has a significant physical, emotional, social and school functioning impact on patients with the condition. [7] The impact of psoriasis on Health related quality of life (HRQoL) is greater during childhood compared to adulthood, and this burden comparable to other chronic childhood diseases such diabetes or epilepsy.[8] The psychosocial burden of psoriasis is associated with the visibility of skin lesions. Visible skin disease in paediatric patients have a detrimental impact on their quality of life including disrupting family and social relationships, impeding every day activities, and affecting normal development.[9] Results from the adalimumab pivotal study (M04-717)[6] in a paediatric population with plaque psoriasis, indicated that in patients receiving initial treatment with adalimumab 0.8 mg/kg, CDLQI and PedsQL measures improved from baseline (a change of –6.6 for CDLQI and 10.8 for PedsQL). This is indicates a comprehensive improvement in skin-related QoL for subjects treated with adalimumab 0.8 mg/Kg, compared to MTX. These data demonstrate that adalimumab helps to improve quality of life in a paediatric population with plaque psoriasis relative to standard of care (MTX).

Adalimumab has a well-defined long-term safety and tolerability profile

The safety profile of adalimumab in the paediatric population across indications has been extensively studied in both randomised controlled trials, as well as observational studies. The evidence base from the adalimumab pivotal trial (M04-717)[6] suggested that after 16 weeks of treatment, adalimumab was statistically significant in clinical efficacy outcomes over MTX; adalimumab was generally well tolerated and had a similar safety profile to MTX with no new safety risks identified relative to drug administration and treatment. These results are in line with existing peer reviewed literature by Seyger et al. (2016)[10], indicating that adalimumab is a well-tolerated drug in the paediatric population based on the similarity in rates of treatment-emergent adverse events detected across various chronic immune diseases, including plaque psoriasis, at 7.4 events per 100 person-years. Furthermore, no reports of treatment related malignancies, demyelinating disorders, cardiovascular events, pulmonary embolism, hepatitis B reactivation, Stevens-Johnson syndrome, or erythema multiform were observed.

Across other indications such as crohns disease and enthesitis-related arthritis in a paediatric population treated with adalimumab, results indicate a similar trend in tolerability and safety profiling with no treatment related malignancies reported, respectively.[11, 12]

2.5.2 Other evidence for the established use of adalimumab outside of the paediatric population [Adults ≥18 years]

Adalimumab clinical trials

One active-comparator study (CHAMPION) [13] involved patients with plaque psoriasis who were candidates for systemic therapy or phototherapy. Adults with moderate to severe disease for at least one year were randomised 2:2:1 to adalimumab 40mg every other week (eow), methotrexate dose escalation from 7.5mg to 25mg (if required and tolerated) or placebo over 16 weeks in a double blind, double dummy fashion. The primary endpoint was the proportion of subjects achieving 75% improvement in PASI from baseline to 16 weeks (PASI 75) in the intention to treat (ITT: as randomised) population. If superiority of adalimumab over placebo was established, superiority of adalimumab over methotrexate was tested. The results showed that the proportion of subjects achieving PASI 75 was 80% in the adalimumab group, 36% in the methotrexate group and 19% in the placebo group. The risk difference was significant for the comparisons of adalimumab versus placebo (60%; 95% confidence intervals [CI] 44% to 77%) and for adalimumab versus methotrexate (44%; 95% CI 31% to 57%). Differences were also significantly in favour of adalimumab over both groups for PASI 90 and PASI 100 at week 16, as were the percentages of patients reporting good or complete disease severity control.

In a second trial (n=1212) (REVEAL) [14] involving patients with moderate to severe plaque psoriasis for at least six months, adalimumab was significantly superior to placebo in achieving a PASI 75 response over a 16-week double-blind period (71% versus 6.5%) and showed sustained response over an open-label period of 17 weeks during which all patients who responded in the first phase received adalimumab. Patients with sustained response were re-randomized to adalimumab or placebo in a second 19-week double-blind period during which loss of adequate response was defined as <PASI 50 compared with week 0 and at least a 6-point increase in PASI score relative to week 33. Adalimumab was associated with a significantly lower rate of loss of response than placebo (4.9% versus 28%).

Open label extension data have shown sustained efficacy for up to 120 weeks. In both pivotal studies, quality of life was assessed using the Dermatology Quality of Life Index (DLQI). Adalimumab was significantly superior to all comparators for change from baseline in DLQI score and to placebo for the proportion of patients with a score of 0 (no dermatology-specific impairment in quality of life)

Therefore, the observed consistency in the relative efficacy rates of adalimumab versus MTX in CHAMPION[13] and the M04-717[6] clinical trials are broadly comparable.

Adalimumab observational studies

Findings from a real-world prospective observational research study of UK adult patients (≥18 years) conducted in the dermatology units of 19 UK secondary and tertiary care NHS trusts, showed that adalimumab significantly improved the physical and psychosocial variables, as well as the general quality of life of patients with psoriasis.[15] Additionally, treatment effects for psychosocial variables were maintained at the 6 month time-point following 16 weeks of initial therapy with adalimumab. Therefore these results indicate that in adult patients with severe chronic plaque psoriasis, adalimumab helps to improve both signs and symptoms of psychosocial variables, which may be more prominent with increased disease severity.

In an ongoing, multicentre, post marketing, 10-year, international, observational registry[16] designed to prospectively evaluate the long term safety and effectiveness of adalimumab in adult patients with chronic plaque psoriasis, results indicate that the vast majority of patients after the first 5 years persisted on adalimumab therapy with 76.5% and 69.2% of the all-treated and new-prescription populations, respectively. None of the patients had permanently discontinued adalimumab. In terms of safety, the rates of any serious TEAE and serious TEAEs of special interest reported were low, and rates of serious TEAEs and serious infections decreased with increasing adalimumab exposure.

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

Plaque psoriasis is an inflammatory skin condition characterised by an accelerated rate of turnover of the upper layer of the skin (epidermis); symptoms often leading to morbidity and reduced quality of life.

Adalimumab is also the only biologic treatment indicated in paediatric plaque psoriasis who has not failed prior systemic therapies. As such, adalimumab can be prescribed as a first line biologic in patients who inadequately respond or are contraindicated to topical treatments and have no prior exposure to systemic treatments.

Adalimumab is the only monoclonal antibody currently licenced for plaque psoriasis in children aged 4 to 17 years; therefore fulfilling an un-met need for treatment in a sub category of a paediatric population (4 to 6 years of age), contrast to etanercept and ustekinumab who are licenced to treat patients ≥6 years or ≥12 years, respectively.

Adalimumab has been recognised by other UK HTA bodies as an effective technology which offers value for money to the NHS. It has been approved for use by the Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG) for the treatment of severe chronic paediatric plaque psoriasis.

Adalimumab is the only biologic comparing its clinical effectiveness rates against those of methotrexate (UK standard of care for psoriasis). With adalimumab demonstrating superiority in efficacy over standard of care, this indicates a favourable profile for adalimumab as a first line biologic.

Adalimumab is an effective treatment associated with statistically significant rapid and sustained PASI 75 responses in disease activity, health related quality of life and function in paediatrics with severe chronic plaque psoriasis.

There is currently no explicit guidance/guideline for the treatment and management of paediatric plaque psoriasis, hence the variation in the treatment of the condition across clinical setting. Therefore, this highlights the need for an explicit treatment pathway and/or guidance for paediatric plaque psoriasis. Patients can be initiated on adalimumab in childhood and are able to continue therapy in to adulthood through a well-defined transitional care treatment pathway.

Adalimumab offers an additional treatment option for children and young people with severe chronic plaque psoriasis.

2.6.1 Description of the disease

Psoriasis is a common chronic immune-mediated relapsing-remitting skin disease.[17] Plaque psoriasis is by far the most common form of the condition (about 90% of people with psoriasis).[18] Plaque psoriasis is characterised by well-delineated red, scaly plaques that vary in extent from a few patches to generalised involvement. Plaque psoriasis at some 'difficult-to-treat sites' such as the face, flexures, genitalia, scalp, palms and soles may result in functional impairment, requires particular care when prescribing topical therapy and can be resistant to treatment. The disease is characterised by an unpredictable course, due to the intermittent exacerbations/flare-ups or remissions.

2.6.2 Epidemiology

The prevalence rates for plaque psoriasis may vary subject to gender, age, geographical location and prevalence definition across studies.[19] Best estimates indicate a worldwide prevalence rate of between 2.5–3%, representing one of the most common dermatological diseases.[20] In the UK, the prevalence rate of plaque psoriasis is estimated to be between 1.3 and 2.2%.[19]

2.6.3 Aetiology and risk factors

The explicit cause of psoriasis remains unclear thus, not fully understood.[17] Psoriasis can occur at any age, but the majority of occurrences are before the age of 35 years.[21] Several triggers such as genetic disposition, environmental and immunological factors may play a role in the manifestation of psoriasis.[22] Additionally, in up to 54% of patients, bacterial infections may induce or exacerbate the condition. [21] According to estimates published by the World Health Organization (WHO), paediatric psoriasis is similar to adult psoriasis in terms of symptoms, and occurs in 0.70% of the paediatric population.[17]

2.6.4 Diagnosis

Diagnosis of plaque psoriasis is undertaken by a specialist medical professional such as a dermatologist by thoroughly examining the skin, scalp and nails of a patient for any signs of psoriasis.[5] Furthermore, patients are asked about family history of the condition in combination to ascertaining the history of the symptoms based on the patient's lifestyle choices or health status i.e. taking or discontinuation of certain medications such as interferons or corticosteroids, respectively. In some cases, the dermatologist may remove a bit of skin from the patient and examine it under a microscope which may in turn confirm the presence or absence of psoriasis.[5]

2.6.5 Assessment of paediatric plaque psoriasis

In patients presenting with psoriasis, the assessment tool to guide treatment therapy is based on the establishment of disease severity using a validated clinical tool such as the Psoriasis Area and Severity Index (PASI).[5] Although the tool is commonly used in clinical practice in patients with psoriasis across all age groups, it has not been validated in the paediatric population.[23] Also, the choice of therapy may be influenced by disease severity, due to the lack of a validated assessment tool in paediatrics and therefore, clinical challenges in establishing the grade severity

remain a common occurrence.[5] Adalimumab in line with its MA[4] for paediatric psoriasis, the severity of disease is defined by a total Psoriasis Area Severity Index (PASI) score of ≥10 and a Dermatology Life Quality Index (DLQI) of >10, as approved by SMC2 and AWMSG.[3]

Furthermore, as part of the management of the condition, the impact on the physical, psychological and social wellbeing domains of patients is also assessed. For example, the Children Dermatology Life Quality Index (cDLQI) is the gold standard tool used in children and young people.[24]

2.6.6 Treatment guidelines/guidance for paediatric plaque psoriasis

There is currently no explicit guidance/guideline detailing the treatment and management of paediatric plaque psoriasis thus, the clinical evaluation for the condition is guided by the existing NICE CG153 on the management of psoriasis in adults, children and young people.[5] The generic guideline covers all age groups as well as all types of psoriasis; with a reference to term 'people' indicating all age groups, and children referred to as those up to the age of 12 years who later on become 'young adults' before becoming adults at age of 18 years. Despite this categorisation, general emphasis of the evidence base in the guideline is derived from the adult population with psoriasis, thus recommendations are not specific to the paediatric population. For example, very few of the recommended drugs in the guideline are licensed for paediatric patients. Therefore, there remains a need for an explicit guideline and guidance, detailing an explicit treatment pathway, for the treatment of plaque psoriasis in children and young people.

2.7 Clinical pathway of care

2.7.1 Current treatment and management pathway for plaque psoriasis

The management of paediatric patients with plaque psoriasis is complicated due to the lack of guidance on treatment, therefore measuring disease severity and response to therapy specifically for this population remains a challenge. For the majority of patients with psoriasis, the condition is managed in primary care, although specialist referral is often required in about 60% of the patients during the course of the disease.[5] Furthermore, in the minority of patients with complex/rare psoriasis, supra-specialist (level 4) tertiary care is required.[25] Evidence from a UK audit in the care of adult patients in psoriasis in secondary care, indicated that there was variation in accessibility to care, particularly specialist care such as access to biologic therapy, specialist nurse support, psychological care as well as appropriate drug monitoring.[26] Given the challenges experienced in the adult population despite the volume of evidence, it is likely that accessibility to specialist services i.e. biologic therapy is likely to be even more challenging for the paediatric population and their carers as a whole.

A wide range of treatment options are available, but some are associated with high acquisition costs and others can only be accessed through specialist care; but all requiring routine monitoring. The current pathway, in line with the NICE CG153[5, the] initiation of treatment is with the use of active topical therapies such as emollients; a recommendation passed as a result of the wide spread use of topical therapies such as emollients within clinical practice at the time of drafting of the guideline.

In UK clinical practice, treatment of psoriasis in children, young people and adults, follows a stepped approach in line with the NICE CG153[5] as described below;

First line: Use of traditional topical therapies such as vitamin analogues, corticosteroids, dithranol.

Second line: Use of phototherapies (such as broad-or narrow-band ultraviolet B light and psolaren plus UVA light [PUVA]) and systemic non-biological agents such as methotrexate

Third line: Use of systemic biological therapies such as tumour necrosis factor antagonists such as adalimumab, etanercept, and the IL12/23 antagonist ustekinumab.

2.7.2 Position of adalimumab in the treatment pathway

The aim of treatment with adalimumab is to improve disease severity, psychosocial variables and QoL.[4] Adalimumab as a first choice systemic biologic may be a treatment option for paediatric patients, from 4–17 years of age, with severe chronic plaque psoriasis; defined by a total Psoriasis Area Severity Index (PASI) score of ≥10 and a Dermatology Life Quality Index (DLQI) of >10 in England. Therefore, adalimumab offers a favourable benefit/risk profile in relation to standard of care (MTX) and other biologics in the treatment of plaque psoriasis for patients aged between 4 and 17 years of age who have an inadequate response to, or are inappropriate candidates for topical therapy and phototherapies.

A comparison of the proposed treatment pathway for adalimumab within the current clinical pathway of care is described in Table 5 below.

Table 5: Position of adalimumab in the clinical treatment pathway for plaque psoriasis in the paediatric population

Patient group	Existing pathway[5]	Clinical pathway for adalimumab[4]
Treatment of severe chronic plaque psoriasis in children and young people	**As per NICE CG135, the following is recommended;** • **First line**: Use of traditional topical therapies such as vitamin analogues, corticosteroids, dithranol. • **Second line:** Use of phototherapies (such as broad- or narrow-band ultraviolet B light and psolaren plus UVA light [PUVA]) and systemic non-biological agents such as methotrexate • **Third line:** Use of systemic biological therapies such as tumour necrosis factor antagonists such as adalimumab, etanercept, and the monoclonal antibody i.e. ustekinumab.	• Adalimumab can be prescribed as a first line biologic in patients who inadequately respond to, or are contraindicated to topical treatments and have no prior exposure to systemic treatments; therefore a first choice biologic. • Adalimumab is the only monoclonal antibody currently licenced for plaque psoriasis in children aged 4 to 17 years; therefore fulfilling an un-met need for treatment in a sub category of the paediatric population (4 to 6 years of age), contrast to etanercept and ustekinumab who are licenced to treat patients ≥6 years or ≥12 years, respectively. • Adalimumab is superior in efficacy over standard of care (MTX), thus indicates a favourable profile as first line biologic in the treatment of severe chronic plaque psoriasis. A similar safety profile between adalimumab and MTX was established in the pivotal trial.

Other agents are also licenced in the UK for the treatment of paediatric plaque psoriasis, although there are some differences in marketing authorisation for the respective indication.

A summary of the licenced technologies in line with the NICE final scope is presented in Table 6 below.

Table 6: Biological agents licensed in the treatment of paediatric plaque psoriasis

Biological agent	Licenced patient population and formulation
Adalimumab[4] (Humira, AbbVie)	A fully human immunoglobulin G1 monoclonal antibody that inhibits the activity of tumour necrosis factor (TNF). **UK Marketing authorisation:** Treating severe chronic plaque psoriasis in children and adolescents from 4 years of age who have an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.
Etanercept[27] (Enbrel, Pfizer)	A recombinant human TNF receptor fusion protein that inhibits the activity of TNF. **UK Marketing authorisation:** Treating chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.
Ustekinumab[28] (Stelara, Janssen)	Fully human monoclonal antibody that acts as a cytokine inhibitor by targeting interleukin‑12 and interleukin‑23. **UK Marketing authorisation:** Treating moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.
All 3 technologies are administered by subcutaneous injection.	

2.8 Equality Issues

No equality issues are expected in this appraisal. Of note, in comparison to other interventions (etanercept and ustekinumab), adalimumab is the only licenced agent for use in the sub-category of the paediatric population aged between 4 and 6 years of age; with the full licence covering the age category of 4 to 17 years of age in the paediatric population with severe chronic plaque psoriasis.

3 Clinical effectiveness

Summary of efficacy, interventional study

Adalimumab demonstrates sustained PASI responses throughout the course of treatment for plaque psoriasis.

- Results from the M04-717 trial[6], indicate that a statistically significantly higher proportion of patients receiving 0.8 mg/kg ADA achieved PASI75 response at week 16 vs. patients receiving MTX (57.9% vs. 32.4%; *P* = 0.027). The 25.5% treatment difference between 0.8 mg/kg ADA and MTX is clinically relevant.

- Patients treated with 0.8mg/kg ADA achieved PASI75 responses earlier than patients treated with MTX; at week 4, PASI75 response rates were 23.7% and 0%, respectively.

- A numerically higher proportion of patients receiving 0.8mg /kg ADA achieved a PASI90 or PASI100 response at week 16 than patients receiving MTX.

The results from the paediatric trial M04-717[6] are consistent with those of an observational study in the adult UK population with plaque psoriasis, which indicated that there was a significant positive correlation between the change in SAPASI score from baseline at 16 weeks following adalimumab initiation and the corresponding change in PASI (r=0.50, n=55, p<0.001). Improvements in disease severity were accompanied by significant improvements in psychosocial variables and QoL, following adalimumab initiation. Effects at 16 weeks were maintained at 6 months.

Adalimumab demonstrates sustained PGA responses throughout the course of treatment for plaque psoriasis.

- Approximately 20% more patients receiving 0.8mg/kg ADA achieved PGA 0/1 (clear, minimal) at week 16 (60.5%) than patients receiving MTX (40.5%; p-0.083). The magnitude of the treatment effect with o.8mg/kg is considered clinically relevant.

- Patients treated with 0.8mg/kg ADA achieved PGA 0/1 (clear, minimal) responses earlier than patients treated with MTX; at week 4, PGA 0/1 response rates were 28.9% and 8.1%, respectively.

Adalimumab use is associated with improved health related quality of life (HRQoL) in the long term.

3. 1 Identification and selection of relevant studies

3.1.1 Study identification

A single systematic literature review was conducted to identify relevant evidence assessing the efficacy and safety of adalimumab, etanercept and ustekinumab against relevant comparators, in children and young people with plaque psoriasis, in line with the NICE final scope.[23] The search strategy for the systematic review is presented in Appendix 1.

The systematic review process adhered to the recommendations by the Centre for Reviews and Dissemination (CRD) guidance[29] for undertaking systematic reviews in health care, as well as the reporting guidance by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) reporting checklist[30], thus ensuring transparency and a reproducible method of conducting and reporting data from the systematic review.

The electronic databases were searched from inception of the database to 10th August 2016. No limitations on publication status (published, unpublished or on-going) were applied; however only publications in English were included. Furthermore, only studies in human subjects were eligible for inclusion.

The following electronic databases were searched:

- MEDLINE
- MEDLINE-IN-PROCESS and Daily Update
- EMBASE
- The Cochrane Library, incorporating;
    - Cochrane Database of Systematic Reviews (CDSR)
    - Database of Abstracts of Reviews of Effects (DARE)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Health Technology Assessment (HTA)
    - NHS economic Evaluation Database (NHS EED)
    - PubMed (for E-publications ahead of print)

To retrieve further articles not identified through the electronic database search, reference lists of included studies were scanned, and searches for grey literature as well as completed and on-going trials, was also carried out.

Furthermore, the following key conference proceedings covering the last 3 years (2013 to August 2016) were searched.

- American Academy of Dermatology (ADD)
- International Congress on Psoriasis (ICP)
- Society for Investigative Dermatology (SID)
- World Congress of Dermatology (WCD)
- British Association of Dermatologists (BAD)
- Psoriasis International Network (PIN)
- Psoriasis and psoriatic arthritis conference
- Gene to clinic
- European Society for Dermatological Research (ESDR)
- British society of paediatric dermatology
-

3.1.2 Study selection

The screening process (titles ± abstracts and full paper stages) for both RCT and non-RCT evidence involved two reviewers working independently. Any disagreements were resolved through the involvement of a third reviewer or through team discussion until a consensus was reached.

The identified studies were initially assessed based on titles ± abstracts. Thereafter, full papers of the eligible studies were obtained and assessed further for inclusion/exclusion. The reasons for exclusion of the studies excluded at full paper stage are documented in the Appendix 2.

A summary of the eligibility criteria for the systematic review of RCT evidence, in line with the NICE final appraisal for this appraisal, is outlined in Table 7 below.

Table 7: Eligibility criteria used in the search strategy for the clinical effectiveness evidence

Population	Children and young people with plaque psoriasis (<18 years old)
Intervention(s)	• Adalimumab, etanercept, ustekinumab
Comparator(s)	• Placebo, any active drug
Outcome(s)	Efficacy and safety outcomes included, but not restricted to: • Severity of psoriasis (e.g., PASI, IGA, PGA) • Response and remission rate (e.g., proportion of patients achieving PASI 75, PASI 50, PASI 90, PASI 100, IGA 0 or 1, PGA 0 or 1) • Relapse rate (e.g. time to loss of disease control) • Adverse effects of treatment (e.g. number and proportion of patients experiencing adverse events) • Health-related quality of life (e.g., change from baseline in DLQI [or cDLQI], proportion of patients with DLQI [or cDLQI] response of 0,1, change from baseline on EQ-5D, change from baseline on PedsQL)
Study type(s)	Prospective, randomised clinical trials, with open label and/or double-blind designs.

cDLQI=Children's Dermatology Quality of Life Index; DLQI=Dermatology Quality of Life Index; EQ-5D=EuroQoL 5 Dimension; IGA=Investigator's Global Assessment; PedsQL=Paediatric Quality of Life Inventory; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment

The electronic database search identified 393 articles, including key conference abstracts, of which 325 were screened (after de-duplication). In total, 296 publications were excluded on the basis of titles ± abstract. A total of 29 articles were screened at full paper stage, of which a further 12 were excluded. Therefore, 17 publications (corresponding to 6 unique trials) met the inclusion criteria and were included in the systematic review, of which 1 was relevant to adalimumab, three for etanercept and two for ustekinumab.

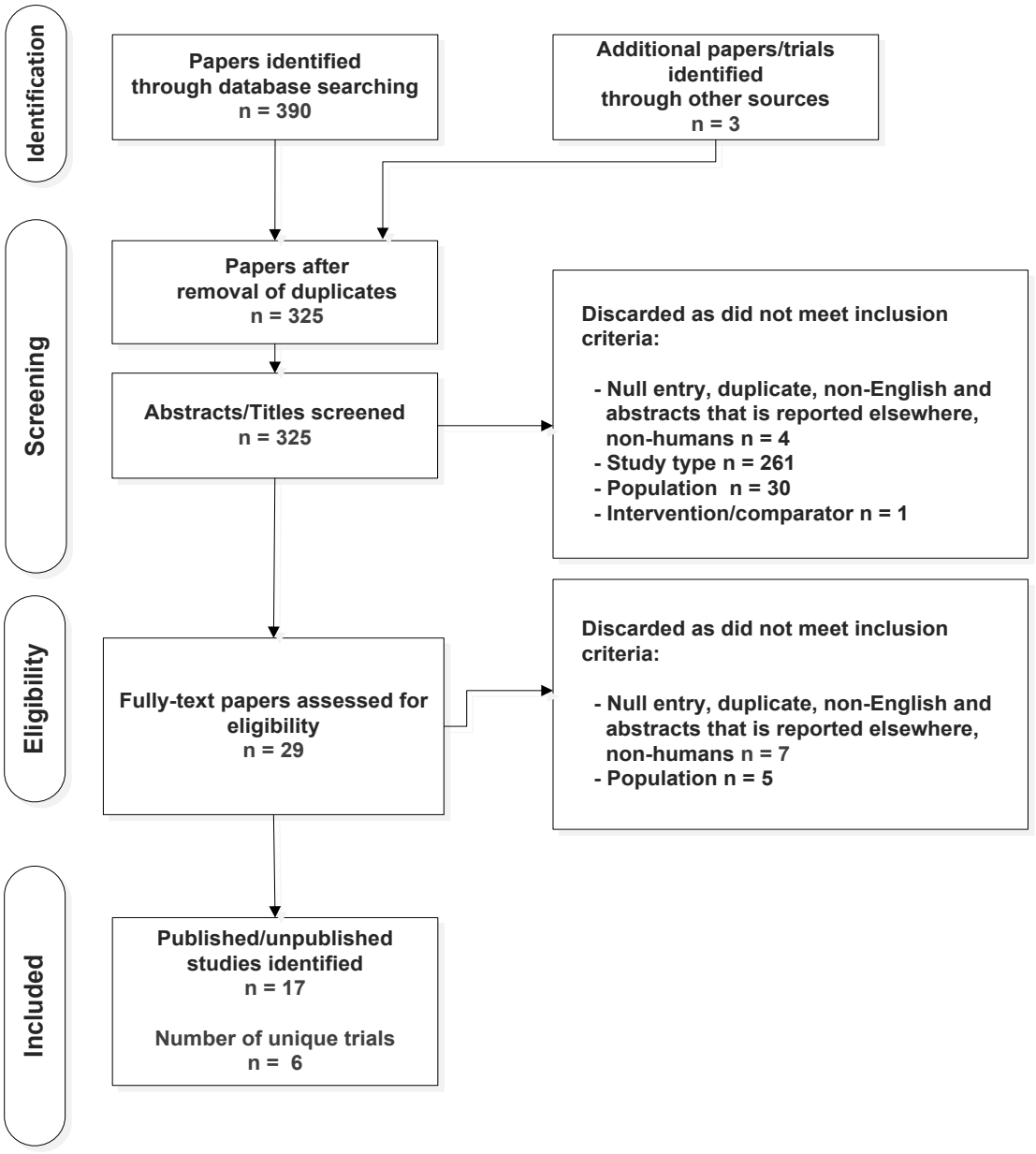
The adalimumab trial had seven corresponding publications, although the majority were in abstract form, thus limited data for disclosure. Nevertheless, unpublished information and/or data (AbbVie data on file) from relevant studies have also been included for completeness.

Only data for adalimumab informs the evidence base of this submission and/or appraisal.

The schematic for the study selection process for the RCT evidence is shown in Figure 1 below.

Figure 1: Schematic for the systematic review of RCT evidence

Of the 6 unique trials identified through the electronic search, adalimumab n=1, ustekinumab n=2 and etanercept n=3. Only the evidence base for the adalimumab trial is presented in the submission. Therefore, non-specific adalimumab studies have been excluded from the evidence base informing this appraisal.



3.1.3 Data extraction

The eligibility criteria for the clinical effectiveness data were in line with the NICE final scope.[23] In all cases, inclusion was restricted to studies that used the licenced dose of adalimumab. The data were extracted in pre-pilot tested Excel data extraction form by one reviewer, and checked for accuracy and consistency by another reviewer. Where disagreements were experienced, a discussion between the reviewers until a consensus was reached was undertaken, or the involvement of a third reviewer was sought where a consensus could not be reached.

4 List of relevant randomized controlled trials

The efficacy and safety of adalimumab in plaque psoriasis in the paediatric population has been studied in both randomised and non-randomised interventional studies as well as observational studies. The evidence for non-randomised interventional studies is presented in section 4.11

Seven publications relating to one clinical trial using the licensed does of adalimumab in paediatric population were identified. The evidence informing the marketing authorisation of adalimumab in the patient population under consideration in this appraisal were depicted from only one trial (M404-717).[6]

A summary of the relevant interventional studies (randomised controlled clinical trials) is presented in Table 8 below.

Table 8: List of relevant interventional studies (RCTs only)

Study ID	Intervention	Comparator	Study design	Location
M04-717[6] (NCT01251614)	**Period A:** 16-week double-blind treatment, in which patients were randomized 1:1:1 to •0.8 mg/kg ADA up to 40 mg, then every other week (eow) from week 1; •0.4 mg/kg ADA up to 20 mg, then eow (every other week) from week 1	**Period A:** 0.1–0.4 mg/kg MTX weekly up to 25 mg per week	Multicenter, randomized, double-blind study, including 4 study periods	41 study locations across 13 countries including; Belgium, Canada, Chile, Germany, Czech Republic, Italy, Mexico, Poland, Hungary, Netherlands, Spain, Switzerland, Turkey,
	Period B: treatment withdrawal for treatment responders in Period A			
	Period C: ADA re-treatment of patients who lost disease control in Period B			
	Period D: 52-week, long-term follow-up			

ADA- Adalimumab; eow – every other week; MTX – methotrexate; ID- Identity.

Other relevant information

Various peer-reviewed publications have been published in relation to the key clinical trial (N=7), informing the marketing authorisation of adalimumab in paediatric population with plaque psoriasis. These include the following;

- Papp et al. (2016) Adalimumab Long-term Safety/Efficacy Results for Paediatric Patients with Chronic Plaque Psoriasis from a Phase 3 Randomised Studies. 74th Annual Meeting of the American Academy of Dermatology, Washington.[31]
- Papp et al. (2014) Study Design and Baseline Characteristics from a Phase 3, Randomised, Double-Blind Study of Adalimumab versus Methotrexate Treatment in Paediatric Patients with Chronic Plaque Psoriasis. 72nd Annual Meeting of the American Academy of Dermatology, Denver, Colorado.[32]
- Papp et al. (2013) Study Design and Baseline Characteristics from a Phase 3, Randomised, Double-Blind Study of Adalimumab versus Methotrexate Treatment in Paediatric Patients with Chronic Plaque Psoriasis. 4th Congress of the Psoriasis International Network in Paris, France.[33]
- Papp et al. (2014) Baseline Characteristics in Paediatric Patients with Chronic Plaque Psoriasis from a Phase 3, Randomised, Double-Blind Study of Adalimumab versus Methotrexate Treatment. 12th European Society for Paediatric Dermatology Congress, Kiel, Germany.[34]
- Papp et al. (2015) Efficacy and Safety of Adalimumab Versus Methotrexate Treatment in Paediatric Patients With Severe Chronic Plaque Psoriasis: Results From the 16-Week, Randomised, Double-Blind Period of a Phase 3 Study. 23rd World Congress of Dermatology, Canada.[35]
- Phillip et al. (2015) Efficacy and Safety of Adalimumab versus Methotrexate in Paediatric Patients with Severe Chronic Plaque Psoriasis: Results from the Treatment Withdrawal and Double-Blind Retreatment Periods of a Phase 3 Study. 23rd World Congress of Dermatology, Vancouver.[36]
- Thaci et al. (2015) Safety and Efficacy for Paediatric Patients with Chronic Plaque Psoriasis Who Did Not Respond to 16 weeks of Double-Blind Methotrexate Treatment and Switched to Adalimumab. 24th EADV Congress; October 7-10 2015; Copenhagen, Denmark.[37]

4.1 Summary of the methodology of the relevant randomised controlled trial

The methodology of the key RCT provides and overview on the trial conduct and design. The section explores the key parameters of the study design i.e. objective, randomisation methods, inclusion and exclusion criteria, as well as the demographics of the study participants.

Only one randomised controlled trial (M04-717)[6] informs the evidence base for adalimumab use in the treatment of paediatric severe chronic plaque psoriasis, in line with the NICE final scope. The M04-717[6] adalimumab trial was of paediatric patients aged between 4 and 17 years of age, both males and females and weighed ≥13kg. Furthermore, the participants had failed to respond to topical therapy, and therefore had the need for a systemic treatment. The study utilised the low dose (0.4 mg/kg up to a maximum of 20mg) as well as the standard dose (0.8 mg/kg up to a maximum of 40mg every other week), in line with the UK marketing authorisation and the NICE final scope. Furthermore, both doses have been tested in paediatrics, double- trial phase, against methotrexate which is UK standard of care for patients with psoriasis.

A summary of the methodology (trial overview) utilised in the RCT is summarised in Table 9 below.

Table 9: Overview of the randomised controlled trial

Domain	Description
Study name	M04-717[6] (NCT01251614)
Study objective	Evaluates the safety and efficacy of 2 dosing schedules of the TNF inhibitor ADA vs. methotrexate (MTX) in paediatric patients with severe chronic plaque Ps
Location	42 study locations across 13 countries [Belgium, Canada, Chile, Germany, Czech Republic, Italy, Mexico, Poland, Hungary, Netherlands, Spain, Switzerland, Turkey]
Design	Multicenter, randomized, double-blind study, including 4 study periods [Primary Treatment Phase, Treatment Withdrawal Phase, Re-Treatment Phase and Long Term follow-up Phase, in that sequence)
Duration of the study	**Period A**: 16 week study; **Period B:** up to 36 weeks: **Period C:** 16 weeks: **Period D:** Long term follow up – 52 weeks.
Method of randomisation	Parallel Assignment of patients via an [redacted] to receive Standard Dose Adalimumab (0.8 mg/kg), Low Dose Adalimumab (0.4 mg/kg) or MTX. The [redacted] helps to maintain blinding and proper assignment of patients to study arms.
Method of blinding (care provider, patient and outcome assessor)	Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Intervention	Adalimumab
Comparator	Methotrexate (MTX)
Primary outcome measure	The proportion of patients achieving a ≥75% improvement in PASI (PASI75) response at week 16 The proportion of patients achieving a PGA of 0/1 (clear or minimal) at week 16
Secondary outcome measure	The proportion of patients achieving a PASI90 or PASI100 response at week 16

Source: ClinicalTrials.gov; NCT01251614

A summary of the eligibility criteria (inclusion and exclusion criteria) for the key adalimumab trial for this appraisal is presented in Table 10 below.

Table 10: Eligibility criteria for the randomised controlled trial under consideration in this appraisal

Study Acronym (Trial no)	Inclusion criteria	Exclusion criteria
M04-717[6] (NCT01251614)	Key inclusion criteria included the following entities; • Male and female paediatric patients (aged ≥4 to <18 years), with body weight ≥13 kg and a clinical diagnosis of chronic plaque Ps for ≥6 months were eligible • Patients must have failed topical therapy and required systemic therapy to control their disease • Inclusion criteria were at least 1 of the following: ❖ Physician's Global Assessment (PGA) ≥4 (marked to severe Ps) ❖ Body surface area (BSA) involved >20% (or BSA >10% and very thick lesions) ❖ Psoriasis Area and Severity Index (PASI) >20 • PASI >10 and at least 1 of the following: ❖ Active psoriatic arthritis unresponsive to non-steroidal anti-inflammatory drugs ❖ Clinically relevant facial, genital, or hand and/or foot involvement ❖ Children's Dermatology Life Quality Index (CDLQI) >10 (moderate to extremely large effect)	Key Exclusion criteria included the following entities; • Prior use of biologics other than prior treatment with etanercept • Treatment with etanercept within 4 weeks before baseline visit • MTX use within the past year or prior MTX use at any time with an inadequate response or intolerance

4.1.1 Baseline demographics and disease-specific characteristics

A total of 114 patients were enrolled in 41 Dermatology sites across 13 countries. The majority were white (90.4%), 57.0% were female, and the mean age of the study participants was 13.0 years. The mean duration of psoriasis was 5.0 years and about 32.7% of patients had a family history of psoriasis.

A summary of the patient demographics is presented in Table 11 below

Table 11: Baseline demographics of the study participants enrolled in the adalimumab M04-717 trial

Domain, n (%)	MTX (n=37)	Adalimumab		Total (N=114)
		0.4mg/Kg (n=39)	0.8mg/Kg (n=38)	
Female, n (%)	26 (70.3)	18 (46.2)	21 (55.3)	65 (57.0)
White, n (%)	34 (91.9)	34 (87.2)	35 (92.1)	103 (90.4)
Mean (SD) age, y	13.4 (3.5)	12.6 (4.4)	13.0 (3.3)	13.0 (3.8)
BMI percentile, n (%)				
<5th (underweight)	1 (2.7)	1 (2.6)	3 (7.9)	5 (4.4)
<5th to <85th (normal weight)	22 (59.5)	25 (64.1)	21 (55.3)	68 (59.6)
85th to 95th (overweight)	6 (16.2)	4(10.3)	7 (18.4)	17 (14.9)
≥95th (obese)	8 (21.6)	9(23.1)	7 (18.4)	24 (21.1)
Mean (SD) Ps duration, y	5.1 (3.8)	4.8(3.3)	5.0 (3.8)	5.0 (3.6)
Family history of Ps, n (%)	11 (30.6)[a]	15 (38.5)	11 (28.9)	37 (32.7)
Mean (SD) % BSA affected	30.3 (21.2)	26.0 (16.2)	27.7 (20.4)	27.9 (19.3)
Mean (SD) PASI	19.2 (10.0)	16.9 (5.8)	18.9 (10.3)	18.3 (8.8)
PGA, n (%)				
Clear/minimal	0	1 (2.6)	0	1 (0.9)
Mild	1 (2.7)	3 (7.7)	3 (7.9)	7 (6.1)
Moderate	19 (51.4)	18 (46.2)	17 (44.7)	54 (47.4)
Marked	17 (45.9	15 (38.5)	17 (44.7)	49 (43.0)
Severe	0	2 (5.1)	1 (2.6)	3 (2.6)

BMI, body mass index; BSA, body surface area; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; Ps, psoriasis. aData missing for 1 patient.

4.2 Statistical analysis and definition of study groups in the relevant randomized controlled trials

Only one RCT informs the evidence base for adalimumab for this appraisal. Data on statistical analysis are extracted from an abstract publication, thus further data will be extracted from the study clinical report (CSR) and marked accordingly in line with NICE's guide to the processes of technology appraisal.

A summary of the statistical analysis of study groups in the RCT are reported in Table 12 below.

Table 12: Statistical analysis employed in the adalimumab RCT

Study	Hypothesis objective	Statistical analysis	Sample size and power	Data management, patient withdrawals
M04-717[6] (NCT01251614)	To determine the safety and efficacy of 2 doses of adalimumab versus MTX in paediatrics with chronic plaque psoriasis. Determine time to loss of disease control. Evaluate the ability to regain response upon re-treatment. =	Efficacy analyses were to be conducted in the intent-to-treat (ITT) population. [redacted] [redacted] Descriptive statistics were calculated for all outcomes. Treatment differences were compared using a chi-square test or Fisher's exact test [redacted]	[redacted]	[redacted]

4.3 Participant flow in the relevant randomized controlled trials

In the M04-717 trial[6], 4 treatment phases were employed; Primary Treatment Phase, Treatment Withdrawal Phase, Re-Treatment Phase and Long Term follow-up Phase.

The main focus for this section is on the Primary treatment phase of the study, 16 weeks duration, comparing low and standard doses of adalimumab with MTX.

Results indicated that at the 16 week time-point, no patients experienced serious adverse events relating to the study drugs (both adalimumab and MTX). Furthermore, across all treatment arms, no adverse events leading to discontinuation from the study or drug were observed. Also, no deaths were reported during the 16 week double blind treatment phase.

A summary of the patient disposition in the key adalimumab trial is depicted in Table 13 below.

Table 13: Summary of the participant flow in the adalimumab M04-717 RCT

Study	Number of recruited and/or randomised n (%)	Number of efficacy evaluated population n (%)	Number of patients completing the study n (%)	Overall discontinuation n (%)
M04-717[6] (NCT01251614)	114	114	114	0

4.4 Quality assessment of the relevant randomized controlled trials

The critical appraisal of the RCT evidence was undertaken using a format provided by the NICE submission template which adhered to the CRD guidance.[29]

The study informing the evidence base of adalimumab for this appraisal was of very high quality based on the responses for each category indicating very low risk of bias in study conduct and design. A complete assessment of the M04-717 RCT evidence against the relevant comparators is provided in Appendix 3.

Table 14: Quality assessment of the key adalimumab trial (M04-717): (NCT01251614)

Study question	M04-717[6] (NCT01251614)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No
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; [redacted]

4.5 Clinical effectiveness results of the relevant randomized controlled trials

All efficacy analyses were based on the ITT population (analysed as randomized). Only one randomized controlled trial (M404-717)[6] informs the evidence base for this Appraisal The objective of the study was to evaluate the clinical effectiveness of adalimumab versus methotrexate (MTX) based on the proportion of patients achieving primary and secondary outcomes such as PASI75/90/100 responses as well as PGA 0/1 (clear and minimal).

