NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]

Committee papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted. The Assessment Group appendices discussing the confidential comparator Patient Access Schemes in this appraisal are completely confidential and have therefore not been included in these papers.

Premeeting briefing
Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs

The pre-meeting briefing document was prepared before the consultation on the Assessment Group report closed

This slide set is the premeeting 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 Assessment Group (AG) 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 AG before the company has checked the AG report for factual inaccuracies.

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

COMMON ABBREVIATIONS (shaded rows contain comparator technologies)	
ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse event
AG	assessment group (for MTAs)
APR	apremilast
BSC	best supportive care
cDMARD	conventional disease modifying anti-rheumatic drugs
CG	clinical guideline
CZP	certolizumab pegol
DLQI	Dermatology Quality of Life Index
EQ-5D	EuroQol Group measure of health states (including mobility, self-care, usual activities, pain/discomfort, anxiety/depression) at 5 levels from no problems to extreme problems
ETA	etanercept
HAQ	Health Assessment Questionnaire
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
INF	infliximab
GOL	golimumab
MTA	multiple technology assessment
MTX	methotrexate
NMA	network meta-analysis
NSAID	non-steroidal anti-inflammatory drug

COMMON ABBREVIATIONS (shaded rows contain comparator technologies)	
PAPAA	Psoriasis and Psoriatic Arthritis Alliance
PAS	Patient Access Scheme
PASI	Psoriasis Area and Severity Index score
PLA	placebo
PNR	placebo non-responders
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
QALY	Quality adjusted life year
RCT	randomized controlled trial
SC	subcutaneous
SEC	secukinumab,
SF-36	Short Form (36) health survey
Subpopulation 1 (as per AG model)	patients who are biologic-naïve but have tried one previous cDMARD
Subpopulation 2 (as per AG model)	patients who are biologic-naïve but have tried two or more previous cDMARD
Subpopulation 3 (as per AG model)	patients who are biologic-experienced
Subpopulation 4 (as per AG model)	patients who are contraindicated to TNF-alpha inhibitors
TA	technology appraisal
TNF	tumour necrosis factor
UST	ustekinumab

Psoriatic arthritis

- Psoriatic arthritis (also called psoriatic arthropathy) is an inflammatory arthritis closely associated with psoriasis which affects joints and soft tissues.
- It is a chronic condition that progresses in the joints, its course may be erratic, with flare-ups and remissions. Arthritis symptoms can range from inflammation of the synovial membrane surrounding a joint (synovitis), ligaments and tendons (enthesitis and tendonitis), and inflammation of digits (dactylitis) to severe progressive erosion of the joints.
- An estimated 5–7% of all people with psoriasis, and up to 40% of those with extensive skin disease, have psoriatic arthritis

Relevant NICE guidance (I)

Published guidance

- **TA 372 (2015) 'Apremilast for treating active psoriatic arthritis'.**
  - Not recommended within its marketing authorisation for treating adults with active psoriatic arthritis that has not responded to prior DMARD therapy, or such therapy is not tolerated
  - Currently under Rapid Review
- **TA 340 (2015) 'Ustekinumab for treating active psoriatic arthritis'**
  - Recommended as an option alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only when:
    - treatment with tumour necrosis factor (TNF) alpha inhibitors is contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis) or
    - the person has had treatment with 1 or more TNF–alpha inhibitors.
    - And if the company provides the 90 mg dose of ustekinumab for people who weigh more than 100 kg at the same cost as the 45 mg dose, as agreed in the patient access scheme.

Continued…

Relevant NICE guidance (II)

- **TA 340 continued:**
  - Ustekinumab treatment should be stopped if the person's psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 24 weeks. An adequate response is defined as an improvement in at least 2 of the 4 criteria (1 of which must be joint tenderness or swelling score), with no worsening in any of the 4 criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response (see NICE technology appraisal guidance on ustekinumab for the treatment of adults with moderate to severe psoriasis).
  - When using the Psoriatic Arthritis Response Criteria (PsARC) healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate.
  - Proposed to be transferred to the ‘static list guidance’: August 2016

Relevant NICE guidance (III)

- **TA220 (2011) 'Golimumab for the treatment of psoriatic arthritis'.**
  - Recommended for the treatment of active and progressive psoriatic arthritis in adults only if:
    - It is used as described for other tumour necrosis factor (TNF) inhibitor treatments in etanercept, infliximab and adalimumab (TA 199)
    - The company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose
  - When using the PsARC, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate
  - Proposed to be transferred to the 'static list guidance': August 2016

Relevant NICE guidance (IV)

- **TA199 (2010) 'Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review of TA104 and 125)'**
  - Recommends all three drugs for the treatment of active and progressive psoriatic arthritis if :
    - the person has peripheral arthritis with three or more tender joints and three or more swollen joints, and the psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination.
  - Treatment should start with the least expensive drug
  - Treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response using the PsARC at 12 weeks. People whose disease has a PASI 75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response
  - Proposed to be transferred to the 'static list guidance': August 2016

Relevant NICE guidance (V)

Related Guidelines:

- CG153 (2012) 'Psoriasis: assessment and management'. Review Proposal Date December 2016.
- Guideline in development 'Spondyloarthritis'. Expected Publication Date March 2017

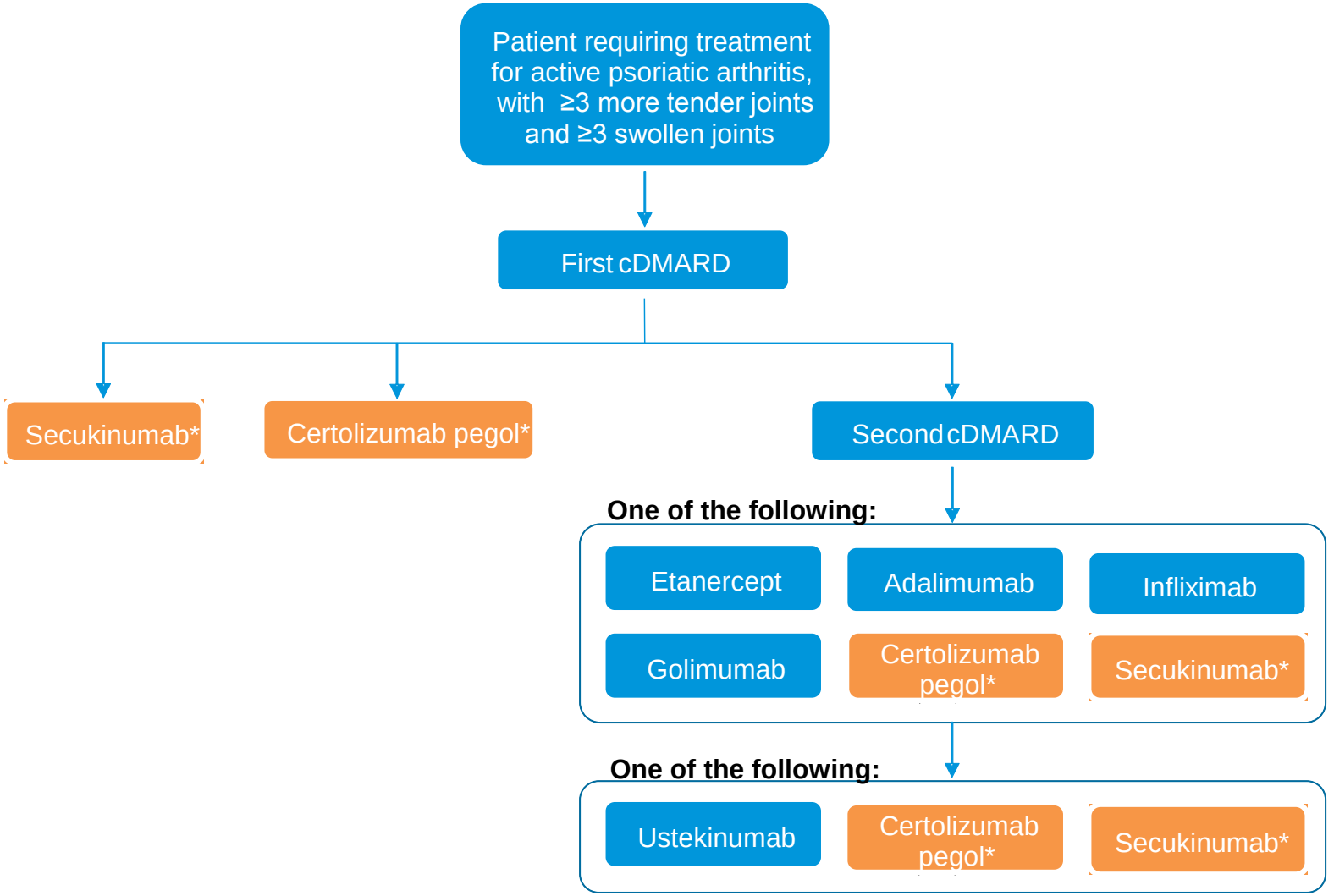
Related Quality Standards:

- QS40 (2013) 'Psoriasis'. Review Proposal Date TBC

Related NICE Pathways:

- NICE Pathway: Musculoskeletal conditions, Pathway last updated June 2015

Position of certolizumab pegol (CZP) and secukinumab (SEC) in the treatment pathway



Abbreviations: cDMARD, conventional disease modifying anti-rheumatic drugs. *Technologies under consideration in this appraisal

Source: adapted from figure 5 p.43 of UCB's submission

pre-meeting briefing document

Impact on patient and carers

Psoriasis and Psoriatic Arthritis Alliance (PAPAA) and the Psoriasis Association

- Most of people affected by PsA are young and mid adults
- Symptoms include pain, stiffness, fatigue and swelling that can flare and subside unpredictably making it difficult to carry out normal everyday tasks and maintaining relationships causing a reduction in quality of life
- Willingness for treatments that keep disease activity to a minimum, reduce pain, fatigue swelling and improve mobility
- ACR20 is unlikely to make people with PsA feel significantly better
- Current treatment includes NSAIDs and DMARDs:
  - NSAIDs can improve symptoms in the short-term but they do not prevent long-term irreversible damage. It can also cause a flare-up in psoriasis which can further affect quality of life.
  - DMARDs can prevent progression and irreversible damage but not all of them improve extra-articular symptoms such as enthesitis, fatigue and skin psoriasis. People taking DMARDs can still experience pain. Most suitable DMARD for a person is sometimes identified by trying a range of treatments; however, it noted that some clinical commissions groups limit the number of DMARDs available to each person.

Impact on patient and carers

Psoriasis and Psoriatic Arthritis Alliance (PAPAA) and the Psoriasis Association

- Certolizumab pegol (CZP) and secukinumab (SEC)
  - slow down or stop the progression of PsA
  - reduce symptoms
  - improve disease stability and mental HRQoL
  - could benefit people who have tried other DMARDs and did not have acceptable results
  - have other benefits related to psoriasis
  - DMARDs are known to have potential toxicity, however people are willing to tolerate a certain level of side-effects for an improvement in quality of life
  - could be beneficial in pregnant women with severe PsA in whom the severity of the disease can prevent pregnancy
  - there is some reluctance to self-inject or phobia of injecting
  - SEC has a different mechanism of action from available treatments
  - CZP has a good track record in rheumatoid arthritis which may suggest that it will have positive benefits on other types of inflammatory arthritis, including PsA

Clinician perspectives

British Association of Dermatologists (also endorsed by the Royal College of Physicians)

- Choice and sequencing of drugs can be influenced by the presence of skin disease thus both psoriasis and PsA should be considered before making changes of treatment.

- PASI and DLQI outcomes should be considered to account for people with concurrent skin disease.

DETAILS OF THE TECHNOLOGY

	CERTOLIZUMAB PEGOL (Cimzia, UCB Pharma)	SECUKINUMAB (Cosentyx, Novartis)
MA	Inhibitor TNF-alpha • with MTX: active PsA in adults when the response to previous DMARD therapy has been inadequate • monotherapy: in case of intolerance to MTX or when continued treatment with MTX is inappropriate	Inhibitor IL-17A: • with or without MTX: 'active PsA in adult patients when the response to previous DMARD therapy has been inadequate'
Admin.	Subcutaneous injection once every 2 weeks - initial 400 mg at weeks 0, 2 and 4 - maintenance 400 mg every 4 weeks Continued therapy should be reconsidered in people who show no evidence of therapeutic benefit within first 12 weeks	Subcutaneous injection weekly • For people with both PsA and Psoriasis or TNF-alpha inhibitor inadequate responders: initial 300 mg at 0, 1, 2 and 3 weeks; maintenance 300 mg monthly • For all other people: initial 150 mg at weeks 0, 1, 2 and 3; maintenance 150 mg monthly Discontinued therapy should be reconsidered in people who show no evidence of therapeutic benefit within first 16 weeks
Costs	£357.50 per 200 mg prefilled syringe Company has proposed a complex PAS: this is not currently approved by the DH	£1,218.78 per 2 x 150 mg prefilled pen or syringe Available at lower cost through confidential PAS: Simple discount

Key: DMARD, disease modifying anti-rheumatic drugs ; MTX, methotrexate; PAS, patient access scheme; PsA, psoriatic arthritis

DECISION PROBLEM (I)

	FINAL SCOPE	AG COMMENTS
Pop.	Adults with active psoriatic arthritis whose disease has not responded adequately to previous DMARD drug therapy	
Int.	• CZP alone or in combination with MTX • SEC alone or in combination with MTX	
Com.	For people who have only received 1 prior non-biological DMARD • DMARDs For people whose disease has not responded adequately to at least 2 DMARDs: • Biological therapies (+/- MTX including ETA, ADA, INF, GOL, APR [subject to ongoing NICE appraisal]) For people whose disease has not responded adequately to DMARDs and not adequately responded to biological therapies (including ETA, ADA, INF, GOL) or biological therapies are contraindicated: • UST • APR [subject to ongoing NICE appraisal] • BSC	AG included the following comparators: • Placebo • DMARDs: MTX, sulfasalazine, leflunomide, hydroxychloroquine, azathioprine and ciclosporin • Biologic therapies: ETA, ADA, INF, GOL and UST, including any licensed biosimilars • APR • BSC

- The AG did not look at biological therapies +/- MTX as specified in the final scope

DECISION PROBLEM (II)

	FINAL SCOPE	AG COMMENTS
Out.	The outcome measures to be considered include: • disease activity • functional capacity • disease progression • periarticular disease (for example enthesitis, tendonitis, dactylitis) • mortality • adverse effects of treatment • health-related quality of life	AG considered the following outcomes: • disease activity, using the following multi-domain measures: PsARC, ACR 20/50/70 • functional capacity (assessed using HAQ) • radiographic assessment of disease progression • response of psoriatic skin lesions (assessed using PASI) • measures of dactylitis, enthesitis, and tendonitis • mortality • HRQoL (assessed using EQ-5D or SF-36) • AEs of treatment, focusing on the key AEs identified from previous studies of biologics: malignancies, serious infections, reactivation of latent tuberculosis, injection site reactions, and withdrawals due to adverse events
Other	Availability and cost of biosimilars should be taken into consideration. If evidence allows the following subgroups will be considered: • the reason for treatment failure (for example due to lack of efficacy, intolerance or AEs).	AG's searches included biosimilars If evidence allows, AG will evaluate the following: • different patient positions in the care pathway • different reasons for previous treatment failure (e.g. due to lack of efficacy, contraindication, or AEs)

Abbreviations: AG, assessment group, AEs, adverse events; ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; DMARD, disease modifying anti-rheumatic drugs ; ETA, etanercept; HRQoL, health related quality of life; INF, infliximab; MTX, methotrexate; SEC, secukinumab; UST, ustekinumab

CLINICAL EFFECTIVENESS

Key clinical issues (I)

- What is the Committee's view on the 'placebo creep' (placebo response rates appear to have increased over time) and its impact on the indirect comparison?
- What is the Committee's view on the exclusion of certolizumab pegol treatment data from the biologic experienced network?
- A class effect has been considered between apremilast and secukinumab although they have distinct mechanism of action (targets IL-17A vs. target p40 of IL-12 and IL-23). What does the Committee think of the relevance of the class effect?
- What is the Committee's view on the safety profile of both certolizumab pegol and secukinumab based on the long-term studies and the systematic review conducted by the Assessment Group?
- What is the Committee's view in considering the subgroups by psoriasis severity as the base case populations?
- What is the Committee's view on the inclusion of BSC as a comparator for subpopulation 1 (patients who have failed 1 DMARD) and not another DMARD?
- What is the Committee's view on the limitations of the long-terms studies of SEC and CZP's with regards to efficacy and safety?

Results of clinical evidence

The following slides report

1. Short term efficacy from:
   - Company submission (pivotal RCTs for CZP and SEC)
   - Assessment Group report (results from network meta analysis)
2. Long term efficacy from:
   - Company submission (open-label extensions RCTs for CZP and SEC)
3. Adverse events from:
   - Company submission (short and long term RCTs for CZP and SEC)
   - Assessment Group report (results from systematic review)
4. Health related quality of life from
   - Company submission (pivotal RCTs for CZP and SEC)

Certolizumab pegol (UCB submission)

- 'RAPID-PsA' was the only eligible RCT identified: compares CZP 200mg every 2 weeks or 400mg every 4 weeks against placebo up to 24 weeks
  - Dose blinded to 48 weeks and open-label to 216 weeks
- Patients with primary failure of a previous anti-TNF were excluded (primary failure was defined as no response within the first 12 weeks of treatment with the anti-TNF)
- Placebo patients who failed to achieve a 10% improvement from baseline in both swollen and tender joints at week 14 and 16 were re-randomised to active treatment at week 16. At week 24 all the remaining placebo patients were re-randomised to receive 200mg or 400mg of CZP
- Subgroups were defined according to:
  - number of previous DMARDs
  - biologic-naïve and biologic-experienced

Source: adapted from section 4.5 p 90 from AG's report

pre-meeting briefing document

CZP 'RAPID-PsA' results: ACR 20, 50 and 70

UCB submission

Time-point		TNF inhibitor naïve				Prior TNF inhibitor exposure		Overall population	
		Only 1 prior cDMARD		All TNF inhibitor naïve					
		Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined
		N=75	N=135	N=110	N=219	N=26	N=54	N=136	N=273
ACR 20 (%)	wk 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24.3	54.9*
	wk 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23.5	60.1*
ACR 50 (%)	wk 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11.0	34.4*
	wk 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12.5	42.1*
ACR 70 (%)	wk 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.9	18.7*
	wk 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.4	26.0*

Abbreviations: [redacted] ACR, American College of Rheumatology; CZP, certolizumab pegol; cDMARD, conventional disease-modifying anti-rheumatic drug; TNF, tumour necrosis factor

Note: 'CZP combined' associate CZP 200 mg Q2W (every 2 weeks) + 400 mg Q4W (every 4 weeks)

Source: adapted from tables 16 and 17 from UCB's submission

CZP 'RAPID-PsA' results: PASI 50, 75 and 90 for people with ≥ 3% BSA of psoriasis at baseline

UCB submission

Time-point		TNF inhibitor naïve				Prior TNF inhibitor exposure		Overall population	
		Only 1 prior cDMARD		All TNF inhibitor naïve					
		Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined
		N=46	N=81	N=66	N=130	N=20	N=36	N=86	N=166
PASI50 (%)	wk 12	[redacted]	[redacted]	27.3	61.5*	25.0	83.3*	26.7	66.3
	wk 24	[redacted]	[redacted]	30.3	68.5*	20.0	91.7*	27.9	73.5
PASI75 (%)	wk 12	[redacted]	[redacted]	16.7	43.1*	5.0	61.1*	14.0	47.0*
	wk 24	[redacted]	[redacted]	19.7	56.2*	0.0	80.6	15.1	61.4*
PASI90 (%)	wk 12	[redacted]	[redacted]	4.5	19.2*	5.0	27.8**	4.7	21.1*
	wk 24	[redacted]	[redacted]	7.6	36.9*	0.0	58.3	5.8	41.6*

Abbreviations: [redacted]; CZP, certolizumab pegol; cDMARD, conventional disease-modifying anti-rheumatic drug; PASI, Psoriasis Area and Severity Index; TNF, tumour necrosis factor

Note: 'CZP combined' associate CZP 200 mg Q2W (every 2 weeks) + 400 mg Q4W (every 4 weeks)

Source: adapted from tables 23 to 25 in UCB's submission

CZP 'RAPID-PsA' results: PsARC response

UCB submission

Time-point	TNF inhibitor naïve				Prior TNF inhibitor exposure		Overall population	
	Only 1 prior cDMARD		ALL TNF inhibitor naive					
	Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined	Placebo	CZP combined
	N=75	N=135	N=136	N=273	N=26	N=54	N=136	N=273
PsARC at week 12 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38.2	69.6*
PsARC at week 24 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33.1	77.7*

Abbreviations: [redacted]; CZP, certolizumab pegol; cDMARD, conventional disease-modifying anti-rheumatic drug; PsARC, psoriatic arthritis response criteria; TNF, tumour necrosis factor

Note: 'CZP combined' associate CZP 200 mg Q2W (every 2 weeks) + 400 mg Q4W (every 4 weeks)

Source: adapted from table 19 in UCB's submission

Secukinumab (Novartis submission)

- 4 phase 3 RCTs: FUTURE 2, ERASURE, FIXTURE and CLEAR
  - FUTURE 2 provides the main evidence, include patients with psoriatic arthritis
    - compared SEC 150mg or 300mg with placebo
  - ERASURE, FIXTURE and CLEAR trials were trials of patients with psoriasis which reported subgroup data for patients who also had psoriatic arthritis.
    - EARSURE compared SEC 150mg or 300mg with placebo
    - FIXTURE compared SEC 150mg or 300mg with etanercept (100mg/week) and placebo
    - CLEAR compared SEC 300mg with UST 45 or 90mg (dosing was as per license: 45mg in patients weighing ≤100kg and 90mg for patients weighing >100kg)
- FUTURE 1 not included in evidence synthesis as studied non-licensed dose, but reports data on radiographic progression of joint damage
- 3 ongoing trials for which results are not yet available (FUTURE 3, 4 and 5)

Source: adapted from section 4.4 p 80 from AG's report

SEC 'FUTURE 2': ACR 20, 50 and 70

Novartis submission

Time-point		Biologic naive						Biologic experienced			Overall population		
		Only 1 prior cDMARD			All biologic naive								
		Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300
		[redacted]	[redacted]	[redacted]	N=63	N=67	N=67	N=35	N=37	N=33	N=98	N=100	N=100
ACR 20 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26	56	57
	wk 24	[redacted]	[redacted]	[redacted]	16	63	58	14	30	45	15	51	54
ACR 50 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5	32	30
	wk 24	[redacted]	[redacted]	[redacted]	6	44	39	9	19	27	7	35	35
ACR 70 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	wk 24	-	-	-	2	27	22	0	11	15	1	21	20

Abbreviations: ACR, American College of Rheumatology; cDMARD, conventional disease-modifying anti-rheumatic drug; SEC, secukinumab

Source: adapted from tables 8 and 10 from AG report and table 8 from Novartis' submission

SEC 'FUTURE 2': PASI 50, 75 and 90 for people with ≥ 3% BSA of psoriasis at baseline

Novartis submission

Time-point		Biologic naive						Biologic experienced			Overall population		
		Only 1 prior cDMARD			All biologic naive								
		Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300
		[redacted]	[redacted]	[redacted]	N=31	N=36	N=30	N=12	N=22	N=11	N-41	N=58	N=41
PASI 50 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12	83	83
	wk 24	-	-	-	-	-	-	-	-	-	-	-	-
PASI 75 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5	53	59
	wk 24	[redacted]	[redacted]	[redacted]	19	56	63	8	36	64	16	43	63
PASI 90 (%)	wk 12	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5	33	39
	wk 24	[redacted]	[redacted]	[redacted]	10	39	53	8	23	36	9	33	49

Abbreviations: cDMARD, conventional disease-modifying anti-rheumatic drug; PASI, Psoriasis Area and Severity Index; SEC, secukinumab

Source: adapted from tables 9 and 11 from AG report and table 8 from Novartis' submission

SEC 'FUTURE 2': PsARC

Novartis submission

Time-point	Biologic naive						Biologic experienced			Overall population		
	Only 1 prior cDMARD			All biologic naive								
	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300	Placebo	SEC 150	SEC 300
	[redacted]	[redacted]	[redacted]	N=63	N=67	N=67	N=35	N=37	N=33	N=98	N=100	N=100
PsARC at week 12 (%)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PsARC at week 24 (%)	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	30	62	63

Abbreviations: cDMARD, conventional disease-modifying anti-rheumatic drug; PsARC, psoriatic arthritis response criteria; SEC, secukinumab

Source: adapted from tables 8 and 10 from AG report and table 8 from Novartis' submission pre-meeting briefing document