The M404-717[6]adalimumab trial was categorized in to four periods namely;

Period A: 16 week study – Double blind primary treatment phase (ADA vs. MTX)

Period B: up to 36 weeks – Withdrawal/no medication

Period C: 16 weeks – Double blind re-treatment phase

Period D: 52 weeks - Long term follow up

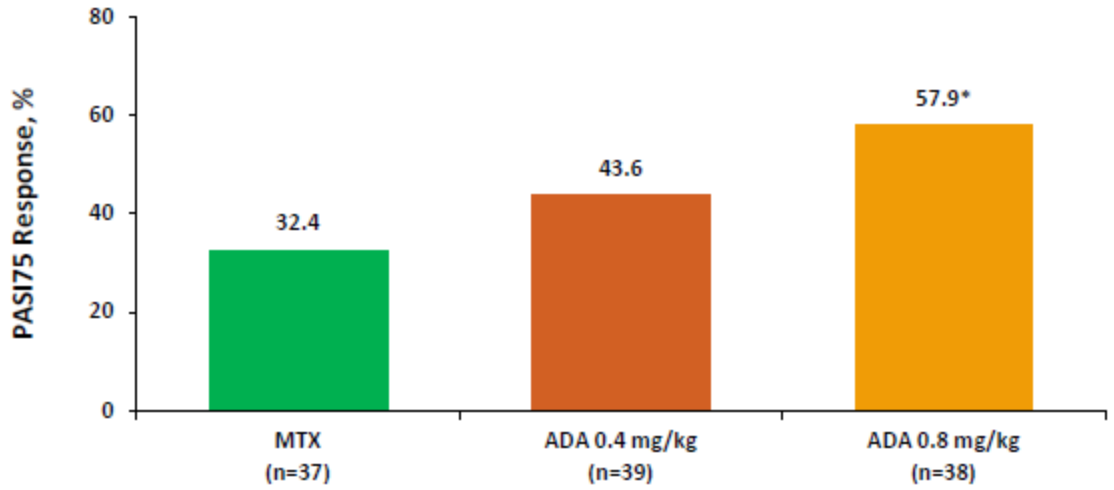
The efficacy results from each treatment period of the trial are presented below.

Period A: Double blind primary treatment phase (ADA vs. MTX); 16 weeks

PASI75 responses: A statistically significantly higher proportion of patients receiving 0.8 mg/kg ADA achieved PASI75 response at week 16 vs. patients receiving MTX (57.9% vs. 32.4%; *P* = 0.027). The 25.5% treatment difference between 0.8 mg/kg ADA and MTX is clinically relevant. PASI75 response rates between patients randomized to 0.8 and 0.4 mg/kg ADA were not statistically significantly different. Patients treated with 0.8mg/kg ADA achieved PASI75 responses earlier than patients treated with MTX; at week 4, PASI75 response rates were 23.7% and 0%, respectively.

Figure 2 below presents a graphical representation of the responses across trial arms.

Figure 2: PASI75 responses at week 16 for ADA vs. MTX



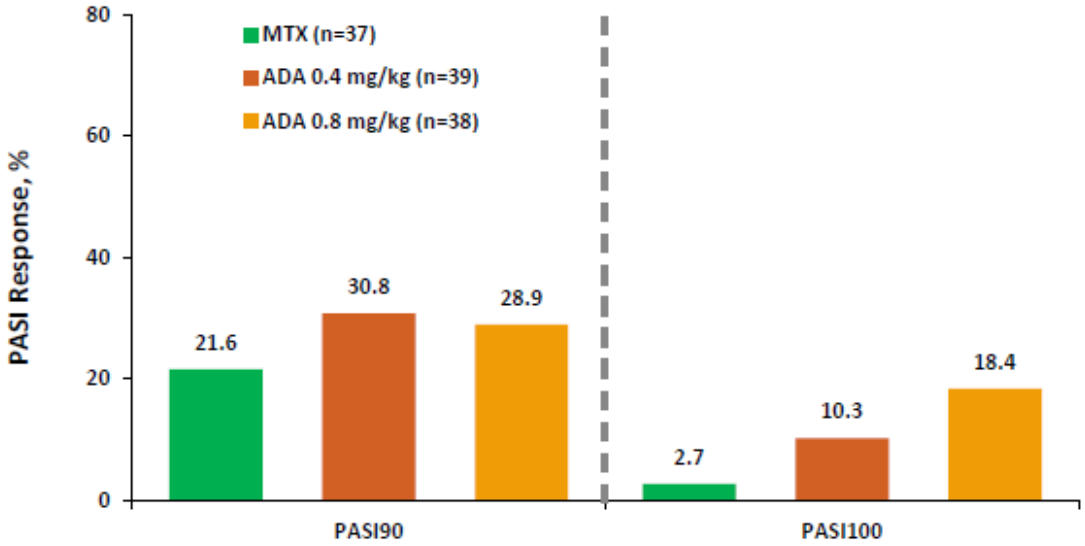
ADA, adalimumab; MTX, methotrexate; PASI75, ≥75% improvement in Psoriasis Area and Severity Index.
*P<0.05 ADA 0.8 mg/kg vs. MTX.

Note: 0.8mg/kg is the licensed dose for adalimumab in the paediatric population for plaque psoriasis and therefore of consideration in this appraisal; information on the 0.4mg/kg has been included for data completeness.

PASI90/100: A numerically higher proportion of patients receiving 0.8mg /kg ADA achieved a PASI90 (28.9%) or PASI100 (18.4%) response at week 16 than patients receiving MTX at 21.6% and 2.7%, respectively.

Figure 3 below presents a graphical representation of the responses across trial arms.

Figure 3: PASI90/100 responses at week 16 for ADA vs. MTX



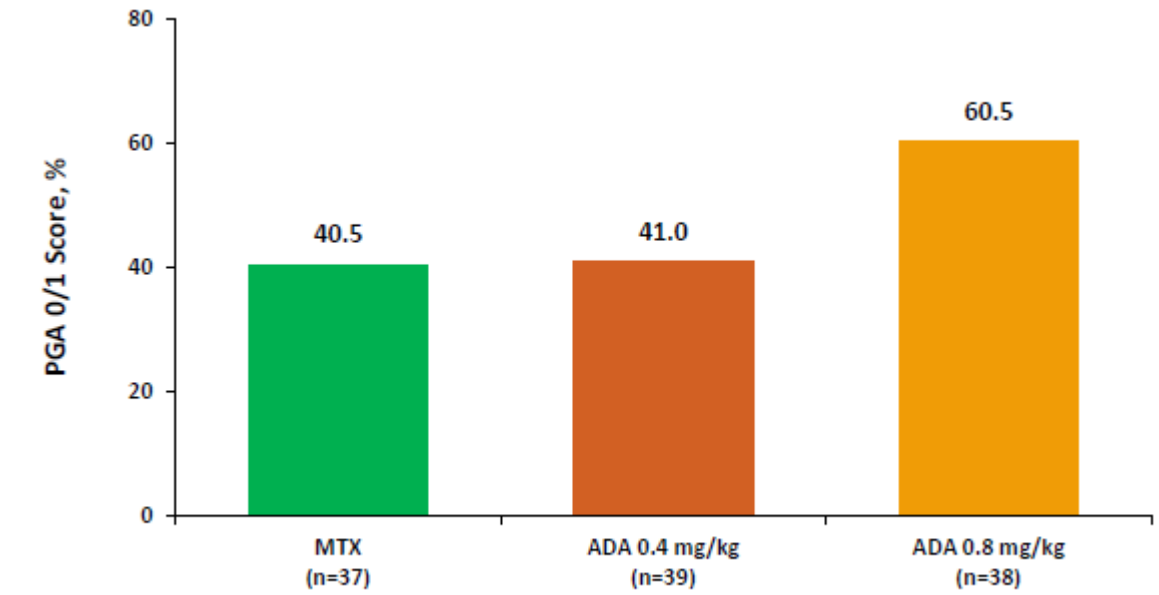
ADA, adalimumab; MTX, methotrexate; PASI90/100, ≥90%/100% improvement in Psoriasis Area and Severity Index.

Note: 0.8mg/kg is the licensed dose for adalimumab in the paediatric population for plaque psoriasis and therefore of consideration in this appraisal; information on the 0.4mg/kg has been included for data completeness.

PGA responses: Approximately 20% more patients receiving 0.8mg/kg ADA achieved PGA 0/1 (clear, minimal) at week 16 (60.5%) than patients receiving MTX (40.5%; p-0.083). The magnitude of the treatment effect with o.8mg/kg is considered clinically relevant. Patients treated with 0.8mg/kg ADA achieved PGA 0/1 (clear, minimal) responses earlier than patients treated with MTX; at week 4, PGA 0/1 response rates were 28.9% and 8.1%, respectively.

Figure 4 below presents a graphical representation of the responses across trial arms.

Figure 4: PGA 0/1 (clear, minimal) responses at week 16 for ADA vs. MTX



ADA, adalimumab; MTX, methotrexate; PGA, Physician's Global Assessment. PGA 0/1 is defined as PGA clear or minimal.

Note: 0.8mg/kg is the licensed dose for adalimumab in the paediatric population for plaque psoriasis and therefore of consideration in this appraisal; information on the 0.4mg/kg has been included for data completeness.

Improvement in PedsQL scores:

[redacted]

Period B: Withdrawal/no medication treatment phase (ADA vs. MTX); up to 36 weeks

PASI and PGA

Responses: [redacted]

Period C: Double blind re-treatment phase; 16 weeks

PASI Responses:

[redacted]

PGA responses:

[redacted]

[redacted]

Improvement in PedsQL scores:

[redacted]

Period D: Long term follow up; 52 Weeks

PASI Responses:

[redacted]

PGA responses:

[redacted]

Improvement in PedsQL scores:

[redacted]

4.6 Subgroup analysis

The pre-planned sub-group analyses were conducted in line with the study hypotheses i.e. determine time to loss of disease control and ability to regain response upon re-treatment. A summary of some of the pre-planned sub-group analyses and their corresponding justifications is presented below.

[redacted]PASI 50/75/90/100 Responses:

[redacted]

[redacted]PGA 0, 1 (Cleared, Minimal) Responses:

[redacted]

[redacted]

CDQI Responses:

[redacted]

PedsQL Responses:

[redacted]

4.7 Meta-analysis

A meta-analysis was deemed neither feasible nor appropriate to conduct due to the differences in; study designs, comparators, inclusion/exclusion of study participants, variations in the reporting of study outcomes, as well as outcome measures across the biologics studies.

4.8 Indirect and mixed treatment comparisons

In the absence of head to head trials comparing adalimumab to etanercept and ustekinumab, AbbVie considered undertaking an indirect comparison. However, this was deemed unfeasible to the substantial differences in the respective marketing

authorizations across the biologics treatments relevant to this appraisal, scarcity of high quality studies as well as significant heterogeneity across the relevant studies.

Examples of heterogeneity including, but not limited to, differences in;

- Classification of severity in plaque psoriasis, including end-point definitions across studies
- Patient demographics i.e. age categories in line with the respective MAs
- treatment and/or clinical trial durations
- Study designs i.e. lack of common comparator, open label, single arm studies
- Type and nature of concomitant treatments used across trials i.e. impact on observed treatment effects.

Due to the considerable heterogeneity across trials, AbbVie decided within the submission to only present the evidence base for adalimumab from the robust interventional and observational study data on paediatric plaque psoriasis for this MTA.

4.9 Non-randomised and non-controlled evidence

No adalimumab specific observational studies within the paediatric population were identified through the electronic literature search. Furthermore, no AbbVie data on file are available to address the data gap(s). Nevertheless, for completeness, data from key observational studies relating to patients with adult plaque psoriasis are presented; two studies were identified through a tailored literature search.

Leman et al. (2015) study[15] was a prospective observational research study of UK adults with plaque psoriasis. The main objective of the study was to assess change in patient reported Dermatology Life Quality Index (DLQI) measurement after initiating therapy with adalimumab in patients with severe psoriasis. The results

indicate that hospital anxiety and depression scale (HADs), SF-12 (short-form-12), SAPASI and cutaneous body image scale (CBI) scores were significantly lower at both 16 weeks and 6-month post adalimumab initiation compared to baseline. Therefore adalimumab is associated with improvements in disease severity, psychosocial wellbeing leading to an increased quality of life in patients with plaque psoriasis. Similarly, the Menter et al. (2015) study[16] assessed the long-term safety and effectiveness of adalimumab treatment in routine clinical practice for patients with moderate to severe chronic psoriasis in adult patients in UK and Canada. Interim results [5 year time-point] indicate that adalimumab was well tolerated and no new safety signals were identified. Furthermore, the results are comparable with the adalimumab clinical trials, informing the marketing authorisation, and post marketing surveillance.

Given the evidence base across the adult and paediatric populations, the safety profile of adalimumab remains unchanged.

A summary of the key observational studies in the adult population with plaque psoriasis is presented in Table 15 below.

A summary of the key observational studies is presented in Table 15 below.

Table 15: List of key observational studies for adalimumab in the adult population with plaque psoriasis

Study ID	Study design	Intervention	Total sample size recruited	Study duration	Location	Notes
Leman et al. (2015)[15]	Prospective observation research study	Adalimumab	153	Unclear	UK	Abstract data only
Menter et al. (2015)[16] ESPRIT	Observational registry	adalimumab	N=6059	Median registry exposure was between 765 and 677 days	USA and Canada	On-going [10 yr.-study]; 5-year analysis of data available.

4.10 Adverse reactions

Summary of findings; Safety

Adalimumab has a long-term safety and tolerability profile established in at least 10 years of real-world use in the paediatric population. [redacted].[1]

Data on the short and long term safety and tolerability are available from both clinical trials and observational studies.

Adalimumab has a similar safety profile to MTX (UK standard of care for psoriasis). This was demonstrated in a head to head, double blind randomised trial indicating that adalimumab was generally well tolerated and had a similar safety profile to MTX, and no new safety risks were identified.

In the paediatric population, the adalimumab trial (M04-717)[6] is the first and only study comparing its efficacy and safety to that of methotrexate. Therefore, this provides an insight in to how adalimumab may fit in to the current treatment pathway for the treatment of plaque psoriasis in children and young people.

Low rates of serious adverse events are reported across the clinical trials. No deaths were reported in the (M04-717)[6] trial which informs the evidence base for this appraisal. Also, there were no study and/or drug discontinuations during the treatment phase.

4.10.1 Interventional studies

Only one randomised double blind controlled clinical trial (M04-717)[6] informs the evidence base on safety of adalimumab compared to methotrexate (standard of care for psoriasis), for this appraisal. The observed adverse events were categorised as mild, moderate and severe, although infectious adverse events were of special concern.

Adverse events: Only 73.7% (84/114) of patients experienced any adverse events; 28 patients from MTX arm, 30 from adalimumab 0.4mg/kg and 26 patients from adalimumab 0.8mg/kg. Infectious adverse events were the most common adverse events of interest, and incidences were relatively similar across the treatment arms. A total of 60 (52.6%) patients reported some sort of infection (serious infection, malignancy, allergic reaction and injection site reaction) during the treatment phase of the study.

Discontinuations: No patients prematurely discontinued from the study owing to an adverse event, and no deaths during the treatment phase of the study were observed.

A summary of the adverse events observed in the treatment phase of the M401-717 adalimumab trial is presented in Table 16 below.

Table 16: Adverse events, AE [treatment phase of the trial – Period A; 16 weeks]

Domain, n (%)	MTX (n=37)	Adalimumab		Total (N=114)
		0.4 mg/Kg (n=39)	0.8 mg/Kg (n=38)	
Any AE	28 (75.7)	30 (76.9)	26 (68.4)	84 (73.7)
Any severe AE	2 (5.4)	5 (12.8)	1 (2.6)	8 (7.0)
Any serious AE	0	3 (7.7)*	0	3 (2.6)
Any serious AE at least possibly related to study drug	0	0	0	0
Any AE leading to discontinuation	0	0	0	0
Death	0	0	0	0
All infections	20 (54.1)	22 (56.4)	18 (47.4)	60 (52.6)
Serious infections	0	1 (2.6)	0	1 (0.9)
Malignancy	0	0	0	0
Allergic reaction	2 (5.4)	1 (2.6)	0	3 (2.6)
Injection site reaction	3 (8.1)	3 (7.7)	4 (10.5)	10 (8.8)

AE- adverse event; MTX, methotrexate; Safety analysis was evaluated in all patients who received ≥1 dose of the study drug(s).

* One infection event (gastrointestinal infection, noted by the investigator as food poisoning) reported by a patient in the 0.4-mg/kg ADA group was serious.

4.11 Interpretation of clinical effectiveness and safety evidence

Adalimumab is an effective treatment in the treatment of paediatric patients, from 4 years of age with severe chronic plaque psoriasis who have an inadequate response to or are inappropriate candidates for topical therapy and phototherapies. Both in the short/long term, patients using adalimumab experienced a significantly clinically relevant PASI75/90/100 response rates versus methotrexate. Also, a range of tools such as CDLQi demonstrate that positive PASI responses were associated with improved health related quality of life in children and young people. Furthermore, adalimumab has a long term safety and tolerability profile established in at least 10 years of real-world use both in the paediatric and adult populations.

Adalimumab has already received positive recommendation(s) from the SMC and AWMSG UK HTA bodies for the treatment of plaque psoriasis in paediatrics, in line with its marketing authorisation. Therefore, adalimumab should continue to be recommended as an effective treatment for the treatment of children and young people with plaque psoriasis.

The high quality body of evidence has shown that adalimumab is an effective and well tolerated treatment in plaque psoriasis within its licensed indication. The pivotal adalimumab trial had a unique design which included 4 study periods, including the treatment phase that allowed for a head to head comparison with MTX; thereby demonstrating superiority in efficacy over MTX which is the UK standard of care for patients with psoriasis. This means that adalimumab may be used as a first choice systemic therapy as well as a first choice biologic in children, as young as 4 years of age, and young people with plaque psoriasis.

Nonetheless, there are several limitations to the evidence base. Very few observational/real-world evidence studies within the paediatric population were identified which may limit observation beyond clinical trial settings. Furthermore, no head to head trials with relevant biologics (etanercept and ustekinumab) were identified. Additionally, due to the variations in the respective marketing authorisations, as well as variations in clinical study trial designs, lack of common comparators, study/treatment durations, this limited the feasibility of undertaking a meta-analysis and/or indirect comparison of the respective interventions.

Despite these limitations, the robust adalimumab clinical trial (M404-717)[6] in combination with other relevant peer reviewed literature and at least 10 years of use in the paediatric population, means that adalimumab has a comprehensive evidence base to support its clinical effectiveness profile, and represents good value for money to the NHS i.e. no requirement for additional resource use above and beyond current clinical practice following adalimumab recommendation for use in a population under consideration in this appraisal.

4.12 Ongoing studies

There are no on-going studies for adalimumab in this patient population.

5 Cost effectiveness

Adalimumab is clinically effective and represents value for money to the NHS

- **Adalimumab has previously been found to be both a clinically and cost-effective technology for the use of NHS Scotland and Wales resources by the Scottish Medicines Consortium (SMC) and All Wales Medicine Strategy Group (AWMSG), respectively. Both recommendations are in children and young people with plaque psoriasis, in line with the adalimumab marketing authorisation.**
- **Adalimumab is an established treatment in the treatment of adults with plaque psoriasis following a positive recommendation from NICE [TA146][38] based on the clinical and cost effectiveness evidence base from the adult population.**
- **AbbVie undertook a feasibility assessment which identified that data limitations remain particularly in the identification of key model attributes such as utilities and natural history data that are required for modelling a life-time horizon in a paediatric population, as per the NICE Reference Case.**
- **For these reasons, any cost-effectiveness evidence submitted would continue to be associated with considerable and unresolvable uncertainty. Therefore, AbbVie have not submitted a cost-effectiveness model for this appraisal.**

AbbVie have undertaken a targeted review of publications and major HTA bodies that report cost-effectiveness analyses for adalimumab in paediatric patients with plaque psoriasis. Our findings confirm that there is a paucity of robust data in this field. Nevertheless, one relevant study assessing number needed to treat and the corresponding incremental costs was identified.

Langley et al. (2014)[39] undertook a Bayesian network meta- analysis and calculated the numbers need to treat for efficacy measures between adalimumab, etanercept, infliximab and ustekinumab. Based on this analysis, the number needed to treat to achieve PASI-75 response was 1.28 for infliximab 5 mg/kg, 1.49 for ustekinumab using weight based dosing, 1.58 for adalimumab 40 mg EOW; 2.10 [1.86- 2.38] for etanercept 50 mg BIW, and 3.05 for etanercept 25 mg BIW. The incremental cost per PASI-75 responder based on this analysis was found to be £6,130 [£5,572 to £7,020] for adalimumab, £7,221 [£6,740 to £7,817] for ustekinumab, £7,570 [£7,091 to £8,101] for infliximab, £8,019 [£6,573 to 9,930] for etanercept 25 mg, and £10,188 [£9,007 to £11,544] for etanercept 50 mg. Although Infliximab was found to require the lowest number needed to treat to achieve PASI-75 response, adalimumab was found to be the most cost-effective treatment option in terms of incremental cost per PASI-75 responder.

5.1 Assessment of factors relevant to the NHS and other parties

Patient care/service flexibility

Adalimumab, equally to etanercept and ustekinumab, is administered subcutaneously, which means that the treatment may be self-administered by the patient and/or carer at home. This offers flexibility to patients and their families, and therefore has no cost impact for the NHS.

Cost analysis

Given that adalimumab is an established clinical and cost-effective technology in the treatment of adults with plaque psoriasis within Wales and Scotland, the long term treatment costs in the adult population are relatively generalizable to the paediatric population following 12 months of initial therapy. For-example, the cost acquisition for humira in paediatrics in the first 12 months of treatment is lower than that of an adult patient due to a different loading dose therefore paediatrics will have one dose less than their adult counterparts. Consequently, adalimumab offers good value for money to the NHS in the paediatric population.

A comparison between the adalimumab acquisition costs in both the adult and paediatric populations is presented in Table 17 below

Table 17: Acquisition costs for adalimumab in both the paediatrics and adult populations

	Cost per vial/year	Total annual drug acquisition cost (exc VAT)
Year 1 [paediatrics]	£352.14 per vial @ 27 vials / year	£9507.78
Year 1 [Adults]	£352.14 per vial @ 28 vials / year	£9,856.92
Year 2 [paediatrics]	£352.14 per vial @ 26 vials / year.	£9155.64
Year 2 [Adults]	£352.14 per vial @ 26 vials / year.	£9155.64
Drug acquisition costs are exclusive of value added tax (VAT)		

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people

Company evidence submission

September 2016

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1. Executive summary

Background

This submission relates to the management of young people (aged 12 years old and over) suffering from moderate to severe psoriasis (i.e. with raised, red and coarse scaly plaque lesions covering approximately 10% to 30% or more of body surface). (1) Severe psoriasis in young people can have a profound long-term impact on the psychological health of affected young people and is often associated with multiple comorbidities. (2),((3),(4))

Due to the lack of clinical guidelines in children and young people and of licensed treatments in this population, effective therapies are needed, and this NICE appraisal will fill an important gap.

Ustekinumab is a newly licensed biological treatment for young people with moderate to severe PsO, providing an alternative therapy with a broader license and a different mode of action a different mode of action to currently licensed TBF-inhibitors, namely etanercept and adalimumab. (5),(6) Ustekinumab is administered every 12 weeks in its maintenance phase (after the first 4 weeks of treatment), a less stringent dosing schedule compared to other biologics. (5), (7), (8)

While effective, TNF inhibitors are perceived to be a less refined treatment for PsO compared to the more advanced biologics which achieve better results and a recent international survey (MAPP) of patients with PsO or psoriatic arthritis (PsA) highlighted UK patients' dissatisfaction with current systemic treatment options (see Section 3. .

Clinical Evidence

There are a limited number of rigorous clinical trials in paediatric PsO, especially for systemic treatments, although the clinical evidence available suggests that ustekinumab is an important treatment option to consider. (2)

The efficacy and safety of ustekinumab in PsO adolescents has been studied in the pivotal phase III, international randomised controlled clinical trial, CADMUS comparing ustekinumab to placebo. (2) Patients enrolled in the trial were followed up to week 52 for efficacy and week 60 for safety. CADMUS primary endpoint was measured at 12 weeks, following which all placebo patients crossed over to ustekinumab:

- At week 12, 25 (69.4%) of ustekinumab patients achieved a PGA 0/1 (i.e. absence of any lesion to minimal raised plaque to 0.25 mm with fine / faint lesion) compared with 2 (5.4%) in the placebo group (P < .001); of those 25 patients, 17 (47.2%) achieved a PGA score of 0 (cleared of all lesions), compared to 1 (2.7%) patient in the placebo arm. (9)
- At Week 12, 29 (80.6%) patients in the ustekinumab group achieved a PASI 75 response, i.e. a 75% reduction in their baseline PASI score, compared with 4 (10.8%) in the placebo group (p<0001). (9)
- At Week 12, 22 (61.1%) of ustekinumab patients achieved a PASI 90 response, corresponding to a 90% reduction in their baseline PASI score, compared with 2 (5.4%) in the placebo group (p<0.001). (9)

Furthermore, patients treated with usketinumab reported a significantly higher improvement in their health-related quality of life (HRQoL), as measured by the Children's Dermatology Life Quality Index (CDLQI), at week 12 and maintained this improvement to week 52. (9)

These results reported in the CADMUS trial in young people with PsO are consistent with the results reported in the adult population (PHOENIX 1 and PHOENIX 2 trials). (10),(9)

In the absence of long-term extension studies in the adolescent population, observational studies (BADBIR, PSOLAR) and clinical trials (PHOENIX 1 and PHOENIX 2) of ustekinumab in adults were considered. PASI 75 response rates at week 28, when steady state was achieved, from the CADMUS trial and the PHOENIX adult ustekinumab studies showed that the response observed was similar to (or higher than) that in adults. (10),(9),(11) Long term data from PHOENIX 1 & 2 and the two

registries suggest that the efficacy benefits with ustekinumab are likely to be maintained over time (particularly when adolescents become adults). (12),(13),(10),(11)

There are no head-to-head trial data available comparing ustekinumab to any other biologics or best supportive care (BSC) in young people with PsO. (14) Only three randomised clinical trials were identified during the systematic literature review and an adjusted indirect comparison (AIC) was undertaken to compare the efficacy of ustekinumab against etanercept. (14) Results of an adjusted indirect comparison (AIC) for ustekinumab against etanercept showed a positive trend in favour of ustekinumab in each comparison, i.e. PASI 50, PASI 75, PASI 90, and PGA 0-1(see Section 5.6. . The positive trend for ustekinumab compared to etanercept in young people is further supported by the adult head- to- head ACCEPT study of etanercept compared to ustekinumab in adults, which was sufficiently powered and demonstrated a significant improvement of ustekinumab compared to etanercept: 68% of patients treated with ustekinumab 45mg achieved PASI 75 response compared to 57% treated with etanercept 50mg twice weekly (p<0.001). (15)

A naïve comparison of the week-16 response rates on PGA, PASI 75, 90 and 100 suggests a higher clinical response with ustekinumab compared to adalimumab and methotrexate (see **Error! Reference source not found.**), although these results should be interpreted with caution in light of the differences in baseline characteristics of the study populations (e.g. difference in age range, baseline PASI severity, etc.) and differences in trial design.

Table 1 Response rates on PGA, PASI 75, 90, 100 and change in CDLQI score reported at week 16 ((16) and (9))

	M04-717 trial		CADMUS trial
Response rates at 16 weeks	Adalimumab 0,8 mg/kg	Methotrexate	Ustekinumab standard dose
PGA (cleared or minimum) 0/1	23/38 (60.5%)	15/37 (40.5%)	[redacted]
PASI 75	22/38 (57.9%)	12/37 (32.4%)	[redacted]
PASI 90	11/38 (28.9%)	8/37 (21.6%)	[redacted]
PASI 100	7/38 (18.4%)	1/37 (2.7%)	[redacted]
Change in CDLQI score	-6.60	-5.00	[redacted]

* CDLQI scores for ustekinumab were reported at week 12 (CDLQI scores were not reported at week 16 in CADMUS trial).

Furthermore, BADBIR and PSOLAR registries demonstrated consistently better results in terms of long term maintenance of efficacy and safety for ustekinumab compared to the other biologics (i.e. etanercept, adalimumab and infliximab) in the adult population. (12), (13). Although these registries are conducted in an adult population, these results provide a good indication of what the long term efficacy of ustekinumab would be when the adolescents become adults.

From a safety point of view, 44.4% of the young people treated with ustekinumab reported ≥1 AE at week 12 compared to 56.8% in the placebo group. Most AEs were mild or moderate. In general, AE rates were similar across treatment groups. At week 60, infections and infestations was the most common category of AEs, with naso-pharyngitis (34.5%), upper respiratory tract infection (12.7%), and pharyngitis (8.2%) occurring most often. The safety profile of ustekinumab in this adolescent PsO population was generally consistent with that observed in the adult PsO populations, and no new safety issues were identified (see section 4.3.1.).

Ustekinumab presents the added advantage of a lower frequency of injections (every 12 weeks, after the initial loading doses at weeks 0 and 4) compared to etanercept (every week) and adalimumab (weekly for the first 2 doses, then every other week), which reduces the burden to patients and carers who administer the subcutaneous injections (see section 2.2.) and is linked to a reduction in injection site infections; only 1 out of a total 508 of ustekinumab injections results in a mild injection site reaction and that was in the SD arm (see Section 4.6.2.), compared to the NCT00078819 study which reported 62 injection site reactions in the etanercept arm (17).

Expected Cost-effectiveness

As explored in Section 6. , despite previous UK HTA submissions in children and adolescents with PsO, there remains a paucity of data available to develop a cost effectiveness model for the young population. However, given the similarities between the young (from 12 to 17 years old) and the adult populations in terms of response rates in the CADMUS trial compared to the PHOENIX trials up to 52 weeks (see Sections 4.5. and 4.8.3.), long term efficacy in the adolescent population could be extrapolated. Ustekinumab responses rates in PASI 50, 75 and 90 and PGA 0-1 are higher to those reported by etanercept and adalimumab (naïve comparison), whilst having equivalent drug and administration costs (see Sections 5.5. 5.6.). This is further supported by the withdrawal rate in long-term adult registries which demonstrate that adult patients remain on ustekinumab longer than assumed in previous NICE appraisals (see Sections 4.8.1. and 4.8.2.).

Under these conditions, it is expected that ustekinumab in young people aged 12 years and older with moderate to severe psoriasis is a more cost-effective use of NHS resources that in the adult population.

Budget Impact Analysis

The net budget impact of introducing ustekinumab as an alternative treatment option to TNF inhibitor for young people with moderate to severe psoriasis in the UK is expected to range between £40,491 in year 1, to £43,962 in year 5. With its three-monthly dosing schedule, ustekinumab's drug acquisition costs would be partially offset by savings in administration costs should a nurse be involved.

2. The technology

2.1. Description of the technology

On the 21st May 2015 ustekinumab became the first cytokine inhibitor to receive market approval for the treatment of moderate to severe plaque psoriasis in young people (ages 12 -18 years) (5).

Ustekinumab is classed as a biologic drug and is the only available treatment option with a mode of action different from the 2 alternative TNF-α inhibitor biologics in the treatment of plaque psoriasis. TNF-α is produced by a wide range of immune and non-immune cells and accordingly TNF-α inhibitors have broad anti-inflammatory effects. More recently, IL-12 and IL-23, cytokines that induce naive CD4+ lymphocytes to differentiate into type 1 helper T cells (Th1 cells) and type 17 helper T cells (Th17 cells), respectively, have been identified as key mediators of psoriasis. This suggests that IL-12/23 blockers, such as ustekinumab, may provide a more effective treatment of PsO, due to them being further down the inflammatory cascade and are thus better at targeting the part of the inflammatory cascade most relevant to PsO, while leaving the part of the inflammatory cascade less specific to PsO intact. (15)

There is a need for new, practical, safe, systemic therapies for paediatric PsO (2):

- A third of PsO patients develop symptoms before age 20
- PsO prevalence increasing in the paediatric population
- Emotional impairment of children <17 comparable to that in paediatric patients with arthritis, asthma and diabetes
- Limited treatments available for children with PsO
- Limited number of rigorous clinical trials in paediatric PsO, especially for systemic treatments
- Many common therapies for PsO are not practical for young people

In a disease with few licensed drugs for the younger population, having a therapy with a different mode of action will offer an alternative option to young people, in a disease area where few therapies are licensed and recommended.

2.2. Licensed indication and dose

Ustekinumab is currently indicated for:

- the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A),
- the treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies, and
- the treatment of active psoriatic arthritis in adult patients either alone or in combination with MTX, when the response to previous non-biological disease modifying anti-rheumatic drug (DMARD) therapy has been inadequate. (5)

This multiple technology appraisal (MTA) is specific to the treatment of plaque psoriasis in children and young people. As a result, this submission will focus on any evidence for ustekinumab within young people.

NICE have previously recommended ustekinumab for the treatment of adults with moderate to severe psoriasis and for treating active psoriatic arthritis (Technology appraisals TA180 and TA340, respectively).

Ustekinumab is available in the UK as a 45mg pre-filled syringes and vials and 90mg pre-filled syringes with a recommended weight-based dose of 0.75 mg/kg for patients < 60 kg, 45mg for patients ≥ 60-≤ 100 kg; and 90mg for patients > 100kg. For young people with moderate to severe plaque psoriasis, the recommended posology of ustekinumab is an initial subcutaneous dose of 0.75 mg/kg, 45mg or 90mg at weeks 0 and 4, followed by maintenance dosing every 12 weeks (see Table 2). (18) The frequency of dosing, compared to that of adalimumab (weeks 0, 1 and then every other

week) and etanercept (weekly) would reduce the administrative burden to carers and patients. (19), (20)

Table 2 Recommended dose of STELARA for paediatric psoriasis (5)

Body weight at the time of dosing	Recommended Dose
< 60 kg	0.75 mg/kg
≥ 60-≤ 100 kg	45 mg
> 100 kg	90 mg

To calculate the volume of injection (ml) for patients with a weight below 60 kg, the following formula is used: body weight (kg) x 0.0083 (ml/kg) or see Table 3. The calculated volume should be rounded to the nearest 0.01 ml and administered using a 1 ml graduated syringe.

Table 3 Injection volumes of ustekinumab for paediatric psoriasis patients < 60 kg (5)

Body weight at time of dosing (kg)	Dose (mg)	Volume of injection (mL)
30	22.5	0.25
31	23.3	0.26
32	24.0	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27.0	0.30
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30.0	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33.0	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36.0	0.40
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39.0	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42.0	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

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

Psoriasis is a chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations. It is characterised by scaly skin lesions, which can be in the form of patches, papules, or plaques. Plaque psoriasis is the most common type of psoriasis, representing 90% of cases. (21)

Plaque psoriasis in young adults clinically exhibits both similar and different characteristics compared with adult PsO; the lesions are usually smaller, thinner and less scaly than those seen in adults, with the scalp and face the most affected areas, followed by the extensor surfaces of knees and elbows, the trunk and the groin. On the other hand, adolescent PsO may be associated with significant comorbidity (hyperlipidemia, obesity, hypertension, diabetes mellitus, rheumatoid arthritis and Crohn's Disease), as is the case with adults. (6)

The overall severity of PsO is assessed by the how much of the body surface area is covered, induration (thickness) of the psoriasis, extent of scaling and erythema (redness of the skin that results from capillary congestion). (6)

Clinical assessment of PsO severity is evaluated using the Psoriasis Area and Severity Index (PASI), the generally accepted standard, and the Physician's Global Assessment (PGA) of particular relevance in children of a younger age. (22)

- **Psoriasis Area and Severity Index (PASI) -** The PASI combines assessments of the extent of body-surface involvement in four anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque thickness in each region, yielding an overall score of 0 (no psoriasis) to 72 (severe disease). A PASI 50 response is defined as ≥50% improvement in PASI score from baseline; PASI 75 and PASI 90 are similarly defined as achievement of thresholds of % improvements in PASI.
- **Physician's Global Assessment (PGA) -** The PGA rates the patient's psoriasis overall relative to baseline as 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (marked) or 5 (severe), and considers involvement of body surface area, induration (thickness), scaling, and erythema.

A patient presenting with moderate PsO at baseline (a PASI score of 7-12), is likely to have a lower body surface area covered in plaques and are likely to score 'severe' in one of the 3 assessment critera. (1) Therefore we would expect a patient with moderate PsO to be more likely to achieve clear skin (i.e. PASI 100) or nearly clear skin (i.e. PASI 90), after treatment, compared to a patient with severe PsO, who would have nearly a third of their body surface area covered in plaque.

The impact of psoriasis on quality of life is particularly evident in young people, as they deal with a potentially disfiguring and lifelong disease, which could permanently impair their psychological development. Even relatively mild forms of the disease could have a major impact in the quality of life of young people, who can be severely affected psychosocially, underlying the need for prompt, effective treatment, and long-term disease control. (6)

Severe PsO is usually present in post-pubescent young people, and in comparison is rarely seen in children younger than 10 years old, with a prevalence of 0.55%, although the reason for this is unclear. (23) This appears to be substantiated by one-year period prevalence rates per 1,000 patients reported: 5 children age 5-9, 9 children in ages 10-14 and 15 adolescents age 15-19 years old (24). A population-based study designed to determine prevalence in the UK reported the prevalence of psoriasis in those aged between 10 and 19 years is around 1.4% in the UK, and varies between boys and girls. (25), (24)

The estimated prevalence of people with severe psoriasis currently eligible for biological therapy in England is 1.1% of those with psoriasis. (26)

While the prevalence of plaque psoriasis is relatively low in numbers, it is a disease which carries a burden for healthcare services; in 2014-15, for all age groups there were 1,253 hospital admissions due to plaque psoriasis (psoriasis vulgaris, with an ICD10 code of L40.0) in England, equating to 1,341 finished consultant episodes and 3,727 bed days. There were a total of 11 finished consultant episodes for patients aged up to 18 years in 2014-15 (27).

Current treatment pathway follows the NICE Clinical Guideline (CG153), which offers evidence-based advice on the management of psoriasis in adults, young people and children (28).
While not specific to children and young people with plaque psoriasis, these guidelines are generally followed for such patients in clinical practice (6). Key recommendations from CG153 are summarised below (28):

- Topical therapy should be offered as first-line treatment;
- Phototherapy should be offered to people with plaque psoriasis that cannot be controlled with topical therapy alone;
- Non-biological systemic therapy should only be offered when topical therapy fails to control disease and the disease is extensive or localised but associated with significant functional impairment and/or high levels of distress or phototherapy has been ineffective or cannot be used.

In clinical practice biologics are generally used after the failure of topical and non-biological systemic therapies (29). Therefore, we do not believe that topical therapies represent a relevant comparator for biologics in the model for this reason. Furthermore, ustekinumab is licensed for use in young patients (age 12 years and older) who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. (5) Therefore, in keeping with our license, the suitable comparators for consideration in this submission are other biologics.

It is estimated that currently only 50% of patients who satisfy the NICE eligibility criteria to receive biologic therapy for their psoriasis in England and Wales receive therapy, suggesting that a significant proportion of patients are undertreated and may be sub-optimally managed in clinical practice. (29) One reason for this could be patient preference for avoiding injectable therapy and avoiding the risk of serious adverse events, highlighted by a recent conjoint-analysis study in the UK (29).

Moreover, a definition for moderate disease lacks consensus, a recent publication has stated that patients with moderate psoriasis are defined as having disease that is too extensive for topical therapy alone but not severe enough to be eligible for biological therapy. (30)
Thus, there is a significant unmet need in patients who fail on or are contraindicated to conventional systemic non-biological therapy but who do not meet the eligibility criteria for biologic therapy due to disease severity.

Thus, there is a significant unmet need in patients with moderate PsO who fail on or are contraindicated to conventional systemic non-biological therapy but who do not meet the eligibility criteria for biologic therapy due to PsO not being severe yet.

Ustekinumab is licensed for use in young people who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. The only other treatment option for such patients in current practice is the use of alternative biological therapy; therefore, alternative biological treatments are the only clinically relevant comparators to ustekinumab in this indication as well as Best Supportive Care (BSC) for patients who have failed or are contra-indicated to systemic conventional (non-biological) therapies.

Biological treatments licensed for treating plaque psoriasis in children and young people that have been considered as part of this submission are summarised in Table 1. Additional biological treatments licensed for treating plaque psoriasis in adults includes infliximab; this treatment does not have marketing authorisation for children and young people and no evidence supports its use in this specific population. This submission will therefore not include any information about infliximab.

Table 4: Summary of biological therapy for treating plaque psoriasis in children and young people

	Treatment class	Indication specifications		
		Disease severity	Age range	Treatment history[a]
Adalimumab	TNF inhibitor	Chronic, severe	4 years +	Topical therapy Phototherapies
Etanercept	TNF inhibitor	Chronic, severe	6 years +	Systemic therapies Phototherapies
Ustekinumab	Cytokine inhibitor	Moderate to severe	12 years +	Systemic therapies Phototherapies
Key: TNF, tumour necrosis factor. **Notes**: [a], inadequately controlled by, or intolerant to.				

As this table shows, ustekinumab is the only cytokine inhibitor specifically licensed for treating PsO in young people with moderate to severe disease. With ustekinumab having the license to treat a wider

severity range than the TNF-inhibitors, it allows biologic treatment across the full moderate-to-severe range without restriction, which allows easier access to treatment for patients. (5)

4. Clinical Effectiveness

4.1. Identification and selection of relevant studies

4.1.1. *Systematic literature review*

A systematic literature review (SLR) was undertaken to identify all relevant clinical efficacy, safety and quality of life evidence for treatments used in paediatric PsO (14).