Systematic review conducted by the AG

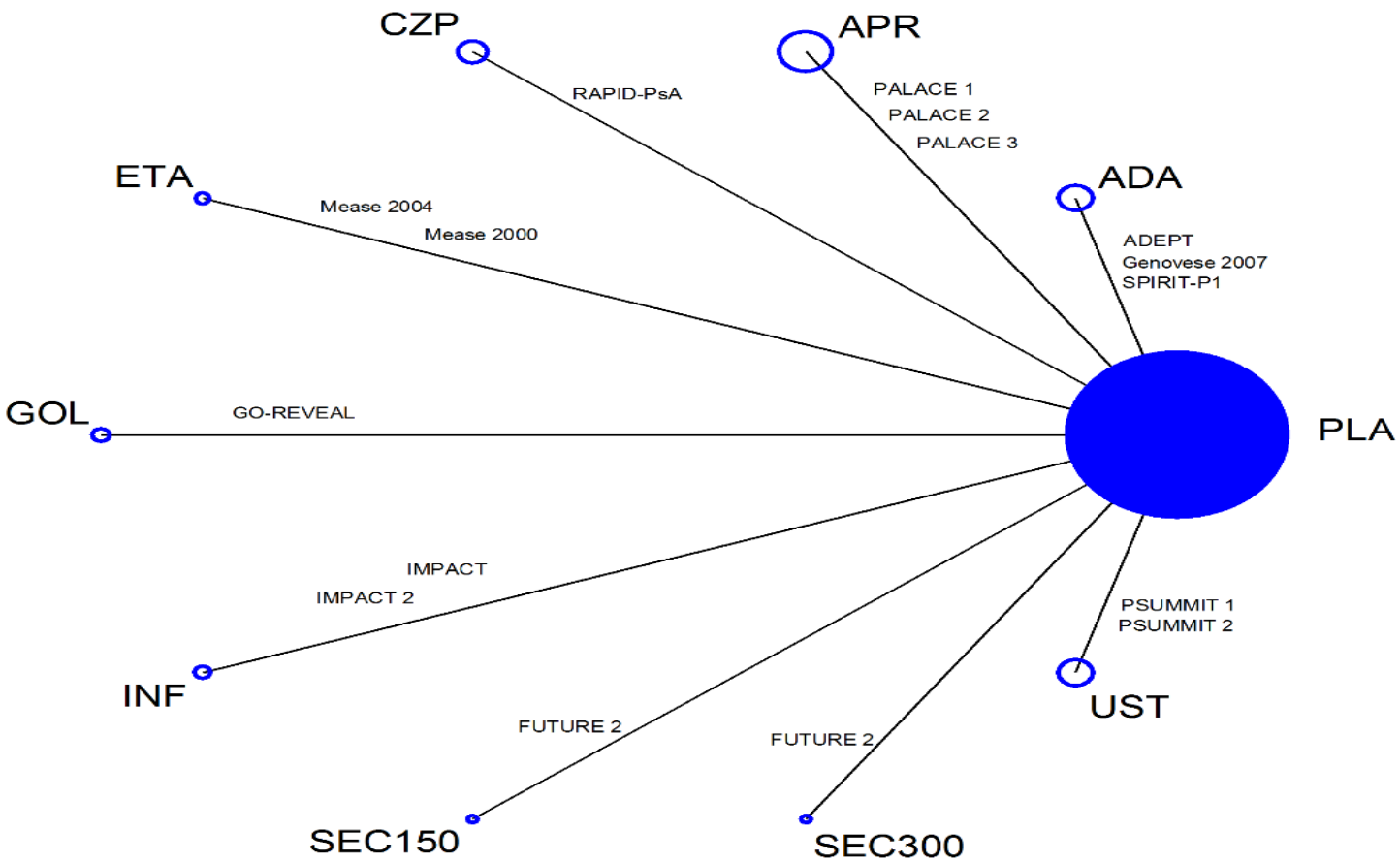
AG report

- The AG conducted a systematic review of short term efficacy:
  - 19 RCTs eligible used to generate short term efficacy for network meta-analysis:
    - 5 eligible pivotal RCTs: 4 for SEC, 1 of CZP (same evidence presented by companies)
      - demonstrated statistically significant improvements in all key clinical outcomes, as well as in HRQoL measures and the resolution of enthesitis and dactylitis
      - but it is not possible to make robust conclusions about any difference in efficacy of these drugs across subgroups (based on previous biologic experience)
    - 14 RCTs including comparators from the NMA (see slide 29)

Source: adapted from section 4.3 p.153 from AG's report

AG network meta-analysis (not outcome or subgroup specific)

AG report



3 outcomes included in the NMA to inform the economic model:

- PsARC response
- change of HAQ score conditional on PsARC response
- PASI 50, 75 and 90 responses

Some additional outcomes were analysed: ACR 20, 50 and 70 responses

ADA=adalimumab 40 mg; APR=apremilast 30mg; CZP=certolizumab pegol; ETA=etanercept 25mg; GOL=golimumab 50mg; INF=infliximab 5mg mg/kg; PLA=placebo; SEC150= secukinumab 150 mg; SEC300=secukinumab 300mg; UST=ustekinumab 45mg

Network meta-analysis (NMA) description

AG report

- Companies conducted their own NMAs, but the AG also developed its own network
- AG's analyses were performed for the biologic naive and experienced subgroups separately
  - ***Biologic naive population network:*** insufficient data to subdivide biologic naïve patients into those who have failed one conventional DMARD and those who have failed two conventional DMARDs, as per NICE scope; rate of placebo response was identified as source of heterogeneity thus several models were explored
    - an independent model was developed (with no baseline adjustment)
    - a model that include meta-regression on baseline risk for placebo effects (to explore placebo response as treatment effect modifier) for PsARC, PASI and ACR outcomes; and within this, whether there was similarity between treatment effects for treatments of the same class (to explore treatment effects as class)
    - For each outcome, the preferred model and its clinical data used in the AG model are presented
  - ***Biologic experienced network :*** exclusion of CZP treatment data in the NMA as the definition of treatment experienced patients in RAPID PsA was different from other trials
- Data from the 12 week time point were used where available, otherwise data relating to the closest time point after 12 weeks were used (14 or 16 weeks) and assumed equivalent to outcomes at 12 weeks
- Assumption of homogeneity/exchangeability between all the trials included in the NMA

Source: adapted from section 5 p.133 from AG's report

pre-meeting briefing document

Probability of PsARC response in biologic experienced patients

- PsARC response data available from 3 trials for 3 active treatments
- No class effect assumption was made because of data limitation
- Exclusion of data from CZP (see slide 30)

	Probability	Odd ratio	Treatment effects (Log odds)
treatments	**Median (95% CrI)**	**Median (95% CrI)**	**Median (95% CrI)**
Placebo	0.266 (0.19 to 0.36)	-	-1.013 (-1.48 to -0.58)
SEC300	0.686 (0.41 to 0.88)	6.033 (2.15 to 18.39)	1.797 (0.77 to 2.91)
UST	0.566 (0.35 to 0.76)	3.559 (1.68 to 7.76)	1.279 (0.53 to 2.07)

Source: adapted from table 45 in AG report

pre-meeting briefing document

Probability of PsARC response in biologic naïve patients

- PsARC response data available from 14 trials for 9 active treatments
- The 2 models presented were preferred by the AG (both used in AG's model)

	Not adjusted for placebo response, independent treatment (Model A1)		Adjusted for placebo response, class effects assumed (Model D2)*	
	Probability	Odd ratio	Probability	Odd ratio
treatments	Median (95% CrI**)	Median (95% CrI**)	Median (95% CrI**)	Median (95% CrI**)
Placebo	0.31 (0.26 to 0.36)		0.31 (0.26 to 0.36)	
SEC300	0.59 (0.40 to 0.76)	3.25 (1.56 to 6.89)	0.73 (0.57 to 0.86)	6.25 (3.15 to 13.31)
SEC150	0.59 (0.40 to 0.76)	3.24 (1.54 to 6.96)	0.73 (0.57 to 0.86)	6.18 (3.10 to 13.30)
UST	0.49 (0.38 to 0.60)	2.13 (1.49 to 3.07)	0.59 (0.48 to 0.70)	3.24 (2.25 to 4.86)
CZP	0.57 (0.44 to 0.69)	2.99 (1.88 to 4.81)	0.71 (0.60 to 0.81)	5.56 (3.59 to 9.11)
GOL	0.82 (0.71 to 0.90)	10.37(5.87 to 18.98)	0.71 (0.58 to 0.81)	5.54 (3.23 to 9.06)
ADA	0.64 (0.53 to 0.75)	4.06 (2.70 to 6.21)	0.60 (0.49 to 0.69)	3.33 (2.30 to 4.70)
INF	0.81 (0.71 to 0.89)	9.93 (5.91 to 17.06)	0.74 (0.63 to 0.83)	6.52 (4.18 to 10.04)
ETA	0.77 (0.65 to 0.86)	7.71(4.53 to 13.58)	0.74 (0.64 to 0.82)	6.50 (4.38 to 9.85)
APR	0.50 (0.41 to 0.59)	2.26 (1.73 to 2.94)	0.49 (0.41 to 0.57)	2.16 (1.76 to 2.64)

*Shrunken estimates are reported to account for the differences between treatments; **CrI, Credible Interval

Source: adapted from table 43 in AG report

HAQ changes conditional on PsARC response/non-response in biologic naïve patients

- HAQ changes data available from 13 trials for 9 active treatments
- The 2 models presented were preferred by the AG, results are considered similar (both used in AG's model)

	Not adjusted, independent treatment (Model E1)		Not adjusted, allowed exchangeability within classes (Model E2)*	
treatments	**PsARC resp vs. non-resp (median)**	**r****	**PsARC resp vs. non-resp (median)**	**r****
Placebo	-0.26	10	-0.26	10
SEC150	-0.31	8	-0.35	8
SEC300	-0.49	1	-0.43	3
UST***	-0.39	4	-0.39	4
CZP	-0.36	6	-0.35	7
GOL***	-0.38	5	-0.37	5
ADA	-0.36	7	-0.37	6
INF***	-0.46	2	-0.46	1
ETA	-0.44	3	-0.45	2
APR	-0.27	9	-0.27	9

*Shrunken estimates are reported to account for the differences between treatments; **r: ranking of treatments according to point estimates; ***outcome data for GOL and INF at 14-16 weeks, and UST at 24 weeks were included in the analysis and assumed equivalent to outcomes at 12 weeks

Source: adapted from table 47 in AG's report

HAQ changes conditional on PsARC response/non-response in biologic experienced patients

- HAQ changes data available from 3 trials for 3 active treatments
- No class effect assumption was made because of data limitation
- Exclusion of data from CZP (see slide 30)

	HAQ changes in PsARC response in relation to PNR		HAQ changes in PsARC non response in relation to PNR	
	Mean	**Median (95% CrI)**	**Mean**	**Median (95% CrI)**
Placebo/ baseline effect	-0.134	-0.134 (-0.288 to 0.021)		
SEC300	-0.385	-0.385 (-0.624 to -0.145)	-0.431	-0.430 (-0.880 to 0.014)
UST	-0.320	-0.320 (-0.552 to -0.086)	0.003	0.002 (-0.269 to 0.274)

Abbreviations: PNR, placebo non-responders

Note: outcomes data at 24 week were included in the analysis and assumed equivalent to outcomes at 12 weeks

Source: adapted from table 49 in AG report

pre-meeting briefing document

PASI in biologic naïve patients

- PASI data available from 13 trials for 9 active treatments
- The model presented was preferred by the AG (used in AG's model)

	Independent treatment, unadjusted for placebo response (Model F1)		
	PASI50	**PASI75**	**PASI90**
	Median (95% CrI)	**Median (95% CrI)**	**Median (95% CrI)**
Placebo	0.153 (0.13 to 0.18)	0.054 (0.04 to 0.07)	0.015 (0.01 to 0.02)
SEC300	0.819 (0.61 to 0.94)	0.627 (0.38 to 0.84)	0.405 (0.19 to 0.67)
SEC150	0.801 (0.59 to 0.93)	0.603 (0.36 to 0.82)	0.380 (0.18 to 0.63)
CZP	0.441 (0.31 to 0.59)	0.231 (0.14 to 0.36)	0.097 (0.05 to 0.18)
UST	0.544 (0.44 to 0.65)	0.317 (0.23 to 0.42)	0.149 (0.09 to 0.22)
GOL	0.732 (0.58 to 0.86)	0.514 (0.35 to 0.68)	0.297 (0.17 to 0.47)
ADA	0.675 (0.55 to 0.78)	0.448 (0.32 to 0.58)	0.242 (0.15 to 0.36)
INF	0.918 (0.84 to 0.96)	0.789 (0.67 to 0.88)	0.593 (0.44 to 0.73)
ETA	0.411 (0.15 to 0.72)	0.209 (0.05 to 0.50)	0.084 (0.01 to 0.29)
APR	0.391 (0.31 to 0.49)	0.195 (0.14 to 0.27)	0.077 (0.05 to 0.12)

Note: outcomes data at 24 week were included in the analysis and assumed equivalent to outcomes at 12 weeks; all trials reported PASI50 and PASI75 except PSUMMIT 2 (UST) and SPIRIT-P1 (ADA) trials which did not report PASI50, a few trials did not report PASI90 (i.e. PALACE trials, RAPID-PsA, Mease 2000 and PSUMMIT 2).

Source: adapted from tables 53 in AG's report

PASI in biologic experienced patients

- PASI data available from 3 trials for 3 active treatments
- No class effect assumption was made because of data limitation
- Exclusion of data from CZP (see slide 30)

	Probability of achieving			
	Treatment effect on probit scale Median (95% CrI)	**PASI50 Median (95% CrI)**	**PASI75 Median (95% CrI)**	**PASI90 Median (95% CrI)**
Placebo	1.354 (0.59 to 2.19)	0.088 (0.01 to 0.28)	0.012 (0.00 to 0.06)	0.002 (0.00 to 0.02)
SEC300	-2.509 (-4.01 to -1.23)	0.875 (0.46 to 1.00)	0.598 (0.23 to 0.89)	0.365 (0.08 to 0.75)
UST	-1.659 (-2.73 to -0.83)	0.628 (0.29 to 0.89)	0.279 (0.07 to 0.61)	0.120 (0.01 to 0.42)

Source: adapted from tables 55 in AG's report

pre-meeting briefing document

ACR response in biologic naïve patients

- ACR responses available from 15 trials for 9 active treatments
- The 2 models presented were preferred by the AG (both used in AG's model)

	Not adjusted for placebo response, independent treatment (Model H1)			Adjusted for placebo response, class effects assumed (Model K2)*		
	ACR20	ACR50	ACR70	ACR20	ACR50	ACR70
Treat-ments	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)
Placebo	0.17 (0.15, 0.19)	0.05 (0.04, 0.06)	0.01 (0.01, 0.02)	0.17 (0.15, 0.19)	0.05 (0.04, 0.06)	0.01 (0.01, 0.02)
SEC300	0.49 (0.33, 0.64)	0.24 (0.14, 0.38)	0.09 (0.04, 0.18)	0.61 (0.46, 0.75)	0.35 (0.22, 0.50)	0.16 (0.08, 0.27)
SEC150	0.49 (0.34, 0.65)	0.25 (0.14, 0.39)	0.10 (0.04, 0.19)	0.61 (0.46, 0.75)	0.35 (0.22, 0.51)	0.16 (0.08, 0.27)
UST	0.35 (0.27, 0.44)	0.15 (0.10, 0.21)	0.05 (0.03, 0.08)	0.41 (0.34, 0.49)	0.19 (0.14, 0.25)	0.07 (0.04, 0.10)
CZP	0.44 (0.34, 0.55)	0.21 (0.14, 0.30)	0.08 (0.04, 0.13)	0.58 (0.49, 0.69)	0.33 (0.24, 0.43)	0.14 (0.09, 0.22)
GOL	0.68 (0.55, 0.80)	0.43 (0.30, 0.57)	0.21 (0.12, 0.33)	0.53 (0.40, 0.66)	0.28 (0.18, 0.40)	0.11 (0.06, 0.19)
ADA	0.55 (0.47, 0.62)	0.29 (0.23, 0.36)	0.12 (0.09, 0.17)	0.56 (0.50, 0.63)	0.31 (0.26, 0.37)	0.13 (0.10, 0.17)
INF	0.75 (0.65, 0.83)	0.50 (0.39, 0.62)	0.27 (0.18, 0.38)	0.62 (0.51, 0.72)	0.36 (0.26, 0.47)	0.17 (0.10, 0.24)
ETA	0.66 (0.55, 0.76)	0.40 (0.29, 0.52)	0.19 (0.12, 0.29)	0.61 (0.51, 0.69)	0.35 (0.27, 0.43)	0.16 (0.11, 0.21)
APR	0.33 (0.27, 0.39)	0.13 (0.10, 0.17)	0.04 (0.03, 0.06)	0.35 (0.30, 0.41)	0.15 (0.12, 0.19)	0.05 (0.03, 0.07)

Note: outcomes at 14 and 16 weeks were included in the analysis and assumed equivalent to outcomes at 12 weeks; all 15 trials reported all three categories of ACR response (20/50/70)

*Shrunken estimates are reported to account for the differences between treatments

Source: adapted from tables 59 in AG's report

ACR response in biologic experienced patients

- ACR responses available from 15 trials for 9 active treatments
- No class effect assumption was made because of data limitation
- Exclusion of data from CZP (see slide 30)

	Probability of achieving			
	Treatment effect on probit scale Median (95% CrI)	**ACR20 Median (95% CrI)**	**ACR50 Median (95% CrI)**	**ACR70 Median (95% CrI)**
Placebo	1.06 (0.76, 1.38)	0.14 (0.08, 0.22)	0.03 (0.01, 0.06)	0.01 (0.00, 0.02)
SEC300	-0.71 (-1.36, -0.08)	0.36 (0.19, 0.57)	0.11 (0.04, 0.25)	0.03 (0.01, 0.11)
UST	-0.85 (-1.34, -0.37)	0.42 (0.26, 0.59)	0.14 (0.06, 0.27)	0.05 (0.01, 0.12)

Source: adapted from table 61 in AG's report

	Key findings of the NMA	
	Biologic naïve	**Biologic experienced**
PsARC response	• Uncertain relative effectiveness of SEC and CZP vs. other biologics and with each other • SEC and CZP seem more effective than APR	• CZP excluded, only SEC and UST included in analyses • SEC and UST significantly more effective than placebo in all outcomes • SEC may be better than UST although uncertainty
HAQ conditional on PsARC response	• Results from adjusted model similar to unadjusted • Significant reductions in mean HAQ score with response to all nine treatments and response to placebo (improvement in response to placebo is < minimum clinically significant threshold for PsA of -0.35) • Highest median HAQ change with INF and ETN, followed by SEC300 mg, but SEC150 mg and CZP were worse than all treatments except for APR	
PASI	• Uncertain difference between treatment • Adjusted results (for placebo response): highest probabilities of achieving PASI 50,70 and 90 responses for SEC 300 • Probabilities of achieving PASI 50,70 and 90 responses for CZP lower than all other treatments except APR and ETN	
ACR	• Uncertain difference between treatment • Unadjusted results: lower probabilities of response than other biologics for SEC and CZP • Adjusted results (for placebo response): increased probabilities of response for SEC and CZP	

Source: adapted from section 5.6 p.156 in AG's report

Long-term efficacy of CZP (Rapid PsA) and SEC (FUTURE 2)

UCB and Novartis submissions

- Open label extension studies FUTURE 2 (to 52 weeks) and RAPID PsA (to 216 weeks)
- Patients who were responders at 12 or 16 weeks appear to be the most clinically relevant and useful (for the dichotomous outcomes), although such data were only available for CZP and SEC
- Radiographic assessments of joint damage
  - FUTURE 1 indicates that, after two years of treatment, SEC effectively reduces disease progression with results being similar to those observed in the open-label studies of the other anti-TNFs
  - For SEC, fewer result details were available at two years although the results also indicated effective reduction in radiographic disease progression

Source: adapted from section 4.7 p 102 from AG's report

Adverse reactions

Company submissions and AG report

Occurrence of adverse events (AE)	RAPID-PSA (CZP, 24 week period)		FUTURE 2 (SEC, 16 week period)	
	CZP pooled	Placebo	SEC pooled	Placebo
Overall	28%	27%	54%	58%
Mild AEs	51%	54%	[redacted]	[redacted]
Moderate AEs	30%	36%	[redacted]	[redacted]
Severe AEs	6.6%	4.4%	1.7%	0%
Most common AE are [redacted]	[redacted]	[redacted]	[redacted]	7% 8%

- From AG systematic review:
  - Additionally, results from 3 systematic reviews suggested that CZP was associated with statistically significantly more serious AEs and serious infections when compared with placebo
  - SEC seems to have a favourable safety profile although there is uncertainty around SEC's safety because only a few trials are available

Source: adapted from section 4.10 p.128 from AG's report

Other efficacy outcome

Company submissions and AG report

- Treatment with CZP and SEC resulted in statistically significantly improvements in the resolution of both dactylitis and enthesitis.

Outcome mean change from baseline	RAPID-PSA (CZP, 24 week period)			FUTURE2 (SEC, 16 week period)		
	CZP 200 mg	CZP 400 mg	Placebo	SEC 150mg	SEC 300 mg	Placebo
Dactylitis count ±SD*	-40.7 ± 34.6	-53.5 ± 69.1	-22.0 ± 46.9	-3.1 ± 4.5	-2.3 ± 4.0	-0.6 ± 2.4
Enthesitis count ±SD*	-2 ± 1.8	-1.8 ± 1.9	-1.1 ± 1.8	-1.5 ± 2.0	-1.7±1.8	-0.9 ± 2.1

*SD, standard deviation

Source: adapted from tables 15 and 28 from AG's report

Health-related quality of life (HRQoL)

UCB and Novartis submissions

- RAPID PsA (CZP) and FUTURE2 (SEC) reported HRQoL using EQ-5D and SF-36. Treatment with CZP and SEC resulted in statistically significantly improvements in health-related quality of life measures
- CZP:
  - At week 12, EQ-5D VAS scores were higher in CZP treated groups
  - At week 24, there was a significant improvement with pooled CZP in all domains of the SF-36 regardless of the dose regimen and prior TNF inhibitor status.
- SEC:
  - At week 24, SEC 150 mg and 300 mg were better than placebo for improving EQ-5D overall health state
  - At week 24, there were greater improvements with SEC 150 and 300mg in self-reported quality of life and physical functioning compared to placebo as measured by SF36-PCS scores.

Source: adapted from section 4.4.1 p.86 and 4.5.3 p.89 p.95 from AG's report

Summary of AG comments of CZP and SEC trials

- RAPID-PsA and FUTURE 2 had low overall risk of bias
- Results demonstrated short-term efficacy of CZP and SEC in treating PsA
  - Full trial population: CZP and SEC was associated with statistically significant improvements in all key outcomes
  - Subgroups: no reliable conclusions in efficacy results because of low numbers of placebo patients in the biologic-experienced subgroup coupled with higher placebo response rates in the biologic-naïve subgroup
  - Similar efficacy between 1 prior cDMARD group and all biologic naïve subgroup at 24 weeks
- Variation across trials with respect to previous biologic use:
  - Populations recruited in clinical trials have changed over time, with earlier trials excluding biologic-experienced patients and later trials including them
  - RAPID-PsA trial (CZP) was more selective than the FUTURE 2, PSUMMIT 2 and PALACE trials in recruiting its biologic-experienced patients
- Increase of placebo response rates over time across in all trials, not justified by the baseline characteristics

Source: adapted from section 4.4.4 p.89, 4.5.4 p 96 and 4.6 p.98 from AG's report

Summary of registry studies

- AG conducted searches for patient registry studies
  - Patients taking biologics
    - Expected benefit from anti-TNFs diminishes after switching, with a reduced chance of response and reduced drug survival (from 12 studies reporting data on drug survival and switching of anti-TNFs)
    - Treatment with anti-TNFs seems to be associated with improvement on radiographic progression and HAQ score (although only 4 studies and uncertainty around measure used to estimate HAQ change)
  - Patients not taking biologics
    - Paucity of observational data on natural history of PsA
    - In patients with PsA who do not receive any treatment, HAQ change over time is yet to be properly measured

Key clinical issues (I)

- What is the Committee's view on the 'placebo creep' (placebo response rates appear to have increased over time) and its impact on the indirect comparison?
- What is the Committee's view on the exclusion of certolizumab pegol treatment data from the biologic experienced network?
- A class effect has been considered between apremilast and secukinumab although they have distinct mechanism of action (targets IL-17A vs. target p40 of IL-12 and IL-23). What does the Committee think of the relevance of the class effect?
- What is the Committee's view on the safety profile of both certolizumab pegol and secukinumab based on the long-term studies and the systematic review conducted by the Assessment Group?
- What is the Committee's view in considering the subgroups by psoriasis severity as the base case populations?
- What is the Committee's view on the inclusion of BSC as a comparator for subpopulation 1 (patients who have failed 1 DMARD)?
- What is the Committee's view on the limitations of the long-terms studies of SEC and CZP's with regards to efficacy and safety?