The systematic literature review was performed to robust methodological standards in order to meet the requirements of NICE, and followed the guidance of the Centre for Reviews and Dissemination. Details of this SLR are presented in the appendix (see Section **Error! Reference source not found.**

4.2. List of relevant randomised controlled trials

The clinical SLR identified two published RCTs, considered relevant to this submission. Both RCTs are presented in below in Table 5**.** The main studies identified were CADMUS for ustekinumab and NCT00078819 for etanercept. (9), (17)

Table 5 Studies included in this review

Study	Full reference
CADMUS (31)	CADMUS clinical study report
(9)	Landells I, Marano C, Hsu MC, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: Results of the randomized phase 3 CADMUS study. Journal of the American Academy of Dermatology. 2015; 73:594-603.
(2)	Landells I, Marano C, Hsu MC, et al. Safety and efficacy of ustekinumab in adolescent patients with moderate to severe plaque psoriasis: Results through 1 year of the phase 3 CADMUS trial. Journal of the American Academy of Dermatology. 2015; 72: AB202.
NCT00078819(17)	Paller AS, Siegfried EC, Langley RG, et al. Etanercept Treatment for Children and Adolescents with Plaque Psoriasis. New England Journal of Medicine. 2008; 358:241-51.
(32)	Landells I, Paller AS, Pariser D, et al. Efficacy and safety of etanercept in children and adolescents aged ≥ 8 years with severe plaque psoriasis. European Journal of Dermatology. 2010; 20:323-8.
(33)	Langley RG, Paller AS, Hebert AA, et al. Patient-reported outcomes in paediatric patients with psoriasis undergoing etanercept treatment: 12-week results from a phase III randomized controlled trial. Journal of the American Academy of Dermatology. 2011; 64:64-70.
(34)	Paller AS, Siegfried EC, Eichenfield LF, et al. Long-term etanercept in paediatric patients with plaque psoriasis. Journal of the American Academy of Dermatology. 2010; 63:762-8.
(35)	Siegfried EC, Eichenfield LF, Paller AS, et al. Intermittent etanercept therapy in pediatric patients with psoriasis. Journal of the American Academy of Dermatology. 2010; 63:769-74.

An additional reference for the NCT00078819 study, presenting subgroup data for young people (aged 12-17) in a letter to an editor, was identified by the SLR, but did not meet the inclusion criteria, because it was published in a letter (letters are usually considered a lesser source of evidence with higher risk of bias and poorer reporting of data). However, this publication provided useful evidence to allow a comparison to NCT00078819 using the same age group as the CADMUS study, and was therefore included in the analysis alongside the evidence base. (36)

In addition, the European Medicines Agency (EMA) Assessment Report for Enbrel (20 November 2008) reported further subgroup data for the NCT00078819 study, including PASI 90 response rates and was therefore also included in the analysis alongside the main trial data. (37)

Finally, the European Medicine Agency (EMA) also produced an Extension of indication variation Assessment Report for (adalimumab**)** Humira (26 February 2015), which reported some data from the yet unpublished clinical trial versus methotrexate (M04-717), which was felt to be significant enough for inclusion, as it was a comparator in the NICE scope. (16) The M04-717 study is a multicentre, randomised, double-dummy, double-blind study evaluating two doses of adalimumab versus methotrexate in paediatric subjects with chronic plaque PsO.

No other trials for methotrexate or ciclosporin were found.

4.2.1. *Quality assessment of the relevant randomised controlled trials*

Table 6: Quality appraisal of studies included in this submission

Quality Appraisal	CADMUS	NCT00078819	M04-717
1. Was randomisation carried out appropriately?	Yes	Yes	Yes
2. Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
3. Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
4. Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
5. Were there any unexpected imbalances in drop-outs between groups?	No	No	No
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
7. 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	Yes	Yes
Source: CADMUS (9, 31), NCT00078819 (17) and M04-717 (38)			

Overall, the differences between the study populations were minimal and are considered to be comparable.

4.3. Summary of methodology of the relevant randomised controlled trials

The efficacy of ustekinumab was studied in one randomised, multicentre, double-blind, placebo controlled phase 3 study (CNTO 275PSO3006 [CADMUS]) carried out in young people and is presented here as primary evidence in support of this submission.

As a key limitation of the CADMUS trial in the paediatric population was the lack of long term efficacy data beyond a 1-year follow up, the CADMUS trial is further supported by results taken from the British Association of Dermatologists Biologic Interventions Register (BADBIR), a prospective observational cohort study on the differential drug survival of biologic therapies for the treatment of psoriasis in adults (12). This registry was originally set up to gather observational data for patients age 16 years and older, although it has recently extended inclusion to patients younger than 16 years old (NICE Stakeholder Meeting, 11th August 2016).

In addition, the CADMUS trial is also further supported by five-year follow-up data from two trials in the adult population C0743T08 (PHOENIX 1) and C0743T09 (PHOENIX 2), used to validate that the

response observed in CADMUS is likely to be sustainable for adolescents becoming adults, as observed in the PHOENIX trials.

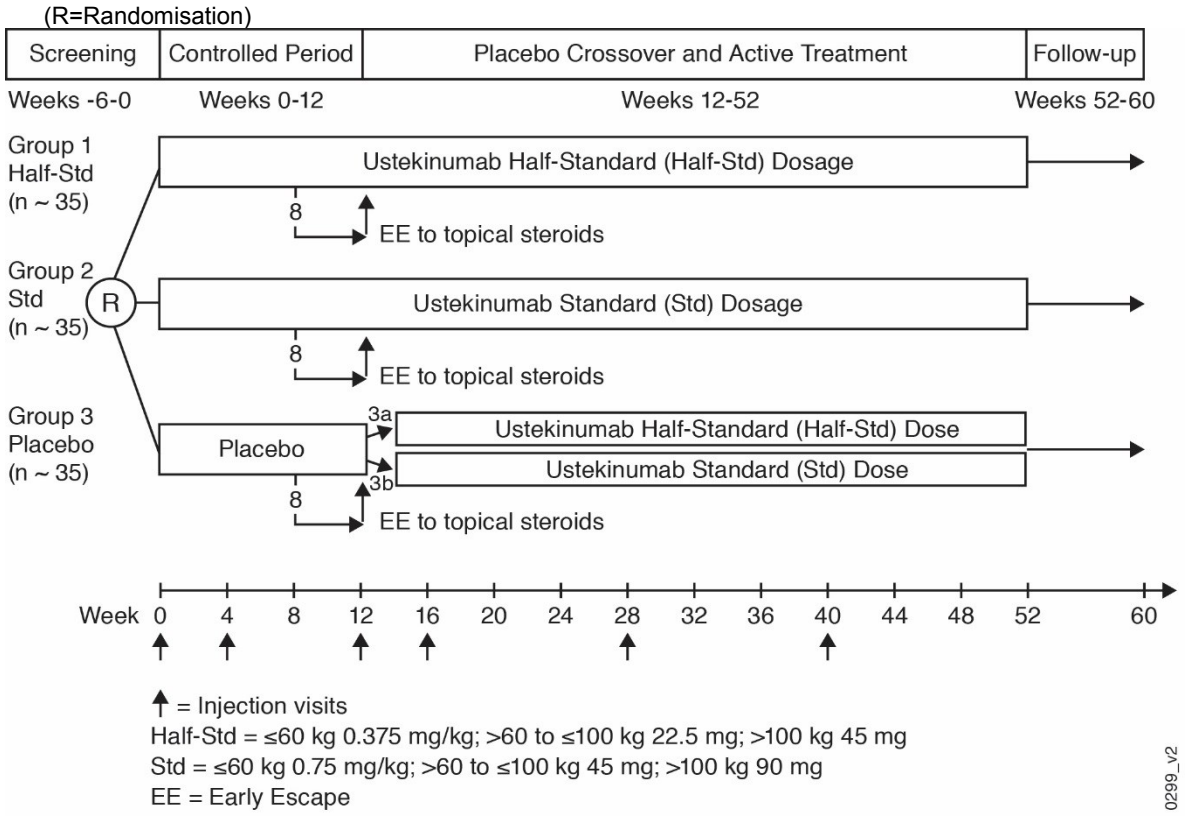
4.3.1. *Main study CNTO1275PSO3006 (CADMUS)*

Data for this section is drawn from the published paper by Landells et al, 2015 (9), the final Clinical Study Report (CSR) (31) and an oral presentation at the American Academy of Dermatology (AAD) 2015 congress (2).

4.3.1.1. Study design

CADMUS (CNTO1275PSO3006) was a phase 3 multi-centre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of ustekinumab in the treatment of young people with moderate to severe plaque-type psoriasis. The trial recruited 110 patients and was conducted at 36 sites in 10 countries in Canada and Europe; 3 sites were UK based with a total of 6 subjects. See schematic in Figure 1.

Figure 1 Study schema through week 60



At Week 0, 110 Patients were randomly assigned (2:2:1:1) to receive ustekinumab Standard Dose (SD) (n=36) or Half Standard Dose (HSD) (n=37) at weeks 0, 4, and 16 and thereafter every 12 weeks through week 40 or placebo (n=37) at weeks 0 and 4, with crossover to either ustekinumab SD (n=18) or HSD (n=19) at weeks 12 and 16 and every 12 weeks through week 40. In keeping in line with the license for ustekinumab, only the results for the standard dose arm are presented as part of this submission.

Subjects were followed for efficacy through to Week 52 and for safety and immunogenicity through to Week 60.

<u>Early Escape</u>

At Week 8, subjects whose PASI scores increased ≥50% from their baseline PASI score were allowed to early escape to the use of moderate to high potency topical steroid preparations through Week 12. It was recommended that subjects use no more than 60 grams per week. Class I (very-high potency) steroids were not allowed. After Week 12, subjects were encouraged to decrease and discontinue use of the moderate to high potency steroid by Week 16.

Full details of the methodology of CADMUS are presented in Table 7 below.

Table 7 Summary of methodology of CADMUS

Variable	CADMUS trial
Location	Belgium, Canada, France, Germany, Hungary, Portugal, Russia, Sweden, Ukraine and United Kingdom (6/110 patients)
Inclusion criteria	Adolescent subjects ≥12 to <18 years of age (excluding those who were pregnant or nursing or planning pregnancy [both males and females]) were eligible for this study if: • They had moderate to severe plaque-type psoriasis (defined by PASI ≥12, PGA ≥3, and BSA involvement ≥10%) • Were candidates for phototherapy or systemic treatment of psoriasis • Had psoriasis considered by the investigator as poorly controlled with topical therapy after an adequate dose and duration of therapy.
Exclusion criteria	• If they had non-plaque forms of psoriasis (e.g. erythrodermic, guttate, or pustular) or drug-induced psoriasis (e.g. a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium). • If they had used topical medications/treatments that could affect psoriasis or PASI evaluation within two weeks of first administration of study agent, or had received phototherapy or any systemic medications/treatments that could affect psoriasis or PASI evaluation within four weeks of the first administration of study agent. • If they had received any systemic immunosuppressants within four weeks of the first administration of study agent; had received any biologic agent within the previous three months or five times the half-life of the agent (whichever was longer); or had received natalizumab, efalizumab, or agents that deplete B or T cells within twelve months of screening. • If they had used any therapeutic agent targeted at reducing IL-12 or IL-23. • If they had any known malignancy or a history of malignancy, or known to be infected with human immunodeficiency virus, hepatitis B, or hepatitis C. Subjects with a history of the following were not eligible for enrolment into this study: • Chronic or recurrent infectious disease; serious infection; latent or active granulomatous infection (including TB); a nontuberculous mycobacterial infection or opportunistic infection; an immune deficiency syndrome; or a lymphoproliferative disease.
Design	Multi-centre, randomized, double-blind, placebo-controlled phase 3 study
Patient population	Adolescents (ages 12-17 years) with moderate to severe plaque psoriasis
Duration of study	March 2010 to January 2014
Method of randomisation	Dynamic central randomization was implemented in conducting this study. Subjects were randomly assigned to 1 of 4 treatment groups based on an algorithm implemented in the Interactive Voice/Web Response System (IVRS or IWRS) before the study. Dynamic central randomization minimizes the imbalance in the distribution of the number of subjects across treatment groups within the levels of each individual stratification factor: investigational site and baseline weight (≤60 kg, >60 kg). Based on the algorithm, the IVRS/IWRS assigned a unique treatment code, which dictated the treatment assignment. The randomization method was a minimization with a biased-coin assignment in a 2:2:1:1 ratio, to assign subjects to groups 1, 2, 3a, and 3b (see Figure 1)
Method of blinding (care provider, patient and outcome assessor)	The Sponsor, investigative study sites, and subjects remained blinded to treatment assignment until the last subject enrolled completed the Week 60 evaluations and the database was locked. To maintain the blind, all randomised subjects received each administration of study agent as two subcutaneous (SC) injections in two different locations. Therefore, subjects received both the half-standard and standard dosage volumes according to their randomised treatment group and body weight category The investigator was not provided with randomization codes. The codes were maintained within the IVRS or IWRS, which had the functionality to allow the investigator to break the blind for an individual subject.
Intervention(s) and	Ustekinumab (standard dosage) and ustekinumab (half standard dosage), versus placebo

comparator(s)	
Primary outcomes (including scoring methods and timings of assessments)	The proportion of subjects who achieve a PGA score of cleared (0) or minimal (1) at Week 12. Assessments done at week 0 and every 4 weeks after.
Secondary outcomes (including scoring methods and timings of assessments)	• The proportion of subjects who achieve a PASI 75 response at Week 12 • The change from baseline in CDLQI at Week 12 • The proportion of subjects who achieve a PASI 90 response at Week 12 All assessments were done at week 0 and every 4 weeks after.
Planned analyses	To examine the consistency of treatment effect for the primary and secondary endpoints, the proportion difference of the half-standard dosage and the standard dosage groups versus the placebo group and the corresponding 95% confidence intervals were provided for predefined subgroups as follows (see Section 4.5.3. : • Baseline demographic characteristics Baseline psoriasis disease characteristics Psoriasis medication history
Duration of follow-up	Weeks 52-60
Sources: CADMUS CSR (31)	

4.3.1.2. Treatments

The pharmacokinetics of ustekinumab is affected by body weight, although no clinically meaningful impact of age on the pharmacokinetics of ustekinumab was reported to date. (9) Since limited data from subjects with a body weight ≤60 kg were available in the two pivotal phase 3 adult studies (C0743T08/C0743T09) and ustekinumab has not been tested in subjects with a body weight <37.4 kg, body weight adjusted doses are considered to be appropriate for subjects with a body weight ≤60 kg (see Table 8).

The standard dosage was intended to provide ustekinumab exposure in the adolescent psoriasis population comparable to that achieved in the adult psoriasis population with the approved adult dosage.

The half-standard dosage was intended to provide ustekinumab exposure comparable to half of the approved psoriasis adult dosage, and was included to allow the ustekinumab pharmacokinetic-pharmaco-dynamic relationship between adult and adolescent psoriasis to be better defined, so that an appropriate adolescent psoriasis dosage approach could be efficiently determined.

Table 8 Ustekinumab Dosages in CADMUS

Subjects' BodyWeight	Standard Dosage	Half-Standard Dosage
≤60 kg	0.75 mg/kg	0.375 mg/kg
>60 kg through ≤100 kg	45 mg	22.5 mg
>100 kg	90 mg	45 mg

There were more patients with adverse events related to lack of efficacy in the half-standard dosage group when compared with the standard dosage group through 60 weeks. As a result, the EMA recommended that the standard dose should be the only one licensed for use in paediatric population. (5)

Therefore, in keeping with the licensed dose, only the results for the standard dose arm are presented as part of this submission, although full results are available in the CADMUS CSR. (5), (31)

4.3.1.3. Study outcomes: definitions

The definitions of the outcomes used in CADMUS are presented in Table 9

Table 9 Validity and clinical use of outcomes used in CADMUS

Outcome	Definition	Reliability/validity/current use in clinical practice
Primary outcome		
PGA	A score of either 0 (cleared) or 1 (minimal) measured at week 12	The PGA documents the physician's assessment of the subjects' psoriasis status according to the following categories: induration, scaling, and erythema. Higher scores indicate worse disease.
Secondary/exploratory outcomes		
PGA	A score of either 0 (cleared) or 1 (minimal) measured over time up to week 52. Proportion of subjects achieving a PGA score of mild or better (≤ 2) will be summarized over time. Sub-group analyses over demographics, baseline disease characteristics and prior medications.	As above
PASI 75	A PASI 75 response is defined as ≥75% improvement in PASI score from baseline, at week 12 (main secondary endpoint) and over time up to week 52.	The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy (39). The PASI produces a numeric score that can range from 0 to 72, with higher scores indicating worse disease. A PASI 75 response is defined as ≥75% improvement in PASI score from baseline; PASI 50 and PASI 90 are similarly defined.
PASI 90	A PASI 90 response is defined as ≥90% improvement in PASI score from baseline, at week 12 (main secondary endpoint) and over time up to week 52.	See above for a description of the relevance of the PASI 90 outcome.
CDLQI	Change from baseline in CDLQI at week 12 and subsequent assessments at week 28 and week52. Proportion of subjects with CDLQI = 0 at week 12.	The CDLQI is an adapted version of the Dermatology Life Quality Index for the paediatric population. The adaption and validation of the CDLQI was undertaken by the original developer of the Dermatology Life Quality Index to ensure it addressed the specific needs of the paediatric population. The CDLQI questionnaire is frequently used to assess the patient's perspective on the impact of skin disorders on daily living. The CDLQI, a 10-item instrument, has 4 item response options and a recall period of 1 week. Scores range from 0 to 30 and higher scores indicate worse health-related quality of life.
PedsQL	Mean change from baseline in PedsQL scores for each post baseline assessment (i.e. week 12, 28 and 52).	The Pediatric Quality of Life Inventory (PedsQL™) is a general health-related quality of life measure developed for use in children and adolescent populations (40). The Generic Core Scale contains 23 items and is comprised of 4 domains: physical, social, emotional, and school functioning. Each domain can be scored independently. Additionally, a Psychosocial Health and Physical Health Summary Score can be calculated as well as a total score. The measure is applicable for healthy school and community populations, as well as with paediatric populations with acute and chronic health conditions and has versions for both parent and teen report. The tool is a reverse score (higher scores are better) and takes less than 5 minutes to complete with a recall of 1 month.
Safety	Assessments were based on reported AEs, clinical laboratory tests, physical examinations, vital signs measurements, waist circumference, injection-site reactions, allergic reactions, TB evaluations and concomitant medication usage.	Safety and toxicity of therapies are important to understand both for patients and for clinical decision-makers.
Source: CADMUS CSR (31).		

4.3.2. *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

Sample size

The planned sample size was approximately 150 subjects, however due to challenges with subject enrolment, the STELARA pediatric investigation plan (PIP) was modified to include a target sample size of 105 subjects randomized to receive treatment with ustekinumab (standard dosage or half-standard dosage) or placebo at Weeks 0 and 4, followed by q12w doses with the last dose at Week 40. (31)

A summary of the statistical analyses in the CADMUS study, including study hypothesis and sample size calculation, is provided in Table 10.

Table 10: Summary of statistical analyses in CADMUS

Primary hypothesis	The hypothesis in this study is that at least 1 of the 2 ustekinumab dosing tiers (standard dose [SD] or half standard dose [HSD]) is superior to placebo in the proportion of subjects who achieve a PGA score of cleared or minimal at Week 12.
Calculation of study sample size	Simulation studies were performed to evaluate the power of the primary analysis, the CMH chi-square test stratified by weight (≤ 60 kg, > 60 kg) for detecting a significant difference in the proportion of subjects who achieve PGA score of cleared or minimal between at least 1 ustekinumab group and the placebo group at Week 12 (at an overall 5% significance level). With 33 subjects in each treatment group, the power was calculated for the following assumptions based on the results observed in the Phase 3 trials of ustekinumab in adults with moderate to severe psoriasis: • The proportion of subjects with baseline weight ≤ 60 kg is between 40% and 60%,inclusive. • The proportion of subjects with a PGA score of cleared or minimal at Week 12 in the placebo group is 10% regardless of weight (≤ 60 kg, > 60 kg). • The proportion of subjects with a PGA score of cleared or minimal at Week 12 in the ustekinumab SD group is 60% for subjects with weight ≤ 60 kg and 55%, 50%, 45% for subjects with weight > 60 kg. • The proportion of subjects with a PGA score of cleared or minimal at Week 12 in the ustekinumab HSD group is 50% for subjects with weight ≤ 60 kg and 45%, 40%, 35% for subjects with weight > 60 kg. In all cases, the power to detect a difference between at least 1 ustekinumab group and placebo group in the proportion of subjects with a PGA score of cleared or minimal at Week 12 was greater than 95%.
Primary analysis	In the primary analysis, data from all randomized subjects will be analysed according to their assigned treatment group regardless of the actual treatment received. The number and proportion of subjects achieving a PGA score of cleared (0) or minimal (1) at Week 12 will be summarised and compared between the ustekinumab HSD group and the placebo group and between the ustekinumab SD group and the placebo group using the CMH chi-square test stratified by weight (≤ 60 kg or > 60 kg). The p-values will be ordered. To maintain an overall Type I error rate of 0.05, the Holm's procedure will be used. The smaller p-value will be compared to 0.025. If this test is significant, then the other p-value will be compared to 0.05. Otherwise, if the smaller p-value is greater than 0.025, both tests are considered not significant. To establish the efficacy of ustekinumab compared with placebo, at least 1 of the comparisons must be statistically significant (i.e. at least the smaller p-value must be ≤0.025). To assess the robustness of the primary endpoint analysis results, the following two sensitivity analyses will be conducted. • For subjects who do not return for evaluation at Week 12, a last observation carried forward (LOCF) procedure (e.g. PGA score from the closest visit prior to Week 12) will be used to impute the missing data at Week 12, after applying: - Treatment failure rules: Subjects who discontinue study treatment due to lack of efficacy, an adverse event (AE) of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could affect their psoriasis are considered as treatment failures.

	- Early escape rules: Subjects who use a moderate to high potency topical steroid as a result of being eligible to early escape will be considered as non-responders at Week 12 for binary endpoints and their continuous outcomes at Week 12 will be imputed by the last value at or prior to Week 8. The analysis at Week 16 will use the observed data without imputation. After Week 16, if subjects continue to use a moderate to high potency topical steroid, treatment failure rules will be applied to those subjects. • For subjects who do not return for evaluation at Week 12, the missing PGA score at Week 12 will not be imputed. That is, the analysis will be performed using observed data, after applying treatment failure rules (Subjects who discontinue study treatment due to lack of efficacy, an adverse event (AE) of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could affect their psoriasis are considered as treatment failures) and early escape rules. For each of the subgroups (see below), the difference between the ustekinumab treatment groups and placebo group in the proportion of subjects achieving PGA score of cleared (0) or minimal (1) at Week 12 and its 95% confidence interval will be calculated. **Definition of Subgroups:** To evaluate the consistency of efficacy in the primary endpoint over demographic, baseline disease characteristics, and psoriasis medication history, subgroup analyses will be performed when the number of subjects in the subgroups permits. • **Baseline demographics:** - Sex (male, female) - Baseline Age (≤ 15 years, > 15 years) - Baseline weight (≤ 60 kg, > 60 kg to ≤ 100 kg, > 100 kg) • **Baseline disease characteristics:** - Age at diagnosis (years) (< 10, ≥ 10) - Psoriasis disease duration (years) (< 5, ≥ 5) - Baseline PASI (< 20, ≥ 20) - Baseline PGA (< 4, ≥ 4) - Baseline BSA (< 20%, ≥ 20%) - Baseline CDLQI (< 10, ≥ 10) • **Psoriasis medication history:** - Phototherapy (Ultraviolet B light [UVB] or psoralen-ultraviolet-light [PUVA]) o Never used o Ever used - Conventional systemics (PUVA, methotrexate [MTX], acitretin, or ciclosporine) o Never used o Ever used The proportion of subjects achieving a PGA score of cleared (0) or minimal (1) at Week 12 will also be summarized by investigational site. Due to the anticipated small sample sizes within subgroups, no p-value will be provided; and the continuity correction will be included in the confidence limits. Subgroup analyses will not be stratified by subjects' baseline weight. All above subgroup analyses will also be performed on the proportion of PASI 75 responders at Week 12.
Data management, patient withdrawals	If a patient withdrew from the study prior to completion, the reason for withdrawal was documented. Patients who withdrew after randomisation were not replaced.
SD: standard dose, HSD: half standard dose	

4.4. Participant flow in the relevant randomised controlled trials

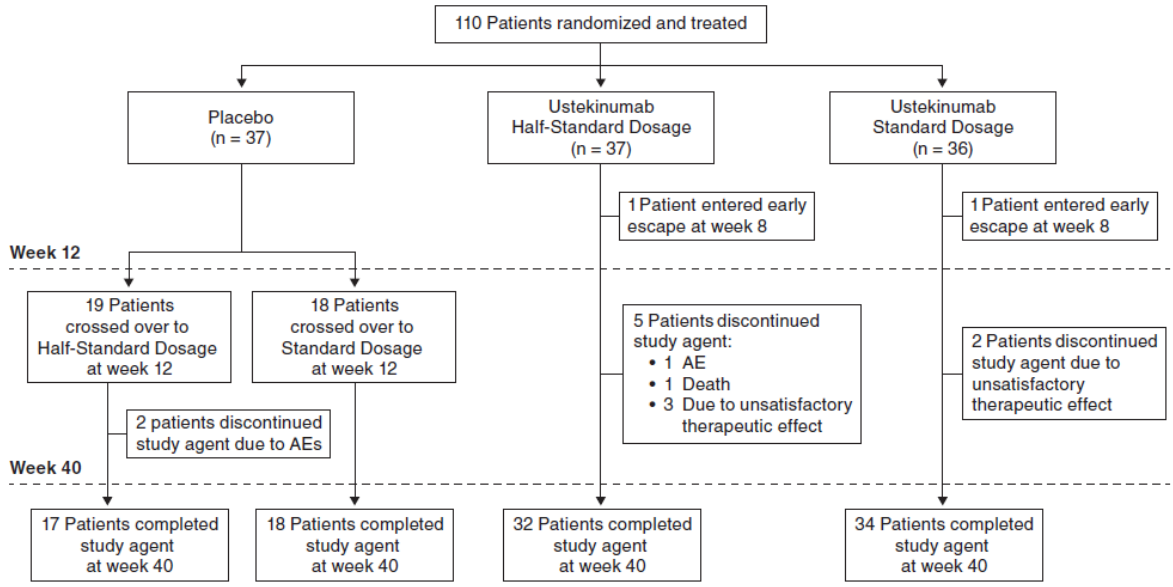
A total of 110 subjects were randomised in CADMUS. All randomised subjects were treated and all received their assigned treatment (see Figure 2).

- 37 subjects to placebo

- 37 subjects to ustekinumab half-standard dosage
- 36 subjects to ustekinumab standard dosage

The 110 randomised subjects were from 10 countries in Europe and Canada, with 6 subjects recruited from 3 sites in the United Kingdom.

Figure 2 Subject disposition through week 40



4.4.1. *Treatment discontinuation and crossover*

No subject discontinued study agent through week 12 and through week 40 nine subjects (8.2%) discontinued study agent (see Table 11).

Table 11 Number of subjects who discontinued study agent through week 40; all randomised subjects (CADMUS CSR) (31)

			Ustekinumab		
	Placebo → Half-Standard Dosage	Placebo → Standard Dosage	Half-Standard Dosage	Standard Dosage	Combined
Analysis set: subjects randomized	19	18	37	36	110
Subjects who discontinued study agent	2 (10.5%)	0	5 (13.5%)	2 (5.6%)	9 (8.2%)
Reason for discontinuation					
Adverse event	2 (10.5%)	0	1 (2.7%)	0	3 (2.7%)
Worsening of psoriasis	1 (5.3%)	0	1 (2.7%)	0	2 (1.8%)
Withdrawal of consent	0	0	0	0	0
Death	0	0	1 (2.7%)	0	1 (0.9%)
Lack of efficacy	0	0	3 (8.1%)	2 (5.6%)	5 (4.5%)
Lost to follow-up	0	0	0	0	0
Other	0	0	0	0	0

The single death in the HSD arm was due to a motor vehicle accident and assessed as not related to the study agent (the subject was a passenger in the car).

In total, three adverse events led to treatment discontinuation. Two patients (one in the placebo → half-standard dosage group and one in the half-standard dosage group) withdrew due to worsening psoriasis and one patient who crossed over to half-standard dosage withdrew due to toxoplasmosis infection.

4.4.1.1. Termination of study participation

Up to and including week 60, seventeen subjects (15.5%) terminated study participation. The most common reason for termination was withdrawal of consent (9 subjects, 8.2%). See Table 12.

Table 12 List of subjects who terminated study participation through Week 60; all randomised subjects (CADMUS CSR) (31)

Treatment Group	Subject ID	Early Escape	Last Scheduled Visit	Study Day of Termination	Study Day of Last Study Agent Administration	Primary Reason
Placebo → Ustekinumab Half-Std		No	Week 52	393	281	WITHDRAWAL OF CONSENT
		No	Week 48	337	281	WITHDRAWAL OF CONSENT
Placebo → Ustekinumab Std		No	Week 52	309	281	WITHDRAWAL OF CONSENT
Ustekinumab Half-Std		No	Week 32	225	197	DEATH
		No	Week 32	227	184	WITHDRAWAL OF CONSENT
		No	Week 52	378	292	LOST TO FOLLOW-UP
		No	Week 52	338	264	WITHDRAWAL OF CONSENT
		No	Week 32	225	189	WITHDRAWAL OF CONSENT
		No	Week 32	213	119	OTHER (PSORIASIFORM DERMATITIS WITH VASCULOPATHY; BILATERAL ANCLE EDEMA)
		No	Week 20	141	113	OTHER (DISCONTINATION DUE TO LOSS OF EFFICACY.)
		No	Week 48	337	281	WITHDRAWAL OF CONSENT
		No	Week 52	387	285	OTHER (EARLY WITHDRAWN DUE TO RELAPSE)
		No	Week 44	312	283	WITHDRAWAL OF CONSENT
Ustekinumab Std		No	Week 52	379	288	OTHER (SUBJECT CALLED SITE TO SAY HE WAS TOO BUSY TO COME IN FOR APPOINTMENT)
		No	Week 20	141	113	LOST TO FOLLOW-UP
		No	Week 48	337	281	WITHDRAWAL OF CONSENT
		No	Week 20	142	108	OTHER (LACK OF EFFICACY)

4.4.1.2. Imputation Methods

Patients who discontinued study treatment because of an unsatisfactory therapeutic effect or an AE of worsening psoriasis or used protocol prohibited therapies for psoriasis were classified as non-responders for dichotomous endpoints or as zero change for continuous endpoints thereafter. Patients with missing PGA or PASI at week 12 were classified as non-responders. Patients who used a moderate-to-high potency topical steroid after entering early escape, were considered non-responders at week 12 for binary endpoints; the last value at or before week 8 was used to impute continuous endpoints. (2)

4.4.2. *Baseline Characteristics*

The subject population was comprised of adolescent subjects (excluding those who were pregnant or nursing or planning pregnancy [both males and females]) ≥12 to <18 years of age, who had a diagnosis of plaque-type psoriasis for at least 6 months prior to first study agent administration and who had moderate to severe disease defined by a PASI ≥12, a Physician's Global Assessment (PGA) ≥3, and body surface area (BSA) involvement ≥10%.

Baseline demographics and disease characteristics were well balanced across the treatment groups (see Table 13).

Table 13 Baseline demographics and disease characteristics

		Ustekinumab			
	Placebo	Half-standard dosage*	Standard dosage†	Combined	Total
Patients randomized, n	37	37	36	73	110
Males, n (%)	20 (54.1)	18 (48.6)	16 (44.4)	34 (46.6)	54 (49.1)
Age, y					
Mean (SD)	15.6 (1.5)	15.1 (1.7)	14.8 (1.7)	14.9 (1.7)	15.2 (1.7)
Body weight, kg					
Mean (SD)	64.7 (14.7)	68.2 (24.5)	62.0 (17.1)	65.1 (21.2)	65.0 (19.2)
Race, n (%)					
White	34 (91.9)	30 (81.1)	34 (94.4)	64 (87.7)	98 (89.1)
Psoriasis disease duration, y					
Mean (SD)	6.2 (5.0)	5.9 (4.0)	5.6 (3.8)	5.7 (3.9)	5.9 (4.3)
Age at diagnosis, y					
Mean (SD)	9.5 (5.0)	9.2 (4.5)	9.3 (4.3)	9.2 (4.4)	9.3 (4.6)
BSA, %					
Mean (SD)	27.4 (16.4)	33.6 (21.4)	31.9 (23.2)	32.7 (22.1)	30.9 (20.5)
PASI score (0-72)					
Mean (SD)	20.8 (8.0)	21.0 (8.5)	21.7 (10.4)	21.3 (9.4)	21.1 (8.9)
PGA score, n (%)					
Marked or severe (≥4)	15 (40.5)	15 (40.5)	12 (33.3)	27 (37.0)	42 (38.2)
CDLQI (0-30), n	33	36	32	68	101
Mean (SD)	9.1 (6.4)	9.4 (6.5)	10.3 (6.6)	9.8 (6.5)	9.6 (6.5)
Prior medications for psoriasis, n (%)					
Topical agents	34 (91.9)	31 (83.8)	33 (91.7)	64 (87.7)	98 (89.1)
Conventional systemic therapies	16 (43.2)	14 (37.8)	17 (47.2)	31 (42.5)	47 (42.7)
UVB	11 (29.7)	15 (40.5)	13 (36.1)	28 (38.4)	39 (35.5)
Methotrexate	8 (21.6)	8 (21.6)	6 (16.7)	14 (19.2)	22 (20.0)
Biologics	5 (13.5)	4 (10.8)	3 (8.3)	7 (9.6)	12 (10.9)
PUVA	0	3 (8.1)	4 (11.1)	7 (9.6)	7 (6.4)

BSA, Body surface area; *PUVA*, psoralen with ultraviolet light A; *SD*, standard deviation; *UVB*, ultraviolet B.
*Ustekinumab half-standard dosage: 0.375 mg/kg for patients weighing ≤60 kg, 22.5 mg for patients weighing >60 kg to ≤100 kg, and 45 mg for patients weighing >100 kg.
†Ustekinumab standard dosage: 0.75 mg/kg for patients weighing ≤60 kg, 45 mg for patients weighing >60 kg to ≤100 kg, and 90 mg for patients weighing >100 kg.

The study population had moderately to severely active psoriasis, with median psoriasis duration of 5.29 years. The median age at onset of disease was 10.0 years, and the majority of subjects (57.3%) had ≥20% of BSA affected with psoriasis. The median PASI score was 18.8. The majority of subjects (61.8%) had PGA scores of moderate and 38.2% of subjects had a PGA score of marked or severe.

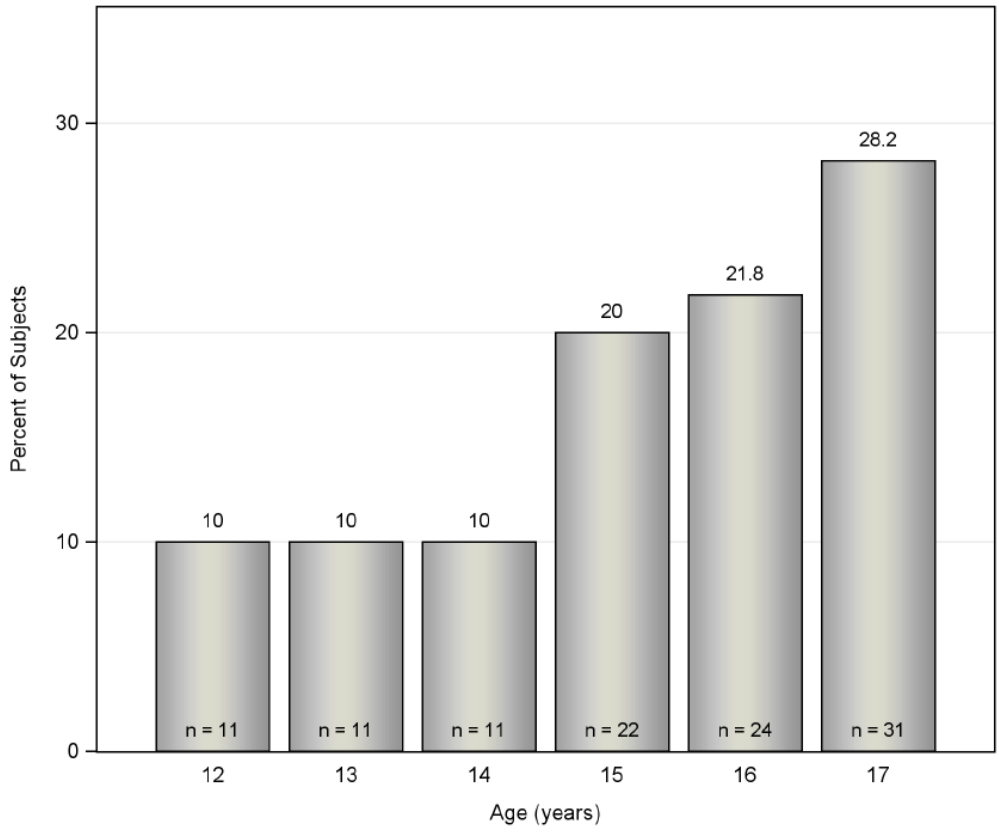
Disease activity scores at baseline were consistent with moderate-to-severe disease; mean CDQLI (9.6) indicated a moderate effect of psoriasis on HRQoL.
Prior psoriasis medication use was as follows: topical agents (89.1%); conventional systemic agents (PUVA, methotrexate, acitretin, and cyclosporine; 42.7%); ultraviolet B (35.5%); PUVA (6.4%); biologics (10.9%); and conventional systemic agents or biologics (46.4%).

As permitted by the protocol, few (6) subjects received concomitant corticosteroids for short-term use for indications other than psoriasis through Week 60.

The study population was approximately half male and half female; most subjects were Caucasian (89.1%), and generally CADMUS' patients can be considered representative of the UK target population.

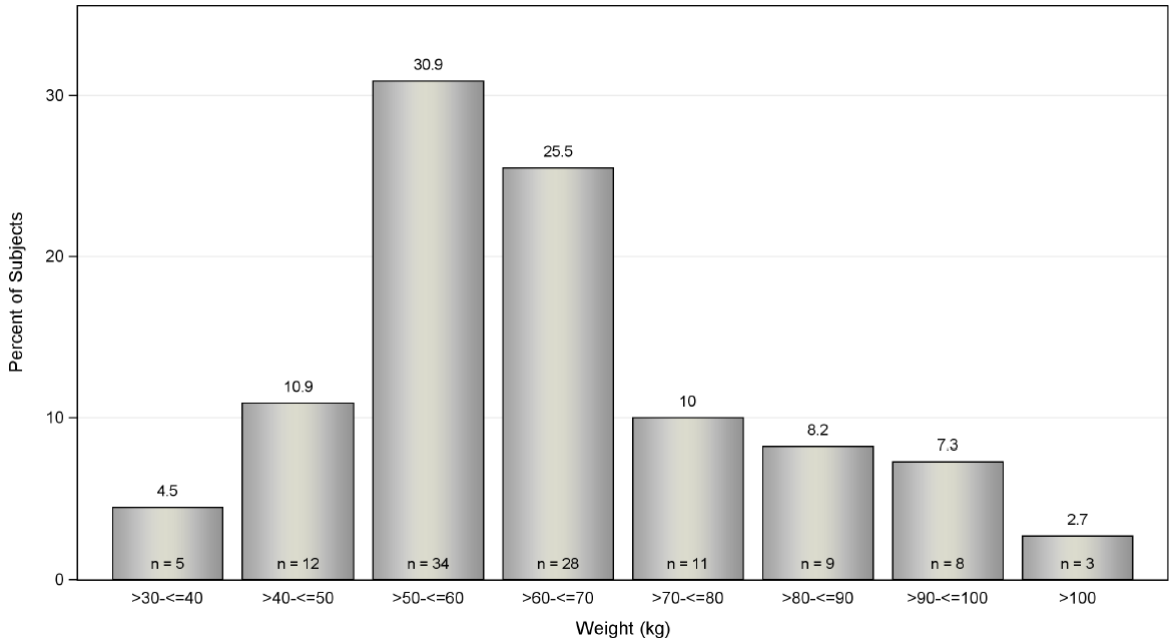
Mean age was 15.2 years, with most patients 15 to 17 years of age (n=77; 70%) (Figure 3Error! Reference source not found.).

Figure 3 Distribution of age (years) at baseline; all randomised subjects



Mean body weight was 65.0 kg; 51 (46.4%) patients weighed ≤60 kg, 56 (50.9%) weighed greater than 60 to ≤100 kg and 3 (2.7%) weighed greater than 100 kg (**Error! Reference source not found.**Figure 4).

Figure 4 Distribution of weight (kg) at baseline; all randomised subjects Distribution of weight (kg) at baseline; all randomised subjects



CADMUS is a well-designed RCT with a low risk of bias. Table 6 presents the quality assessment of the studies included in this submission.