COST EFFECTIVENESS

Note: results in part 1 do NOT reflect the unapproved and approved patient access schemes for CZP or SEC respectively. Please see AG's confidential appendix for PAS vs. PAS ICERS

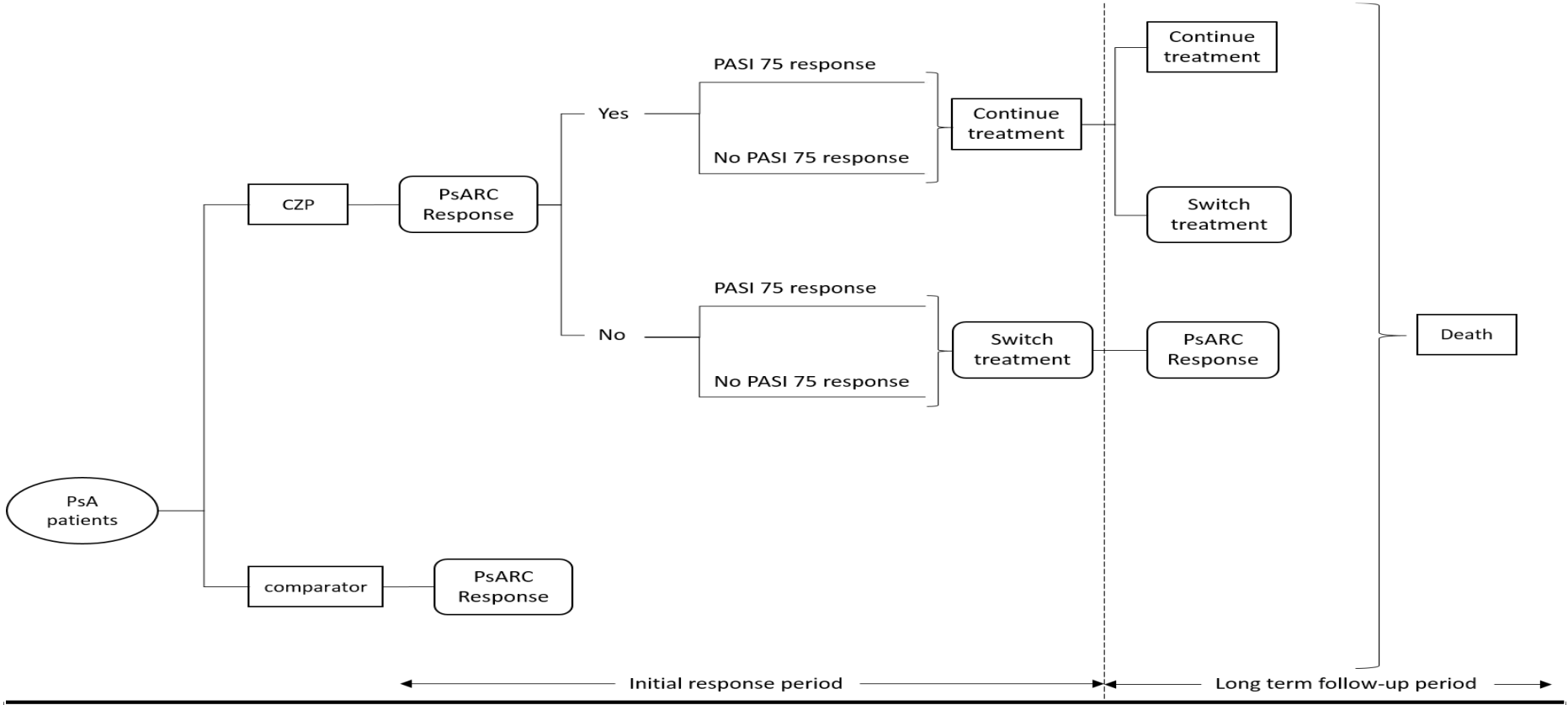
Key cost effectiveness issues

- Are the following inputs and assumptions in the AG model considered reasonable?
  - After withdrawal, the “rebound” of HAQ and PASI is assumed to be equivalent to the gain
  - The use of the York algorithm to generate utilities when both RAPID-PsA and FUTURE 2 collect EQ-5D data
  - PsARC repsonses and PASI75 assumed to be correlated
  - Change in baseline HAQ score assumed to be conditional on PsARC response status
  - Use of Poole et al. study as a source for disease management costs, given the fact that costs are being derived from comparable patients with PsA (rather than deriving costs from a RA population and adding separate assumptions for PASI costs).

COMPANIES' MODELS

1- UCB, CERTOLIZUMAB
2- NOVARTIS, SECUKINUMAB

UCB model structure for CZP

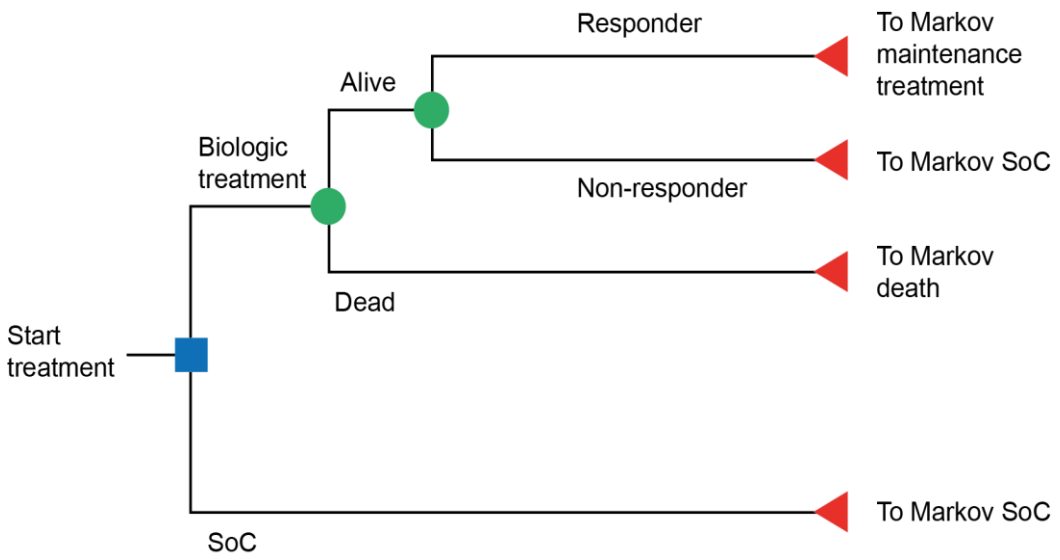


- Cohort Markov model with 3 periods
  - short-term, in which the initial response to treatment is determined (12 or 24 weeks depending on the treatment)
  - treatment continuation (up to 36 weeks post initial response)
  - long term period (50 years)
- 3 subgroups: only one prior cDMARD, all biologics-naïve, anti-TNF experienced

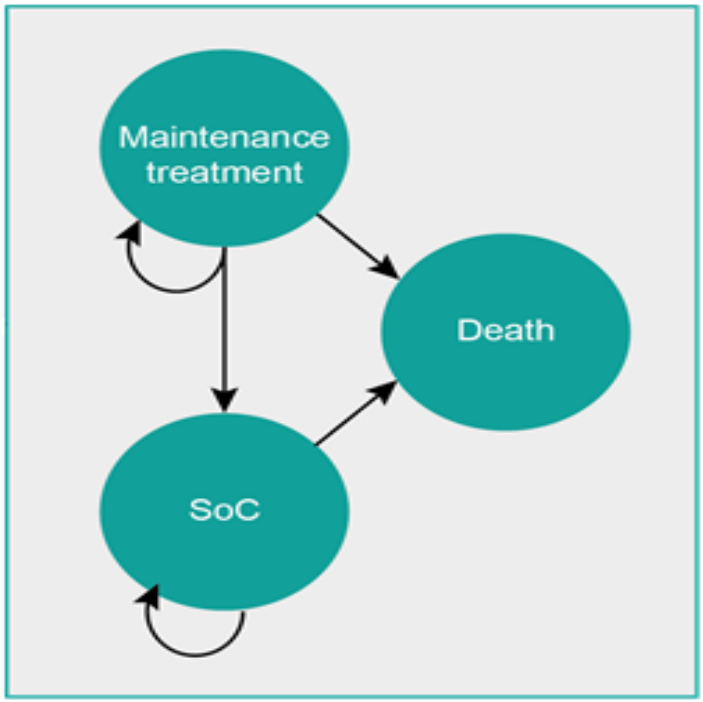
Source: adapted from figure 10 in AG's report

NOVARTIS model structure for SEC

Decision tree structure



Markov model structure (base case)



- Short-term (3-month) decision-tree, leading into a long-term (40 year) Markov cohort model
- 3 subgroups: biologic-naïve (1 prior cDMARD), biologics-naïve (≥2 prior DMARDs), biologic-experienced

Source: adapted from figure 11 in AG's report

Key differences between Novartis and UCB models (I)

	Novartis submission	UCB submission

Struc-ture	• Response defined at 3 months by PsARC and PASI 75
	  • consistent with previous NICE appraisal and BSR/BHPR guidelines and to maximise the data included in the NMA
	• HAQ improvement in responding patients derived from trial data at 12-16 week time period and assumed to remain constant from 3 months
	• For patients that withdraw from treatment, PASI and HAQ both rebounds back to the baseline value in the cycle after stopping active treatment.
	• Withdrawal rate data from FUTURE 2 for 1st year and subsequent year
		• Response defined at 24 weeks by PsARC
		  • based on EULAR (2011) guidelines
		  • 3 months used in sensitivity analysis
		• HAQ improvements in responding patients derived from week 4 trial data for the initial 9 months after which HAQ gain remains constant
		• For patients that withdraw from treatment, PASI rebounds back to the baseline value in the cycle after stopping active treatment, but HAQ rebounds to a worse position.
		• Withdrawal rate applied same as York model for initial 4 years only
		  • lack of longer term evidence reported for withdrawal

Seque ncing	• Not addressed in the base case analysis. Included as a scenario in which patients move to a subsequent "basket" of biologics before switching to SoC. This was applied only in the anti TNF naïve population.	• Full sequence model of biologics followed by the mix of palliation, the sequence differs based on the subpopulation, ranging from one to three lines of treatments. Switching can only occur in the first four years, after which patients remain on treatment indefinitely, accounting for mortality.

Key differences between Novartis and UCB models (II)

	Novartis submission	UCB submission
Pop.	Subpopulation 2 defined in accordance with NICE scope Subpopulation 3 include only biologic experienced patients and therefore do not include people who are contraindicated to biologic therapies	Subpopulation 2 defined as "all-biologic naïve" people Subpopulation 3 include only biologic experienced patients and therefore do not include people who are contraindicated to biologic therapies
Patient inputs	HAQ and PASI score: FUTURE2 use baseline average characteristics assuming a PASI≤10 or PsA patient with concomitant mild to moderate psoriasis • Baseline HAQ = [redacted] • Baseline PASI = [redacted] These baseline values were applied to each of the 3 subpopulations	HAQ and PASI score: RAPID-PsA use baseline average characteristics assuming a PASI>10 or PsA patient with concomitant moderate to severe psoriasis <u>Biologic naïve (1 prior DMARD):</u> • Baseline HAQ = [redacted] • Baseline PASI = [redacted] <u>Biologic naïve (1 or more prior DMARDs)</u> • For anti TNF naïve pop baseline HAQ = 1.29 • Baseline PASI = 11.58 <u>Biologic experienced</u> • Baseline HAQ = 1.37 • Baseline PASI = [redacted]

Key differences between Novartis and UCB models (III)

	Novartis submission	UCB submission
Costs	• Costs associated with HAQ and PASI based on the same sources and assumptions previously used in the York model (Kobelt et al.)	• Costs based on a separate study by Poole et al • PsA population included was more appropriate than deriving costs based on a RA population and employing separate assumptions for PASI costs.
Utilities	• Algorithm derived from patient-level data of FUTURE2 in which utility is a function of HAQ, PASI, age, gender and anti-TNF response state.	• Algorithm derived from patient-level data of RAPID-PsA in which utility is a function of HAQ and PASI

Abbreviations: BHRP/BSR, British Society for Rheumatology/British Health Professionals in Rheumatology; DMARD, disease-modifying antirheumatic drugs; HAQ, Health Assessment Questionnaire; NMA, network meta-analysis; PASI, Psoriasis Area Severity Index ; PsARC, psoriatic arthritis response criteria; SoC, standard of care; TNF, tumor necrosis factor

Source: adapted from table 65 in AG's report

Base case result for subpopulation 1

Subpopulation 1 (Novartis and UCB): biologic naïve - 1 prior DMARD

UCB submission

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
cDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	-
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£23,666

Novartis submission

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC*	[redacted]	[redacted]	[redacted]	[redacted]	-
SEC 150	[redacted]	[redacted]	[redacted]	[redacted]	£12,189

*SoC is defined as 100% use of methotrexate, dose 25mg per week

Source: adapted from tables 72 and 73 in AG's report

Base case result for subpopulation 2

Subpopulation 2 (UCB): 1 or more prior DMARDs

UCB submission

Treatment	Total costs (£)	Total QALYs	Incremental costs vs next least costly interventions	Incremental QALYs vs next least costly interventions	ICER vs next least costly interventions (£)
CZP	[redacted]	[redacted]	[redacted]	[redacted]	-
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
SEC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
INF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Source: adapted from tables 74 in AG's report

Base case result for subpopulation 2

Subpopulation 2 (Novartis): 2 or more prior DMARDs

Novartis submission

Treatment	Total costs (£)	Total QALYs	Incremental costs vs next least costly interventions	Incremental QALYs vs next least costly interventions	ICER vs next least costly interventions	ICER vs. next least costly intervention
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
SEC 150	[redacted]	[redacted]	[redacted]	[redacted]	£10,549	£10,549
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£28,432	Dominated by SEC
ETN	[redacted]	[redacted]	[redacted]	[redacted]	£31,280	Dominated by SEC
GOL	[redacted]	[redacted]	[redacted]	[redacted]	£33,802	Dominated by SEC
ETN	[redacted]	[redacted]	[redacted]	[redacted]	£32,706	Dominated by SEC
INF	[redacted]	[redacted]	[redacted]	[redacted]	£53,223	£220,558

Source: adapted from tables 75 in AG's report

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Base case result for subpopulation 3

Subpopulation 3 (Novartis and UCB): biologic experienced

UCB submission

Treatment	Total costs(£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Mix*	[redacted]	[redacted]	[redacted]	[redacted]	-
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£8,894
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by CZP
SEC 300mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by CZP

*Mix is a mixture of cDMARDs and palliative care

Novartis submission

Treatment	Total costs(£)	Total QALYs	Incremental costs vs SoC(£)	Incremental QALYs vs SoC	ICER vs. SoC (£)	ICER vs. next least costly intervention
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£29,538	Extendedly dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£37,228	Extendedly dominated
SEC 300	[redacted]	[redacted]	[redacted]	[redacted]	£27,562	£27,562

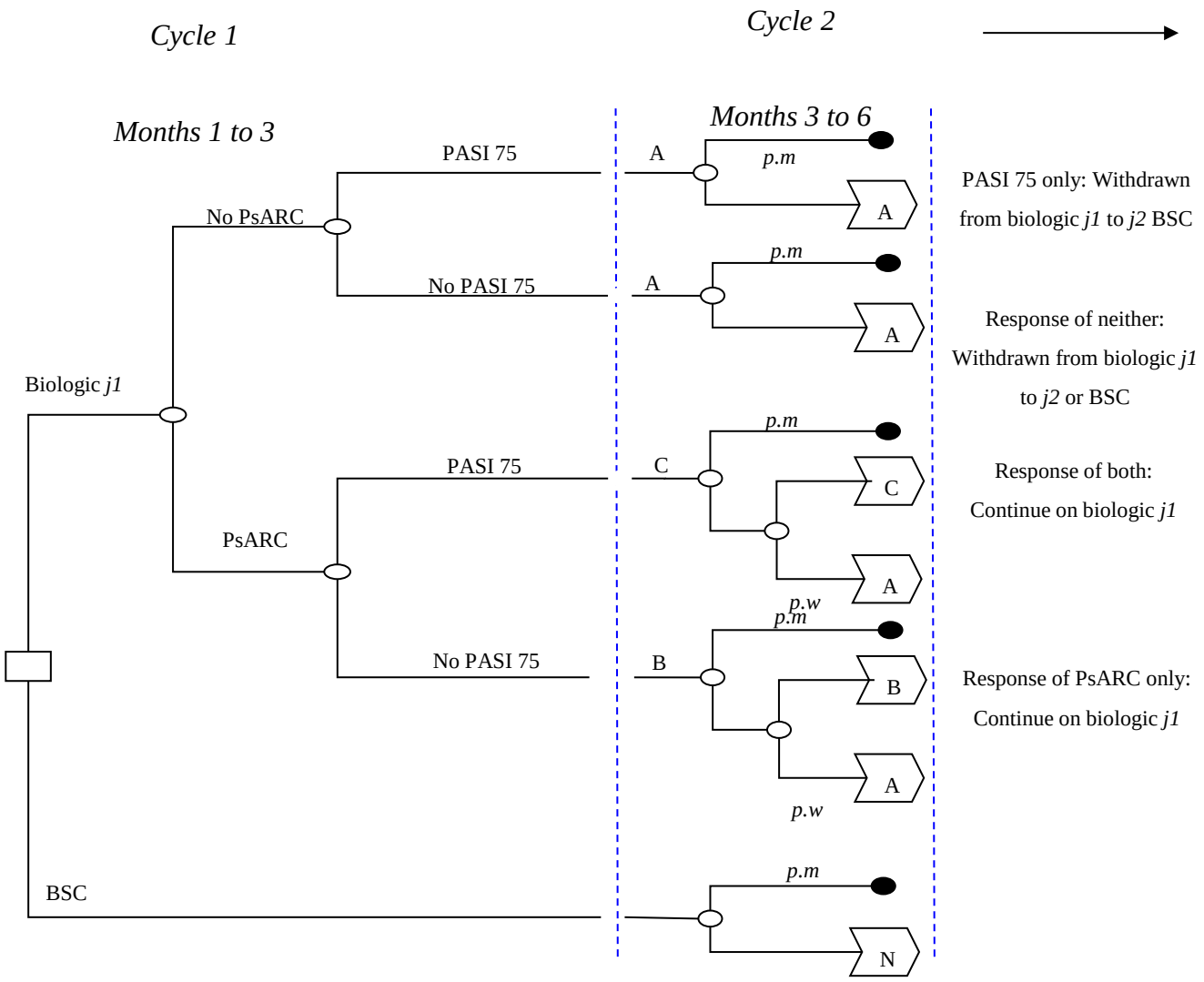
Source: adapted from tables 76 and 77 in AG's report

AG's critique of UCB and Novartis models

- Differences in approaches and data sources
- No comparison possible between subpopulations
- Lack of consistency with previous NICE technology appraisals for Novartis results (subpopulations 1 and 2); UCB's results for subpopulation 3 are consistent with previous NICE technology appraisals
- Contradictory findings reported for several of the subpopulations in terms of the relative cost-effectiveness of SEC and CZP
- Neither company incorporated the full range of interventions and comparators as stated in the NICE final scope across all three subpopulations
- Uncertainty regarding both the cost-effectiveness of SEC and CZP in each subpopulation and potential implications for the NHS

ASSESSMENT GROUP (AG) MODEL

AG model structure



- Markov cohort model with 3-monthly cycles
- Costs and HRQoL differ by state
- lifetime horizon (40-years)
- NHS and PSS perspective
- Costs and outcomes discounted at an annual rate of 3.5%
- BSC is a mix of cDMARDs and palliative care

Key: A – Withdrawn from biologic *j1* to *j2* or BSC. B – Continue on biologic *j1* with response of arthritis but not of psoriasis. C – Continue on biologic *j* with response of both arthritis and psoriasis. N – No treatment.
P.m – Probability of mortality (any cause) P.w – Probability of withdrawal from biologic after first 3 months.

Source: adapted from figure 15 in AG report

AG model description

Update of the previous York model (TA199) - structure similar but a few key differences:

- inclusion of subsequent treatments following primary lack of response or secondary failure
- models all subpopulations specified in the NICE scope, including patients contraindicated to existing biologic treatments (subpopulation 4).
- subpopulation 4 patient population:
  - exclusion of CZP because it was assumed that patients that are contraindicated to other TNF-alpha inhibitors are also contraindicated to CZP
  - SEC, UST, BSC included as comparators
  - patients likely to be a combination of biologic naïve and biologic experienced who have experienced a significant AEs; however because of lack of effectiveness data specific to these patients, analysis was undertaken using biologic naïve population
- takes into account heterogeneity in terms of baseline PASI with results for 3 subgroups within each subpopulation:
  - PsA without concomitant psoriasis
  - PsA with concomitant mild to moderate psoriasis (≥3% of BSA and PASI ≤10)
  - PsA with concomitant moderate to severe psoriasis (≥3% of BSA and PASI >10).

Source: adapted from section 7.2 and 7.3 p. 197 in AG's report

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Model assumptions

- Response defined as PsARC response, only PsARC response used to determine continuation on treatment
- Correlation between PsARC response and HAQ score
- Adjustment for placebo response (same methods employed in the previous York model for TA199)
- Probability of withdrawal due to AEs or loss of efficacy are assumed to be independent of HAQ and PASI scores, and constant over time (0.165 per year)
  - After withdrawal, the “rebound” of HAQ and PASI is assumed to be equivalent to the gain
- Effectiveness used in the economic model utilises 2 combinations of results (independent analysis and meta-regression) of PsARC response, HAQ conditional on PsARC response and PASI response. Means (instead of medians) are used in order to inform a decision regarding the expected cost-effectiveness of competing treatment (see section 7.2.6.4 p.210 in AG’s report)

Source: adapted from section 7.2.2 p. 199 in AG’s report

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HRQoL

- HRQoL measured as a function of HAQ and PASI
- It is assumed that HAQ and PASI capture all the relevant information regarding a PsA patient's quality of life (based on previous York model for TA 199), therefore these 2 functions, at each cycle of the model, must be mapped onto the utility scores associated with particular HAQ and PASI combinations in order to generate an estimate of the lifetime QALYs for each of the treatments.
- No published sources offered a mapping function that would allow the disease specific measure (HAQ and PASI) or be mapped onto a utility score. Therefore the existing York algorithm was used in the model.
- Utility changes based on the York algorithm
  - Applied to all subpopulations, subgroups and treatments
  - No separate scenarios as very similar to the previous York model

$$Expected\ Utility = 0.897 - 0.298 * HAQ - 0.004 * PASI$$

Source: adapted from section 7.2.8 p. 214 in AG's report

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Resources & costs (list prices)

Agent	Annual costs							
	1st cycle (13 weeks)				Subsequent cycles			
	Acquisition *(biosimilar)*	Administration	Monitoring	Total	Acquisition *(biosimilar)*	Administration	Monitoring	Total
ETN	£2,332 *(2,139)*	£43	£166	£2,541	£2,332 *(2,139)*	0	£4	£2,336
INF	£7,147 *(6,432)*	£574	£166	£7,887	£3,395 *(3,056)*	£273	£4	£3,672
ADA	£2,297	£43	£166	£2,506	£2,297	0	£4	£2,301
GOL	£2,289	£43	£166	£2,498	£2,289	0	£4	£2,293
CZP	£3,575	£43	£166	£3,784	£2,145	0	£4	£2,149
SEC 150	£4,266	£43	£166	£4,475	£1,828	0	£4	£1,832
SEC 300	£8,532	£43	£166	£8,741	£3,656	0	£4	£3,661
UST	£4,294	£43	£166	£4,503	£2,147	0	£4	£2,151
Sources	MIMS BNF (MTX)	PSSRU	PSSRU		MIMS BNF (MTX)	PSSRU	PSSRU	

Source: adapted from table 83 in AG report

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Health state costs

- Data should report mean costs conditional on HAQ and PASI (see Appendix 12.11 of AG's report)
- Previous NICE TA 372 (apremilast) identified HAQ costs and/or PASI based on Poole et al. (only source of cost specific to PsA)
  - used in scenario analyses
- As base case, the final HAQ costs were based on the same function used in the previous York model
  - HAQ scores address only the arthritis component of PsA, therefore additional costs were required to capture the psoriasis element of the disease

Description	Without psoriasis	Mild to moderate	Moderate to severe
Baseline PASI	0.0	7.3	12.5
Costs of uncontrolled psoriasis (£)	0.0	223	638
Costs of controlled psoriasis (PASI75 response)	0.0	18	18
Source		NHS unit costs of phototherapy and a UK RCT	Dutch RCT adjusted to UK price levels (Hartman et al)

Source: adapted from table 83 in AG report

Application of price discounts

- CZP and SEC are being appraised by NICE in the context of this MTA, they both have Patient Access Scheme (PAS)
  - CZP: unapproved complex scheme
  - SEC: approved simple scheme
- Infliximab is available to the NHS at confidential contract prices agreed with the Commmercial Medicines Unit (CMU)
- Approved schemes have been incorporated in the base case cost-effectiveness analysis for the comparators ustekinumab and golimumab
- Because the PAS (for CZP and SEC) and the CMU contract price (for infliximab) are confidential, cost-effectiveness analyses in the AG report use the list prices for CZP, SEC and infliximab
  - *Note: these results are not reflective of the true cost effectiveness of CZP and SEC*
- In its confidential appendix, the AG has developed its base case using the confidential PAS for CZP (unapproved), SEC and the CMU contract price discount for infliximab.
- The results presented in this premeeting briefing document reflect list prices of the CZP, SEC and infliximab. Exact ICERs using the discount cannot be published for analyses which contain CZP or SEC as intervention or infliximab as comparator, to protect the confidentiality of the commerical discounts.
- The AG presented pairwise comparisons versus BSC, as well as comparison versus the next best option for 4 subpopulations. Therefore, for analyses which contain CZP and SEC as intervention or infliximab as comparator, incremental results with the PAS prices for CZP and SEC and the CMU contract price for infliximab are not available.