4.5. Clinical effectiveness results of CADMUS

4.5.1. *Primary endpoint*

At week 12, 25 (69.4%) of ustekinumab patients achieved a PGA 0/1 (i.e. absence of any lesion to minimal raised plaque to 0.25 mm with fine / faint lesion) compared with 2 (5.4%) in the placebo group (p<0.001); of those 25 patients, 17 (47.2%) achieved a PGA score of 0 (cleared of all lesions), compared to 1 (2.7%) patient in the placebo arm (p<0.001). (9) See Table 14.

Table 14 Primary and select secondary endpoints at week 12 (9)

		Ustekinumab	
	Placebo	Half-standard dosage*	Standard dosage†
Patients randomized, n	37	37	36
PGA 0/1, n (%)	2 (5.4)	25 (67.6)‡	25 (69.4)‡
PGA 0	1 (2.7)	12 (32.4)‡	17 (47.2)‡
PASI 75, n (%)	4 (10.8)	29 (78.4)‡	29 (80.6)‡
PASI 90, n (%)	2 (5.4)	20 (54.1)‡	22 (61.1)‡
Change from baseline in CDLQI, n	32	35	32
Mean (SD)	−1.5 (3.2)	−5.6 (6.4)§	−6.7 (5.6)‡
Patients with CDLQI score 0/1, n (%)	4/30 (13.3)	12/31 (38.7)¶	17/30 (56.7)‡

SD, Standard deviation.
*Ustekinumab half-standard dosage: 0.375 mg/kg for patients weighing ≤60 kg, 22.5 mg for patients weighing >60 kg to ≤100 kg, and 45 mg for patients weighing >100 kg.
†Ustekinumab standard dosage: 0.75 mg/kg for patients weighing ≤60 kg, 45 mg for patients weighing >60 kg to ≤100 kg, and 90 mg for patients weighing >100 kg.
‡$P < .001$ vs placebo.
§$P < .01$ vs placebo.
¶$P < .05$ vs placebo.

4.5.2. *Results of secondary analyses of primary endpoint and analyses of relevant secondary endpoints*

4.5.2.1. Sensitivity analyses

Two sensitivity analyses were conducted to test the robustness of the primary endpoint and to assess the impact of missing data. An additional sensitivity analysis was also conducted to evaluate the effect of re-randomisation.

Results in all three sensitivity analyses were similar to the main analysis and demonstrate the robustness of the primary endpoint analysis (see Appendix, section **Error! Reference source not ound.**).

4.5.2.2. PASI 75 responders at week 12

At Week 12, 29 (80.6%) patients in the ustekinumab group achieved a PASI 75 response, i.e. a 75% reduction in their baseline PASI score, compared with 4 (10.8%) in the placebo group ($p<0.001$). (9)

4.5.2.3. PASI 90 responders at week 12

At Week 12, 22 (61.1%) of ustekinumab patients achieved a PASI 90 response, corresponding to a 90% reduction in their baseline PASI score, compared with 2 (5.4%) in the placebo group ($p<0.001$). (9)

4.5.2.4. Change from baseline in CDLQI score at week 12

At Week 12, the change from baseline in mean CDLQI was significantly greater in the ustekinumab group (-6.7) compared to the placebo group (-1.5), with $p<0.001$. Among patients with CDLQI greater than 1 at baseline, significantly greater proportions of ustekinumab treated patients achieved a CDLQI 0/1 (indicative of minimal impact of psoriasis on HRQoL) compared with placebo, with 17 (56.7%) and 4 (13.3%) of patients respectively. (2)

4.5.2.5. Change from baseline in PedsQL score at week 12

At Week 12, the change in baseline in mean total score PedsQL was significantly greater in the ustekinumab group (8.03) compared to the placebo group (3.35), with $p<0.028$. Across all subscales, patients in the standard dose group showed greater changes from baseline in the mean scores compared with patients in the placebo group (see appendix, Section **Error! Reference source not ound.**.

4.5.2.6. Response through week 52

In the ustekinumab SD group, the proportions of patients who achieved PGA 0/1, PASI 75 or PASI 90 were maintained from week 12 through 52 (see Figure 5, Figure 6 and Figure 7). Data for CDLQI and for PedsQL is reported in the appendix, see Section 9.5.

Onset of response was rapid; approximately one third of patients in the ustekinumab SD group achieved PGA 0/1 at week 4 (the first post baseline visit) compared with 1 (2.7%) patients in the placebo group (see Figure 5).

Figure 5 Ustekinumab in adolescent patients with psoriasis. Proportions of patients with a PGA 0/1 in the ustekinumab half-standard and standard dose groups (A) and the placebo group (B) through week 52 (Landells et al, 2015)

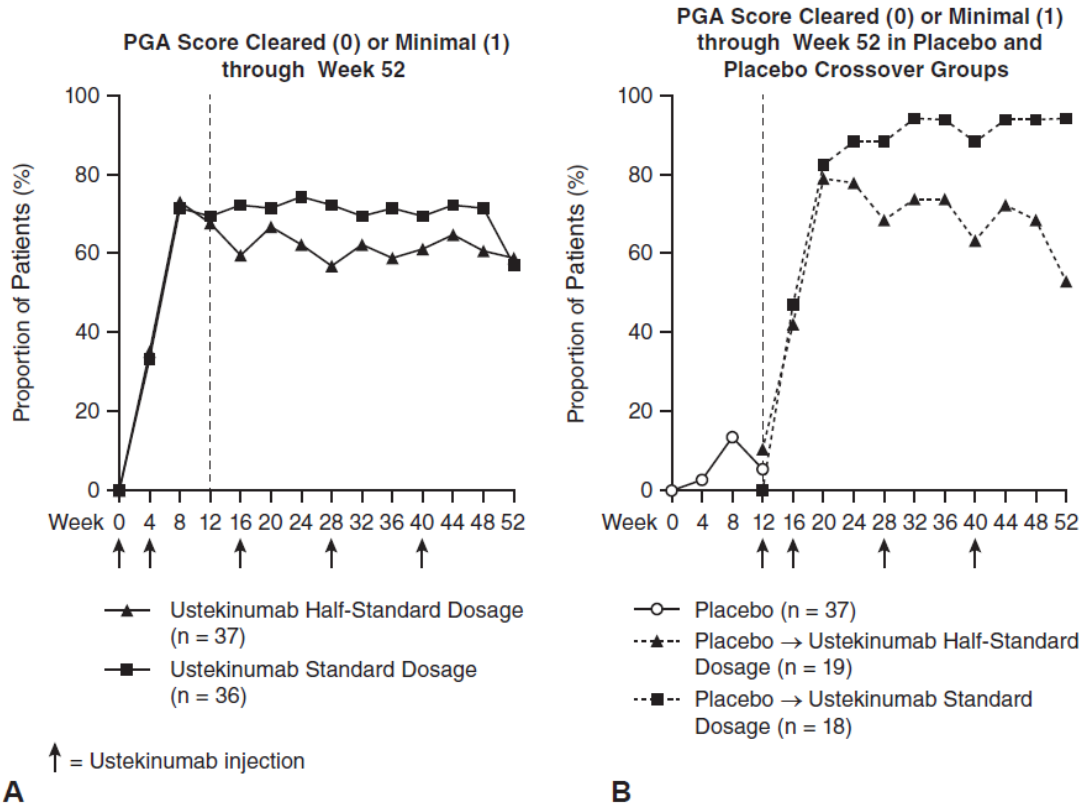


Figure 6 Ustekinumab in adolescent patients with psoriasis. Proportions of patients with a PASI 90 response through week 52

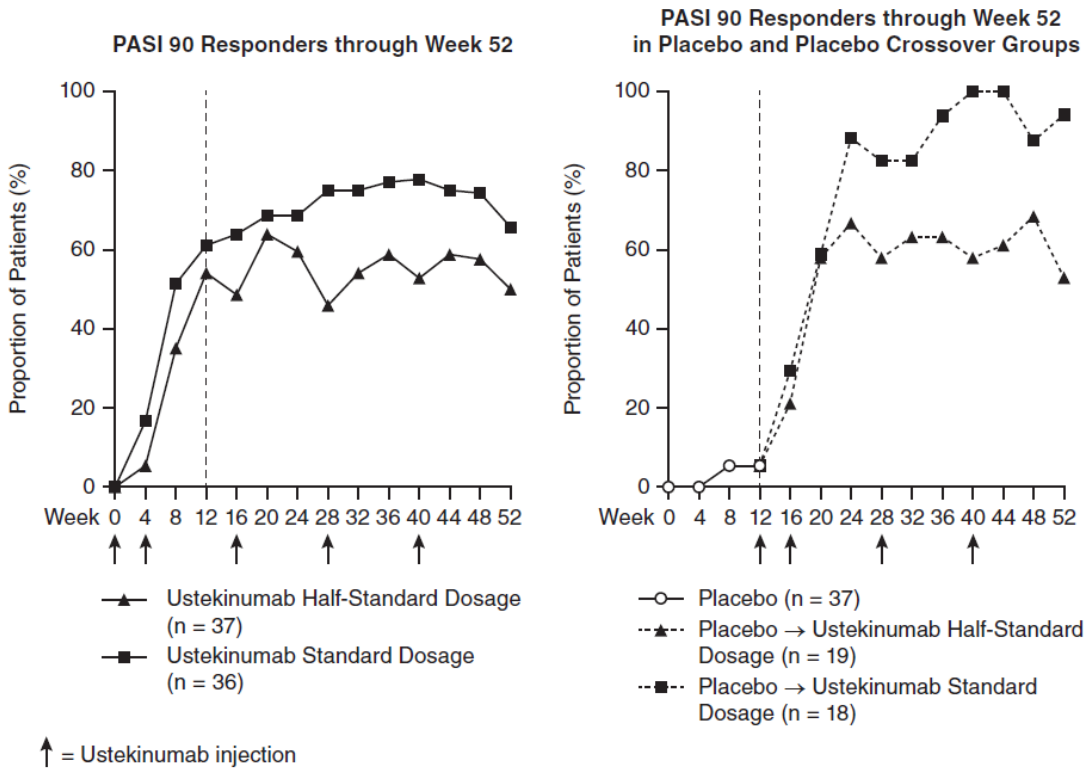


Figure 7 Percent of subjects achieving PASI 75 response through Week 52 by visit; all randomised subjects

4.5.3. *Subgroup analyses*

To examine the consistency of treatment effect for the primary and secondary endpoints, the proportion difference of the standard dosage groups versus the placebo group and the corresponding 95% confidence intervals were provided for three predefined subgroups and are presented below.

- Baseline demographic characteristics
- Baseline PsO disease characteristics
- PsO medication history

4.5.3.1. Proportion difference and 95% confidence interval for comparing proportions of subjects achieving a PGA score of Cleared (0) or Minimal (1) at Week 12, who received ustekinumab standard dose versus placebo

Table 15 Proportion difference and 95% confidence interval for comparing proportions of subjects achieving a PGA score of Cleared (0) or Minimal (1) at Week 12, who received ustekinumab standard dosage versus placebo by baseline demographic characteristics; all randomized subjects (CADMUS (31))

Table 16 Proportion difference and 95% confidence interval for comparing proportions of subjects achieving PGA score of cleared (0) or minimal (1) at week 12, who received ustekinumab standard dosage versus placebo by baseline psoriasis disease characteristics (CADMUS (31))

Table 17 Proportion difference and 95% confidence interval for comparing proportions of subjects achieving PGA score of cleared (0) or minimal (1) at week 12, who received ustekinumab standard dosage versus placebo by baseline psoriasis medication history

4.5.3.2. Proportion difference and 95% confidence interval for comparing proportions of subjects achieving a PASI 75 response at Week 12, who received ustekinumab standard dose versus placebo

Table 18 Proportion difference and 95% confidence interval for comparing proportions of subjects achieving a PASI 75 response at week 12, who received ustekinumab standard dosage versus placebo by baseline demographic characteristics; all randomized subjects (CADMUS (31))

Table 19 Proportion difference and 95% confidence interval for comparing proportions of subjects achieving PASI 75 response at week 12, who received ustekinumab standard dosage versus placebo by baseline psoriasis disease characteristics (CADMUS(31))

Table 20 Proportion difference and 95% confidence interval for comparing proportions of subjects achieving a PASI 75 response at week 12, who received ustekinumab standard dosage versus placebo by psoriasis medication history; all randomized subjects (CADMUS (31))

The treatment effect of the standard dosage group versus placebo was substantial and generally consistent across demographic characteristics, psoriasis disease characteristic, and psoriasis medication history.

4.6. Clinical safety

4.6.1. *Adverse events in the placebo-controlled period (through week 12)*

Through week 12, 44.4% (16) of subjects in the SD group, and 56.8% (21) in the placebo group reported ≥1 AE (see Table 21). Most AEs were mild or moderate.

In general, AE rates were similar across treatment groups, and no dose effect was observed.

AEs in the infections and infestations category were the most common (SD, 25.0%; placebo, 40.5%); none was considered serious. Through week 12, the most common AEs were nasopharyngitis (SD, 2.8%; placebo, 27.0%) and headache (SD, 8.3%; placebo, 5.4%).

Table 21 Number of subjects with 1 or more treatment-emergent adverse events (with frequency of 5% or greater in any treatment group) through week 12 by MedDRA preferred term; treated subjects (31)

[redacted]

4.6.2. *Adverse events through week 60*

Through week 40, all 110 patients received ≥1 injection of ustekinumab; among these, 81.8% reported an AE through week 60 in the ustekinumab combined group (see Table 22). For a fully detailed table of number of subjects with 1 or more treatment emergent adverse events through week 60, please refer to the appendix, Section 9.4. **Error! Reference source not found.**

[redacted] occurring most often. After week 12, 5 additional singular SAEs were reported (total, 6; SD, 1) through week 60. One serious infection was reported (ear infection [SD]). Of the 508 ustekinumab injections, only one was associated with an injection site reaction; this mild reaction occurred at baseline in the SD group (9). There were no malignancies, active tuberculosis cases, opportunistic infections, anaphylactic reactions, or serum sickness-like reactions through week 60.

Table 22 Adverse Events (9)

Adverse events through week 12 (placebo-controlled period)				
		Ustekinumab		
	Placebo	Half-standard dosage	Standard dosage	Combined
Patients, n	37	37	36	73
Mean duration of follow-up, wk	12.2	12.2	12.4	12.3
Mean exposure, wk	4.2	4.2	4.1	4.1
Patients with ≥1 AE	21 (56.8)	19 (51.4)	16 (44.4)	35 (47.9)
Patients who discontinued due to AE	0	0	0	0
Infections	14 (37.8)	12 (32.4)	8 (22.2)	20 (27.4)
Patients with ≥1 SAE	0	1 (2.7)	0	1 (1.4)
Serious infections	0	0	0	0
Malignancies	0	0	0	0

Adverse events through week 60					
	Ustekinumab				
	Placebo → Half-standard dosage	Placebo → Standard dosage	Half-standard dosage	Standard dosage	Combined
Patients, n	19	18	37	36	110
Mean duration of follow-up, wk	45.9	46.9	55.2	58.0	53.2
Mean exposure, wk	27.3	28.1	38.0	39.0	34.9
Patients with ≥1 AE	15 (78.9)	13 (72.2)	33 (89.2)	29 (80.6)	90 (81.8)
Patients who discontinued due to AE	2 (10.5)	0	2 (5.4)	0	4 (3.6)
Infections	13 (68.4)	11 (61.1)	26 (70.3)	24 (66.7)	74 (67.3)
Patients with ≥ 1 SAE	0	0	5 (13.5)	1 (2.8)	6 (5.5)
Serious infections	0	0	1 (2.7)	1 (2.8)	2 (1.8)
Malignancies	0	0	0	0	0

Data presented as n (%) unless otherwise noted.

4.7. Conclusions of CADMUS

CADMUS provides high quality evidence confirming the efficacy and safety of ustekinumab in PsO adolescents compared to placebo. A total of 110 patients were enrolled in the trial and were followed up to week 52 for efficacy and week 60 for safety.

Efficacy responses in terms of PGA 0 (absence of any lesions except for residual discoloration) and 0/1 (absence of any lesion to minimal raised plaque to 0.25 mm with fine / faint lesion), PASI 75 (meaning a 75% reduction to the baseline PASI score) and PASI 90 (meaning a 90% reduction to the baseline PASI score) were reported as early as week 4 and maintained through to week 52 for the patients randomised on ustekinumab: (9)

At week 12, 25 (69.4%) of ustekinumab patients achieved a PGA 0/1 (i.e. absence of any lesion to minimal raised plaque to 0.25 mm with fine / faint lesion) compared with 2 (5.4%) in the placebo group ($p<0.001$); of those 25 patients, 17 (47.2%) achieved a PGA score of 0 (cleared of all lesions), compared to 1 (2.7%) patient in the placebo arm. (9) This result is further supported by 29 (80.6%) patients in the ustekinumab group achieving a PASI 75 response at week 12, i.e. a 75% reduction in their baseline PASI score, compared with 4 (10.8%) in the placebo group ($p<0.001$) and by 22 (61.1%) of ustekinumab patients achieving a PASI 90 response at week 12, corresponding to a 90% reduction in their baseline PASI score, compared with 2 (5.4%) in the placebo group ($p<0.001$). This response was maintained through to week 52. (9)

Ustekinumab made a positive impact on HRQoL, with a significant proportion of ustekinumab treated patients reporting a CDLQI score of 0/1 (indicative of minimal impact of psoriasis on HRQoL) compared with placebo at week 12 and was maintained through to week 52. (see Table 14).

4.8. Supporting Studies

Due to the paucity of long term studies in the paediatric PsO population and because half of the CADMUS population (i.e. 50 out of the 100 patients included in CADMUS) were aged 16 -17 (see Figure 3) and thus, clinically speaking, 'adults', the results of CADMUS were compared to the results in PHOENIX trials. It should also be noted that the young people population considered in CADMUS would become adults within a timeframe of 1 to 4 years. Therefore, the results of PHOENIX trials would help understand the efficacy and safety of ustekinumab in the long term.
BADBIR and PSOLAR studies are both registries conducted in patients aged 16 and above. (12), (41)

The inclusion of both observational and clinical studies is considered here to more completely capture and consider treatment persistence, long term safety and sustained efficacy / response in both the clinical trial and real world for biologic treatments.

4.8.1. ***BADBIR***

(Warren RB, Smith CH, Yiu ZZN, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol 2015 Nov; 135(11):2632-40).

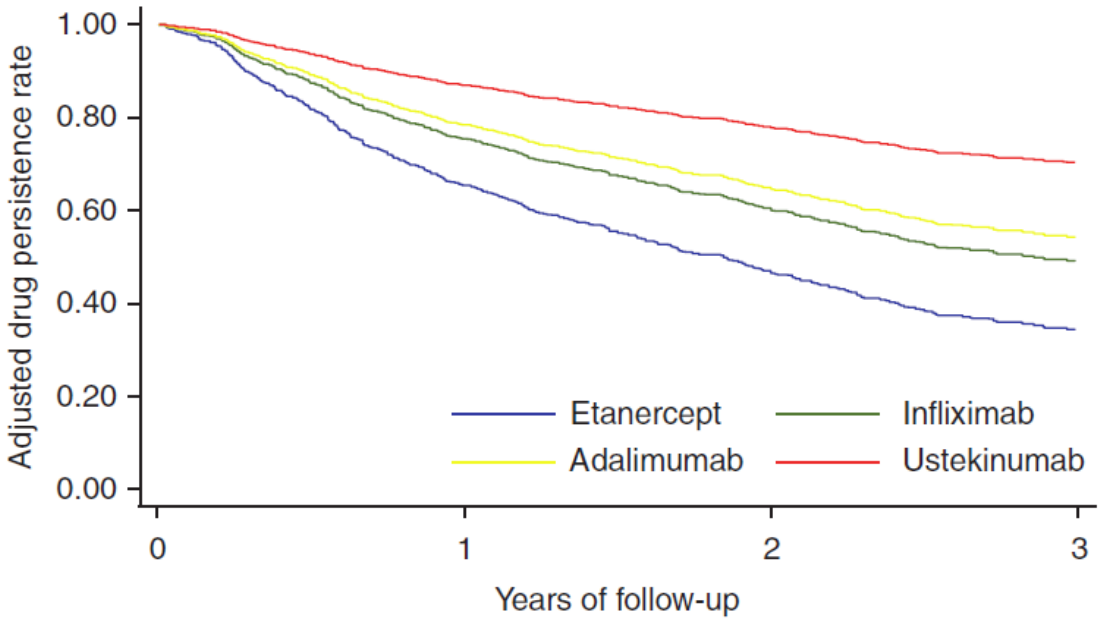
BADBIR is a prospective, UK and Eire observational study which seeks to assess the long-term safety of biologic treatments for patients age 16 and above, with PsO. This study represents the largest observational real-world cohort study assessing the drug survival (i.e. drug effectiveness, safety and tolerability) with biologics in psoriasis to date (12).

The survival rates of the first course of biologics for 3,523 biologic-naive patients with chronic plaque psoriasis were compared using survival analysis techniques and predictors of discontinuation analysed using a multivariate Cox proportional hazards model. Data for patients on adalimumab (n=1,879), etanercept (n=1,098), infliximab (n=96), and ustekinumab (n=450) were available.

The study focuses on biologic-naive patients and shows that the survival with biologic therapies decreases over time, from 77% in the first year to 53% in the third year. One of the most notable findings is that ustekinumab had a significantly higher survival rate than anti-TNFs (see Figure 8). (12) This difference persisted after controlling for clinical factors likely to cause systematic bias in biologic-naive patients. (12).

Possible reasons contributing to the higher drug survival shown by ustekinumab as compared with the TNF inhibitors, based on the literature and known licensing information, are high effectiveness, lower immunogenicity, lower drug discontinuation due to AEs, dosing regimen, and method of administration (12).

Figure 8 Adjusted drug survival curves (12).



As the BADBIR database grows, it is expanding their remit to include the paediatric population, in order to obtain some real world data for the younger PsO patients (NICE Stakeholder Meeting, 11th August 2016).

The results seen in the BADBIR study were comparable to results seen in the company sponsored registry, PSOLAR.

4.8.2. *PSOLAR study*

(Menter A, et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Eur Acad Dermatol Venereol, 2016 Jul;30(7):1148-58)

The Psoriasis Longitudinal Assessment and Registry (PSOLAR) is a multi-centre, non-interventional observational study, which was set up in order to evaluate safety and clinical outcomes in adult patients with moderate to severe PsO (41).

With 12,095 PsO patients enrolled, the registry has a duration of 8 years (enrolment stopped on 23 August 2013). Physicians prescribe treatment (biologic or non-biologic) based on usual clinical practice and standard of care; patients are not randomised to treatment groups. The registry captures real world experience in the treatment of PsO in adults, with 989 patients enrolled in Europe, 1,896 in Canada, 8,981 in US, 46 Mexico, 119 in South America and 64 in Israel.

As of the 2013 data cut, 12,095 patients with psoriasis were enrolled in PSOLAR. Of the 4,000 patients initiating any new biologic therapy, approximately 3,500 started a first-line, second-line or third-line biologic therapy. Lack of effectiveness was the most common reason for discontinuation across biologic therapies. Based on the multivariate analysis, significantly shorter times to discontinuation were observed for infliximab [HR (95%CI) = 2.73 (1.48-5.04), p=0.0014]; adalimumab [4.16 (2.80-6.20), p<0.0001]; and etanercept [4.91 (3.28-7.35) p<0.0001] compared with ustekinumab [reference treatment]) for first-line biologic use; results were similar for treatment effects for second/third-line therapies. Although limited in power, analyses in patients with concurrent psoriatic arthritis confirmed by a rheumatologist reflect observations in the overall psoriasis population. (41)

Drug survival was superior for ustekinumab compared with infliximab, adalimumab and etanercept in patients with psoriasis. (41)

4.8.3. *PHOENIX 1 and PHOENIX 2*

(PHOENIX 1:
Leonardi C. et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet, 2008; 371: 1665-1674
Kimball A et al. Long term efficacy of ustekinumab in patients with moderate to severe psoriasis treated for up to 5 years in the PHOENIX 1 study. J Eur Acad Dermatol Venereol. 2013 Dec;27(12):1535-45)

(PHOENIX 2:
Papp K. et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet, 2008; 371: 1675-1684
Langley RG, et al. Long term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate to severe psoriasis: results from the PHOENIX 2 study through 5-year follow-up. Br J Derm. 2015:172;1371-1383)

Two long term studies (PHOENIX 1 and PHOENIX 2), designed with long term extensions (LTE) of up to 5 years of continuous exposure and follow up, provides long term efficacy and safety of ustekinumab in the adult PsO population.

In order to demonstrate that these studies are supportive studies to the main study in young people (CADMUS), details of the PHOENIX 1 and PHOENIX 2 studies with 5 year follow up data are summarised briefly in
Table 23. ((42), (11))

Table 23 Overview of ustekinumab supportive phase 3 psoriasis studies in adults ((42), (11))

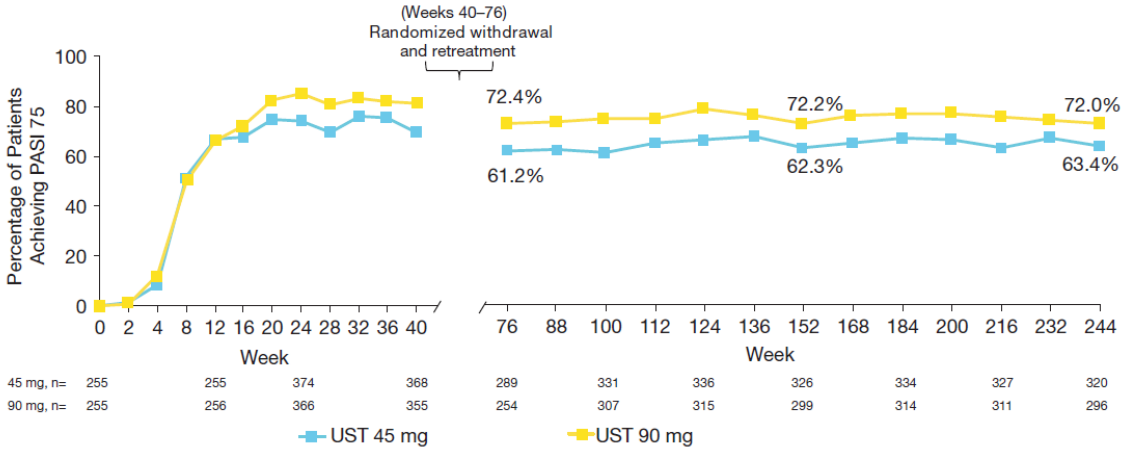
Design elements	**C0743T08 - PHOENIX 1 (43)**	**C0743T09 - PHOENIX 2 (44)**
Study population	Adults with moderate to severe plaque-type psoriasis	Adults with moderate to severe plaque-type psoriasis
Study sites	Europe and North America	Europe and North America
Duration of efficacy follow-up	264 weeks	264 weeks
Subjects randomised	766	1,230
Treatment groups (n)	Placebo (n=255) - Placebo → 45mg (n=123) - Placebo → 90mg (n=120) Ustekinumab - 45mg SC Weeks 0, 4 then q12w (n=255) - 90mg SC Weeks 0, 4 then q12w (n=256)	Placebo (n=410) - Placebo → 45mg (n=197) - Placebo → 90mg (n=195) Ustekinumab - 45mg SC Weeks 0, 4 then q12w (n=409) - 90mg SC Weeks 0, 4 then q12w (n=411)
Primary endpoint	PASI 75 response at week 12	PASI 75 response at week 12
Primary endpoint results at week 12	USK 45mg: 171/255 (67.1%) USK 90mg: 170/256 (66.4%) Placebo: 8/255 (3.1%)	USK 45mg: 273/409 (66.7%) USK 90mg: 311/411 (75.7%) Placebo: 15/410 (3.7%)
Major secondary endpoints	- PGA score of cleared (0) or	- PGA score of cleared (0) or

Design elements	C0743T08 - PHOENIX 1 (43)	C0743T09 - PHOENIX 2 (44)
in order of statistical testing	minimal (1) at Week 12 - Change in DLQI score from baseline at Week 12 - Time to loss of PASI 75 response	minimal (1) at Week 12 - Change in DLQI score from baseline at Week 12 - Number of visits with PASI75 response from Week 40 to Week 52
Major secondary endpoint results at week 12	- PGA score of cleared (0) or minimal (1) at Week 12 USK 45mg: 154/255 (18.04%) USK 90mg: 158/256 (61.7%) Placebo: 10/255 (3.9%) - Change in DLQI score from baseline at Week 12 USK 45mg: 254/255 (-8.0) USK 90mg: 249/256 (-8.7) Placebo: 252/255 (-0.6)	- PGA score of cleared (0) or minimal (1) at Week 12 USK 45mg: 278/409 (68.0%) USK 90mg: 302/411 (73.5%) Placebo: 20/410 (4.9%) - Change in DLQI score from baseline at Week 12 USK 45mg: 401/409 (-9.3) USK 90mg: 402/411 (-10.0 Placebo: 400/410 (-0.5)

4.8.3.1. Efficacy through year 5 for PHOENIX 1 (42)

In PHOENIX 1, high levels of clinical response were achieved at week 12 (see Table 23) and maintained through Week 244 for patients treated with ustekinumab 45mg and 90mg: at Week 244, PASI 75 responses were achieved by 63.4% and 72.0% of patients receiving ustekinumab 45mg and 90mg, respectively (Figure 9). (42)

Figure 9 Overall population (all patients who received one dose of ustekinumab): maintenance of clinical response through week 244 (42)

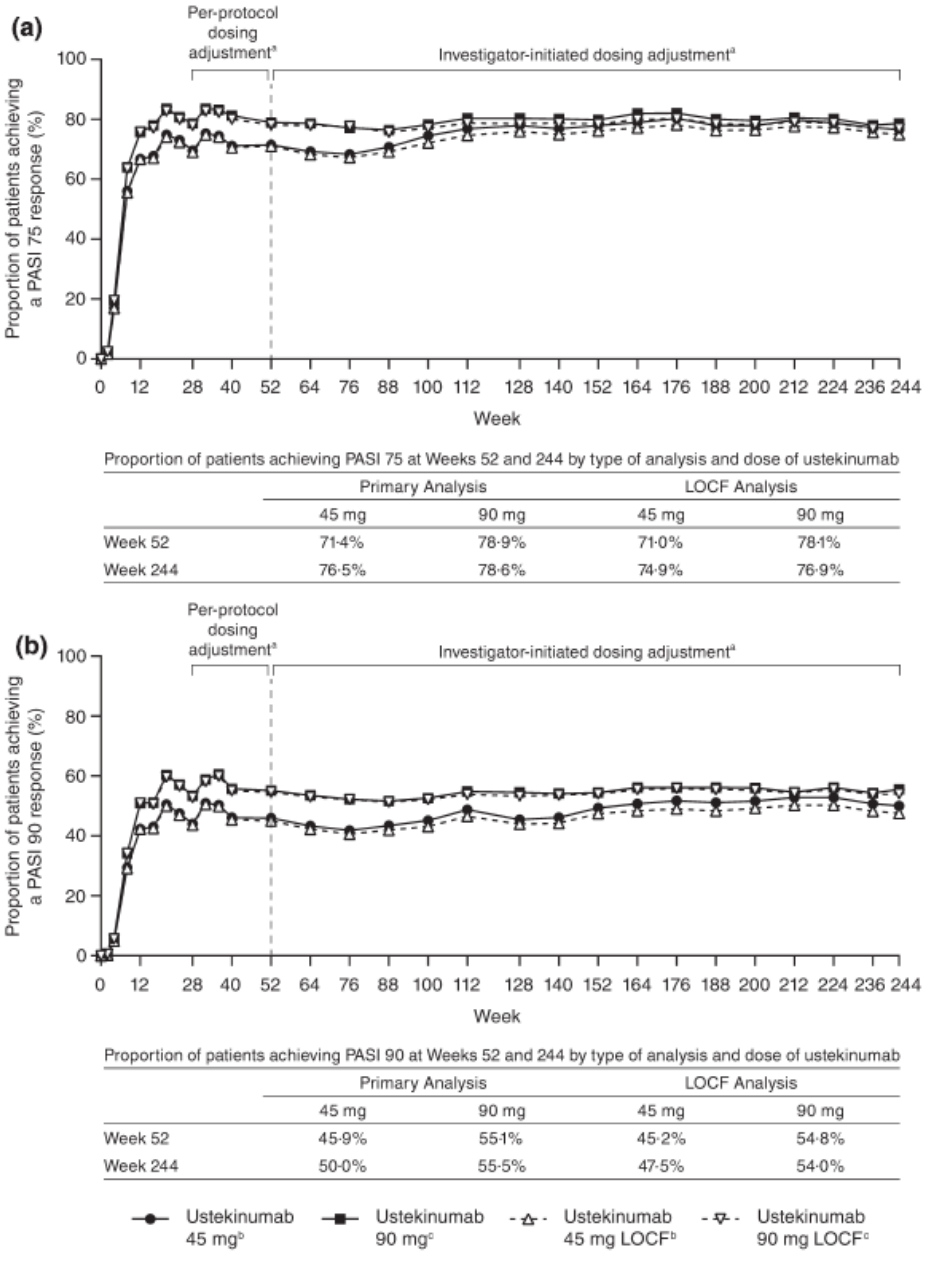


Note: Placebo cross-over patients are included beginning week 24 (ie 12 weeks after ustekinumab treatment). Analyses were not conducted between weeks 40 and 76 when the majority of the population was withdrawn from treatment per study design. Analyses resumed at week 76 when about half of the withdrawn patients had reinitiated UST for at least 12 weeks. Patients who reinitiated treatment after Week 76 were re-included after at least 12 weeks of re-treatment.

4.8.3.2. Efficacy through year 5 for PHOENIX 2 (11)

In PHOENIX 2, high levels of clinical response were achieved and maintained through year 5 in the overall population, which included patients with and without dosing adjustment. At week 244, 76.5% and 78.6% of patients initially randomised to 45mg and 90mg, respectively, achieved PASI 75. (11)

Figure 10 Proportion of patients achieving (a) 75% improvement in PASI and (b) PASI 90 response through week 244 (5 years) in patients randomised to ustekinumab 45mg and 90mg by primary and last-observation-carried-forward (LOCF) (11)



Proportion of patients achieving PASI 75 at Weeks 52 and 244 by type of analysis and dose of ustekinumab

	Primary Analysis		LOCF Analysis	
	45 mg	90 mg	45 mg	90 mg
Week 52	71·4%	78·9%	71·0%	78·1%
Week 244	76·5%	78·6%	74·9%	76·9%

Proportion of patients achieving PASI 90 at Weeks 52 and 244 by type of analysis and dose of ustekinumab

	Primary Analysis		LOCF Analysis	
	45 mg	90 mg	45 mg	90 mg
Week 52	45·9%	55·1%	45·2%	54·8%
Week 244	50·0%	55·5%	47·5%	54·0%

[a]Refer to the Methods section and study design figure in the publication for further details regarding dosing adjustment(11)
[b]The 45-mg group included patients who adjusted their dose interval from q12wk to q8wk at weeks 28 or 40 based on clinical response per protocol as well as a subgroup of patients who made a two-step adjustment from 45mg q8wk to 90mg q8wk in the long-term treatment period.
[c]The 90-mg group included patients who adjusted their dose interval from q12wk to q8wk at weeks 28 and 40 based on clinical response per protocol.

4.8.3.3. Safety through Year 5 for PHOENIX 1 (42)

Ustekinumab was generally well-tolerated through 5 years with 3,104 patient years (PY) of follow-up. Comparable rates of key safety events were observed between the ustekinumab 45mg and 90mg groups (Table 24).The rates of AEs leading to discontinuation, SAEs, serious infections, non-melanoma skin cancer (NMSC), other malignancies, and major adverse cardiovascular events (MACE) per 100 PY of follow-up remained generally stable over time from Year 1 through Year 5 (data not shown, refer to Kimball, et al. 2013) (42).

Table 24 Cumulative rates of key safety events per 100 patient years (PY) of follow up through year 5 (PHOENIX 1) (42)

	UST		
	45 mg	90 mg	Combined
Patients treated, n	378	375	753
Avg. duration of follow-up (weeks)	211.8	216.9	214.4
PY of follow-up (years)	1539.9	1564.2	3104.2
Adverse events (AEs)	220.92	209.05	214.94
AEs leading to discontinuation	2.03	2.26	2.13
Serious adverse events (SAEs)	5.26	5.43	5.35
Infections	83.71	81.64	82.66
Infections requiring treatment	28.44	30.37	29.41
Serious infections	0.84	1.21	1.03
Malignant neoplasms	1.24	0.64	0.93
Non-melanoma skin cancers (NMSCs)	0.65	0.26	0.45
Malignancies (excluding NMSC)	0.59	0.38	0.48
Major adverse cardiovascular events (MACE)*	0.52	0.13	0.32

**Adjudicated MACE included myocardial infarction, stroke, and cardiovascular death*

4.8.3.4. Safety through Year 5 for PHOENIX 2 (11)

Through week 264, safety event rates did not increase and event rates were generally comparable between dose groups and between patients with and without dosing adjustment.
No dose response was observed between 45mg and 90mg in overall AEs, AEs leading to treatment discontinuation and AEs of interest at year 5.

Through week 264, the cumulative rates of AEs, SAEs and AEs of interest were generally comparable between the 45-mg and 90-mg groups in the overall population (see Table 23), and between the non-adjusters and adjusters (data not shown, please refer to Langley, et al. 2015) (11).

Table 25 Summary of safety events per 100 patient-years of follow-up through week 264 (5 years) by dose received; overall population treated with at least one dose of ustekinumab

	Ustekinumab 45 mg[a]	Ustekinumab 90 mg[a]	Combined
Patients treated, n	606	809	1212
Average duration of follow-up (weeks)	167	198	216
Patient-years of follow-up	1952	3085	5037
Adverse events, n	222	195	206
% of patients with:	2·17	2·58	2·43
Adverse events leading to discontinuation, %			
Serious adverse events, %	7·99	6·87	7·31
Overall infections, %	85·6	75·9	79·7
Infections requiring treatment	26·0	23·6	24·5
Serious infections	1·08	0·88	0·95
Overall malignancies, %	1·08	1·07	1·08
NMSC	0·57	0·32	0·42
Other malignancies (excludes NMSC)	0·51	0·75	0·66
MACE, %	0·56	0·42	0·48

MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer. [a]Patients who adjusted their dose from 45 to 90 mg were included in the 45-mg or 90-mg group based on the dose received at the time the event was reported.

4.8.4. *Conclusions from supporting studies*

The response rates at week 12 in the CADMUS trial for ustekinumab compared to placebo (see Section 4.5.2.) are similar or better than those reported in the adult PHOENIX trials (See Table 23).

In PHOENIX 1 and PHOENIX 2, the majority of patients remained on ustekinumab through up to 5 years of therapy and maintained high levels of clinical response. (42) (11) The safety profile of ustekinumab remains consistent with previously reported safety data through to year 3. (10) Through Year 5, ustekinumab was well-tolerated, in general, without evidence of cumulative toxicity with increased duration of exposure (42), (11)

Under the assumption that young people will spend the majority of their lives living with psoriasis as an adult, the extension to use usketinumab in young people only adds 6 years of additional treatment with ustekinumab. The expectation of continuation of response for adolescent patients beyond one year is evident and is supported by real world evidence gathered in the BADBIR and PSOLAR registries ((12), (41)) as well as the longer-term data from the adult studies, PHOENIX 1 and 2 trials. (11), (42)

5. Indirect treatment comparisons

No direct head-to-head trial clinical evidence for ustekinumab against other biologics in the treatment of PsO was identified, and therefore an indirect treatment comparison (ITC) approach was considered (see Section 4.1. . The only study identified by the SLR that contained a potentially relevant comparator and permitted an ITC to ustekinumab via a shared placebo comparator with the CADMUS trial was the etanercept study (NCT00078819) (see section 4.2. .

Baseline characteristics were not available for the subgroup of patients the NCT00078819 study aged 12-17 years so no assessment could be made as to the similarity of this subgroup to the CADMUS study.

There was no common comparator arm between the adalimumab trial (M04-717) and the CADMUS study; the former compared against methotrexate and the latter against placebo, therefore it was not possible to establish an indirect comparison between ustekinumab and adalimumab (16), (31)). A naïve comparison is presented in Section 5.5. .

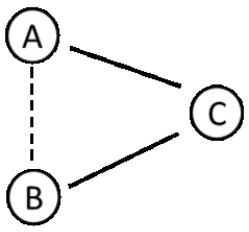
5.1. ITC Methods

Bucher indirect comparisons were conducted in this case due to the small network and number of trials. A frequentist indirect treatment comparison was also undertaken using an ordered logistic model (using a fixed effect to create the indirect link and maintain the randomisation).

This method simply compares results from 2 or more randomised controlled trials (RCTs), each with a common comparator arm. This allows a comparison to be made between two interventions which have not been directly compared in head-to-head trials, whilst preserving randomisation of the RCTs. AICs do not account for study differences and there is an underlying assumption that the trials included within an AIC are deemed similar and comparable. There should be no important differences between the sets of trials that could bias the estimated indirect effect, resulting in an overestimate or underestimate of the true treatment effect.

In this case, odds ratios [OR] were used for estimating relative treatment effects of the dichotomous outcomes and mean differences were used for the change from baseline outcome.
The outcome measures from each trial should be identical and on the same scale for an AIC to be conducted. Figure 11 shows an example of where an adjusted indirect comparison may be used. In this scenario, C is the common comparator treatment and an indirect estimate of A vs. B is calculated using direct trials comparing A vs. C and B vs. C.

Figure 11: Example indirect comparison of A vs. B



5.2. Outcomes of interest

There were five outcomes reported in both CADMUS and the NCT00078819 study on the full population; PASI 50, PASI 75, PASI 90, PGA Score 0/1 and change from baseline in CDLQI. CADMUS further reported PASI 100. In addition, PASI 50, PASI 75 and PASI 90 were reported for the population sub grouped by age for the NCT00078819 study and were also compared to the

corresponding outcomes in the CADMUS study. The only time point where it was possible to compare evidence across studies is Week 12, as the CADMUS study re-randomised placebo patients between the two ustekinumab doses after this time. Table 26 shows outcome availability by study and for the subgroup of patients aged 12-17 years in the NCT00078819 study.

AE rates were reported in NCT00078819 at week 48. AE rates for the double-blind period in the CADMUS study were curtailed at Week 12. It was considered prone to bias to compare rates over a 48-week period with those over a 12-week period, as it was possible that AEs occurred soon after the start of treatment and so the rate would be higher at earlier time points.

The M04-717 study reported the following outcomes: PGA 0/1, PASI 75, PASI 90 and PASI 100 and change from baseline in CDLQI. Adverse events are first reported at 16 weeks.

Table 26 Outcome availability

Study	Ustekinumab Standard dose: 0.75 mg/kg [≤60 kg], 45 mg [>60-≤100 kg], and 90 mg [>100 kg])	Adalimumab High dose: 0.8mg/kg	Adalimumab Low dose: 0.4mg/kg	Etanercept 0.8mg/kg (max 50mg)	Placebo	PASI					PGA	HRQoL		
						50	75	90	100	Score % Improvement	Score 0/1	CDLQI CFB mean/SD	CDLQI mean % CFB	CDLQI Score 0/1
CADMUS	✓				✓	✓	✓	✓	✓		✓	✓		✓
NCT00078819				✓	✓	✓	✓	✓		✓	✓	✓	✓	
NCT00078819 (subgroup for patients aged 12-17 years)				✓	✓	✓	✓							
M04-717		✓	✓				✓	✓	✓		✓		✓	

Key: PASI; Psoriasis Area and Severity Index, PASI 50; at least 50% improvement in PASI (similarly for PASI 75, 90 and 100), PGA; Physician's Global Assessment, HRQoL; health-related quality of life, CDLQI; Children's Dermatology Life Quality Index, CFB; Change from baseline, SD; standard deviation

5.3. Data inputs and results

The trials identified by the systematic literature review (see Section 4.1.1.) are used to inform an indirect comparison, comparing ustekinumab with the other biological treatment options for adolescent psoriasis that are included in the NICE MTA scope.

The relevant treatments are:

- Ustekinumab (Stelara); Standard dose [SD]: 0.75 mg/kg [≤60 kg], 45 mg [>60-≤100 kg], and 90 mg [>100 kg])
- Etanercept (Enbrel®); 0.8mg/kg (max 50mg)
- Adalimumab (Humira®); 0.8mg/kg or 0.4mg/kg
- Best supportive care [BSC]

The CADMUS study has been described in detail in Section 4.3.1.

The NCT00078819 study has been referred to previously, and the full publication is referenced in the bibliography (17).

In addition, a third study (M04-717) is included in this section for completion; this study was not captured in the SLR, due to it not yet being published (study was completed in August 2015). The EMA report published October 2015 is included in the reference (16). The M04-717 study is a multicentre, randomized, double-dummy, double-blind study evaluating two doses of adalimumab versus methotrexate in paediatric subjects with chronic plaque PsO. Again the M04-717 does not provide a common comparator link to the CADMUS study to allow for standard ITC.

Best supportive care is a combination of active treatments, such as topical therapies, ciclosporin, methotrexate and phototherapy and is usually given to patients after cycling through biologic treatments. Due to a lack of clinical trials available with a BSC arm, it was not possible to make any comparisons of ustekinumab versus BSC and in line with the ERG report for the apremilast appraisal it was assumed that patients on BSC would be quivalent to the placebo response seen in the trials. (29).

5.4. Baseline Characteristics

To assess the underlying assumption of similarity between studies, key baseline characteristics of the patient populations are presented in

Table 27, by study and treatment.

Table 27 Key baseline characteristics by study and treatment

Study ID	Treatment	Total N	Male (%)	Age	Duration of psoriasis	PASI score	Psoriasis BSA %	Body weight, kg	PGA Score ≥4 n (%)	Prior therapy n (%)
CADMUS	Ustekinumab (standard dose)	36	44.4	Mean 14.8 (Median 15.0)	Mean 5.55 (Median 5.54)	Mean 21.7 (Median 16.8)	Mean 31.9 (Median 21.5)	Mean 62 (Median 61.7)	36 (100)	Topical agents = 33 (91.7); Conventional systemic therapies = 17 (47.2); UVB = 13 (36.1); Methotrexate = 6 (16.7); Biologics = 3 (8.3); PUVA = 4 (11.1)
	Placebo	37	54.1	Mean 15.6 (Median 16.0)	Mean 6.18 (Median 5.11)	Mean 20.8 (Median 19.6)	Mean 27.4 (Median 21)	Mean 64.74 (Median 60.30)	37 (100)	Topical agents = 34 (91.9); Conventional systemic therapies = 16 (43.2); UVB = 11 (29.7); Methotrexate = 8 (21.6); Biologics = 5 (13.5); PUVA = 0 (0)
NCT00078819	Etanercept	106	52	Median 14	Median 6.8	Median 16.7	Median 21	Median 59.6	105 (99)	Previous systemic therapy or phototherapy = 58 (55)
	Placebo	105	50	Median 13	Median 5.8	Median 16.4	Median 20	Median 59.8	104 (99)	Previous systemic therapy or phototherapy = 62 (59)
M04-717	Adalimumab (high dose)	38	44.7	2 children were 7 yrs old; 3 were 8 yrs old; 33 were 9-18 yrs old	Not reported by treatment arm. The average subject had been diagnosed with plaque psoriasis for 5 years before participating in this study before participating in this study.	Mean 18.9 (Median 15.3)	Not reported by treatment arm. The average subject had 28% of the body surface area affected by psoriasis lesions	Mean 50.8 Median 48.5	35 (92.1)	Etanercept = 4 (10.5) Systemic nonbiologic therapy = 14 (36.8) Topical agent = 38 (100) Phototherapy = 17 (44.7)
	Adalimumab (low dose)	39	53.8	2 children were 5yrs old; 4 were 6 yrs old; 2 were 7 years old; 1 was 8 yrs old; 30 were 9-18 years old		Mean 16.9 (Median 15.6)		Mean 50.2 Median 53.0	35 (92.1)	Etanercept =4 (10.3) Systemic nonbiologic therapy = 11 (28.2) Topical agent = 39 (100) Phototherapy = 23 (59.0)
	Methotrexate	37	29.7	2 children were 7 yrs old; 1 was 8 yrs old; 34 were 9-18 years old		Mean 19.2 (Median 17.5)		Mean 53.1 Median 52.0	36 (97.3)	Etanercept = 3 (8.1) Systemic nonbiologic therapy = 9 (24.3) Topical agent = 37 (100) Phototherapy = 19 (51.4)

Table 28 Response rates and HRQoL results as Week 12

			Number of responders at Week 12 *					Change from baseline	
Study ID	**Treatment**	**Dose**	**N**	**PASI50 (%)**	**PASI75 (%)**	**PASI90 (%)**	**PGA01 (%)**	**N**	**CDLQI Mean (SD)**
CADMUS	Ustekinumab	Standard dose: 0.75 mg/kg [≤60 kg], 45 mg [>60-≤100 kg], and 90 mg [>100 kg])	36	32 (88.9)	29 (80.6)	22 (61.1)	25 (69.4)	36	-6.7 (5.63)
	Placebo	.	37	11 (29.7)	4 (10.8)	2 (5.4)	2 (5.4)	37	-1.5 (3.18)
NCT00078819	Etanercept	0.8mg/kg (max 50mg)	106	79 (74.5)	60 (56.6)	29 (27.4)	56 (52.8)	106	-5.4 (5.6)
	Placebo	.	105	24 (22.9)	12 (11.4)	7 (6.7)	14 (13.3)	105	-3.1 (5.1)
NCT00078819 (Age 12-17 years subgroup population)	Etanercept	0.8mg/kg (max 50mg)	68	50 (73.5)	38 (55.9)	NR	NR	NR	NR
	Placebo	.	67	16 (23.9)	8 (11.9)	NR	NR	NR	NR
M04-717	Adalimumab	0.8mg/kg (up to a maximum of 40mg)	38	NR	22 (57.9)	11 (28.9)	23 (60.5)	38	-6.6 (6.22)
	Adalimumab	0.4mg/kg (up to a maximum of 20mg)	39	NR	17 (43.6)	12 (30.8)	16 (41.0)	38	-4.9 (6.16)
	Methotrtexate	0.1-0.4mg/kg weekly (up to maximum of 25mg)	37	NR	12 (32.4%)	8 (21.6%)	15 (40.5%)	36	-5.0 (7.11)

Key: PASI; Psoriasis Area and Severity Index, PASI 50; at least 50% improvement in PASI (similarly for PASI 75, 90 and 100), PGA; Physician's Global Assessment, PGA01; PGA Score 0/1, N; number of patients, NR; not reported, SD; standard deviation.
*Week 16 response rates reported for M04-717

Table 29: Key inclusion criteria

Study ID	Inclusion criteria				Study Duration	Duration of treatment
	Age	**Diagnosis**	**Moderate-to-severe defined as:**	**Other**		
CADMUS	12-17 years incl.	Moderate-to-severe plaque psoriasis	PASI ≥12, PGA ≥3; and BSA≥10, with a history of psoriasis for ≥6 months	Were candidates for phototherapy or systemic treatment, or had psoriasis that was poorly controlled with topical therapy.	60 weeks	52 weeks

Study ID	Inclusion criteria				Study Duration	Duration of treatment
	Age	Diagnosis	Moderate-to-severe defined as:	Other		
NCT00078819	4-17 years	Moderate-to-severe plaque psoriasis at screening	PASI score ≥12, static PGA ≥3, BSA≥10% with a history of psoriasis for ≥6 months, previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids) or psoriasis considered by the investigator as poorly controlled with topical therapy	Previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids) or psoriasis considered by the investigator as poorly controlled with topical therapy	48 weeks	48 weeks
M04-717	4-17 years	Severe plaque psoriasis at screening	PASI score >20, BSA >20% and PGA ≥4, PASI >10 and at least one of the clinical features[a]	Subject needed systemic treatment to control their disease	120	Two separate periods of 16 weeks (with an intermittent period of up to 36 weeks).

Key: PASI; Psoriasis Area and Severity Index, PGA; Physician's Global Assessment, BSA; Body surface area

[a]active PsA unresponsive to non-steroidal anti-inflammatory drugs (NSAIDs); clinically relevant facial involvement; clinically relevant genital involvement; clinically relevant hand and/or foot involvement; CDLQI >10

A thorough examination of the patient/baseline characteristics of the studies was made in order to establish whether differences were of clinical relevance.

The less severe a patient's PsO is at baseline, then the more likely they would achieve a PASI score of 90 or 100 after treatment (see section 3.). Baseline absolute median PASI scores for the CADMUS population were more severe than those observed for either the etanercept or adalimumab clinical trial populations (16.8 standard dose arm, 19.6 placebo arm for CADMUS compared to 16.7 etanercept, 16.4 placebo for NCT00078819; 15.3 high dose adalimumab, 15.6 low dose adalimumab and 17.5 placebo in the M04-717). Moreover, CADMUS patients reported a higher number of treatment with prior biologics, which would imply that they could be more severe than the ones recruited in NCT00078819 and M04-717 studies.
In this context, we believe that there may be a bias in the trial against ustekinumab, due to the higher baseline severity of the placebo group compared to the ustekinumab group, which may disfavour ustekinumab when the trial data is entered in the indirect comparison versus etanercept.

The input data used for all comparative analyses are presented in Table 28 and key inclusion criteria for each study is presented in Table 29.

5.5. Comparison of ustekinumab versus adalimumab

Adalimumab is compared within an RCT to methotrexate (M04-717 study) which was recently presented at the annual meeting of the American Academy of Dermatology. (45) As there are no RCTs for methotrexate linking to the network in this population, an AIC could not be completed between M04-717 study and CADMUS trial.

Timing of reported outcomes and baseline characteristics of the two trials are summarised in Table 26 and Table 27. The majority of patients in the M04-717 study were age 9-18 years (33/38 in the high dose arm, 30/39 in the low dose and 34/37 in the methotrexate arm), which suggests that the two studies may have comparable populations from an age perspective. However, M04-717's full study results would be required in order to determine exactly how many of the patients were aged 12 and above as in CADMUS.

Given the absence of published data, a naïve comparison of the week 16 efficacy data is presented below (See

Table 30, based on the PGA 0/1, PASI 75, PASI 90 and PASI 100 response rates and the change in CDLQI scores reported in the EMA report for Humira ((16)) and CADMUS' published results ((9).

Although naïve comparison should be interpreted with caution, due to confounding bias due to cross-trial differences, the above comparison suggests that young people treated with ustekinumab have higher response rates than those treated with adalimumab or methotrexate, despite the ustekinumab population being more severe at baseline (as measured by baseline PASI scores – See Table 27.

It should be noted that while the change in CDLQI score was recorded at week 16 for adalimumab, it is comparable to ustekinumab scores at week 12, as reported in CADMUS ((9) and (16)).

Table 30 Response rates on PGA, PASI 75, 90, 100 and change in CDLQI score reported at week 16 ((16) and (9))

	M04-717 trial		CADMUS trial
	Adalimumab 0,8 mg/kg	Methotrexate	Ustekinumab standard dose
PGA (cleared or minimum) 0/1	23/38 (60.5%)	15/37 (40.5%)	[redacted]
PASI 75	22/38 (57.9%)	12/37 (32.4%)	[redacted]
PASI 90	11/38 (28.9%)	8/37 (21.6%)	[redacted]
PASI 100	7/38 (18.4%)	1/37 (2.7%)	[redacted]
CDLQI	-6.60	-5.00	[redacted]

* CDLQI scores for ustekinumab were reported at week 12 (CDLQI scores were not reported at week 16 in CADMUS trial).

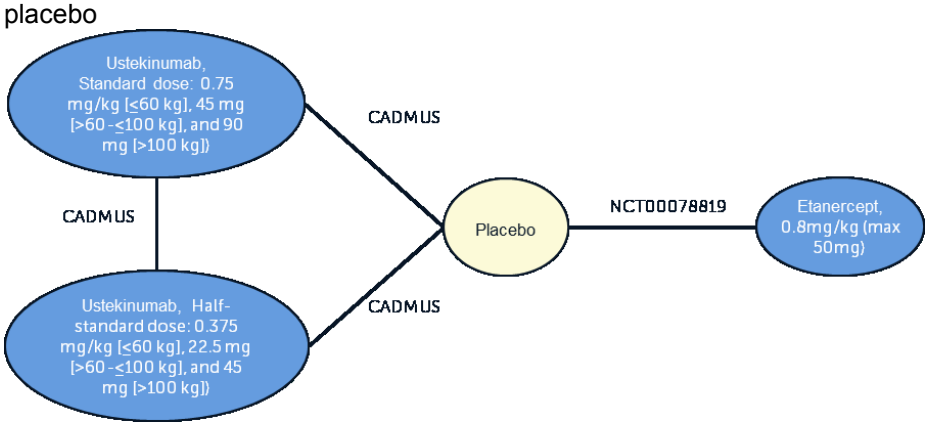
5.6. Comparison versus etanercept

The comparison between ustekinumab and BSC can be made from direct head to head randomised controlled trial (RCT) evidence, CADMUS (see section 5.2.). AICs between etanercept and ustekinumab (standard dose) have been formed using placebo as a common comparator.

The available network for each of the analyses is shown in

Figure 1, where included studies are linked into the network via a common comparator.

Figure 1: Diagram of the AIC between ustekinumab (CADMUS) and etanercept (NCT00078819) via placebo



5.6.1. *Presentation of AIC results for ustekinumab vs etanercept*

Table 31 presents the direct trial outcomes for each treatment versus placebo.

As the outcomes PASI 50, 75, 90 and PGA01 are positive outcomes, odds ratios >1 favour the active treatment (see Table 31). All odds ratios (ORs) in Table 31 are larger than 1, so in all cases the active treatment is favoured over placebo. As none of the 95% confidence intervals span the reference line of 1, the differences shown are also statistically significant, however there is a high level of variability surrounding these estimates shown by the size of these intervals, particularly for the CADMUS trial, due to the small patient numbers in each arm, which result in large variability for the within-trial treatment effect estimates.

Table 31 presents the direct trial outcomes for each treatment versus placebo, for each dichotomous outcome (PASI 50, 75, 90 and PGA01), ustekinumab results in the highest OR for ustekinumab

compared to placebo. The direct trial ORs for etanercept compared to placebo in the full and 12-17 years subgroup populations are reasonably similar for PASI50,75 and 90 , 9.88 [5.25, 18.56] and 8.85 [4.07, 19.28] for PASI50. 10.11 [4.95, 20.63] and 9.34 [3.87, 22.52] for PASI75 and 5.27 [2.19,12.68} and 5.25 [1.66,16.58] for PASI 90 in the full and subgroup populations respectively, suggesting that the treatment effect of etanercept is not substantially different for the full and subgroup populations.

The more positive the PASI outcome is (i.e. PASI 75 is a better outcome than PASI 50) the more pronounced the difference becomes between ustekinumab and etanercept (full or subgroup population), there are also a large difference shown for the PGA01 outcome in favour of ustekinumab.

Lower scores of CDQLI indicate better health related quality of life (HRQoL) so negative mean changes from baseline correspond to improvements in CDLQI therefore mean differences which are < 0 favour the active treatment (see Table 31). All active treatments are favoured versus placebo for CFB in CDLQI, the differences are also significant as none of the confidence intervals cross the reference line, which is 0 in this case. Ustekinumab results in the largest mean difference in change from baseline of CDLQI.

Table 31: Direct Trial Outcomes

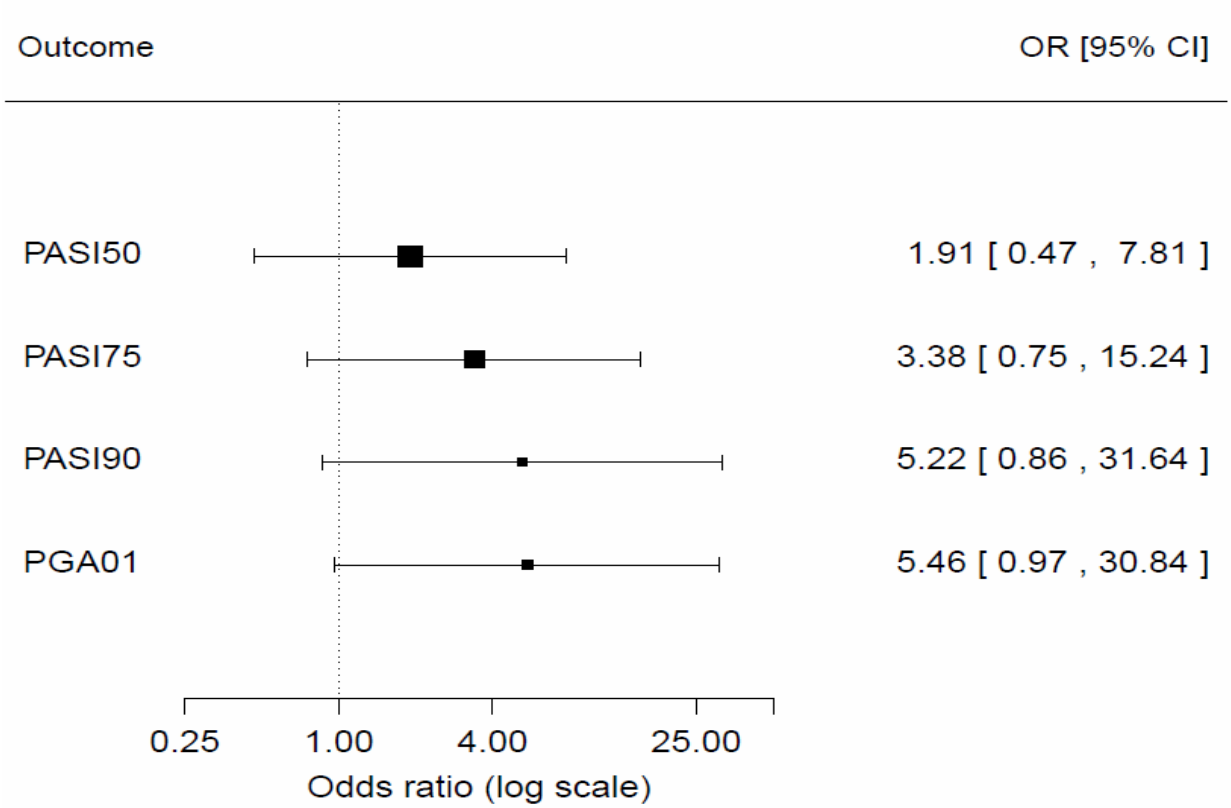
Odds ratios (Dichotomous outcomes)					
Outcome	**Comparison**	**OR**	**95% CI**	**Log OR**	**Log OR SE**
PASI50	Ustekinumab SD vs Placebo	18.91	(5.39, 66.39)	2.94	0.64
	Etanercept vs Placebo (full population)	9.88	(5.25, 18.56)	2.29	0.32
	Etanercept vs Placebo (Age 12-17 years subgroup population)	8.85	(4.07, 19.28)	2.18	0.40
PASI75	Ustekinumab SD vs Placebo	34.18	(9.08, 128.71)	3.53	0.68
	Etanercept vs Placebo (full population)	10.11	(4.95, 20.63)	2.31	0.36
	Etanercept vs Placebo (Age 12-17 years subgroup population)	9.34	(3.87, 22.52)	2.23	0.45
PASI90	Ustekinumab SD vs Placebo	27.50	(5.69, 132.8)	3.31	0.80
	Etanercept vs Placebo (full population)	5.27	(2.19, 12.68)	1.66	0.45
PGA0/1	Ustekinumab SD vs Placebo	39.77	(8.10, 195.36)	3.68	0.81
	Etanercept vs Placebo (full population)	7.28	(3.69, 14.37)	1.99	0.35
Mean difference (Continuous outcome)					
		Mean difference	**95% CI**		**SE**
Change from baseline - CDLQI	Ustekinumab SD vs Placebo	-5.2	(-7.44-2.96)		1.14
	Etanercept vs Placebo (full population)	-2.3	(-3.75-0.85)		0.74

Key: SD; standard dose, PASI; Psoriasis Area and Severity Index, PASI 50; at least 50% improvement in PASI (similarly for PASI 75, 90 and 100), PGA; Physician's Global Assessment, PGA01; PGA Score 0/1, OR; odds ratio, SE; standard error, CI; confidence interval.

5.6.1.1. Results of the ITC

The comparisons for all dichotomous outcomes for ustekinumab SD compared to etanercept (full population) are shown in
Figure 12. Although multiple outcomes are presented in 1 forest plot, these are the result of separate ITCs. As before, ORs>1 favour the first treatment, which is ustekinumab. As indicated in the direct trial results, ustekinumab becomes more favourable against etanercept as the PASI outcome improves as well as for PGA01, though the high uncertainty shown in the direct trial estimates is reflected here in the lack of statistical significance for each outcome at the 5% level (although this becomes very close for PGA0/1).

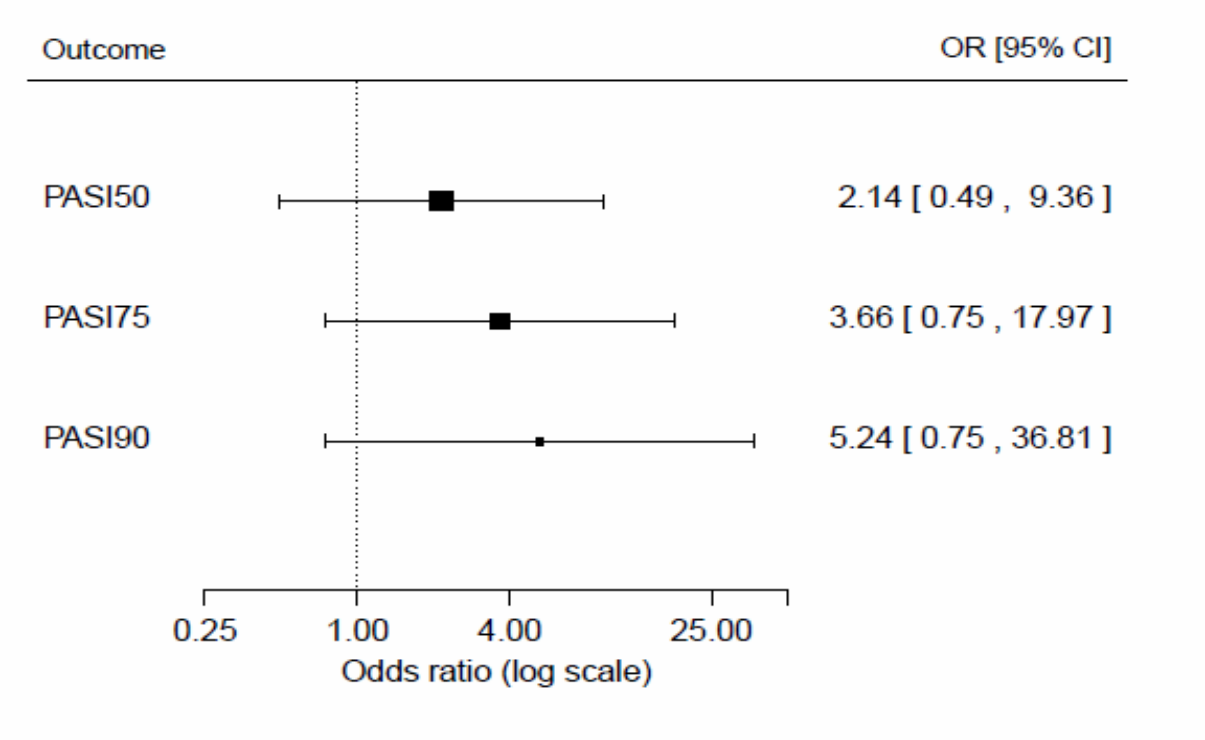
Figure 12: AIC Ustekinumab vs Etanercept (full population): All dichotomous outcomes



Legend: PASI; Psoriasis Area and Severity Index, PASI 50; at least 50% improvement in PASI (similarly for PASI 75, 90 and 100), PGA; Physician's Global Assessment, PGA01; PGA Score 0/1, OR; odds ratio, CI; confidence interval. Odds ratios greater than 1 favour ustekinumab SD.

Figure 5 shows the results of the AICs for all dichotomous outcomes for ustekinumab compared to etanercept (Age 12−17 years subgroup population). The indirect estimates of the OR for PASI 50, 75 and 90 again favour ustekinumab , and show a slight improvement over the results based on the etanercept full population case, however, due to the reduction in sample size caused by the subgrouping - 68 and 67 in the etanercept and placebo arm respectively compared to 106 and 105 using the full population - the uncertainty in these estimates is increased (shown in the wider confidence intervals).

Figure 5: AIC Ustekinumab vs Etanercept (Age 12−17 years subgroup population): PASI 50, 75 and 90

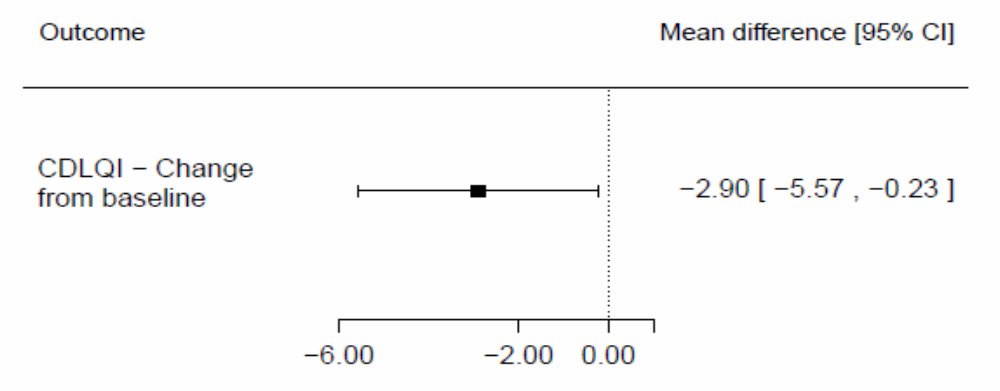


Legend: PASI; Psoriasis Area and Severity Index, PASI 50; at least 50% improvement in PASI (similarly for PASI 75), OR; odds ratio, CI; confidence interval.

Odds ratios greater than 1 favour ustekinumab SD

Figure 6 shows the AIC for the change from baseline in CDLQI for ustekinumab SD compared to etanercept. As before, negative values for the mean difference in change from baseline in CDLQI favour the first treatment. The indirect estimate of the mean difference is less than 0 and so favours ustekinumab, this difference is also statistically significant as the confidence interval does not cross the reference line of 0.

Figure 6: AIC Ustekinumab Standard Dose vs Etanercept (full population): Change from baseline in CDLQI



Legend: CDLQI; Children's Dermatology Life Quality Index, CI; confidence interval

Mean differences less than 0 favour ustekinumab SD.

Indirect treatment comparison using an ordered logistic model

A frequentist indirect treatment comparison was undertaken using an ordered logistic model (using a fixed effect to create the indirect link and maintain the randomisation). The model included a covariate for the trial and the average estimated relative treatment effect across the two trials. The analysis has been conducted for the full and sub group etanercept population.

The outputs include the probabilities and CIs for each PASI category by treatment, along with ORs (for each treatment versus placebo) and associated confidence intervals. ORs were outputted as opposed to RRs given that a logistic regression has been performed. Please note, the estimates for the CIs around the ORs may be overestimated, as no standard form was available for the log OR variances given the model that was used.

The results demonstrate that for etanercept, 23.9% in the full population and 25.6% in the sub group analyses did not achieve at least a PASI 50 response compared to only 10.4% in the full population and 10.0% in the subgroup analysis for ustekinumab. Furthermore the results demonstrate that more patients with ustekinumab (57.6% and 57.9%) achieved a PASI 90 response compared to etanercept (33.5% and 30.8%) in both the full and sub group populations respectively. However, the wide confidence intervals illustrate are reflective of the small patients numbers used in the analysis.

Table 32 Full population output

PASI	Treatment	Probability	Lower95CI	Upper95CI	OddsRatio	LowerCI.OR	UpperCI.OR
PASI<50	Placebo	0.738344	0.642272	0.816007	1	NA	NA
	Ustekinumab standard dose	0.104362	0.050666	0.202808	0.041293	0.01675	0.101799
	Etanercept	0.239258	0.143854	0.370547	0.111455	0.051454	0.241422
50<PASI<75	Placebo	0.121738	0.084066	0.173103	1	NA	NA
	Ustekinumab standard dose	0.098084	0.054282	0.170848	0.784566	0.366728	1.678477
	Etanercept	0.167314	0.117713	0.232312	1.449595	0.810755	2.591815
75<PASI<90	Placebo	0.086739	0.056001	0.131991	1	NA	NA
	Ustekinumab standard dose	0.221259	0.153896	0.307396	2.991481	1.564168	5.721224
	Etanercept	0.258358	0.201676	0.324494	3.667789	2.074484	6.484828
PASI>90	Placebo	0.053178	0.031531	0.08833	1	NA	NA
	Ustekinumab standard dose	0.576295	0.395221	0.738962	24.21699	9.713214	60.37781
	Etanercept	0.335071	0.213037	0.484015	8.972239	3.925283	20.50835

Table 33 Subgroup population output

PASI	Treatment	Probability	Lower95CI	Upper95CI	OddsRatio	LowerCI.OR	UpperCI.OR
PASI<50	Placebo	0.734841	0.633795	0.816095	1	NA	NA
	Ustekinumab standard dose	0.100785	0.047526	0.201127	0.040443	0.015858	0.103146
	Etanercept	0.256301	0.145139	0.411607	0.124356	0.053141	0.291009
50<PASI<75	Placebo	0.120571	0.080301	0.177145	1	NA	NA
	Ustekinumab standard dose	0.092288	0.049031	0.167007	0.741579	0.328162	1.675815
	Etanercept	0.167567	0.112903	0.241493	1.468241	0.77167	2.793593
75<PASI<90	Placebo	0.091934	0.057848	0.143056	1	NA	NA
	Ustekinumab standard dose	0.228105	0.154282	0.323731	2.918891	1.457001	5.847578
	Etanercept	0.267241	0.201182	0.345607	3.602327	1.93349	6.711572
PASI>90	Placebo	0.052654	0.029928	0.091018	1	NA	NA
	Ustekinumab standard dose	0.578821	0.394548	0.743474	24.72593	9.558651	63.96001
	Etanercept	0.308891	0.180608	0.475424	8.041429	3.204927	20.17661

5.6.1.2. Heterogeneity and inconsistency assessments

Points of possible heterogeneity between studies were:

- Inclusion criteria for age were different between studies, NCT00078819 allowed a much larger age range of patients (4-17 years) compared to CADMUS (12-17 years). (17),(33)
  - Data were available on two outcomes for the subgroup of patients aged 12-17 in the NCT00078819 study, analyses were also conducted using the subgroup population compared to the CADMUS study
- Study/treatment duration were different between studies
  - However, as the analysis endpoints were only comparable at week 12 this did not impact the comparability of the studies.

Limitations:

- There is a lot of uncertainty in both the within-trial treatment effect estimates and the indirect estimates obtained from the AICs. This is likely due to the small sample sizes in each arm of the CADMUS study, reflected in the wide confidence intervals in both the direct and indirect (AIC) relative treatment effect estimates. This is exacerbated in the subgroup analyses as in this case there is a reduction in the sample sizes of etanercept trial arms. There may not be enough statistical power in the majority of AIC analyses to able to detect true differences between the treatments, likely attributed to the low patient numbers.
- There is an underlying assumption when conducting AICs that the included studies are comparable. No formal assessment of heterogeneity was made as there were no closed loops within the network, however clinical opinion was sought to assess whether the differences between trials were of clinical relevance (see section 5.4.). A further assumption was also necessary about the comparability of this etanercept subgroup population to the full CADMUS population as no information was available of the baseline characteristics of this subgroup.

5.7. Discussion

The direct trial results were presented for each treatment and outcome in Table 28.
These results tend to favour the active treatment over placebo and these differences were statistically significant for each comparator.

Although naïve comparison should be interpreted with caution, due confounding bias due to cross-trial differences, the results suggests that young people treated with ustekinumab have higher response rates than those treated with adalimumab or methotrexate, despite the ustekinumab population being more severe at baseline (as measured by baseline PASI scores – SeeTable 27).

Due to significant differences in baseline characteristics between the population of the three main trials (see Table 27), there is a likely bias against ustekinumab when considering comparative efficacy, which disfavour ustekinumab, especially in the indirect comparison versus etanercept. To the difference in baseline population, the small number of patients in each arm of the CADMUS trial also impact the results of the indirect comparison. The indirect estimates for the ORs favoured the corresponding ustekinumab dose for all outcomes although the differences were not statistical significance (See Section 5.6.1.1.). The AICs for the change from baseline in CDLQI also favoured ustekinumab over etanercept, for both doses.

Given the level of uncertainty in the results of the AIC between ustekinumab and etanercept (mainly due to small sample size in the relevant age group), the results of the adult phase 3 Active Comparator (CNTO 1275/Enbrel) Psoriasis Trial (ACCEPT) trial could be considered to further illustrate the expected difference in efficacy between ustekinumab and etanercept (15). The ACCEPT trial is a randomised, head to head trial, designed to compare the efficacy of ustekinumab (at both 45mg and 90mg standard doses) versus etanercept (50mg twice weekly); results showed ustekinumab was significantly more effective than etanercept at both doses, by week 12: (15)

- 67.5% of patients treated with ustekinumab 45mg and 73.8% of patients treated with ustekinumab 90mg achieved PASI 75 response compared to 56.8% treated with etanercept 50mg twice weekly (p=0.01). Significantly more patients achieved the more stringent response criteria of PASI 90 at week 12 for the ustekinumab groups versus etanercept 50mg twice weekly (p<0.001).
- A significantly higher proportion of patients treated with ustekinumab 45mg and ustekinumab 90mg also achieved a PGA 0/1 (e.g. cleared or minimal) (65.1% and 70.6% respectively) compared with (49.0%) treated with etanercept 50mg twice weekly (p<0.001 for both comparisons).
- Safety patterns were similar between ustekinumab 45mg, 90mg and etanercept arms as well as before and after crossover from etanercept to ustekinumab.

6. Cost effectiveness

6.1. Background

The possibility of constructing an economic model to assess the cost effectiveness of ustekinumab for the treatment of moderate to severe PsO in young people was explored. An informal search of the literature was undertaken and did not identify any published economic evaluations of biologics in a paediatric PsO population. Previous UK HTA assessments by the Scottish Medicines Consortium (SMC) and All Wales Medicines Group (AWMSG) were identified. A brief summary has been presented in 6.2. , as these appraisals were the most relevant and generalisable economic evidence identified to inform the NICE decision problem.

Given the lack of economic evidence, and the limited clinical evidence identified in the systematic review presented in Section 4.1. , Janssen decided not to pursue the development of an economic model.

Previous HTA evaluations of adolescents with plaque PsO from the UK and in other countries have also encountered similar issues when developing specific paediatric economic evaluations, which have resulted in either adaptations of adult models or simplified cost-analyses ((46), (47)) Due to the limitations of the evidence base, we believe that any estimation of the cost effectiveness of biologics in children with young people with plaque PsO will be subject to a number of irrevocable uncertainties and will largely be based upon a number of assumptions taken from an adult population. Instead, in Section 6.3. , we have provided a review of the known available literature children and adults which will hopefully be of use to the Assessment Group (AG) in the development of their economic model.

6.2. UK HTA submission in children and adolescents with psoriasis

A number of previous SMC abbreviated or AWMSG limited submissions were identified for adalimumab, etanercept and ustekinumab for the treatment of children and young people with plaque PsO ((46), (48), (49), (50), (51), (52), (53),(54)). A summary of the previous AWMSG and SMC appraisals are presented in Table 34. It is noted that the majority of appraisals have led to a positive AWMSG and SMC recommendation for the biologics in children with plaque PsO. The appraisal process for SMC abbreviated and AWMSG limited submissions does not require an economic evaluation to be submitted. Therefore, there is limited economic evidence available from those SMC and AWMSG submissions to inform any model development for this appraisal.

However, one AWMSG full submission was identified for etanercept for the treatment of chronic severe plaque psoriasis in children and young people from the age of eight years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (46). A cost effectiveness model was submitted by Pfizer to support this submission.

The AWMSG final appraisal report (FAR) describes that there was a lack of detail regarding the modelling methods with the model appearing to be adapted from an adult population (46). The AWMSG concluded that the cost effectiveness data presented was insufficient to recommend etanercept. A brief description of the modelling approach, inputs and results is provided in Section 6.2.1. given this is the only economic evaluation identified.

Table 34 Summary of UK HTA recommendation of licensed biologics in children and adolescents with moderate to severe psoriasis

UK HTA submission	Submission	Economic evidence	Recommendations
AWMSG advice No.138. Etanercept (Enbrel®). March 2010. (46)	AWMSG Full submission	Adaptation of adult etanercept model in psoriasis submitted. See Section 6.2.1. for further details.	Etanercept (Enbrel®) is not recommended for use within NHS Wales for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of eight years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. The cost effectiveness data presented was insufficient for AWMSG to recommend the use of etanercept (Enbrel®) in NHS Wales.
AWMSG advice No.1245. Etanercept (Enbrel®). April 2012. (48)	Non Submission	N/A	In the absence of a submission from the holder of the marketing authorisation, etanercept (Enbrel®) cannot be endorsed for use within NHS Wales for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.
AWMSG advice No.2571. Adalimumab (Humira®) . December 2015. (49)	AWMSG Limited submission	Limited submission so no economic evaluation presented. Budget impact analysis included.	Adalimumab (Humira®) is recommended as an option for restricted use within NHS Wales for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to, or are inappropriate candidates for, topical therapy and phototherapies. Prescribing should be restricted to clinical situations as specified within the National Institute for Health and Care Excellence (NICE) guidance for adults.
AWSMG advice No.2068 Ustekinumab (Stelara®) March 2016 (50)	AWMSG Limited Submission	Limited submission so no economic evaluation presented. Budget impact analysis included.	Ustekinumab (Stelara®) is recommended as an option for use within NHS Wales for the treatment of chronic moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.
SMC advice 570/09. Etanercept (Enbrel®). August 2009. (51)	SMC Abbreviated submission	Abbreviated submission so no economic evaluation presented. No further details presented in the SMC DAD.	Etanercept (Enbrel®) is accepted for restricted use within NHS Scotland. Indication under review: for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. It should be used only when the following criteria are met: SMC restriction: The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10; The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments; Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks.
SMC advice 781/12. Etanercept (Enbrel®). May 2012. (52)	SMC Abbreviated submission	Abbreviated submission so no economic evaluation presented. Budget impact analysis included.	Etanercept (Enbrel®) is accepted for restricted use within NHS Scotland. Indication under review: for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. SMC restriction: The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10; The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments; etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks.
SMC advice 1068/15 adalimumab (Humira®) July 2015 (53)	SMC Abbreviated submission	Abbreviated submission so no economic evaluation presented. Budget impact analysis included	adalimumab (Humira®) is accepted for restricted use within NHS Scotland. Indication under review: Treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies SMC restriction: Patients with severe disease as defined by a total Psoriasis Area Severity Index (PASI) score of ≥10 and a Dermatology Life Quality Index (DLQI) of >10. Treatment with adalimumab in a paediatric population improves both signs and symptoms of psoriasis and quality of life.
SMC advice 1115/15 Uskinumab (Stelara®) January 2016 (54)	SMC Abbreviated submission	Abbreviated submission so no economic evaluation presented. Budget impact analysis included	ustekinumab (Stelara®) is accepted for restricted use within NHS Scotland. Indication under review: treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. SMC restriction: continued treatment should be restricted to patients who achieve at least 75% improvement in their Psoriasis Area and Severity Index (PASI 75) within 16 weeks. Ustekinumab has previously been accepted for restricted use in adults for this indication. For the small number of adolescent patients weighing >100kg that require a dose of 90mg, a 90mg prefilled syringe is available at the same price as the 45mg prefilled syringe.