Independent analysis results (list price) – ICER analysis

Subpopulation 1: biologic naïve - 1 prior DMARD

	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC
Moderate – severe psoriasis						
BSC	£95,965	5.312	-	-	-	-
CZP	£159,951	8.377	£63,987	3.066	£20,870	£20,870
SEC 300*	£179,692	8.524	£19,741	0.146	£134,783	£26,064
Mild – moderate psoriasis						
BSC	£67,000	5.676	-	-	-	-
CZP	£135,946	8.667	-	-	D	£23,052
SEC 150*	£132,500	8.685	£65,500	3.009	£21,772	£21,772
No concomitant psoriasis						
BSC	£51,436	6.188	-	-	-	-
SEC 150*	£120,303	9.067	£68,866	2.878	£23,928	£23,928
CZP	£122,832	9.074	£2,529	0.007	£346,785	£24,744

* SEC 150 is licensed for no concomitant and mild to moderate psoriasis, SEC 300 is licensed for moderate to severe psoriasis

Source: adapted from tables 90-92 in AG's report

Summary of differences between independent and meta regression approaches (list price)

Subpopulation 1: biologic naïve - 1 prior DMARD

	ICERs vs BSC			Optimal treatment (£20,000)	Optimal treatment (£30,000)
	CZP	SEC 150*	SEC 300*		
Moderate – severe psoriasis					
Independent analysis	£20,870	-	£26,064	BSC	CZP
Meta regression	£19,908	-	£27,033	CZP	CZP
Mild – moderate psoriasis					
Independent analysis	£23,052	£21,772	-	BSC	SEC 150MG
Meta regression	£22,446	£21,287	-	BSC	SEC 150MG
No concomitant psoriasis					
Independent analysis	£24,744	£23,928	-	BSC	SEC 150MG
Meta regression	£24,388	£23,408	-	BSC	SEC 150MG

* SEC 150 is licensed for no concomitant and mild to moderate psoriasis, SEC 300 is licensed for moderate to severe psoriasis

Source: adapted from table 93 in AG's report

Independent analysis results (list price) – ICER analysis

Subpopulation 2: biologic naïve - 2 prior DMARDs

	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC
Moderate – severe psoriasis						
BSC	£95,965	5.312	-	-	-	-
CZP	£137,240	7.226	-	-	ED	£21,564
SEC 300mg	£157,086	7.379	-	-	D	£29,569
ADA	£138,109	7.411	£42,144	2.100	£20,074	£20,074
GOL	£142,850	7.637	£4,741	0.226	£20,976	£20,161
ETN	£144,585	7.719	£1,735	0.082	£21,215	£20,197
INF	£167,126	7.890	£22,541	0.171	£131,716	£27,599

* SEC 150 is licensed for no concomitant and mild to moderate psoriasis, SEC 300 is licensed for moderate to severe psoriasis

D = dominated, ED = extendedly dominated

Source: adapted from tables 94 in AG's report

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Independent analysis results (list price) – ICER analysis

Subpopulation 2: biologic naïve - 2 prior DMARDs

	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC
Mild – moderate psoriasis						
BSC	£67,000	5.676	-	-	-	-
CZP	£111,856	7.537			D	£24,103
SEC 150mg	£108,508	7.560	£41,508	1.884	£22,032	£22,032
ADA	£114,039	7.708			ED	£23,149
GOL	£119,624	7.923			D	£23,419
ETN	£119,326	8.025	£10,818	0.465	£23,256	£22,274
INF	£145,569	8.161	£26,243	0.136	£193,063	£31,616

* SEC 150 is licensed for no concomitant and mild to moderate psoriasis, SEC 300 is licensed for moderate to severe psoriasis

D = dominated, ED = extendedly dominated

Source: adapted from tables 95 in AG's report

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Independent analysis results (list price) – ICER analysis

Subpopulation 2: biologic naïve - 2 prior DMARDs

	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC
No concomitant psoriasis						
BSC	£51,436	6.188	-	-	-	-
CZP	£95,632	7.972	-	-	ED	£24,773
SEC 150mg	£98,060	7.974	-	-	ED	£26,105
ADA	£100,893	8.125	-	-	ED	£25,532
GOL	£106,895	8.325	-	-	D	£25,951
ETN	£105,592	8.456	£54,156	2.268	£23,883	£23,883
INF	£133,664	8.543	£28,071	0.087	£324,502	£34,930

* SEC 150 is licensed for no concomitant and mild to moderate psoriasis, SEC 300 is licensed for moderate to severe psoriasis

D = dominated, ED = extendedly dominated

Source: adapted from tables 96 in AG's report

Summary of differences between independent and meta regression approaches (list price)

Subpopulation 2: biologic naïve - 2 prior DMARDs

	ICERs vs BSC							Optimal treatment (£20,000)	Optimal treatment (£30,000)
	CZP	SEC 150*	SEC 300*	ADA	GOL	ETN	INF		
Moderate – severe psoriasis									
Independent analysis	£21,564	-	£29,569	£20,074	£20,074	£20,197	£27,599	BSC	ETN
Meta regression	£19,923	-	£30,456	£20,092	£20,767	£20,552	£29,138	CZP	CZP
Mild – moderate psoriasis									
Independent analysis	£24,103	£22,032	-	£23,149	£23,419	£22,274	£31,616	BSC	ETN
Meta regression	£22,939	£21,177	-	£23,130	£23,408	£22,750	£32,703	BSC	SEC 150
No concomitant psoriasis									
Independent analysis	£26,105	£24,773	-	£25,532	£25,951	£23,883	£34,930	BSC	ETN
Meta regression	£25,275	£23,768	-	£25,485	£25,475	£24,460	£35,689	BSC	SEC 150

* SEC 150 is licensed for no concomitant psoriasis and mild to moderate psoriasis, SEC 300 is licensed for moderate to severe psoriasis

Using biosimilar list prices for ETN and INF decrease the ICERs for ETN vs. BSC and INF vs. ETN and ETN vs. next best alternative (BSC) in the moderate-severe subgroup (falls below £20,000), therefore using the biosimilar list prices for ETN switches the optimal treatments from BSC to ETN.

Source: adapted from table 97 in AG's report

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Independent analysis results (list price)

Subpopulation 3: biologic experienced

	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC
Moderate – severe psoriasis						
BSC	£95,965	5.312	-	-	-	-
UST	£118,127	6.334	£22,162	1.022	£21,684	£21,685
SEC 300	£143,534	6.632	£25,407	0.299	£85,013	£36,013
Mild – moderate psoriasis						
BSC	£67,000	5.676	-	-	-	-
UST	£91,246	6.666	£24,246	0.989	£24,510	£24,510
SEC 300	£118,564	6.945	£27,318	0.280	£97,713	£40,639
No concomitant psoriasis						
BSC	£51,436	6.188	-	-	-	-
UST	£76,712	7.132	£25,275	0.943	£26,797	£26,797
SEC 300	£104,973	7.384	£28,261	0.252	£111,927	£44,774

Source: adapted from tables 98-100 in AG's report

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Independent analysis results (list price)

Subpopulation 4: patients contraindicated to existing TNF-alpha inhibitors

- Analysis undertaken using the naïve populations from the SEC and UST trials
- Exclusion of CZP because it was assumed that patients that are contraindicated to other TNF-alpha inhibitors are also contraindicated to CZP

	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC
Moderate – severe psoriasis						
BSC	£95,965	5.312	-	-	-	-
UST	£115,216	6.276	£19,252	0.964	£19,969	£19,969
SEC 300	£137,936	6.530	£22,720	0.254	£89,302	£34,445
Mild – moderate psoriasis						
BSC	£67,000	5.676	-	-	-	-
UST	£88,280	6.613	D		-	£22,708
SEC 150	£87,559	6.739	£20,558	1.063	£19,349	£19,349
No concomitant psoriasis						
BSC	£51,436	6.188	-	-	-	-
UST	£73,717	7.088	-	-	ED	£24,781
SEC 150	£73,798	7.190	£22,362	1.001	£22,334	£22,334

D = dominated, ED = extendedly dominated

Source: adapted from table 101-103 in AG's report

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Base case results using biosimilar list prices (ETN & INF)

- This analysis only applies to subpopulation 2, for which comparators include ETN and INF
- Overall, the ICERs for ETN vs. BSC, and for INF vs. ETN are reduced
  - moderate-severe subgroup: ICER < £20,000 for ETN vs. its next best alternative (BSC), therefore at this threshold, using the biosimilar list prices for ETN, the optimal treatments switches from BSC to ETN
  - mild-moderate and no concomitant psoriasis subgroups: optimal treatments remains unchanged.
- The optimal treatment was not sensitive to the use of biosimilar list prices for ETN and INF

Source: adapted from section 7.3.2 p.240 in AG's report

Scenario analyses

	Impact on ICER		
Scenarios	Subpopulation 1	Subpopulation 2	Subpopulation 3
Using Poole et al. cost	Consistent with base case	Reduce ICER for all treatment relative to BSC: • ETN becomes the most cost-effective treatment at a threshold of £20,000 per QALY • At a threshold of £30,000 per QALY, UST remains the optimal treatment despite the reduced ICERs across all treatments.	Reduce ICER for all treatment relative to BSC: • UST becomes the most cost-effective treatment at a threshold of £20,000 per QALY • at a threshold of £30,000 per QALY, UST remains the optimal treatment despite the reduced ICERs across all treatments.
Using alternative withdrawal rate[1]	Consistent with base case	Consistent with base case	Consistent with base case
Using a subpopulation specific to baseline HAQ[2]	Consistent with base case	Consistent with base case	Consistent with base case
Biologic experienced secondary failures[3]	CZP seems to be cost effective treatment compared to BSC, with ICERs of £16,573, £19,113 and £20,973 for moderate-severe, mild-moderate and no concomitant psoriasis patients respectively.		

Note: Withdrawal scenarios and use of Poole costs were only conducted for subpopulations 2 and 3

[1]SEC withdrawal rate assumed to be 50% of the base case value from year 2 (same as Novartis assumption); all treatments withdrawal rate assumed to be equivalent to 50% of the base case values from year 5, assumed that patients who remained on therapy at 5 years would no longer be at risk of subsequent withdrawals (similar to UCB assumption); [2]similar to UCB assumption; [3]only includes CZP and BSC

Probabilistic sensitivity analyses (list prices)

- Results from independent approach are presented
- Overall, meta-regression approach produces similar results

	Probability of being less than £20,000 per QALY gained (%)							Probability of being less than £30,000 per QALY gained (%)						
Subpopulation 1	BSC		CZP		SEC			BSC		CZP		SEC		
Moderate to severe psoriasis	51		39*		10			20		53 *		26		
Mild to moderate psoriasis	46		17		37*			20		30		50*		
No concomitant psoriasis	59		13		28*			26		29		45*		
Subpopulation 2	BSC	CZP	ADA	SEC	GOL	ETN	INF	BSC	CZP	ADA	SEC	GOL	ETN	INF
Moderate to severe psoriasis	26	13	16	3	20**	21	1	10	11	16	7	23**	26	8
Mild to moderate psoriasis	28	14	20	11	13	13*	0	13	12	18	13	18	22*	5
No concomitant psoriasis	33	14	19	10	11	12*	0	16	13	17	13	16	22*	3
Subpopulation 3	BSC		UST		SEC			BSC		UST		SEC		
Moderate to severe psoriasis	44		48*		9			34		50*		16		
Mild to moderate psoriasis	47		45*		7%			36		49*		14		
No concomitant psoriasis	50		7*		43			38		13*		49		

Note: SEC is SEC 150 for no concomitant psoriasis and mild to moderate psoriasis, SEC is SEC 300 for moderate to severe psoriasis

*same optimal treatment as results from the deterministic analysis

**different optimal treatment than the results from the deterministic analysis (it switches from ETN to GOL)

Innovation

- **Secukinumab:**
  - The company and a patient organisation stated that the novel mechanism of action (selective IL-17A inhibitor) offers patients an alternative and more targeted mode of action to other biologics currently. It also expands the armamentarium of treatments for clinicians.
  - The company also stated that there was a convenience of administration with the self-administration. The device also has a hidden needle and is therefore more amenable for patients with needle-phobias. Furthermore, treatment with SEC requires a considerably lower frequency of injection (monthly) than etanercept (twice weekly), adalimumab (fortnightly) and CZP (fortnightly).
- **Certolizumab pegol:**
  - The company stated that the structure of CZP was innovative, being the only Fragment crystallisable-free, PEGylated Fab' fragment TNF inhibitor currently available for the treatment of PsA
  - The company also stated that there were some benefits linked to administration with regards to flexible dosing schedule and self-administration
  - CZP provides a rapid response with regards to improving the signs and the symptoms of the disease
  - The company noted some health benefits that would not be captured in the utility assessment: productivity benefit with greater and continued improvements over time (work, household, social, family, leisure activities)

Source: adapted from sections 4.84 (Novartis) and 2.5 (UCB) of companies' submissions

Equalities issues

- No equalities issues were raised.