6.2.1. *Etanercept AWMSG 2009 economic model*

The Pfizer economic model consisted of a Markov model with a 28-day cycle length to represent intermittent treatment with etanercept over a 10-year time horizon of analysis (46). From the description in the AWMSG FAR, the model appears to be based on the York Assessment Group (AG) model developed in TA103 and subsequently used (with adaptations) in other manufacturer submissions to NICE ((46), (55), (56), (57), (58), (59), (29)). Further description of the York AG model is covered in Section 6.3. below.

The AWMSG in their critique of the Pfizer model highlighted the very limited detail submitted to inform the assumptions around the extrapolation of effectiveness and utilities from the short term trial data over the 10-year time horizon of the model. In the model, children were assumed to receive initial therapy for 12 weeks. Those who failed to achieve a PASI 50 response were considered to be treatment failures and stop active therapy. The AWMSG noted that some clinicians in TA103 had felt that the PASI 50 was too low a threshold for clinical response. However, this is broadly consistent with previous modelling in adults and NICE recommendation for biologics, which states that an adequate response can be defined as a PASI 50 and a five-point reduction in DLQI (60).

In the model, those achieving a PASI 50 or more continue treatment for a further 12 weeks, after which those who achieve/maintain a PASI 75 response were eligible to commence intermittent treatment (comprising a treatment-free period, with treatment re-initiated in those who experience relapse), or remain on continuous treatment. It was assumed that 75% of patients commence intermittent treatment. Those children who achieve a PASI 50, but less than a PASI 75 by this point (week 24 of treatment) remain on continuous treatment, i.e. intermittent treatment is not an option. Failure to achieve/maintain a PASI 50 response led to a treatment discontinuation.

The Phase III, placebo-controlled trial of etanercept in patients with moderate to severe PsO was used to model the efficacy of etanercept (17). The AWMSG noted that trial recruited patients aged 4-17 years, with moderate to severe plaque psoriasis and with previous or current treatment with phototherapy or systemic psoriasis therapy or psoriasis considered by the investigator as poorly controlled with topical therapy. In contrast, at the time of the submission, the licensed indication for etanercept was the treatment of chronic severe PsO in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. AWMSG estimated that only 57% of the trial population met the subsequent licensed indication, based on their treatment history.

The model used utility values derived from the adult studies of etanercept through the mapping algorithm between DLQI and EQ-5D. The utility gains were assumed to be the same regardless of the treatment, but too varied according to severity of disease. The AWMSG also reported that the adverse events also seem to be based on the adult population. There was no discussion of the inherent uncertainty in using adult derived utilities to represent a population of children and young people.

The costs of etanercept were reported in the submission and was based on doses used in the phase III trial, at 0.8 mg/kg body weight up to a maximum intended dose of 50mg and delivered in pre-filled syringes. However, upon inspection of the model, the AWMSG suggested that the cost of etanercept was based on weekly doses of 25mg. In the clinical trial, 44% of patients received the maximum dose of 50mg per week and 56% received a weekly dose of 0.8mg per kilogram. The median weight of all patients in the trial was around 60kg which based on a dose of 0.8mg per kilogram per week would have equated to a median dose that approaches 50mg per week. The AWMSG noted that model was very sensitive to the assumed weekly cost of etanercept. The British Association of Dermatologist guidelines informed the model decisions on clinic visit frequency and the data from TA106 AG report informed the length of hospital stay for patients who failed treatment ((55), (61)).

The Pfizer results presented showed that etanercept was both less expensive and more effective than placebo/non-systemic treatment, i.e. etanercept was the dominant treatment strategy. The AWSMG were not able to verify the results from the model that was been provided given the model showed an incremental cost effectiveness ration (ICER) of £1,000-£2,000 per QALY. The reason for this discrepancy was not clear. Given the limitation of the model, plus the lack of detail regarding assumptions and data included in the model, it appears that the AWMSG were unable to recommend etanercept given these uncertainties in the economic case.

6.3. Development of an economic evaluation in children and young people with Psoriasis

Many of the uncertainties highlighted by the previous AWMSG appraisal of etanercept still exist and, despite the AWMSG concerns, any model developed is likely to rely strongly on evidence and assumptions taken from an adult population. Remaining uncertainties in the modelling of children and adolescents include the:

- Limited published clinical data for adolescents with moderate to severe PsO which make comparisons to other interventions included in the NICE scope difficult.
- Lack of long term data on disease progression and maintenance of PASI response available for adolescents with PsO.
- Appropriate threshold for response used in a paediatric population
- No EQ-5D data collected in the clinical trials and a lack of suitable algorithms to map EQ-5D utility values from CDLQI scores.
- Available data on resource use associated with treating children and adolescents in contrast to an adult population.

Below we have provided a discussion of the known available evidence that may help address these uncertainties and to aid the development of an appropriate economic model by the Assessment Group.

6.3.1. *Model Structure*

Children and adolescents present with the same clinical variants of psoriasis seen in adults, though there may be some differences in the distribution, morphology, and natural history (62). The management and approach to care of treatment in children and adolescents and tends to mirror that in adults (28). It is noted that during the development of the NICE CG 153, the guideline development group (GDG) agreed that in most situations it would be reasonable to extrapolate data from adult populations to children when there was no or little data (28). We believe that a similar approach should be taken with regard to the development of the economic model given that there are few significant differences in the posology or management of the disease in children, adolescents and adults.

In adults, the cost effectiveness of biologics in plaque PsO has relied on the York AG model, which was originally developed to assess the cost-effectiveness of etanercept and efalizumab for the treatment of moderate to severe chronic plaque psoriasis in NICE TA103. It was subsequently published in the HTA monograph series, Woolacott and colleagues, 2006 (63). Subsequent manufacturer submissions including adalimumab, infliximab, ustekinumab, secukinumab and apremilast have used a structure based on the Woolacott model. (56), (57), (58), (59), (29)

Janssen believe that the Woolacott structure represents an appropriate way to model a chronic condition like PsO, especially in the context of the limited evidence base in children and young people. The economic evaluation presented in Woolacott and colleagues is a 2-part model comprising a decision-tree to capture the initial response period (which will vary depending on the biological therapy) and a longer-term Markov model to inform longer term response rates and assumptions. (63)
The patient's response to initial treatment uses the combined probabilities of achieving a PASI 50, 75 or 90. The trial period represents a fixed period of time (usually 10 to 16 weeks depending on the treatment)

over which the efficacy of the treatment is monitored. At the end of the trial period, if an adequate response to the treatment is obtained, the Markov structure allows patients to move to continuous use of the treatment and stay at the PASI response level they discontinue treatment (63). In the absence of any other appropriate models identified through the AG literature searching, we believe that the Woolacott model not only represents an appropriate way to model a chronic disease like PsO, but also allows the possibility of a direct comparison to previous NICE assessments in adults.

The development of the model needs to take account of the continuation of the disease from children and adolescents and into adults, as considered in other chronic paediatric conditions ((64), (65)). PsO is a chronic, lifelong condition with no known cure. Treatment goals are to maintain symptomatic disease control and improve patients' HRQoL (66). The model developed should reflect the chronic nature of the disease and should be of sufficient length to follow patients over their lifetime. Previous models based on the York model have used 10-year time horizon ((55), (56), (57), (58), (59), (29)). However, given the population is children and young adults, this may not be a sufficient time horizon to explore the full implications of biologics, especially if a sequential use of treatments is explored.

It is common for patients to cycle through multiple treatment options during their disease course (28). Given the availability of number of biologic and systematic therapies any model should ideally explore the use of sequential biologics and therapies. The most recent manufacturer submission to NICE has departed from the Woolacott model and has allowed the comparison of treatment sequences to be included (29). This amendment to the original York model means that the number of possible treatment sequences could be considered, however, given the limited data available in children and adolescents any modelling of the subsequent lines of treatment in this population would be uncertain. Exploratory analyses could be undertaken using evidence on the sequential use of biologics in adults with Psoriasis, as was undertaken in NICE CG153 (28).

A major assumption of the Woolacott model is that a PASI 50, 75 and 90 responses on a biologic is maintained until the person discontinues treatment (63). There is significant evidence to support this with all three biologics showing a continuation in response over a long period in an adult population ((11), (42), (67), (68)). The trial evidence in pediatric psoriasis patients shows the maintenance of response over the duration of the 48-52 week trials for etanercept, adaliumab and ustekinumab ((17),(2)). The published open-label extension to the paediatric psoriasis etanecept trial (NCT00078819) demonstrates the maintenance of the response in a moderate to severe pediatric population over a 5-year period. However, a major limitation of the study is that only a small proportion of the children were not lost to follow up (34). The available evidence in adults and the limited evidence in children strongly support the long term maintenance of response on biologics.. In addition, the available evidence also suggests that that maintenance of the treatment response is largely consistent across biologics.

6.3.2. ***Population***

The population in the model should reflect the licenses of the three biologics (etanercept, adalimumab and ustekinumab) being appraised by NICE. The three biologic licenses differ in both the age and severity of psoriasis at baseline. Both etanercept and adalimumab can be used in significantly younger patients than ustekinumab, whilst ustekinumab can be used in a moderate to severe population in contrast to etanercept and adalimumab which can only be used in severe patients. See Section 2.2.

The economic evaluation should take into account the difference in the recommended ages in the biologic licenses. To avoid biasing the cost effectiveness results, ustekinumab should only be compared to an equivalent sub group of patients within the etanercept and adalimumab licenses for which the ages are overlap i.e. 12-17 years old. In section 5.6. , a comparison to available subgroup of patients aged 12-17 from the etanercept trial has been provided to allow a direct comparison of etanercept and ustekinumab in that population.

In adults, psoriasis is often described as being mild, moderate or severe. However, there is no consensus on these definitions and moderate disease is particularly poorly defined (29). In children, tools such as PASI and body surface are not validated for use in children and young people, which makes any assessment of disease severity difficult. Assessments using BSA are especially likely to be inaccurate in children, and especially young children (28). NICE technology appraisals (TAs) in adults have recommended therapies for severe psoriasis in a population that has been defined as a PASI score ≥10 and DLQI score >10 (29). Severity measured at baseline shows that children in the CADMUS trial had a similar median PASI scores (18.8) compared to etanercept (16.7) and adalimumab (15.6) Trials ((17),(2), (38)). This is also reflective of the likely use of ustekinumab in clinical practice, as systemic drug therapy, including biologics, in children are generally reserved for severe disease that is resistant to other treatments (62).

Despite the moderate to severe license for ustekinumab, we believe that there is insufficient patient numbers from the CADMUS trial to evaluate the ustekinumab in a more moderate population, as has been attempted in a recent NICE appraisal for another agent (29). Depending on the definition of severe disease in children decided by the AG, the economic evaluation should reflect either a moderate to severe or more likely a severe population. This is especially true given the baseline patients characteristics of the CADMUS trial and the disease severity being comparable to that studied in the etanercept and adalimumab trials ((17), (2), (38)).

6.3.3. *Interventions and comparators*

The NICE scope requested the following comparators to be considered:

- Non-biological systemic therapy (including, but not limited to, ciclosporin and methotrexate)
- Topical therapy (for people in whom nonbiological systemic therapy is not suitable)
- Biological treatments used outside of their marketing authorisation (such as infliximab, adalimumab, etanercept or ustekinumab if used outside of the constraints of the relevant marketing authorisation in children and young people)
- When appropriate, adalimumab, etanercept and ustekinumab will be compared with each other.

Ustekinumab should be compared to TNF-inhibitors (etanercept and adalimumab), but could also be considered as an additional line of therapy in existing treatment pathway after failure of TNF inhibitors (due to the different mode of action). This would extend the time taken for the average adolescent with severe PsO to reach BSC therapy and be aligned to the recommendations in NICE CG 153 around the sequential use of biologics in adults However, we realise that the clinical evidence to look at this question may be insufficient in children and young adults.

We believe that biologics are likely to be used after the failure of systematic conventional (i.e non-biological) therapies), which was supported by our clinical expert and is aligned to the previous positioning considered in adults. Therefore, we believe that either biologics or BSC represents the most relevant comparator to biologics in a population of children and young adults and should be considered as a relevant additional comparator within the decision problem. Further details for the rationale of this comparator are provided below.

Topical therapies

NICE CG153 and psoriasis care pathway recommend that all patients with psoriasis receive first-line treatment with emollients or active topical therapy (28). In clinical practice biologics are generally used after the failure of topical and non-biological systemic therapies (29). Therefore, we do not believe that topical therapies represent a relevant comparator for biologics in the model for this reason.

Non-biological systemic therapies

Non-biological systemic therapies are expected to be used in children, as they are in adults. Therefore, we believe that non-biological systemic therapies are not a relevant comparator to biologics as outlined in NICE CG153 and the NICE treatment pathway (28). In addition, the licenses for biologics in children and young people state that they should be used in people who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Moreover, as reported in Section 4.1. , no evidence was found for non-biological therapies such as ciclosporin and methotrexate in a paediatric population. We discuss the use of non-biological systemic therapies as part of BSC below.

Best supportive care

If treatments are found not to be effective, then adults have been assumed to receive BSC (28), (69), (70)).
The NICE GDG for CG 153 assumed that patient receiving BSC are patients that have exhausted treatment options such as conventional systemic therapy and phototherapy, including PUVA. The GDG felt that even though these therapies had either proved ineffective or given rise to certain toxicities, the patients for whom there was no other option being considered were unlikely to go without treatment altogether. The likelihood is that they would be cycled through different modalities, mainly non-biological systemic therapies, accepting the associated risks. In the economic modelling for CG153, the GDG included treatments comprising of BSC in a pragmatic fashion with a proportion of patients on methotrexate, ciclosporin and patients with no active pharmacological treatment (28). On this basis, we believe that BSC is a relevant comparator to be included in the model and a similar assumption should be used in children and young people.

Biological treatments used outside of their marketing authorisation

Previous evidence for the use of infliximab has been identified in a paediatric population (28). Infliximab is not licensed in children and adolescents and therefore not approved by regulatory authorities for this population. Although infliximab is sometimes used in children and adolescents, we have not considered infliximab further as we do not believe it is appropriate for Janssen to consider infliximab outside of its market authorisation.

No evidence for any of the other biologics included in the scope was identified, see section 4.1.1.

Biological treatments within their market authorisation

We consider etanercept and adalimumab to be relevant biologics to be consider in this appraisal given they are licensed treatments for children and adolescents with psoriasis. As reported in section 5.6. we have undertaken an indirect comparison to compare to etanercept. It was not possible to undertake an indirect comparison with adalimumab, however a naïve comparison has been presented in section 5.5.

6.3.4. *Baseline patient characteristics*

There is limited epidemiology data regarding the patient characteristics of young people with Psoriasis in the UK. The mean weight, age and sex distributions from the CADMUS trial seem to be the most appropriate source to use in the economic model for population of young people aged 12-17 years old (2). The Janssen clinical expert confirmed that the CADMUS trial was likely to be generalised to a UK population of adolescents aged 12-17 years old. An alternative source could be the etanercept sub-group population (17).

6.3.5. *Effectiveness data*

The main evidence for ustekinumab in children and young adults with paediatric psoriasis comes from the CADMUS trial which compares ustekinumab to placebo, as described in section 4.3.1. Landells, 2015 #41}.. We believe that for the purposes of the economic evaluation, placebo should be considered equivalent to BSC, as was assumed in NICE CG153 and previous adult NICE appraisals (28). We realise that this strong assumption that will require exploration by the AG, but to ensure consistency with the adult appraisals this assumption should be considered.

For the comparison of evidence of ustekinumab compared to the other biologics, there is evidence for the effectiveness of ustekinumab in plaque PsO in adolescents. However data availability for the subgroup (age 12-17yrs) population of the etanercept trial is limited (17).Substantial efforts were made to source comparator data suitable to undertake an analysis, however as the full details of the sub group population is not published, it is difficult to determine whether the etanercept sub group population is appropriate and an attempt to produce an adjusted indirect comparison highlighted some uncertainty around the results (see section 5.6.).

In recent models, PASI 75 response has determined treatment continuation, while PASI 50 and PASI 90 response rates (in addition to PASI 75) are used to account for psoriasis severity and thus utility score calculations. PASI 50, 75 and 90 are captured in all clinical studies identified (CADMUS, NCT00078819 and the M04-717) and this would allow an indirect comparison of ustekinumab against etanercept (sub group and full population) and a naïve comparison to adalimumab (full population) bearing in m ((17), (2), (38)).

Older models have also considered PASI 50, as the threshold for a response and this should be explored, especially given the NICE recommendation of response in adults being a PASI 50 and DLQI improvement of 5 or more points. But we realise that data will not be available to model this explicitly based on this decision rule or equivalent decision rule using CDLQI in Children.

In adults, the trial period is 12−16 weeks, depending on the therapy (16 weeks for adalimumab and ustekinumab, 12 weeks and etanercept), as specified in the NICE Technology appraisal guidance (60).. For children, we suggest that trial period for ustekinumab should be 12 weeks based on this being the primary efficacy time point of the CADMUS trial ((31)). It is assumed that the trial periods for adalimumab and etanercept will be the same in children and young people, as in adults.

If the sequential use of biologics is considered in the economic evaluation, then, a reduction in efficacy for additional lines of therapy should be incorporated in the model. A meta-analysis of ustekinumab and infliximab resulted in lower results when used as second line (28). Evidence also suggests that previous treatments do influence the effectiveness of subsequent lines of therapy, which may need to be considered based on adult evidence. Furthermore, a number of studies have shown that switching to a biologic with an alternative mode of action tends to lead to improved responses in contrast to switching to a biologic with a similar mode of action. (71).

6.3.6. *Withdrawal rates*

In previous adult models an annual discontinuation of 20% has been applied for all biologics for those patients who achieve a PASI 50 response of above ((55), ((56), (57), (58), (59), (29)). It has been assumed that this withdrawal probability reflects the risk of treatment discontinuation due to adverse events and loss of efficacy and is assumed to be constant over time. This withdrawal probability is also assumed to remain the same for active all treatments. Evidence from the UK BADBIR registry in adults and presented in Section 4.8.1. suggest that there may be differences in the withdrawal rates amongst different biologics with ustekinumab having a significantly higher survival rate than adalimumab and etanercept (12). This is supported by data from the PSOLAR study which also shows a significant

persistence for ustekinumab compared to adalimumab and etanercept in a large cohort of patients initiated on biologics (n=4,000) (41).

In the sequential use of biologics is considered then the difference in persistence rates based on previous biologic therapy should be taken into account. In the PSOLAR study, the treatment effects for patients who switch to their second and third biologic show that ustekinumab also had a significantly higher survival rate than adalimumab and etanercept (12).

We realise that the evidence in adults may not be directly be generalised to that of children. Nevertheless, we believe that this evidence from both a UK and a large multi-country registry in adults is sufficient for the exploration of differential withdrawal rate across biologics in the paediatric model.

6.3.7. ***Measurement and valuation of health effects***

Patients with moderate to severe psoriasis experience considerable physical discomfort linked with their skin lesions. Symptoms and manifestations include severe itching (pruritis), burning sensations, skin discomfort, skin sensitivity, irritation and pain. The more severe the psoriasis, the greater the degree of skin discomfort. Both the physical symptoms, in particular severe pruritis, and the psychological and social impact of symptoms mean that psoriasis can have a substantial impact on HRQoL (29). Paediatric psoriasis can also have a profound long-term impact on the psychological health of affected young people and is often associated with multiple comorbidities. (2),((3),(4))

In the CADMUS study, health-related quality of life Assessments were collected via the Children's Dermatologic Life Quality Index (CDLQI), and the Pediatric Quality of Life Inventory (PedsQL™) at selected timepoints. EQ-5D or EQ-5D-Y was not collected in the trial. Therefore, any modelling will need to incorporate mapping from either CDLQI or PedsQL™ to incorporate utilities into the economic model. Data reporting CDLQI and PedsQL™ has been reported in section 4.3.1. 4.5.

In the Woolacott model and subsequent models developed in adults with psoriasis, the health effects have been incorporated by using the different levels of PASI response for each treatment and then associating this with an equivalent utility improvement; thus each treatment is associated with a different HRQoL depending on the treatment response ((55), (56), (57), (58), (59), (29)). A similar approach seems reasonable for the modelling of children in the absence of EQ-5D values collected in the trials identified in biologics. The higher levels of responses seen in the CADMUS trial especially at PASI 90 and 100 scores suggests that if this approach is taken then usketinumab will be associated with the largest health improvement compared to etanercept, adalimumab and BSC ((17), (2), (38)).

The utility values used in original AG model and presented in Woolacotte and colleagues (55) were obtained through the mapping of DLQI to EQ-5D through the use of an ordinary least squared (OLS) regression model. This mapping was conducted using data from the Health Outcomes Data Repository (HODaR) which collects both DLQI and EQ-5D. An implicit assumption in using the algorithm is that all treatments are associated with the same change in DLQI within each PASI category. Since Woolacott, several other studies have reported mapping algorithms linking change in DLQI to change in EQ-5D. The mapping algorithms presented in these studies (including the Woolacott re-estimation undertaken by Janssen) are presented in Table 35 and are reproduced from the AG report of a recent NICE appraisal. (29)

From an informal targeted search for studies, Janssen are not aware of any studies that have estimated the relationship between CDLQI and EQ-5D. A recent study has sought to evaluate the both DLQI and CDLQI in 16-17 year olds and demonstrate that they closely correlate, but the mean DLQI score was lower than the mean CDLQI score. (41) This was caused primarily by differences in the answers to questions regarding sexual difficulties and sleep. As the HRQoL impacts experienced by people aged 16–17 may differ from those experienced by children or adults, HRQoL measures designed for use in this age range may have advantages over both child- and adult-specific measure. This difference between DLQI and CDQLI was minor compared with the minimal clinically important difference (MCID) (score change = 4·0) for the DLQI (72)

Given the apparent close relationship between DLQI and CDLQI, then, it may be reasonable to assume that adult utilities could be used as a proxy for at least the adolescent population, especially patients aged 16-17 years old and this should be explored by the AG. For younger children, the extrapolation may be harder to justify.

A further study has sought to map from PedsQL to EQ-5D-Y (EQ-5D youth version). (73) The study is based on data from a cross sectional survey conducted in four secondary schools in England amongst children aged 11-15 years old. The study uses the sub scales of the PedsQL to map between PedsQL and EQ-5D-Y (73), which are not available in the publications associated with the paediatric psoriasis trials. We are aware of the request from the AG to provide the PedsQL data sub scales from the CADMUS trials and we have provided this information in the appendix, Section 9.5. This data should allow the PedsQL values from the CADMUS trlal to be mapped to EQ-5D-Y in the economic model using the algorithm's presented in the Khan and colleagues study. This is therefore a potentially useful source for the AG and increases the generalisability of the economic model to the population of interest in the appraisal. However, the authors, note that the algorithm is likely to only be robust for population comparable to the children in the study (aged 11-15 years old and the performance of the algorithms presented in the study other childhood populations remains uncertain.

6.3.8. ***Adverse events***

Adverse events were not explicitly considered in the Woolacott model. (63) This is consistent with the modelling in other disease areas in which biologics are used. (56), (57), (58), (59), (29)

Table 35 Change in DLQI score to EQ-5D mapping algorithms in adults

Variabe	Norlin PASI<10	Norlin PASI≥10	Blome EQ-5D VAS (1)	Blome EQ-5D vas (2)	Heredi (1)	Heredi (2)	Currie	Ustekinumab MS re-estimation of Woolacott	Ustekinumab MS
R2	Not reported, 0.2799 for combined PASIs		0.242	0.313	0.168	0.488	0.27	0.1315	Not reported
Constant	0.8781	0.8789	77.367	93.002					
DLQI	-0.0197	-0.0201	-1.493	-1.418					
PASI				-0.153					
Active arthritis				-4.728		-0.134			
Concomitant disease				-3.563					
Light/laser therapy				2.252					
age				-0.356					
#psoriasis hospitalisation, year				-1.104		-0.104			
Gender (female)						-0.090			
Psoriasis duration						-0.004			
Chronis plaque psoriasis						-0.089			
Pamoplantar psoriasis						-0.347			
Scalp psoriasis						0.152			
~psoriasis GP visits, month						-0.160			
Use of home help						-0.138			

6.3.9. *Resource identification, measurement and valuation*

Biologics treatment costs

As described in section 2.2. , the management of children and adolescents with psoriasis is similar to that of adults. It seems reasonable to assume that the resource use associated with the administration of the treatment and physician visits for biologic therapies would also be similar to the previous economic evaluations conducted in NICE CG153 in 2012 and used in subsequent NICE submissions ((55), (56), (57), (58), (59), (29), (28)). In these economic evaluations, subcutaneous treatments such as adalimumab, etanercept and ustekinumab are assumed to be self-administered by the patient. In the case of younger children then it is likely that a parent or carer would administer the injection. A similar assumption was made in the recent appraisal of biologics in JIA where there was no cost associated with subcutaneous biologics in children (65).

In the most recent adult NICE psoriasis models, resource use estimates associated with monitoring and routine laboratory tests for biologics have been taken from NICE CG 153 guidelines (2012) (28). Unit costs associated with laboratory tests have been taken from Woolacott and colleagues which used estimates from a publication by the York NHS Trust (63). In the NCGC and recent adult NICE CG 153 and recent adult NICE manufacturer submissions have assumed that biologics will be associated with two outpatient visits during the trial period and four visits per year during continued use based on clinical expert opinion ((55), (56), (57), (58), (59), (29), (28)). The resource use and costs seem appropriate for children and young adults as there is no additional resource expected from administering biologics in children compared to adults. Therefore, we believe that adalimumab, etanercept and ustekinumab should have a similar acquisition and administration cost in a population of adolescents aged 12-17 years old.

BSC treatment costs

BSC is considered as a main comparator in this appraisal and corresponds to the management of adolescents with severe psoriasis after failure on systemic conventional therapies. This population is severe enough to have received biologics and is likely to encounter a high level of healthcare costs due to their condition.

Previous adult models have also used BSC as a relevant comparator (29), although BSC in these models corresponded to management of patients after failure on systemic conventional therapies (i.e. earlier in the treatment pathway of the patients). It would be expected that BSC in this “earlier” treated population would defer from BSC therapies in patients who are severe enough to be considered for a second line of biologics and have failed on it.

The most recent NICE appraisal in adults the AG noted that the costs associated with BSC represents the ‘most significant parameter input which underpins the validity and robustness of the cost-effectiveness results are the cost assigned to patients who receive BSC.’ A search of BSC costing approaches has identified several studies and data sources to be considered (See Table 36).

It should be noted that the Fonia and Driessen studies ((74), (75)) estimated mean inpatient days in the year preceding initiation on a first biologic. However, the total annual cost for BSC estimated by Driessen et al for severe psoriasis patients in the 12 months prior to initiation on biologics was similar to the one estimated by NICE CG 153 in severe psoriasis patients who had failed on a second biologic (£11,071 vs £11,133). Janssen would therefore recommend to consider the total costs of £11,133 from NICE CG 153 for the costs of BSC in severe psoriasis patients who had failed on biologics.

Table 36 Comparison of BSC annual costs from primary data sources

Study	Population considered	Resource use assumption considered				Total cost per year reported*
		Treatment included	Outpatient visits	Day care	Hospitalisations	
NICE CG153 (28)	Post biologic moderate to severe psoriasis	45% of patients received methotrexate, 45% ciclosporin continuously (maximum 2 years), 16% have 24 sessions of NBUVB a year	10% of patients had 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	£10,730 (or £11,133 once inflated)
Fonia et al (74)	Pre-biologics	47% of patients received ciclosporin, 41% methotrexate, 24% acitretin, as well as 2.7 sessions of phytotherapy per patient in the 12 months prior to initiation on biologics	Around 3 outpatient visits per patient	less than 1 day ward admission per patient	6.5 days of inpatient admissions and less than 1 visit to A&E & day ward admission per patient	£4,207.2 (or £4,618 once inflated)
	On biologics	22% received ciclosporin and 35% methotrexate in the 12 months after initiation on biologics	Around 3 outpatient visits per patient	1 day ward admission per patient	Less than 2 days of inpatient admissions per patients	£1,558 (or £1,710 once inflated)
Driessen et al. (75)	Pre-biologics	85% of patients received methotrexate, 51% ciclosporin, 51% acitretin, 58% UVB sessions and various topical therapies in the 12 months prior to initiation on biologics	7.6 visits per patient	5.1 days of day care	14.9 days of hospitalisations	£10,146 (or £11,071 once inflated)
	On biologics	21% of patients received methotrexate, 12% ciclosporin, 12% acitretin, 18% UVB sessions, as well as various topical therapies in the 12 months after initiation on biologics	7 visits per patient	0.3 days of day care	5.4 days of hospitalisations	£3,869 (or £4,014 once inflated)

* costs were inflated to 2014/15 using the hospital & community health services index published in the PSSRU report: Unit costs of Health & Social Care 2015.

6.4. Discussion

The paucity of clinical and economic evidence makes evaluating the cost effectiveness of biologics in children and young people with plaque psoriasis very difficult. Previous HTAs of biologics have either not require an economic model or have submitted an adult psoriasis model with effectiveness data from a paediatric population. Due to the limitations of the evidence base, we believe that any estimation of the cost effectiveness of biologics in children with young people with plaque PsO will be subject to a number of uncertainties which will require strong assumptions. There are many similarities between the clinical presentation and the management of psoriasis in children and adults and in the absence of population specific data; we believe that structure and many of the inputs can be taken from the adult population.

No economic model was presented in this submission. However, it is expected that cost effectiveness of ustekinumab in people aged 12 years and older should improve compared to the adult appraisal in psoriasis, which demonstrated that ustekinumab was a cost effective treatment for severe psoriasis. This is assuming that the AG takes a similar approach to the modelling psoriasis, as was undertaken in adults. We believe this for the following reasons:

- Children and young people will spend the majority of their lives living with psoriasis as an adult, as the extension to young people only adds a maximum of 6 years of additional treatment with ustekinumab. ((31))
- Response rate in the CADMUS trial for ustekinumab compared to placebo is similar or better than that seen in the adult PHOENIX trials which was also compared to placebo (see Sections 4.5. and 4.8.3.
- Ustekinumab has improved PASI 50, 75 and 90 responses compared to etanercept (indirect comparison) and adalimumab (naïve comparison), whilst having equivalent drug and administration costs (see Sections 5.5. 5.6.).
- Available data on the withdrawal rate suggest that patients stay on ustekinumab longer than assumed in previous NICE appraisals and ustekinumab has better persistence compared to adalimumab and etanercept. (see Sections 4.8.1. and 4.8.2.).

Overall, we believe that ustekinumab is a cost effective option for the treatment of people aged 12 years and older with plaque psoriasis and offers an important option to young people who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

7. Budget Impact analysis

7.1. Overview of the budget impact analysis

The budget impact (BI) of introducing ustekinumab for the treatment of chronic plaque PsO in adolescents to the NHSE is estimated based on various sources of information. The BI Analysis presents the difference in total costs to NHSE in treating adolescents with severe PsO with ustekinumab in the following scenarios:

A) Ustekinumab will replace other biologics for the treatment of severe psoriasis adolescents who had failed systemic conventional therapy (i.e. 1st line of biologics)

    - In this scenario, we assumed that all patients who failed systemic conventional therapies are treated with etanercept. This gives an incremental budget impact ranging of using usketinumab from £[redacted] in year 1 to £[redacted] in year 5 (see Table 37**Error! Reference source not found.**).

    - In this scenario, we assumed that all patients who failed systemic conventional therapies are treated with adalimumab. This gives an incremental budget impact of

using usketinumab ranging from £[redacted] in year 1 to £[redacted] in year 5 (see Table 38).

B) Ustekinumab will replace / delay BSC for the treatment of severe psoriasis adolescents who had failed one or more lines of biologics

- In this scenario, we assumed that patients who failed at least 1 to 2 lines of biologics are treated with BSC. This gives an incremental budget impact of using usketinumab ranging from £[redacted] in year 1 to £[redacted] in year 5. (see Table 39)

Table 37 Ustekinumab compared to etanercept (scenario A1) in patients who failed systemic conventional therapies

	Year 1	Year 2	Year 3	Year 4	Year 5
Total costs with Usketinumab	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Total cost if treated with etanercept	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Incremental ustekinumab cost vs etanercept	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]

Table 38 Ustekinumab compared to adalimumab (scenario A1) in patients who failed systemic conventional therapies

	Year 1	Year 2	Year 3	Year 4	Year 5
Total costs with Usketinumab	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Total cost if treated with adalimumab	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Incremental ustekinumab cost vs adalimumab	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]

Table 39 Ustekinumab compared to BSC (scenario B1) in patients who failed at least 2 lines of other biologics

	Year 1	Year 2	Year 3	Year 4	Year 5
Total costs with Usketinumab	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Total cost if treated with BSC	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Incremental ustekinumab cost vs BSC	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]

7.2. Number of adolescents assumed eligible for treatment with ustekinumab in the next 5 years

Overall, there are 3,861,357 adolescents aged 12 to 17 years old living in England and Wales in 2014-15. (76) Of these, 1,882,292 are females and 1,919,065 are males. (76)

Using the prevalence of psoriasis in adolescents from Simpson et al (2002), we estimated that 23,293 female adolescents and 9,961 male adolescents have psoriasis (total of 23,254). (24) Of these, 35.8% have moderate and 12.4% severe psoriasis, giving a total of 11,208 adolescents in needs of therapy. It is estimated that 123 (1.1%) of these adolescents with moderate to severe psoriasis could be eligible for treatment with biologics every year (28).

For the purpose of the calculation of the number of patients expected to be treated with biologics over a period of 5 years, we assumed that the number of adolescents with moderate to severe psoriasis potentially eligible for treatment with biologics remain constant every year. This assumption is based

on the estimation that, out of 1,575 adolescents diagnosed each year with psoriasis, 8 adolescents would be eligible every given year for treatment of their moderate/severe psoriasis with biologics. (23) This number of new patients potentially eligible for biologics would be offset by the number of adolescents who will become adults during the 5-year time horizon period (i.e. these patients would fall be out of scope of this appraisal). The number of eligible adolescents with moderate to severe psoriasis is therefore assumed to remain constant every year at 123 (see Table 40).

Table 40. Number of adolescents with moderate to severe psoriasis receiving a biologic every year (estimates are rounded up to the nearest figure)

	%	12 yrs	13 yrs	14 yrs	15 yrs	16 yrs	17 yrs	Total
Females*		304,380	299,498	308,136	315,218	325,073	329,987	1,882,292
Female adolescents with Psoriasis**								
10-14 years	5/1000	1,522	1,497	1,541				4,560
15-17 years	9/1000				2,837	2,926	2,970	8,733
Males*		320,067	314,445	322,203	332,069	342,463	347,818	1,979,065
Male adolescents with Psoriasis**								
10-14 years	4/1000	1,280	1,258	1,289				3,827
15-17 years	6/1000				1,992	2,055	2,087	6,134
Total number of adolescents with psoriasis		2,802	2,755	2,829	4,829	4,980	5,057	23,254
Adolescents with moderate to severe psoriasis[β]	48%	1,351	1,328	1,364	2,328	2,401	2,437	11,208
Adolescents with severe psoriasis eligible for biologics[¥]	1.10%	15	15	15	26	26	27	123

* Population estimates were obtained from the ONS for males and females aged 12 to 17 years old in England and Wales.
** Simpson et al, 2002
[β] Howa Yeun et al, 2013
[¥] NIHR Horizon Scanning Centre

7.3. Current treatment options and uptake of technologies

Treatment options included in this budget impact model are limited to biologics currently recommended / or under appraisal by NICE, namely adalimumab, etanercept and ustekinumab, and BSC. Biologics are available for adolescents with moderate to severe psoriasis after failure on systemic conventional therapies, while BSC is a treatment option after failure on several lines of biologics, namely TNF-inhibitors.

Ustekinumab being a new therapeutic option for treatment of adolescents with moderate to severe psoriasis, is expected to be used either after failure on systemic conventional therapies (i.e. instead of TNF-α inhibitors) or after failure on currently recommended biologics (instead of BSC).

The budget impact analysis presented in this submission assumes that only a proportion of patients eligible for a biologic will receive ustekinumab. Overall, we estimated that of these patients [redacted] will receive ustekinumab in year 1 rising to [redacted] in year 5 (SeeTable 41).

Table 41 Number of adolescents with moderate to severe psoriasis potentially eligible for ustekinumab over the coming 5 years (estimates are rounded up to the nearest figure)

	Year 1	Year 2	Year 3	Year 4	Year 5
Adolescent patients eligible for biologics	123	123	123	123	123
% of adolescents treated with ustekinumab per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated number of adolescents treated with ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated ustekinumab new patients in Year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated ustekinumab new patients in Year 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated ustekinumab new patients in Year 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated ustekinumab new patients in Year 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated ustekinumab new patients in Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.4. Unit costs assumed as part of the budget impact analysis

7.4.1. *Comparison versus other biologics*

The budget impact analysis measures the impact of using ustekinumab instead of other biologics in adolescents with moderate/severe psoriasis who have failed on systemic conventional therapies. Displaced therapies reflect treatment scenarios where adalimumab or etanercept would normally be used to treat adolescent PsO patients and when ustekinumab will be used instead of these biologics.

The model calculates drug acquisition costs on a 5-year time horizon for PsO patients from a NHS England perspective.

We assume there are no administration costs for any of the biologic drugs, as they can be self-administered. Training in self-administering the biologic is usually provided by a physician or a nurse. However, given that all biologic drugs require training, costs would not change when comparing ustekinumab against any of them. Treatment with any of the biologic drugs would require the same level of monitoring and follow-up. Furthermore, the budget impact analysis does not consider any additional costs incurred such as AEs, follow-up visits, etc. We have, therefore, assumed that these costs would not change when comparing ustekinumab against any of the other biologic drugs.

The average annual costs for biologics that are compared as part of this analysis are drug costs as shown in

Table 42 below.

Table 42 Annual cost of biologics

Drug	Price per vial/ injection	Cost per patient Year 1	Cost per patient Year 2	Cost per patient Year 3	Cost per patient Year 4	Cost per patient Year 5
Ustekinumab	£2,147.00	£12,882	£8,588	£8,588	£10,735	£8,588
Etanercept	£178.75	£9,474	£9,295	£9,295	£9,295	£9,295
Adalimumab	£352.14	£9,508	£9,156	£9,156	£9,156	£9,156

*People for whom a second biologic fails, is not appropriate, or is not used typically progress to 'best supportive care' – a combination of other treatments, mainly conducted in secondary care, and in specialist centres

Drug costs of ustekinumab

The price per injection with ustekinumab is weight dependent. For patients under 60kg, the dose is 0.75mg per kilogram; for patients between 60kg and 100kg the dose is 45mg and for patients above 100kg is 90mg (Table 43).

Table 43 Recommended dose of Stelara for paediatric psoriasis (5)

Body weight at the time of dosing	Recommended Dose	Presentation
< 60 kg	0.75 mg/kg	45 mg vial
≥ 60-≤ 100 kg	45 mg	45 mg Prefilled syringe
> 100 kg	90 mg	90 mg Prefilled syringe

To calculate the volume of injection (ml) for patients with a weight below 60 kg, the following formula is used: body weight (kg) x 0.0083 (ml/kg) or see Table 44. The calculated volume should be rounded to the nearest 0.01 ml and administered using a 1 ml graduated syringe.

Table 44 Injection volumes of ustekinumab for paediatric psoriasis patients < 60 kg (5)

Body weight at time of dosing (kg)	Dose (mg)	Volume of injection (mL)
30	22.5	0.25
31	23.3	0.26
32	24.0	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27.0	0.30
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30.0	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33.0	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36.0	0.40
49	36.8	0.41
50	37.5	0.42

51	38.3	0.42
52	39.0	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42.0	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

For patients less than 60kg, the full cost of the 45mg vial (£2,147) is conservatively assumed as the remaining product cannot be stored. Vial splitting is considered unlikely because in most cases at least three quarters of the vial will be needed per patient and together with the low patient numbers means that patients are unlikely to be treated together.

Table 45 Average weight by age* and recommended ustekinumab dose by weight

AGE	Girls average weight in kg	Boys average weight in kg
12	40	38
13	45	43
14	50	49
15	53	55
16	55	60
17	56	65

KG	UST. DOSE mg
39	29.3
44	33
49	37
54	41
58	44
61	45

*Source: RCPCH 2013

For the purposes of this budget impact calculation, Janssen assumes that no adolescents over 100kg will be treated, as for both boys and girls aged 17, body weight of 100kg is above the 99.6th centile. (77) In the case that an adolescent with a weight > 100kg requires treatment, the price of the 90mg pre-filled syringe is £2,147 equal to the price of the 45mg vial/ pre-filled syringe and would therefore have no impact on the BI analysis.

The recommended frequency of injection of ustekinumab in psoriasis is an initial dose, followed by a dose 4 weeks later, and then every 12 weeks thereafter. This represents 6 injections in year 1, 4 injections in year 2 and 3, 5 injections in year 4 and 4 injections in year 5. The annual drug costs with ustekinumab are presented in

Table 42.

Drug costs for comparators

Drug dosage were based on the summary of product characteristics of each drugs and costs were established using the list price of each drug as reported in MIMs (2016). ((7), (8), (19), (20))

Table 46 Drug costs for other biologics ((7), (8), (19), (20))

ADrug	Frequency of injections			Drug costs		
		Year 1	Subsequent years	Costs per injection	Year 1	Subsequent years
Etanercept	Once weekly	52	52	£178.75	£9,295	£9,295
Adalimumab	Once weekly for the first 2 doses and every other week thereafter	27	26	£352.14	£9,508	£9,156

7.4.2. *Comparisons versus BSC*

The budget impact analysis measures the impact of using ustekinumab instead of BSC in adolescents with moderate/severe psoriasis who have failed on 1 or 2 lines of biologics. These patients typically progress to 'best supportive care' which is defined as a combination of other treatments, mainly delivered in secondary care and in specialist centres.

The costs of BSC is derived from the NICE Clinical Guidelines 153 (2012) and is estimated at £11,133 annually for people for whom a second biologic fails, is not appropriate, or is not used. (28)

The costs of BSC was compared to the drug cost of usketinumab to which we added the healthcare costs of treating severe psoriasis in daily clinical practice. These healthcare costs were estimated by Fonia et al (2010) at £1,710 annually and includes inpatient admissions, A&E visits, outpatient visits, day ward admission, and phototherapy related costs (see Table 36). (74)

The cost of BSC has been actualised based on Unit Cost of Health and Social Care 2015 (PSSRU 2015) and are presented in Table 47. (78)

Table 47 Annual cost of best Supportive Care and ustekinumab ((74), (28))

Therapy	Cost per patient Year 1	Cost per patient Year 2	Cost per patient Year 3	Cost per patient Year 4	Cost per patient Year 5
Ustekinumab costs	**£14,592**	**£10,298**	**£10,298**	**£12,445**	**£10,298**
Drug costs	*£12,882*	*£8,588*	*£8,588*	*£10,735*	*£8,588*
Healthcare costs associated with biologics (74)	*£1,710*	*£1,710*	*£1,710*	*£1,710*	*£1,710*
Best supportive care costs* (28)	**£11,133**	**£11,133**	**£11,133**	**£11,133**	**£11,133**

*People for whom a second biologic fails, is not appropriate, or is not used typically progress to 'best supportive care' – a combination of other treatments, mainly conducted in secondary care, and in specialist centres.

8. Discussion and conclusions

Ustekinumab provides an alternative treatment option with a different mode of action in a disease area with few licensed treatment options and a high burden of illness.

This submission relates to the management of young people (aged 12 years old and over) suffering from moderate to severe psoriasis (i.e. with raised, red and coarse scaly plaque lesions covering approximately 10% to 30% or more of body surface). (1) Severe psoriasis in young people can have a profound long-term impact on the psychological health of affected young people and is often associated with multiple comorbidities. (2),(3), (4))

Due to the lack of clinical guidelines in children and young people and of licensed treatments in this population, effective therapies are needed, and this NICE appraisal will fill an important gap.

Ustekinumab is a newly licensed biological treatment for young people with moderate to severe PsO, providing an alternative therapy with a broader license and a different mode of action a different mode of action to currently licensed TNF-inhibitors, namely etanercept and adalimumab. (5),(6) Ustekinumab is administered every 12 weeks in its maintenance phase (after the first 4 weeks of treatment), a less stringent dosing schedule compared to other biologics. (5), (8), (7)

While effective, TNF inhibitors are perceived to be a less refined treatment for PsO compared to the more advanced biologics which achieve better results and a recent international survey (MAPP) of patients with PsO or psoriatic arthritis (PsA) highlighted UK patients' dissatisfaction with current systemic treatment options (see Section 3. .

There is limited clinical evidence in children but what evidence there is suggests that ustekinumab is an important option (mode of action) and may be more effective than the TNF inhibitors

There are a limited number of rigorous clinical trials in paediatric PsO, especially for systemic treatments, although the clinical evidence available suggests that ustekinumab is an important treatment option to consider. (2)

The efficacy of ustekinumab in young people with moderate to severe PsO is evaluated in the main clinical trial CADMUS, which demonstrated strong efficacy and health-related quality of life responses: 25 (69.4%) of ustekinumab patients achieved a PGA 0/1 (i.e. absence of any lesion to minimal raised plaque to 0.25 mm with fine / faint lesion) compared with 2 (5.4%) in the placebo group at week 12 ($p < .001$). The improvements in disease activity and quality of life were robust (reduction in CDLQI score at week 12 of 6.7 point versus 1.3 points for ustekinumab versus placebo respectively) and sustained through 52 weeks. (9) The safety profile of ustekinumab in this adolescent psoriasis population was generally consistent with that observed in the adult PsO populations, and no new safety issues were identified (see section 4.3.1.).

Results of an adjusted indirect comparison (AIC) for ustekinumab against etanercept showed a positive trend in favour of ustekinumab in each comparison, i.e. PASI 50, PASI 75, PASI 90, and PGA 0-1(see Section 5.6.).

A naïve comparison of the week-16 response rates on PGA, PASI 75, 90 and 100 suggests a higher clinical response with ustekinumab compared to adalimumab and methotrexate (see Section 5.5.), although these results should be cautiously interpreted in light of the differences in baseline characteristics of the study populations (e.g. difference in age range, baseline PASI severity, etc.) and differences in trial design.

Ustekinumab presents the added advantage of a lower frequency of injections (every 12 weeks, after the initial loading doses at weeks 0 and 4) compared to etanercept (every week) and adalimumab (weekly for the first 2 doses, then every other week), which reduces the burden to patients and carers who administer the subcutaneous injections (see section 2.2.) and is linked to a reduction in injection site infections; only 1 out of a total 508 of ustekinumab injections results in a mild injection site reaction and that was in the SD arm (see Section 4.6.2.), compared to the NCT00078819 study which reported 62 injection site reactions in the etanercept arm (17).

There is limited evidence to appraise the cost effectiveness in biologics and much of the evidence and assumptions are based on the adult disease. However, it is expected that use of ustekinumab in young people will be a more cost effective use of NHS resources than in the adult population.

As explored in section 6. despite previous UK HTA submissions in children and adolescents with PsO there is a paucity of data available to develop a cost effectiveness model for the young people population. However, given the similarities between the young people (from 12 to 17 years old) and the adult populations in terms of response rates in the CADMUS trial compared to the PHOENIX trials up to 52 weeks (see Sections 4.5. and 4.8.3.), long term efficacy in adolescent population could be extrapolated from PHOENIX trials. Furthermore, we could assume that young people will spend the majority of their lives living with psoriasis as an adult, as the extension to young people only adds a maximum of 6 years (and less than 3 years on average) of additional treatment with ustekinumab. Ustekinumab responses rates in PASI 50, 75 and 90 and PGA 0-1 are higher to the one reported by etanercept and adalimumab (naïve comparison), whilst having equivalent drug and administration costs (see Sections 5.5. 5.6.). This is further supported by withdrawal rate in long-term adult registries which demonstrate that adult patients stay on ustekinumab longer than assumed in previous NICE appraisals (see Sections 4.8.1. and 4.8.2.).

Under these conditions, it is expected that ustekinumab in young people aged 12 years and older with moderate to severe psoriasis is a more cost-effective use of NHS resources that in the adult population.

With its three monthly dosing schedule, ustekinumab's slightly higher drug acquisition costs would be partially offset by savings in administration costs should a nurse be involved.

The net budget impact of introducing ustekinumab as an alternative treatment option to TNF inhibitor for young people with moderate to severe psoriasis in the UK is expected to range between £40,491 in year 1, to £43,962 in year 5 (using list price). With its three-monthly dosing schedule, ustekinumab's slightly higher drug acquisition costs would be partially offset by savings in administration costs should a nurse be involved.

Therefore, Stelara should be recommended as an alternative therapy alongside the TNF inhibitors for the treatment of young people with moderate to severe PsO.

9. Appendices

9.1. Appendix 1: SLR search strategies

9.1.1. *Medline and EMBASE: EMBASE.com (18th March 2016)*

Disease terms (query 1-4) and intervention terms (query 5-10) were combined with the study design terms [randomised controlled trials (query 12-35) OR Systematic reviews (query 36-63)].

Sr. No.	Query	Hits
1	'psoriasis'/exp	57268
2	psoria*:ab,ti OR 'anti psoria*':ab,ti OR antipsoria*:ab,ti	53361
3	'palmoplantar* pustulosis':ab,ti OR 'pustulosis palmaris et plantaris':ab,ti OR (pustulosis:ab,ti AND palms:ab,ti AND soles:ab,ti)	746
4	1 OR 2 OR 3	69082
5	ustekinumab OR stelara OR 'cnto 1275' OR cnto1275	2695
6	etanercept OR 'tumor necrosis factor receptor igg chimer' OR enbrel	23043
7	adalimumab OR humira OR 'monoclonal antibody d2e7' OR trudexa	19971
8	methotrexate OR 'alpha-methopterin' OR amethopterin OR methotrexatum OR methylaminopterin OR metotrexato OR abitrexate OR folex OR mexate OR rheumatrex OR trexall OR brimexate OR emtexate OR emthexat* OR farmitrexat OR fauldexato OR lantarel OR ledertrexate OR lumexon OR maxtrex OR medsatrexate OR metex OR methoblastin OR metrotex OR novatrex OR texate OR tremetex OR trexeron OR trixilem OR 'cl-14377' OR 'wr-19039'	149020

Sr. No.	Query	Hits
9	ciclosporin OR cyclosporin* OR gengraf OR neoral OR sandimmun* OR sangcya OR '27-400' OR 'ol 27-400'	137968
10	5 OR 6 OR 7 OR 8 OR 9	280299
11	4 AND 10	15749
12	'clinical trial'/exp	1071888
13	'randomized controlled trial'/exp	392861
14	'randomization'/de	69025
15	'single blind procedure'/de	21555
16	'double blind procedure'/de	127311
17	'crossover procedure'/de	45979
18	'placebo'/de	285284
19	(randomi?ed NEAR/2 'controlled trial*'):ab,ti	140235
20	rct:ab,ti	19813
21	'random allocation':ab,ti	1527
22	'randomly allocated':ab,ti	24405
23	'allocated randomly':ab,ti	2113
24	(allocated NEAR/2 random):ab,ti	830
25	(single NEXT/1 blind*):ab,ti	17245
26	(double NEXT/1 blind*):ab,ti	165444
27	((treble OR triple) NEAR/3 blind*):ab,ti	655
28	placebo*:ab,ti	233068
29	'prospective study'/de	316626
30	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29	1626012
31	'case study'/de	38833
32	'case report':ab,ti	311062
33	'abstract report'/de OR 'letter'/de	967327
34	31 OR 32 OR 33	1310396
35	30 NOT 34	1583983
36	'meta analysis'/exp	105183
37	(meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti	114890
38	(systematic NEAR/1 (review* OR overview*)):ab,ti	95428
39	cancerlit:ab	666
40	cochrane:ab	51151
41	embase:ab	51115
42	psychlit:ab OR psyclit:ab	956
43	psychinfo:ab OR psycinfo:ab	12689
44	cinahl:ab OR cinhal:ab	15660
45	'science citation index':ab	2538
46	bids:ab	491
47	'reference lists':ab	12164
48	bibliograph*:ab	16669
49	(hand NEXT/1 search*):ab	5525
50	(manual NEXT/1 search*):ab	3378
51	'relevant journals':ab	974
52	'data extraction':ab	14610
53	'selection criteria':ab	23707
54	52 OR 53	36920
55	review:it	2103783
56	54 AND 55	17648
57	36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 56	246494
58	letter:it OR editorial:it	1409333
59	'animal'/exp	21485745
60	'human'/exp	16856480
61	59 NOT (59 AND 60)	4629265
62	58 OR 61	6007410
63	57 NOT 62	237809
64	35 OR 63	1725306
65	11 AND 64	4196
66	comment:it OR letter:it OR editorial:it OR 'case reports':it OR 'case study':ab,ti OR 'case studies':ab,ti OR 'case report':ab,ti OR 'case reports':ab,ti	1846311
67	review:it OR 'review literature as topic'/de NOT ('meta-analysis':it OR 'meta-	2102194

Sr. No.	Query	Hits
	analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti)	
68	66 OR 67	3914472
69	65 NOT 68	2574

9.1.2. *Cochrane Library: Wiley Interscience (18th March 2016)*

Cochrane Database of Systematic Reviews (CDSR): Wiley Interscience.
Database of Abstracts of Reviews of Effects (DARE): Wiley Interscience.
Cochrane Central Register of Controlled Trials (CCRCT): Wiley Interscience.

Sr. No.	Query	Hits
1	[mh psoriasis]	2071
2	(psoria* or "anti psoria*" or antipsoria*):ti,ab,kw	4295
3	("palmoplantar* pustulosis" or "pustulosis palmaris et plantaris"):ti,ab,kw or (pustulosis and palms and soles):ti,ab,kw	47
4	1 or 2 or 3	4319
5	(ustekinumab or stelara or "cnto 1275" or cnto1275):ti,ab,kw	174
6	(etanercept or "tumor necrosis factor receptor igg chimer" or enbrel):ti,ab,kw	1003
7	(adalimumab or humira or "monoclonal antibody d2e7" or trudexa):ti,ab,kw	936
8	(methotrexate or "alpha-methopterin" or amethopterin or methotrexatum or methylaminopterin or metotrexato or abitrexate or folex or mexate or rheumatrex or trexall or brimexate or emtexate or emthexat* or farmitrexat or fauldexato or lantarel or ledertrexate or lumexon or maxtrex or medsatrexate or metex or methoblastin or metrotex or novatrex or texate or tremetex or trexeron or trixilem or "cl-14377" or "wr-19039"):ti,ab,kw	6519
9	(ciclosporin or cyclosporin* or gengraf or neoral or sandimmun* or sangcya or "27-400" or "ol 27-400"):ti,ab,kw	5655
10	5 or 6 or 7 or 8 or 9	12993
11	4 and 10	941
12	[mh "clinical trial"]	408
13	[mh "randomized controlled trial"]	166
14	randomization:ti,ab,kw	20491
15	"single blind procedure":ti,ab,kw	5891
16	"double blind procedure":ti,ab,kw	32769
17	"crossover procedure":ti,ab,kw	11984
18	[mh placebos]	22822
19	(randomi?ed near/2 "controlled trial*"):ti,ab,kw	191794
20	rct:ti,ab,kw	10279
21	"random allocation":ti,ab,kw	23043
22	"randomly allocated":ti,ab,kw	19724
23	"allocated randomly":ti,ab,kw	1749
24	(allocated near/2 random):ti,ab,kw	784
25	(single next blind*):ti,ab,kw	25777
26	(double next blind*):ti,ab,kw	189333
27	((treble or triple) near/3 blind*):ti,ab,kw	610
28	placebo*:ti,ab,kw	177298
29	[mh "prospective study"]	75934
30	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	466871
31	"case study":ti,ab,kw	1128
32	"case report":ti,ab,kw	996
33	"abstract report":ti,ab,kw or letter:pt	6832
34	31 or 32 or 33	8890
35	30 not 34	462742
36	[mh "meta analysis"]	166
37	((meta near/1 analy*) or metaanalys*):ti,ab,kw	27150
38	(systematic near/1 (review* or overview*)):ti,ab,kw	25751
39	cancerlit:ab	106
40	cochrane:ab	9771
41	embase:ab	6172

Sr. No.	Query	Hits
42	(psychlit or psyclit):ab	131
43	(psychinfo or psycinfo):ab	1338
44	(cinahl or cinhal):ab	2487
45	"science citation index":ab	683
46	bids:ab	29
47	"reference lists":ab	2734
48	bibliograph*:ab	2531
49	(hand next search*):ab	576
50	(manual next search*):ab	187
51	"relevant journals":ab	197
52	"data extraction":ab	1275
53	"selection criteria":ab	7110
54	52 or 53	7575
55	review:pt	4316
56	54 and 55	25
57	36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 56	49117
58	letter:pt or editorial:pt	7234
59	[mh animal]	7366
60	[mh human]	1153
61	59 not (59 and 60)	6213
62	58 or 61	13386
63	57 not 62	48994
64	35 or 63	490468
65	11 and 64	595
66	(comment or letter or editorial or "case reports"):pt or ("case study" or "case studies" or "case report" or "case reports"):ti,ab,kw	11783
67	(review:pt or [mh "review literature as topic"]) not ("meta-analysis":pt or [mh "meta-analysis as topic"] or "systematic review":ti or "systematic literature review":ti or "meta analysis":ti,ab,kw or "meta-analysis":ti,ab,kw)	4192
68	66 or 67	15885
69	65 not 68	585
70	65 not 68 and CDSR	10
71	65 not 68 and DARE	18
72	65 not 68 and CCRCT	539

9.1.3. *Medline in process: PudMed.com (18th March 2016)*

Sr. No.	Query	Hits
1	Psoriasis[mh]	31996
2	psoria*[tiab] OR anti psoria*[tiab] OR antipsoria*[tiab]	36968
3	palmoplantar* pustulosis[tiab] OR pustulosis palmaris et plantaris[tiab] OR (pustulosis[tiab] AND palms[tiab] AND soles[tiab])	637
4	1 OR 2 OR 3	42242
5	ustekinumab[tiab] OR stelara[tiab] OR cnto 1275[tiab] OR cnto1275[tiab]	687
6	etanercept[tiab] OR tumor necrosis factor receptor igg chimer[tiab] OR enbrel[tiab]	5172
7	adalimumab[tiab] OR humira[tiab] OR monoclonal antibody d2e7[tiab] OR trudexa[tiab]	4034
8	methotrexate[tiab] OR alpha-methopterin[tiab] OR amethopterin[tiab] OR methotrexatum[tiab] OR methylaminopterin[tiab] OR metotrexato[tiab] OR abitrexate[tiab] OR folex[tiab] OR mexate[tiab] OR rheumatrex[tiab] OR trexall[tiab] OR brimexate[tiab] OR emtexate[tiab] OR emthexat*[tiab] OR farmitrexat[tiab] OR fauldexato[tiab] OR lantarel[tiab] OR ledertrexate[tiab] OR lumexon[tiab] OR maxtrex[tiab] OR medsatrexate[tiab] OR metex[tiab] OR methoblastin[tiab] OR metrotex[tiab] OR novatrex[tiab] OR texate[tiab] OR tremetex[tiab] OR trexeron[tiab] OR trixilem[tiab] OR cl-14377[tiab] OR wr-19039[tiab]	34639
9	ciclosporin[tiab] OR cyclosporin*[tiab] OR gengraf[tiab] OR neoral[tiab] OR sandimmun*[tiab] OR sangcya[tiab] OR 27-400[tiab] OR ol 27-400[tiab]	46782
10	5 OR 6 OR 7 OR 8 OR 9	85551

Sr. No.	Query	Hits
11	4 AND 10	4955
12	Clinical trial[mh]	287391
13	Randomized controlled trial[mh]	102238
14	randomization[tw]	19320
15	single blind procedure[tw]	16
16	double blind procedure[tw]	206
17	crossover procedure[tw]	38
18	Placebo[mh]	32989
19	(randomised[tiab] OR randomized[tiab]) AND controlled trial*[tiab]	128060
20	rct[tiab]	12160
21	random allocation[tiab]	1286
22	randomly allocated[tiab]	20184
23	allocated randomly[tiab]	23305
24	allocated[tiab] AND random[tiab]	1806
25	single[tiab] AND blind*[tiab]	34723
26	double[tiab] AND blind*[tiab]	127035
27	(treble[tiab] OR triple[tiab]) AND blind*[tiab]	1306
28	placebo*[tiab]	175484
29	Prospective study[mh]	405181
30	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29	950378
31	case study[tw]	49702
32	case report[tiab]	234955
33	abstract report[tw] OR letter[pt]	908087
34	31 OR 32 OR 33	1185125
35	30 NOT 34	925093
36	Meta analysis[mh]	14504
37	(meta[tiab] AND analy*[tiab]) OR metaanlys*[tiab]	93934
38	systematic[tiab] AND (review*[tiab] OR overview*[tiab])	102122
39	cancerlit[tiab]	602
40	cochrane[tiab]	43819
41	embase[tiab]	43520
42	psychlit[tiab] OR psyclit[tiab]	889
43	psychinfo[tiab] OR psycinfo[tiab]	12518
44	cinahl[tiab] OR cinhal[tiab]	14423
45	science citation index[tiab]	2375
46	bids[tiab]	506
47	reference lists[tiab]	11460
48	bibliograph*[tiab]	21895
49	hand[tiab] AND search*[tiab]	9448
50	manual[tiab] AND search*[tiab]	6104
51	relevant journals[tiab]	862
52	data extraction[tiab]	12346
53	selection criteria[tiab]	23337
54	52 OR 53	33899
55	review[pt]	2090590
56	54 AND 55	22037
57	36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 56	222946
58	letter[pt] OR editorial[pt]	1304873
59	Animal[mh]	19856515
60	Human[mh]	15668609
61	59 NOT (59 AND 60)	4187906
62	58 OR 61	5451376
63	57 NOT 62	213298
64	35 OR 63	1076956
65	11 AND 64	943
66	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	412594
67	65 AND 66	18

9.2. Appendix 2: Results of the systematic literature review

9.2.1. *Search Strategy*

The systematic literature review was carried out in three parts: a comprehensive and systematic search of the published literature to identify all potentially relevant studies; systematic selection of relevant studies based on explicit inclusion and exclusion criteria in order to determine eligibility of the studies; and extraction of relevant data from eligible studies in order to assess comparative efficacy, safety and impact on patient quality of life across therapeutic options.

The first stage in the review was to identify all relevant efficacy, safety and quality of life evidence for treatments used in paediatric psoriasis. To this end, a comprehensive literature search was conducted.

The following global electronic databases were all searched from inception and searches were performed on 18th March 2016:

- MEDLINE and MEDLINE In-Process
- EMBASE
- Cochrane library
  - The Cochrane Database of Systematic Reviews
  - Database of Abstracts of Reviews of Effectiveness
  - Cochrane Central Register of Controlled Trials

Table 48 presents the results of the database searches. The specific search strategies that were used for each database are presented in section 9.1. In total 3,159 records were retrieved. Of these records, there were 509 duplicates across the different databases. Removing these duplicates left 2,650 records to progress through the screening process. In addition to this, the clinical study report (CSR) for the CADMUS study was included.

Table 48 Search results by database

S. No.	Database/website	Provider/Interface	Filter used for study design	Coverage	Hits
1.	Medline & EMBASE	EMBASE.com	SIGN-RCT and SR filter	No limit	2574
2.	Medline in process	PubMed.com	SIGN-RCT and SR filter	No limit	18
3.	CDSR	onlinelibrary.wiley.com	SIGN-RCT and SR filter	No limit	10
4.	DARE	onlinelibrary.wiley.com	SIGN-RCT and SR filter	No limit	18
5.	CCRCT	onlinelibrary.wiley.com	SIGN-RCT and SR filter	No limit	539
Total					**3159**
Duplicates					**509**
Total number of hits to screen					**2650**

Key: CCRCT, Cochrane Central Register of Controlled Trials; CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effects; RCT, randomised controlled trials; SIGN, Scottish Intercollegiate Guidelines Network; SR, Systematic Reviews.

Note: No limit was applied for language.

Relevant trials were also identified from reference lists of any included systematic reviews and meta-analyses.

Searches for grey literature (i.e. material that can be referenced but is not typically published in peer-reviewed, database-indexed medical journals) were undertaken to capture evidence presented at

relevant conferences that have not yet been published as full-text journal articles. These searches were limited to conferences within the past 2 years (2014-2016), as any high quality studies should have been reported as journal articles within that time. Only conferences with freely available and searchable abstracts were included.
The following conference websites were considered:

- European Academy of Dermatology and Venereology http://www.eadv.org/eadv-meetings
- European Society for Dermatological Research http://www.esdr.org/annual-meetings
- American Academy of Dermatology https://www.aad.org/meetings

Potentially relevant publications were reviewed and assessed in order to collate a final set of studies, which form the main body of the clinical effectiveness evidence.

9.2.2. ***Study Selection***

At each stage, articles were reviewed against the pre-specified eligibility criteria provided in which were based on the PICOS (Population, Intervention, Comparator, Outcomes, Study design) formula. To determine the final set of studies eligible for review, we applied explicit inclusion and/or exclusion criteria to the literature search results. The inclusion/exclusion criteria are summarised in Table 49. Additional biological treatments licensed for treating plaque psoriasis in adults includes infliximab; this treatment does not have marketing authorisation for children and young people and no evidence supports its use in this specific population.

Table 49 Criteria used in the trial selection process

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Rationale
Population	• Children and adolescent patients (aged 4-17 years) with moderate-to-severe, chronic plaque psoriasis • Patients who have had either an inadequate response to or for whom topical therapy, other systemic therapies and/or phototherapy are inappropriate	• Adult patients (aged ≥18 years) with moderate-to-severe, chronic plaque psoriasis • Patients with non-plaque psoriasis (e.g. guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, nail psoriasis, and psoriatic arthritis) • Patients with mild disease	In line with the NICE final scope.
Intervention	• Ustekinumab • Etanercept • Adalimumab • Methotrexate • Ciclosporin	• Studies that do not include one of the interventions of interest in at least one arm of the trial	In line with the NICE final scope.
Comparators	The comparators used in such studies may have been another of the listed treatments or another treatment option, as long as at least one of the treatment arms included at least one of the interventions of interest.		To allow treatment comparisons to be made, if possible
Outcomes	• Psoriasis Area and Severity Index (PASI50, PASI75, PASI90, PASI100) • Physician's global assessment (PGA) • Quality of life: Children's Dermatology Life Quality Index (CDLQI) • Safety		Appropriate outcomes for psoriasis, in line with the NICE final scope
Study design	• Randomised controlled trials (RCT) • Systematic reviews/meta-analyses[a]	• Non-randomised studies • Single arm studies • Non-systematic reviews • In-vitro studies • Preclinical studies • Studies in animals • Comments • Letters • Editorials • Case reports	
Language restrictions	No language restrictions		
Notes: [a] relevant systematic reviews and meta-analyses were included at Level 1 screening. The most recent and relevant of these were used as a source to cross check for any primary RCTs that may not have been identified in the database searches. These were not included in this systematic review in their own right, and were excluded at Level 2 screening.			

Standardised evidence table shells were developed in Excel®; before commencing data extraction. The data extraction table shell included headings for all relevant baseline characteristics, study characteristics and outcomes that are of interest, as well as data relating to the treatment used (e.g. the dose of the intervention).
Data were extracted from the included full text articles by the one reviewer. All extracted data was quality checked against the original source article by a second reviewer. If study duplication within publications was suspected, author names, location and setting, specific intervention details, participant numbers, baseline data, and date and duration of study were assessed. Should sequential publications from the same trial report on different clinical endpoints, all results were extracted and details of all data sources referenced.

Data were extracted in line with the expected requirements of NICE. The key information that was captured for extraction is presented in, but not limited to, the list below, and was based on the availability of these data:

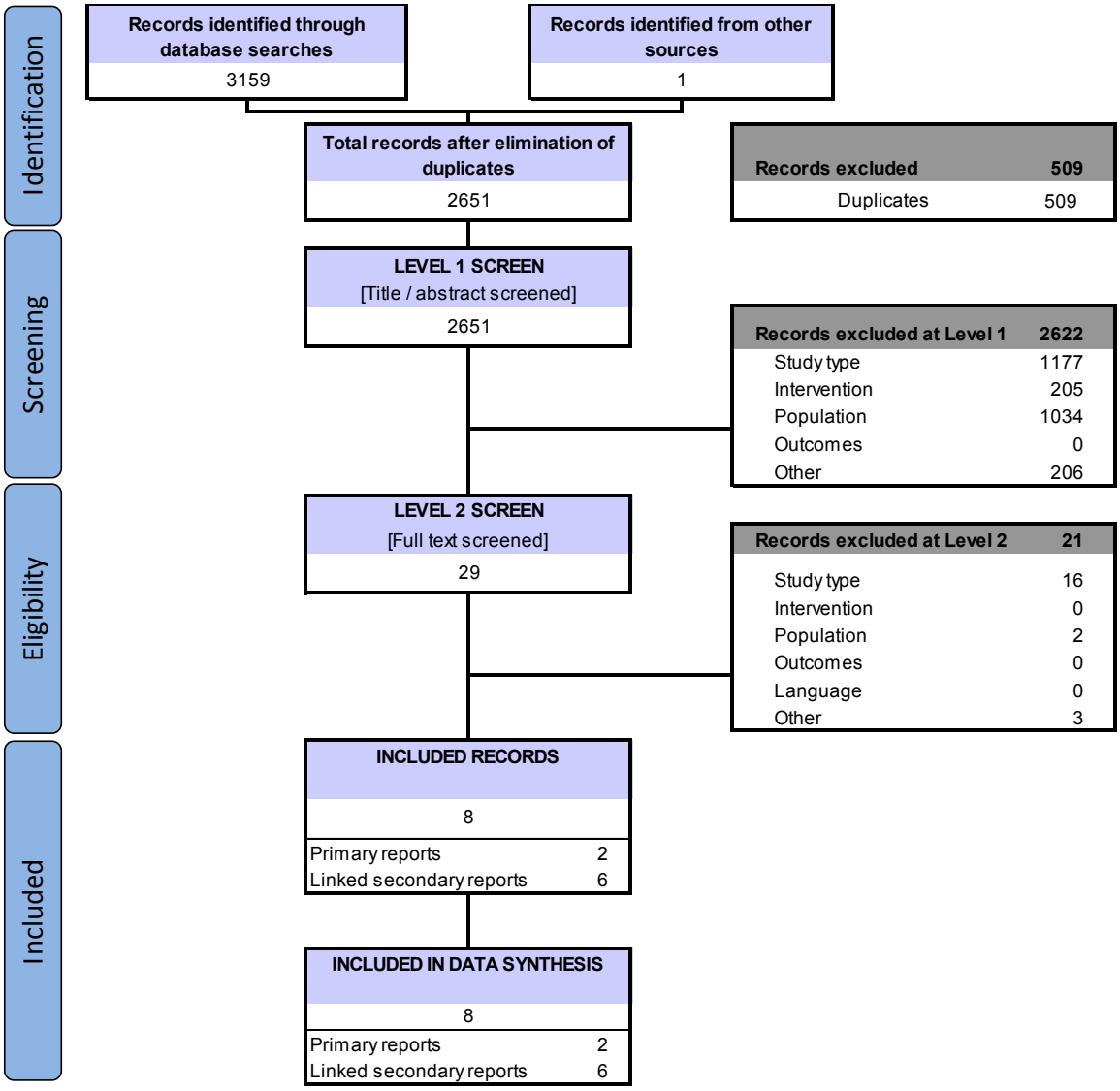
- Study characteristics, including location, setting, study design, study methods, etc.
- Patient demographics/clinical characteristics, including inclusion/exclusion criteria, baseline characteristics, etc.

- Key efficacy data
- Key safety and tolerability data, including adverse events (AEs), Grade 3/4 events, and, serious adverse events. Additionally key AEs such as, fatigue, nausea, dizziness etc., were also extracted. Treatment withdrawals, including withdrawals due to any cause, withdrawals due to AEs, etc. were also extracted
- Quality of life

9.2.3. *PRISMA flow diagram*

A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram presenting the results of the SLR is provided in Figure 13**;** 2,651 titles and abstracts were screened at level 1. Of these 2,622 were excluded. Full text articles were ordered and screened at level 2 for 29 references. Of these 21 were excluded, leaving seven publications and one CSR included in this SLR. These eight references related to two studies (with two primary publications and six secondary publications).

Figure 13: PRISMA diagram



Key: PRISMA, preferred reporting items in systematic reviews and meta-analyses.

Source: Adapted from Moher et al., 2009. (79)

The references for the publications excluded at level 2 screening, along with their reason for exclusion, are presented in the next section.

9.2.4. ***References excluded from the SLR at level 2 screening***

No.	Ref	Reference	Reason for exclusion
1	119	Alsuwaidan SN. Childhood psoriasis: Analytic retrospective study in Saudi patients. Journal of the Saudi Society of Dermatology and Dermatologic Surgery. 2011; 15:57-61.	retrospective study
2	326	Bos JD and De Korte J. Effects of etanercept on quality of life, fatigue, and depression in psoriasis. Lancet. 2006; 367:6-7.	not children/adolescents
3	364	Bulbul Baskan E, Yazici S, Tunali S and Saricaoglu H. Clinical experience with systemic cyclosporine A treatment in severe childhood psoriasis. Journal of Dermatological Treatment. 2015:1-4.	retrospective study
4	429	Cheng S and Murphy R. The use of etanercept in children and adolescents with moderate-to-severe plaque psoriasis: A report of three successful cases. British Journal of Dermatology. 2010; 163:120.	case series
5	492	Constantin T, Foeldvari I, Vojinovic J, et al. Long-term safety and efficacy of etanercept in paediatric subjects with extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis. Arthritis and Rheumatism. 2013; 65:S117-S8.	Extended Oligoarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, Or Psoriatic Arthritis.
6	535	de Jager MEA, de Jong EMGJ, van de Kerkhof PCM and Seyger MMB. Efficacy and safety of treatments for childhood psoriasis: A systematic literature review. Journal of the American Academy of Dermatology. 2010; 62:1013-30.	SR/MA
7	690	Fessler B. Approval expansion: Etanercept for children with severe plaque psoriasis. Deutsche Apotheker Zeitung. 2009; 149:38-9.	approval expansion (German)
8	1132	Kautz J. Psoriasis: Etanercept also for children and adolescents? Aktuelle Dermatologie. 2008; 34:207.	discussion piece (German)
9	1295	Kumar B, Dhar S, Handa S and Kaur I. Methotrexate in childhood psoriasis. Pediatric Dermatology. 1994; 11:271-3.	retrospective record review
10	1479	Mansel L. Severe juvenile plaque psoriasis: Better treatment options after approval of etanercept indication expansion. Medizinische Monatsschrift fur Pharmazeuten. 2009; 32:358-9.	non-systematic review (German)
11	1671	Mrážik P, Martinásková K and Vargová V. Skin-manifested adverse events in children treated with biologics: Single centre experience. Annals of the Rheumatic Disease. 2013; 71.	unable to obtain reference
12	1805	Papp K, Thac¸i D, Landells I, et al. Study design and baseline characteristics from a phase 3, randomized, double-blind study of adalimumab versus methotrexate treatment in pediatric patients with chronic plaque psoriasis. Journal of the European Academy of Dermatology and Venereology. 2013; 27:27-8.	study design and baseline characteristics
13	1806	Papp K, Thaci D, Landells I, et al. Baseline characteristics in pediatric patients with chronic plaque psoriasis from a phase 3, randomized, double-blind study of adalimumab versus methotrexate treatment. JDDG - Journal of the German Society of Dermatology. 2014; 12:37-8.	study design and baseline characteristics
14	1807	Papp K, Williams D, Thaci D, et al. Study design and baseline characteristics from a phase 3, randomized, double-blind study of adalimumab versus methotrexate treatment in pediatric patients with chronic plaque psoriasis. Journal of the American Academy of Dermatology. 2014; 70:AB190.	study design and baseline characteristics
15	1866	Philipp S, Mayer AF, Schulze P and Sterry W. Etanercept as therapy option for plaque psoriasis in childhood and adolescence. Internistische Praxis. 2008; 48:672-7.	non-systematic review (German)
16	2099	Sanclemente G, Murphy R, Contreras J, et al. Anti-TNF agents for paediatric psoriasis. Cochrane Database of Systematic Reviews (2015) DOI: 10.1002/14651858.CD010017.pub2.	SLR/MA
17	2145	Schindler B. Also children profit from etanercept treatment for psoriasis. Arzneimitteltherapie. 2008; 26:177-8.	German language publication of Ref1782
18	2169	Seyger MMB, De Jager MEA, De Jong EMG and Van De Kerkhof PCM. Efficacy and safety of treatments in childhood psoriasis: A systematic literature review. European Journal of Pediatric Dermatology. 2010; 20:58.	abstract of SR; no reference list
19	2192	Shwayder T. Etanercept use in childhood psoriasis. Hong Kong Journal of Dermatology and Venereology. 2009; 17:105-6.	2009 conference presentation
20	2471	Varni JW, Globe DR, Gandra SR, et al. Health-related quality of life of pediatric patients with moderate to severe plaque psoriasis: Comparisons to four common chronic diseases. European Journal of Pediatrics. 2012; 171:485-92.	pooled QoL analysis compared to other conditions

No.	Ref	Reference	Reason for exclusion
21	2487	Vidal D, Salleras M, Romaní J, et al. Adherence of self-administered subcutaneous methotrexate in patients with chronic plaque-type psoriasis. Journal of the European Academy of Dermatology and Venereology. 2015.	letter to the editor

Key: MA, meta-analysis; QoL, quality of life; Ref, reference; SLR, systematic literature review; TNF, tumour necrosis factor.

9.3. Results of the sensitivity analysis

Table 50 Number of subjects with PGA scores of cleared (0) or minimal (1) at week 12 (LOCF); all randomised subjects (CADMUS) (31)

[redacted]

Table 51 Number of subjects with PGA scores of cleared (0) and minimal (1) at week 12; all randomised subjects (observed case) (CADMUS) (31)

[redacted]

Table 52 Number of subjects with PGA scores of cleared (0) or minimal (1) at week 12 (re-randomization test); all randomised subjects (CADMUS) (31)

[redacted]

9.4. Adverse events through week 60

Table 53 Number of subjects with 1 or more treatment-emergent adverse events through week 60 by MedDRA System-organ class and preferred term; subjects treated with ustekinumab (CADMUS)(31)

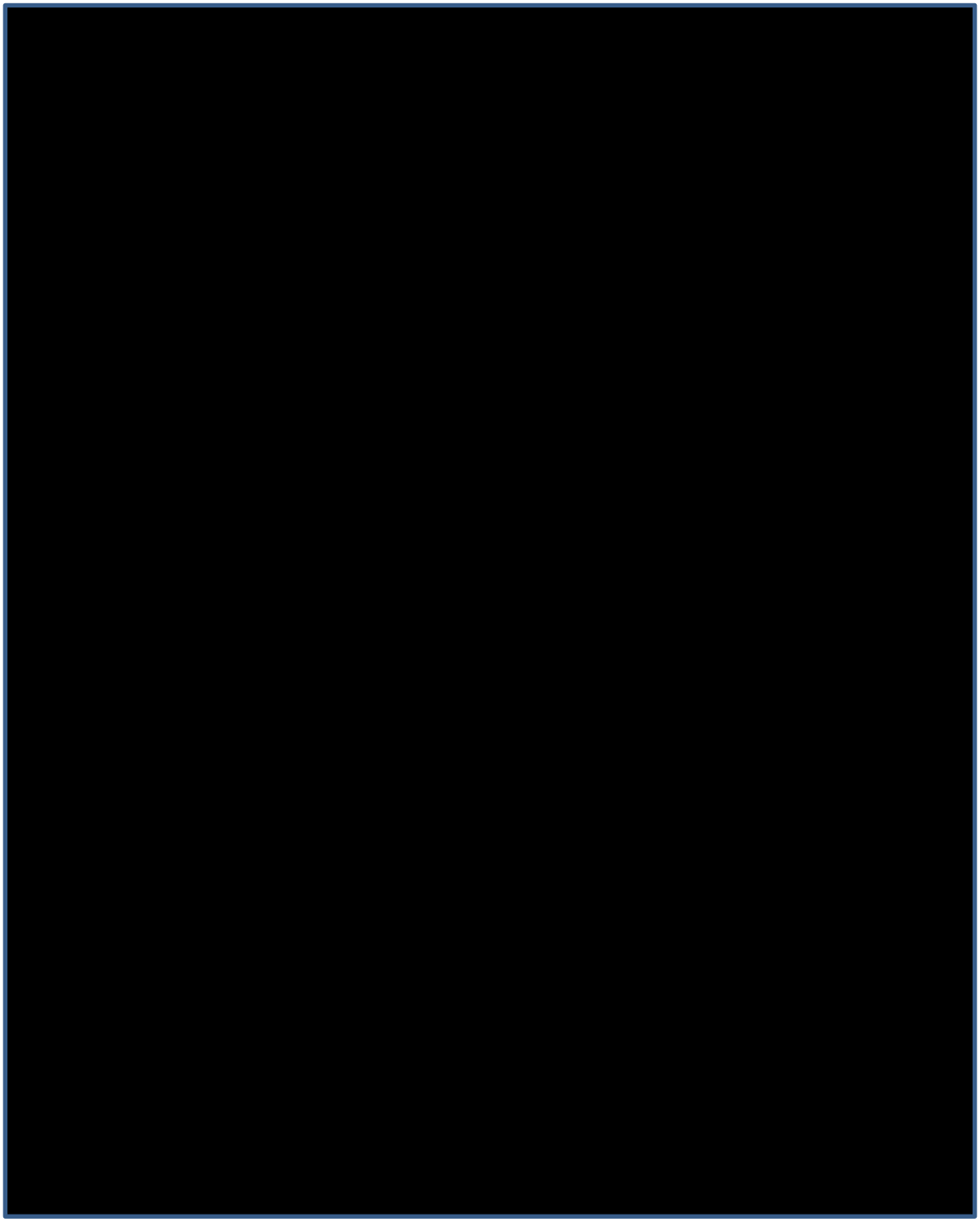


Table 39 (cont'd) Number of subjects with 1 or more treatment-emergent adverse events through week 60 by MedDRA System-organ class and preferred term; subjects treated with ustekinumab (CADMUS)(31)

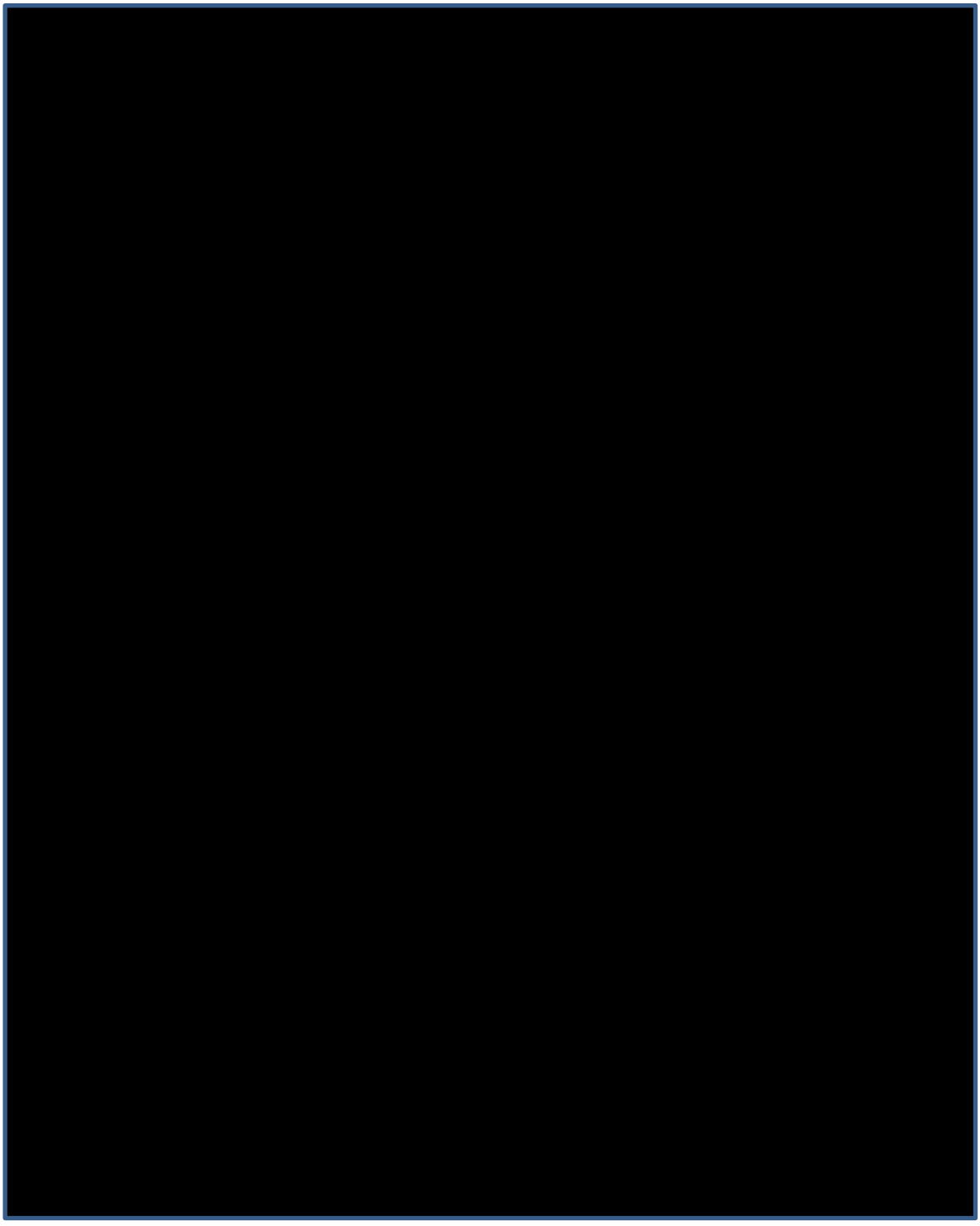


Table 39 (cont'd) Number of subjects with 1 or more treatment-emergent adverse events through week 60 by MedDRA System-organ class and preferred term; subjects treated with ustekinumab (CADMUS)(31)

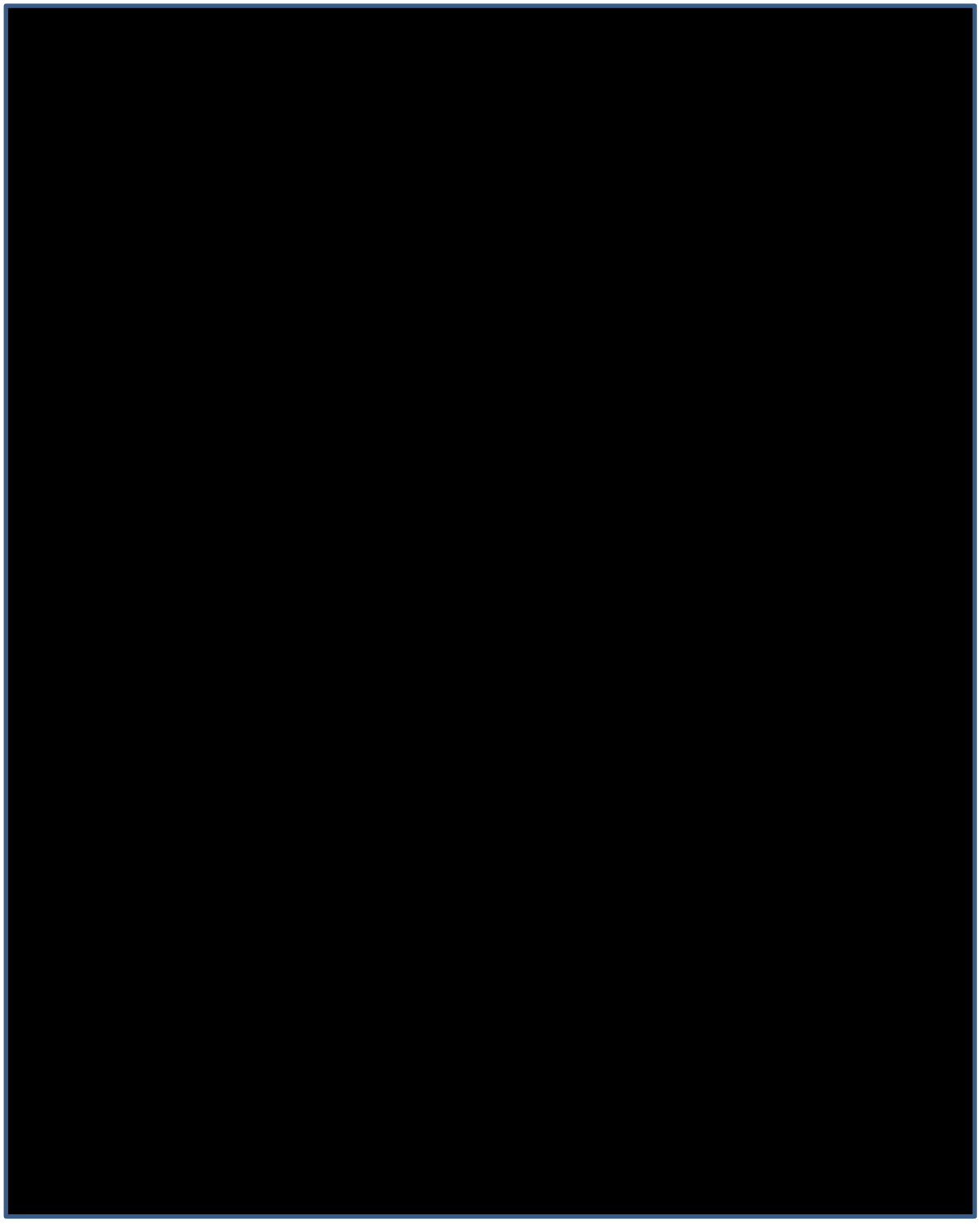


Table 39 (cont'd) Number of subjects with 1 or more treatment-emergent adverse events through week 60 by MedDRA System-organ class and preferred term; subjects treated with ustekinumab (CADMUS)(31)

9.5. NICE Data requested on 25th August 2016

The York Assessment Group anticipates that standard clinical efficacy and health related quality of life data will be included in the company's submission. Our request here is for data we think may not have otherwise been included. The data will be treated under strict confidence. We are grateful to Janssen for their co-operation in providing us with these additional data.

Clinical efficacy data request

1. **Please provide data on the following outcomes (see table below) for the following analyses:**
   a) All randomized subjects
   b) Efficacy evaluable subjects

Table 54 outcomes at 12 weeks

Treatment and trial arm	**CNTO1275PSO3006 CADMUS-Ustekinumab**	
	USK 0.75mg/kg	**Placebo**
Number of patients - all randomized patients	36	37
PASI		
Number of evaluable patients at week 12	36	36
PASI 50 response: N (%)	[redacted]	[redacted]
Mean (SD) PASI score at 12 weeks	[redacted]	[redacted]
Mean (SD) PASI score PERCENT improvement from baseline	[redacted]	[redacted]
CDLQI		
Number of evaluable patients at week 12	32	32
Mean (SD) CDLQI	[redacted]	[redacted]
Mean change from baseline (SD) CDLQI	-6.7 (5.6)	-1.5 (3.2)
PEDSQL		
Number of evaluable patients at week 12	[redacted]	[redacted]
Mean total PedsQL score (SD)	[redacted]	[redacted]
Mean change from baseline (SD) PedsQL	[redacted]	[redacted]

SD: standard deviation

2. **Could you please submit efficacy data for the initial 'trial period' (12 weeks), namely PASI 50/75/90 and PGA 0/1, for subgroups defined by i) age and ii) whether the patients had previous non-biologic systemic therapy?**

Table 55 Sub group Analysis at week 12 – all randomised subjects

Baseline Variable	Placebo		USK SD		*Difference	** 95% CI
	N	N responders (%)	N	N responders (%)		
PGA 0/1 at week 12						
All subjects	37	2 (5.4%)	36	25 (69.4%)	64.00%	(44.6%, 83.5%)
Baseline Age						
=<15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous conventional systemic therapy						
Never used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI >=50						
All subjects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Age						
=<15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous conventional systemic therapy						
Never used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI >=75						
All subjects	37	4 (10.8%)	36	29 (80.6%)	69.70%	(50.7%, 88.8)
Baseline Age						
=<15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline Variable	Placebo		USK SD		*Difference	** 95% CI
	N	N responders (%)	N	N responders (%)		
Previous conventional. systemic therapy						
Never used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI >=90						
All subjects	37	2 (5.4%)	36	22 (61.1%)	55.70%	(35.5%, 76.0%)
Baseline Age						
=<15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous conventional. systemic therapy						
Never used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI >=100						
All subjects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Age						
=<15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous conventional. systemic therapy						
Never used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

USK SD: ustekinumab standard dose
* proportion difference
** 95% CI are based on the Wald approximation with continuity correction

Health related quality of life data request

3. **Given the challenges in estimating utility values for the cost-effectiveness modelling, we would like to request access to individual patient data (IPD) on health-related quality of life from the efficacy trial for ustekinumab (CADMUS, NCT01090427) and conditioned on PASI response. We reiterate that the data will be treated under strict confidence. If IPD is not available, we would like to request the corresponding summary data for PedsQL and CDLQI. In the sections below, we provide a more detailed request of the data required.**

Table 56 Baseline characteristics by sub-groups of PASI responders - all randomised subjects

Time	Baseline		12 weeks									
Treatment allocation	Placebo (N=37)	UST SD (N=36)	Placebo (N=37)					UST SD (N=36)				
PASI*	-	-	<50	50 - <75	75 - <90	90>=	Total	<50	50 - <75	75 - <90	90>=	Total
Age [mean (SD)]	15.65 (1.46), Median= 16	14.83 (1.73), Median= 15	[redacted]	[redacted]	[redacted]	[redacted]	15.65 (1.46), Median= 16	[redacted]	[redacted]	[redacted]	[redacted]	14.83 (1.73), Median= 15
Gender - Males (n, %)	20 (54.1%)	16 (44.4%)	[redacted]	[redacted]	[redacted]	[redacted]	20 (54.1%)	[redacted]	[redacted]	[redacted]	[redacted]	16 (44.4%)

USK SD, ustekinumab standard dose; SD, standard deviation.
*PASI response at 12 weeks (compared to baseline)

Table 57 Summary for PASI score at week 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52

		Placebo					USK Standard dosage				
W	PASI *	<50	50 - <75	75 - <90	90>=	Total	<50	50 - <75	75 - <90	90>=	Total
4	N (%)	[redacted]									
	Mean(SD)	[redacted]									
8	N (%)	[redacted]									
	Mean(SD)	[redacted]									
12	N (%)	[redacted]									
	Mean(SD)	[redacted]									

		Placebo to Standard dosage					USK Standard dosage				
PASI*		<50	50 - <75	75 - <90	90>=	Total	<50	50 - <75	75 - <90	90>=	Total
16	N (%)	[redacted]									
	Mean(SD)	[redacted]									
20	N (%)	[redacted]									
	Mean(SD)	[redacted]									
24	N (%)	[redacted]									
	Mean(SD)	[redacted]									
28	N (%)	[redacted]									
	Mean(SD)	[redacted]									
32	N (%)	[redacted]									
	Mean(SD)	[redacted]									
36	N (%)	[redacted]									
	Mean(SD)	[redacted]									
40	N (%)	[redacted]									
	Mean(SD)	[redacted]									
44	N (%)	[redacted]									
	Mean(SD)	[redacted]									
48	N (%)	[redacted]									
	Mean(SD)	[redacted]									
52	N (%)	[redacted]									
	Mean(SD)	[redacted]									

NOTE all follow-up data are analysed based on the imputed data
N: number of responders change over time
*PASI response at 12 weeks (compared to baseline)

Table 58 summary table for CDLQI and PedsQL scores at baseline and Week 12

	Baseline (0 weeks)									
	Placebo (N= 37)					* USK SD (N= 36)				
PASI *	<50	50 - 75	75 - 90	90>=	Total	<50	50 - 75	75 - 90	90>=	Total
Physical Functioning - Absolute value	[redacted]									
Emotional Functioning - Absolute value	[redacted]									
School Functioning - Absolute value	[redacted]									
Social Functioning - Absolute value	[redacted]									
Total Scale Score - Absolute value	[redacted]									
CDLQI score - Absolute value	[redacted]									

	12 weeks									
	Placebo (N= 32)					USK SD (N=36)				
PASI *	<50	50 - 75	75 - 90	90>=	Total	<50	50 - 75	75 - 90	90>=	Total
Physical Functioning - Absolute value	[redacted]									
Emotional Functioning - Absolute value	[redacted]									
School Functioning - Absolute value	[redacted]									
Social Functioning - Absolute value	[redacted]									
Total Scale Score - Absolute value	[redacted]									
CDLQI score - Absolute value	[redacted]									

*PASI response at week 12

* USK SD- ustekinumab Standard Dosage

NOTE all follow-up data are analysed based on the imputed data

Table 59 Summary table for CDLQI and PedsQL scores at Week 28 and 52

	Week 28									
	Placebo					USK SD				
PASI *	<50	50 - 75	75 - 90	90>=	Total	<50	50 - 75	75 - 90	90>=	Total
Physical Functioning - Absolute value	[redacted]									
Emotional Functioning - Absolute value	[redacted]									
School Functioning - Absolute value	[redacted]									
Social Functioning - Absolute value	[redacted]									
Total Scale Score - Absolute value	[redacted]									
CDLQI score - Absolute value	[redacted]									

	Week 52									
	Placebo					USK SD				
PASI *	<50	50 - 75	75 - 90	90>=	Total	<50	50 - 75	75 - 90	90>=	Total
Physical Functioning - Absolute value	[redacted]									
Emotional Functioning - Absolute value	[redacted]									
School Functioning - Absolute value	[redacted]									
Social Functioning - Absolute value	[redacted]									
Total Scale Score - Absolute value	[redacted]									
CDLQI score - Absolute value	[redacted]									

*PASI response at week 12

NOTE all follow-up data are analysed based on the imputed data

USK SD: ustekinumab standard dose

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Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people [ID854]

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: 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? **YES**
- 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)? **YES. Academic Vice President for the British Association of Dermatologists and President for the British Society of Paediatric Dermatology**
- 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:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people [ID854]

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?

A UK wide audit (Lam et al, BJD 2015) of the current practice in the treatment of children with moderate to severe psoriasis against the published NICE guidelines for the diagnosis and management of psoriasis (TAG 153, 2012) showed that currently there is no formally agreed disease treatment pathway for children. This is largely because none of the standard systemic therapies used to treat psoriasis in adults are licensed to treat psoriasis under 16 years of age. However, the audit showed nationwide use of both standard systemic therapies and biological therapies. These children are treated, largely in line with pathways for adult disease as the draft scope indicates.

There is limited off-license use of biological therapies in the NHS in young people with severe psoriasis who have failed standard systemic therapy. Patterns of use have followed licensing of these agents, and most clinical experience with etanercept. However, ustekinumab and adalimumab are also used. The side effect profile of these drugs compared with standard systemic agents is not known but in 2015 there was agreement to include children below 16 years of age in the UK British Association of Dermatologists biological therapies surveillance register (BADBIR).

Over time this will show whether there are any differences in the safety profiles of standard systemic when compared with biological therapies.

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 drugs where there is fixed dosing, patients who are heavier may be poorer responders. In the adult population there is data to support this with body weight around 85 kg being a rough watershed. There is literature to support that children with psoriasis have a higher risk of obesity. This could translate to etanercept being less effective in this patient sub-group.

Similarly if data is extrapolated from the adult population, in children with psoriatic arthritis and psoriasis, adalimumab and etanercept are more likely to be effective than ustekinumab.

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)?

These drugs should be prescribed by a paediatric dermatologist experience in their use and experienced in the management of psoriasis. This is likely to be in a secondary and tertiary care setting. These drugs should not be prescribed in primary care.

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?

These drugs are being prescribed for severe disease but to date, without NICE approval in dermatology, they have often been prescribed by a paediatric rheumatologist or endocrinologist. Children with psoriasis are at an increased risk of inflammatory bowel disease and the JIA variant of psoriatic arthritis.

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.

The British Association of Dermatologists are just completing their review on the use of biological therapies for the treatment of psoriasis in adults and children. It should be published by December 2016 and it will have relevance to this MTA.

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.

In children with moderate to severe psoriasis who had failed standard systemic therapies, biological therapies would be prescribed. The limiting factor for their use is the necessary funding pending approval from NICE. The drugs can then be prescribed from secondary care and tertiary care settings.

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?

The clinical trial data for the use of these biological therapies in a paediatric population is short term. Most exists for etanercept which was the first to gain its license in the paediatric population. Long term safety and efficacy data for the 'real life' use of these drugs depends on registries such as BADBIR.

The published data from these trials does use PASI and life quality measures which reflects the routine assessment tools used in UK clinical practice. Apart from etanercept, drug efficacy data in this age group beyond 12 months is lacking. There is an increasing trend to look for clear or minimal disease.

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 long term safety data is limited with respect to the use of biological therapies to treat psoriasis in a paediatric population. The long term safety will be compared with standard systemic agents and will be available from national registry data. The UK register for the use of biological therapies is called BADBIR as explained above. Children with psoriasis treated with either standard systemic therapies or biological therapies should have the relevant safety data captured.

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.

The British Association of Dermatologists Biological Guidelines document will be available for review in December 2016. This document should be reviewed before the MTA as it will have some comments specifically about the use of these drugs in the paediatric population.

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people [ID854]

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)?

Paediatric Dermatologists experienced in the treatment of moderate to severe psoriasis will be familiar with these drugs from their adult practice. No further training is required and there should be equity of access to these drugs once there is NICE approval for their use.

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.

Children with psoriasis may have inflammatory bowel disease as well as the JIA variant of psoriatic arthritis. Obviously children are more likely to prefer oral medication than an injection.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people [ID854]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they 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(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Psoriasis and Psoriatic Arthritis Alliance

Your position in the organisation: [redacted]

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.

Primary activity is to provide information, education and support, via a website, information line (both electronic and voice), along with the provision of printed information, produced under The Information Standard scheme. Other activities include a biannual journal called Skin 'n' Bones 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*

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.

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 carried an online survey (29/01/2016 - 18 /06/2016), via the PAPAA website as free text form submissions, and promoted via social media. At the point of producing this submission, the mean age of responders was 47 years old (range 28 - 75) with a split of male 35% female 65%. 74% of respondents live in England.

We asked the following questions:

1. *What is it like to live with psoriasis as an adult, child or young person?*
2. *What do you want a treatment to provide and what is most important?*
3. *What do you think of the current treatments available on the NHS?*
4. *How acceptable are these different treatments and which do you prefer and why?*

All replies were anonymous, with only basic personal data collected of age, gender and location. The responses have been slightly edited to remove patient and professional identifiers. The following are a selection, and reflect the general views of those who responded.

It needs to be taken into consideration that the responders to this survey may be more proactive, in seeking information, have access to the internet and social media, therefore not be 100% representative of the total psoriatic population, where many live with disease, which is well-controlled and adequately managed by the current medications and treatments available.

We had no response from the age group that this appraisal covers, but some response reflected on what is was like to have psoriasis at a younger age.

What is it like to live with psoriasis as an adult, child or young person?

"Very very tiring.I have had it for 20 years now, since I was 17/18 years old."

"It is depressing and produces thoughts of morbidity when you also have other medical issues which limit medication."

"Worried for the future. At the moment the side effects from methotrexate are worse than the condition!"

"Frustrating and embarrassing. I often live in cyclical stress of knowing I could break out and knowing I need to control my stress levels."

"When at its worst and uncontrolled it was unbearable. I used to get it on the back of my head so as it shed it always looked like dandruff. I had it on my back and worst of all around my backside, which used to get so raw I literally could not walk at all. And I am only in my 30s."

"Intrusive. I have found my life has become a lot more insular due to the constant fatigue and attitude towards skin issues."

"It's embarrassing & demoralising for me. I have very bad psoriasis on both knees and elbows. I do wear T shirts & short sleeved tops but I ALWAYS have to wear long dresses, trousers or leggings to hide my unsightly knees, otherwise I notice other people staring at my knees. That's not a good feeling."

"As a teenager horrendous, suicide attempt, eating disorder, still have issues with body image 30 yrs later. Worst comment received: being told by a passing stranger I should kill myself so people didn't have to look at me, but received unpleasant / embarrassing comments most days from total strangers.The shame of smelling of coal tar and leaving piles of scales wherever I was sat. Not forgetting the itching, pain, sleepless nights. Unable to get jobs in anything relating to food/ drink, public facing because of it. First medical to get into nurse training was failed as having psoriasis proves you're mentally incapable of holding a job down (2nd Dr not so antiquated in attitude). Has been less severe over last decade, controlled with tight diet that is slightly restricting socially but prefer this to the psoriasis, even ventured back to dermatology (gave up on them as no topical treatments worked and not offered anything else)"

"I've had it since I was 13, that horrible self conscious age, when you really want to fit in, I've hated it all the years I've had it, I've had it get that bad that I've considered suicide, as an end to the horrible painful, itchy scales and the looks off people that think you have a contagious disease."

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.

What do you want a treatment to provide and what is most important?

"I want treatment that will actually show benefits quickly rather than constantly trying the 'normal' range of medications which take months and for me, have

done nothing to ease up the progress over the past year. This made worse by not being diagnosed for a full year prior to that either."

"*Ideally a cure but failing that a calming of the symptoms. The visual look of psoriasis is awful, but I can live with that if the cracking skin and pain can be reduced. I wish to continue an active lifestyle."*

"A treatment which doesn't require often visits to GPs or hospital. Side effects are an issue but one that is expected. It's hard enough working/living with the condition without adding the pressure of attending physicians on a regular basis."

"I want to feel like I can get up & go for a walk whenever I want & to know that I can hold down a job. I was a solicitor but there was no way I could continue a job that was so highly stressed feeling the way that I did. I now have another job & I work 3 days a week from home as I'm simply not able to make it to the office 5 days a week."

"Stopping the progress of it, minimal side effects"

"A treatment would ideally provide relief from psoriatic based skin complaints with the added bonus of not taking any medication that has been proven to cause quite severe side affects."

"I would like treatment that works! Coal tar cream keeps the crusty skin to pink BUT it never clears it up AND it stains. It's not a very good treatment when you work as a receptionist for general public. Nothing I have tried ever clears it up. I would like a liquid or clear cream to apply at night maybe wash off in morning?"

"Ease of use, accessible when needed. No disabling side effects."

"Relief and a "normalish" life."

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

What do you think of the current treatments available on the NHS?

"In truth they are brutal. The side effects far outweigh the benefits. My overall health has been affected by the diminished immune system I now have. Simple germs make me feel like death for days"

"There are some pretty good ones but actually accessing them is very prohibitive and counterproductive as we deteriorate while jumping through numerous hoops trying to access them."

"I have just started taking methotrexate but don't suppose it is in my system yet however since starting taking the medication my symptoms have got worse"

"I am currently unaware of any other drug(s) than what I'm currently on. I'm constantly told by the GP that there's not much more can be done. So in a word... frustrated."

"I am very lucky as I receive a biological medication and for that I am very grateful. I did have to work my way through all the other different medications first and this process took about two years in all which was a painful process to get to something that did work."

"I have only been offered methotrexate. It is like poisoning yourself once a week - then slowly recovering until it is time to take the dose again...and again. It makes you feel sick and tired."

"Very good. I have been on most anti TNF treatments until I get a bad reaction"

"I am of the view that the medication that I am taking has stabilised my condition and I often wonder what condition I would be in if I did not take the medication. I am taking methotrexate, folic acid, adalimumab. It is the long term use of these medications that concern me. I believe that I have also suffered gastric problems from the medication. I now really have to be aware of my exposure to sunlight as I now sunburn very easily."

"Not the greatest - no focus on this condition."

"There appears to be a reasonable range available, but prescribing guidelines do not seem to be uniform nationwide."

"They're scary. You trade one disease for many others, including cancer. Who wants that?"

"I am lucky. My initial treatments were useless, I used tonnes of creams and all were useless. Only through my own research and demanding to see a specialist in London (I am based in Essex) did I get an effective treatment."

"Nothing works. I have had psoriasis for 27 years and no treatment I have tried has ever worked."

"I love humira I've been on it 6 months and I wish to god I'd of know about it when it first came out!"

"I've been on a lot of topical treatments with no success. And also newer biologics like stelara and otezla, with limited success. I'm about to start cosentyx."

How acceptable are these different treatments and which do you prefer and why?

"Acceptable but have to wait too long before being offered biologics"

"I have tried most, methotrexate on and off for years but suffered with terrible headaches/migraines and nausea. Humira I have tried for over a year but the suppression of my immune system was too much and had constant chest problems and urine infections along with migraines. I am now on Cimzia - been 3-4 months and have been OK so far, except a lot of hair loss."

"Not acceptable at all. Horrific damage to the immune system, which is the whole point."

"I am of the mind that I have no choice if I want to reduce the extent of the condition. There was a period of trial and error to get the right combination and for the most part I am of the view that the right combination has been achieved. I self inject the Humira which has not been a problem so far. I appreciate that there is a cost implication for these medicines."

"Lotions and creams are difficult and time consuming with limited effect. Ciclosproin is the only systemic treatment with any success but already aware I cannot take this for long. Enquired about other treatments (cosentyx) many times but this is not available to me."

"Because I don't have debilitating symptoms the risks don't outweigh the benefits."

"It has cleared my skin and as a woman that loves fashion and clothes, I can finally dress in short sleeves and show my legs. Not be all covered up and worrying about how awful my skin is."

"I have a phobia of needles, so prefer tablets. Though tablets have side effects too."

4. What do patients or carers consider to be the advantages of the treatment(s) 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(s) being appraised.

A reduction in visible symptoms of psoriasis, with 100% clearance being a goal, but with minimal side-effects or at least the ability to manage any adverse events.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

We have no information to answer this question.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

We have no comments to add.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) 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.

The high cost of new therapies appears to limit or delay access. People complain that they often have to wait to qualify, whilst remaining on a failing

treatment with their symptoms worsening. The side effects also worry people, methotrexate appears to be most disliked and feared.

Please list any concerns patients or carers have about the treatment(s) being appraised.

The cost of these treatments and how that cost will limit patient access, is of concern. There are also concerns about the safety and long-term risk benefits, particularly the chance of developing lymphomas or malignancies.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

We have no information on this.

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

Given this is a group, which previously did not have access to these therapies, it is difficult to say. But if a sequence could be found as to who responds to which drug that might prove useful.

Are there any groups of patients who might benefit less from the treatment(s) 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(s)?

✓☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Adalimumab, etanercept are both anti-TNFs whereas ustekinumab is an IL12/23, so different targets that may help give scope for treatment in this young age group. The data appears to show benefit against placebo, but there were patients that did not reach the target of PASI75, so similar to adult trials. Having a range of different targeted drugs would give choice for this unmet need group.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

We have no information on this.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

People want clear skin, with no adverse events, this is probably even more important in the <18 age group, The trial use PASI 75 as a target, which is 75% improvement from base, this still leaves psoriasis present, so does not completely match what patients want

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

No information on this.

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.

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

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Only those who have difficultly with self-injection or needle phobias.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☐ Yes ✓☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

Although for this group it might be argued that they are?

Are there any other issues that you would like the Appraisal Committee to consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- *Psoriasis at any age is distressing, painful and causes psychological issues*
- *In a younger age group the impact can be much more devastating and effect education and future prospects*
- *Clearance should be the goal in psoriasis treatment*
- *There is an unmet need in this group, with limited options*
- *Adverse events and safety must be considered as a priority for this group*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people [ID854]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they 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(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Psoriasis Association

Your position in the organisation: [redacted]

Brief description of the organisation: The Psoriasis Association is a national charity for those affected by psoriasis. Its aims are to raise awareness of psoriasis; to give information, advice and support to those affected by psoriasis; and to promote and fund research into the causes, nature and care of psoriasis. The Psoriasis Association relies on voluntary donations, and receives no government funding. It does receive some funding from pharmaceutical companies, however funding from pharmaceutical company sources cannot exceed 15% of the charity's income in any one year. People can become members of the Psoriasis Association by paying an annual subscription – our current number of members is 2300. However, the Psoriasis Association's reach is considerably greater than its official membership. In 2015, the Psoriasis Association website received 770,000 visits; the number of social media followers/members exceeds 17,000; there are 6500 people registered on the Psoriasis Association's online forums, and 1085 enquiries were made to the Psoriasis Association 'helpline' via telephone, email and letter in 2015.

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?

Psoriasis is a lifelong condition with varying degrees of severity. The patients for whom these treatments are intended – children with severe psoriasis – will have a degree of psoriasis that will not only be visible to others, but will also be itchy, painful and produce excess scales.

Itching, pain and discomfort commonly disturb sleep and concentration, which can have a knock-on effect on school and future employment. The highly visible nature of psoriasis and its unsightliness can cause those who live with the condition to adopt negative coping mechanisms, such as avoiding social situations or instances where their psoriasis might be seen, such as in a swimming pool or gym. This can mean that the condition itself is isolating and lonely. In turn, this can lead to unhealthy lifestyle choices later in life, such as alcohol overuse, lack of exercise and smoking. Psoriasis is associated with significant impacts on quality of life and mental wellbeing, and many adult members and supporters of the Psoriasis Association describe a difficult and lonely childhood with the condition.

Patients with moderate to severe psoriasis have commonly been through a long journey of treatment trial and error and expense. Our latest membership survey found that people often spend up to two hours per day applying topical treatments. This can easily eat into time that might be spent pursuing hobbies or other leisure activities, which could have a detrimental effect on a child's development and the relationship to the family. Parents frequently tell us that they find it difficult to keep up with the treatment regime of a child with psoriasis – applying topical treatments, increased washing – and that they feel helpless and useless when the treatments fail to control the psoriasis, and children start to have problems with their peers, or their schoolwork becomes affected. It must also be recognised that there is a genetic component to psoriasis and so, in a number of cases, parents may also be dealing with quality of life impacts, psychological wellbeing issues and treatment burden of their own psoriasis and/or psoriatic arthritis alongside their child's.

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.

We conducted a short online survey to ask the parents of children with psoriasis about important treatment outcomes. The answer to this question is based on the small number of responses (4) that were received, along with

general experience of the Psoriasis Association's helpline and other interactions with parents and children with the condition.

Parents felt that the most important outcome to their children (the patient) would be a general reduction in the amount of psoriasis, although 'total clearance', 'clearance in visible areas', and 'improvement in flaking' also rated highly. This is understandable, as children are often hyper-aware of their differences to their peers, and are likely to want to look and feel like other children. For parents, the most important outcomes were a reduction in the overall amount of psoriasis, and improvements in symptoms such as redness and flaking. The outcome that was considered the most important for both parents and children was an improvement in itching or pain. It is often mentioned how distressing it is for parents to see their child in pain, and this is also likely to make the child irritable and interfere with sleep, concentration and mood.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

The vast majority of (if not all) children with psoriasis will be prescribed topical treatments in the first instance, and will probably spend quite some time using these, even if they progress onto secondary care and/or use other treatments alongside. Topical treatment is often helpful to treat mild psoriasis, however it is not appropriate alone for treatment of moderate to severe psoriasis covering more than 10% of the body. Topical treatments can be extremely time consuming – as mentioned in Question 2 – and parents noted that they have a limited effectiveness in controlling moderate to severe psoriasis, and can also lose effectiveness over time.

The traditional next stage – and the next stage that is laid out in the NICE guidance on the assessment and treatment of psoriasis (NICE CG153) is ultraviolet light therapy. This requires a significant time commitment, not only from the child but from the rest of the family, as they will be required to attend the Dermatology Department three times a week for up to around 10 weeks. Quite simply, not all families can manage the expense, or take the time out of work to achieve this. This regime can also be significantly disruptive to a

child's schooling. One parent who responded to our survey noted that UVB has so far been the most effective treatment for her child, which is positive, however it is not a long-term fix as psoriasis does rebound at ever-shortening intervals. Additionally, receiving UV therapy in itself can be frightening for children, having to stand naked and alone in a noisy cabinet.

The next stage of treating psoriasis that is moderate to severe would be traditional systemic treatments such as methotrexate, ciclosporin and acitretin. However, these are not licensed for use in children and can have significant long term side effects on major organs. After that would be biologic treatment, of which, up until recently, only Enbrel was licensed for use in children. The advantages and disadvantages of these treatments will be discussed below.

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

The three biologics that are being appraised are all established in the treatment of severe psoriasis in adults, and have proven to be effective. Whilst there is currently no accurate way of predicting individual response to treatment, biologics have shown to provide significant long term improvements in PASI scores (which takes into account physical amount of psoriasis, redness and induration). Therefore, patients and carers could expect to see genuine improvement in psoriasis, and can expect for it to be maintained long term.

Many of our members and supporters describe having difficult, lonely childhoods with psoriasis. They feel that having psoriasis from a young age affected their educational performance, which in turn had an impact on future careers. Issues in relating to peers, bullying, feeling unable to pursue intimate or romantic relationships in their teens, can all have a cumulative impact on mental wellbeing and their life's direction. Many people who have had psoriasis since childhood have told us they feel their life and mental health would have been significantly better had they been able to access effective treatment and gain control of their skin at a young age.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

Biologics are typically administered by injection on a weekly or monthly basis, depending on the particular agent used. This is significantly less time consuming than both topical treatment regimens and ultraviolet light therapy, and will also therefore have less of an associated impact on the wider family. Although long-term safety data is still being gathered, biologics are generally thought to pose less of a threat to major organ systems than traditional systemics and therefore may be safer and more appropriate for children.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

Some parents have expressed apprehension regarding the use of these treatments in children due to the lack of particularly long-term safety data. Whilst particularly young children may not be able to weigh up the risks and benefits, some older children will disagree with their parents and may be willing to accept certain risk for the benefit of improvement in psoriasis.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Please list any concerns patients or carers have about current NHS treatments in England.

One major concern about currently available treatments is a lack of long term efficacy (compared to biologics) in treating psoriasis. Side effects are also a significant concern – over-use of steroid creams can cause skin thinning and unstable psoriasis, ultraviolet light therapy can increase the risk of skin cancers, and traditional systemics can have a negative impact on the liver, kidneys and blood pressure, and can cause difficult-to-manage side effects including nausea. The financial and time impact on the wider family to visit the hospital multiple times a week is a significant barrier to ultraviolet light therapy.

Please list any concerns patients or carers have about the treatment(s) being appraised.

The major concern that patients (children) and their parents may have regarding the treatments being appraised is the lack of particularly long-term safety data. There may also be issues around the administration of the drugs, as they are injected – children may find this frightening, and injections can cause site reactions on the skin such as stinging sensations.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

Children who have particularly severe psoriasis previous treatments have been unable to provide suitable control for. Children who have psoriatic arthritis as well as psoriasis may also see an improvement in their arthritis symptoms and outlook on these treatments. Children whose families are unable to commit the significant time and financial expense to attending ultraviolet light therapy appointments will certainly benefit from their being an additional treatment option after this.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

x☐ 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(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

In general, the biologics being appraised are thought to be quite efficacious and many patients describe their experience of these biologics very positively. As far as we are aware this largely reflects the clinical trial data, although allowances must always be made for the fact that not every treatment will work for every person with psoriasis.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

Clinical trials captured outcomes related to amount/severity of psoriasis including PASI and Physician's Global Assessment, which directly correlate with important patient outcomes of psoriasis reduction/improvement. However, it should be noted that PASI has not been validated in children. It is important that quality of life is measured in this population, and we support the use of the Children's Dermatology Life Quality Index as opposed to the DLQI in this population.

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Not that we are aware of.

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)?

☐x Yes ☐ No

If yes, please provide references to the relevant studies.

A recent survey on the impact of moderate to severe psoriasis by Novartis (https://www.novartis.co.uk/news/media-releases/psoriasis-advocates-support-call-urgent-change-survey-reveals-78-people) data on file. Population was adults with psoriasis rather than children, but does give an up-to-date picture of the quality of life and psychological wellbeing impacts of psoriasis.

8. Equality

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

There is a possibility that children (the patient) who also have psoriatic arthritis might find it difficult to self-administer injections. Children who are too young to self-administer will be reliant upon their parents, and if they have physical disabilities then they may also struggle with the mechanism.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☐x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

These treatments are the first of their kind to be licensed for children with psoriasis.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Psoriasis in children can have a significant impact on physical and psychological health, as well as quality of life. Many Psoriasis Association members and supporters describe a difficult and lonely childhood living with the condition, which has impacted on their life's direction and development as adults.
- Managing and treating psoriasis in a child can have a significant impact on the wider family. Time consuming treatment regimens, excess washing,

and dealing with a child's pain, irritation and distress can all take a toll on the family dynamic.

- Many of the currently-available treatments are not appropriate for a child with severe psoriasis as they are too time consuming, not effective enough, or do not maintain efficacy long term. Traditional systemic treatments which are used for adults before progressing to biologics are not licensed for paediatric populations, and have significant possible side effects and safety concerns.
- The treatments being appraised have been shown to be effective in improving severe psoriasis and do not have the same side effect and safety concerns as traditional systemic therapies. Many adults who have lived with psoriasis since they were child believe that, had they had access to effective long term treatment at a young age, they would have had a different experience which would have had a beneficial effect on their physical health, education, social development and quality of life.
- The treatments being appraised are the first of their kind to be licensed for a paediatric psoriasis population, which makes them a truly new option for children with severe psoriasis. They offer an option for children with psoriasis for whom other available treatments either have not worked or are not suitable, and ustekinumab in particular – as the only interleukin-blocker licensed for use in children – offers an entirely unique treatment method.

Appendix K – Patient expert statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab, etanercept and ustekinumab for treating severe, chronic plaque psoriasis in children and young people [ID854]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **Psoriasis and Psoriatic Arthritis Alliance** and consequently I will not be submitting a personal statement.

Name: .....David Chandler.....

Signed: ....[redacted].....

Date: .....24/1/17.....