Key cost effectiveness issues

- Are the following inputs and assumptions in the AG model considered reasonable?
  - After withdrawal, the “rebound” of HAQ and PASI is assumed to be equivalent to the gain
  - The use of the York algorithm to generate utilities when both RAPID-PsA and FUTURE 2 collect EQ-5D data
  - PsARC repsonses and PASI75 assumed to be correlated
  - Change in baseline HAQ score assumed to be conditional on PsARC response status
  - Use of Poole et al. study as a source for disease management costs, given the fact that costs are being derived from comparable patients with PsA (rather than deriving costs from a RA population and adding separate assumptions for PASI costs).

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Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]

Assessment Report

Commercial in Confidence stripped version for consultation

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

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Assessment Group's Report
Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs

Produced by

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mark Corbett 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.

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Note on the text

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

Abstract

Background

Several biologic therapies are currently approved by the National Institute for Health and Care Excellence (NICE) for treating psoriatic arthritis patients who have had an inadequate response to two or more DMARDs. NICE does not specifically recommend switching anti-TNFs other than the guidance for ustekinumab. The newer biologics secukinumab (SEC) and certolizumab pegol (CZP) have not previously been appraised by NICE.

Objective

To determine the clinical and cost-effectiveness of certolizumab pegol and secukinumab for treating active psoriatic arthritis in adults for whom DMARDs have been inadequately effective.

Design

Systematic review and economic model

Data sources

Fourteen databases were searched for relevant studies up to April 2016

Review methods

Clinical effectiveness data from randomised controlled trials (RCTs) were synthesised using Bayesian network meta-analysis (NMA) methods to investigate the relative efficacy of secukinumab and certolizumab pegol compared with comparator therapies.

Results

Nineteen eligible RCTs were included in the systematic review of short-term efficacy. Most were well-conducted with a low risk of bias. Trials of secukinumab and certolizumab pegol demonstrated clinically important efficacy in all key clinical outcomes; the NMA results for the biologic-naïve subpopulation indicated that their relative effectiveness compared with other biologics and with each other was uncertain. Limited data were available for the biologic-experienced subpopulation. Longer-term evidence suggested these newer biologics effectively reduced disease progression, with the benefits appearing similar to those seen for older biologics.

The de novo model generated ICERs for three subpopulations and three psoriasis subgroups. In subpopulation 1 (which was biologic-naïve with one prior DMARD) CZP appears to be the optimal treatment in the moderate-severe psoriasis subgroup and SEC150mg in the mild-moderate psoriasis and no concomitant psoriasis subgroups. In subpopulation 2 (biologic-naïve with two or more prior DMARDs), ETN is likely to be the optimal treatment in all subgroups, based on the fully incremental analysis. The ICERs for CZP and SEC vs BSC are in the region of £20,000-£30,000. In subpopulation 3 (biologic-experienced or contraindicated), ustekinumab is likely to be the optimal treatment (ICERs

in the region of £21,000-£27,000). The optimal treatment in subpopulation 2 was sensitive to the choice of evidence synthesis model. In subpopulations 2 and 3, results were sensitive to the algorithm for HAQ costs. The optimal treatment is not sensitive to the use of biosimilar prices for ETN and INF.

Conclusions

The results of the economic model indicated that CZP and SEC may be an effective use of NHS resources, depending on the subpopulation and subgroup according to psoriasis severity. There are a number of limitations to this assessment, driven mainly by data availability.

Future work recommendations

Trials are needed to inform effectiveness of biologics in biologic-experienced populations.

Study registration

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List of abbreviations

ACR	American College of Rheumatology
ADA	Adalimumab
ADEPT	Adalimumab Effectiveness in Psoriatic Arthritis Trial
AE	Adverse event
ANOVA	Analysis of variance
APR	Apremilast
BAD	British Association of Dermatologists
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
cDMARD	conventional Disease-modifying antirheumatic drug
CHE	Centre for Health Economics
CI	Confidence interval
CiC	Commercial-in-confidence
CMA	cost-minimisation analysis
CPCI-S	Conference proceedings citation index – science
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CRP	C-reactive protein
CSR	Clinical study report
CUA	Cost–utility analysis
CZP	Certolizumab pegol

DANBIO	Danish Database for Biological Therapies
DARE	Database of Abstracts of Reviews of Effects
df	Degrees of freedom
DIC	Deviation information criterion
DIP	Distal interphalangeal
DLQI	Dermatology life quality index
DMARD	Disease-modifying antirheumatic drug
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence review group
ESR	Erythrocyte sedimentation rate
ETN	Etanercept
FBC	Full blood count
GOL	Golimumab
HAQ	Health assessment questionnaire
HAQ-DI	Health assessment questionnaire-disability index
HEED	Health economic evaluations databases
HLA	Human leucocyte antigen
HODaR	Health outcomes data repository
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IL	Interleukin
I.V.	Intravenous
ICER	Incremental cost-effectiveness ratio (e.g. Incremental cost per qaly gained)
IMPACT	Infliximab Multinational Psoriatic Arthritis Controlled Trial
INF	Infliximab
IPD	Individual patient data
IQR	Interquartile range

ITC	Indirect treatment comparison
ITT	Intention to treat
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
LFT	Liver function test
LOCF	Last observation carried forward
LoE	Lack of efficacy
MeSH	Medical subject heading
MIMS	Online and print prescribing database for health professionals
mRCT	metaRegister of Current Controlled Trials
MTA	Multiple technology appraisal
MTX	Methotrexate
NA	Not applicable
NH	Natural history
NHS EED	NHS economic evaluation database
NICE	National Institute for Health and Clinical Excellence
NMA	Network meta analysis
NOAR	Norfolk arthritis register
NOR-DMARD	Norwegian Anti-rheumatic Drug Register
NR	Not reported
NRI	Non-responder imputation
NRR	National research register
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PALACE	Psoriatic Arthritis Long-term Assessment of Clinical Efficacy
PASI	Psoriasis Area and Severity Index
PBO	Placebo
PDF	Probability density function

PRESTA	Psoriasis Randomized Etanercept study in Subjects with Psoriatic Arthritis
PsA	Psoriatic arthritis
PSA	Probabilistic sensitivity analysis
PsARC	Psoriatic arthritis response criteria
QALY	Quality-adjusted life-year
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RF	Rheumatoid factor
RR	Relative risk
SCI	Science citation index
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SF-36	Short Form questionnaire-36 items
SJC	Swollen joint count
STA	Single technology appraisal
TB	Tuberculosis
TJC	Tender joint count
TNF	Tumour necrosis factor
TSS	Total sharp score
UST	Ustekinumab
VAS	Visual analogue scale
YODA	Yale University Open Data Access Project

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.

American College of Rheumatology Improvement Criteria (ACR 20/50/70) To achieve these response measures, certain measurements of disease severity must have improved beyond the criteria threshold percentage of 20/50/70. A reduction in tender joint count and swollen joint count are required, along with at least three out of the five additional measures, including patient and physician global health assessment, pain, disability, and an acute-phase reactant.

Anti-TNF/biologic experienced Patient has previously undergone treatment with a biologic therapy.

Anti-TNF/biologic naïve Patient has not been previously treated with a biologic therapy.

Apremilast An orally administered small molecule drug which inhibits an enzyme involved in tumour necrosis factor production. Apremilast is not a biologic therapy.

Arthritis A disorder involving inflammation of the joint(s), but which is often used to include all joint disorders. Joints can be permanently damaged through the disease process of arthritis.

Articular Of or relating to joints.

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.

Ciclosporin 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).

C-reactive protein (CRP) Concentrations of this protein in the blood can be measured as a test of inflammation of disease activity, for example in rheumatoid arthritis.

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.

Dactylitis Inflammation of an entire digit caused by simultaneous joint and tendon inflammation.

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.

Dominated A term used in the cost-effectiveness sections. A treatment is said to be dominated by another treatment, if it is associated with higher costs and lower QALYs.

Enthesitis Inflammation of where tendons and ligaments attach to the bone (entheses)

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.

Erythrocyte sedimentation rate (ESR) One of the tests designed to measure the degree of inflammation.

Extendedly dominated A term used in the cost-effectiveness sections. An extendedly dominated strategy has an ICER (incremental cost-effectiveness ratio) higher than that of the next most effective strategy; therefore an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

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.

Leeds Dactylitis Index (LDI) The LDI uses a dactylometer to measure swelling between digital joints, calculating the ratio of circumference between an affected digit and a contralateral unaffected digit or standard reference if both are affected. A difference in circumference of ≥10% is used to define a finger with dactylitis. The tenderness of each digit is also taken into account to generate a score for each, if multiple digits are affected, each score is added together.

Leeds Enthesitis Index (LEI) The LEI examines tenderness over six tendon attachment sites (enthuses), this also includes an assessment for soft-tissue swelling. The LEI is scored from 0-6.

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

Monoclonal antibody An antibody produced using a single clone of cells with affinity for one particular antigen

Modified Total Sharp Score (mTSS) The Modified Total Sharp Score is one of several radiological assessments used to measure joint damage in Psoriatic Arthritis. This method grades all joints of the hand separately for erosions and joint space narrowing for 64 and 52 joints(out of a maximum score of 149), respectively, with higher scores representing greater damage. Total Sharp Score (TSS) is modified to include other joints in the assessment.

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).

Non-steroidal anti-inflammatory drugs (NSAIDs) Consists of a large range of drugs of the aspirin family, prescribed for different kinds of arthritis which reduce inflammation and control pain, swelling and stiffness.

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.

PsARC response is defined as an improvement of at least 30% in tender or swollen joint count as well as a 1-point improvement on a 5-point scale of patient's and/or physician's assessment. NICE define a response as an improvement in ≥2 of the four assessment criteria (with no worsening of any of these four measures)

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.

Remission A lessening or abatement of the symptoms of a disease.

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.

Subpopulation 1 Patients who are biologic-naïve but have tried one previous cDMARD

Subpopulation 2 Patients who are biologic-naïve but have tried two or more previous cDMARD

Subpopulation 3 Patients who are biologic-experienced

Short Form questionnaire-36 items (SF-36) A patient-reported survey of general health status.

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

Tender joint count (TJC) and swollen joint count (SJC) Assessment of the condition of 28 joints important to functional status. Used in the calculation of several composite disease activity scores such as DAS28

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. Plays a key role in onset and persistence of joint and skin inflammation.

1 Scientific Summary

Background

Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory arthritis closely associated with psoriasis of the skin and nails which typically affects joints in the hands, feet and spine. It can cause joint damage so early diagnosis and treatment is important. Current practice typically involves early use of NSAIDs followed by disease-modifying anti-rheumatic drugs (DMARDs) if necessary. When conventional DMARDs are ineffective biologic therapies may be used: anti-TNF biologics such as etanercept, infliximab, adalimumab and golimumab are approved by NICE in patients who have had an inadequate response to two or more DMARDs. Ustekinumab - a different kind of biologic therapy to anti-TNFs - is also recommended as a possible treatment, specifically when DMARDs have not worked well enough, providing that treatment with anti-TNFs is not suitable, or the patient has had an anti-TNF before. NICE does not specifically recommend switching anti-TNFs other than the guidance for ustekinumab and switching decisions can vary depending on local guidelines. The newer biologics secukinumab (an anti-IL) and certolizumab pegol (an anti-TNF) have not previously been appraised by NICE for treating psoriatic arthritis.

Objectives

To determine the clinical- and cost-effectiveness of certolizumab pegol and secukinumab within their marketing authorisations for treating active psoriatic arthritis in adults for whom disease-modifying anti-rheumatic drugs have been inadequately effective.

Methods

For the systematic review of clinical efficacy, randomised controlled trials (RCTs) were eligible, including open-label extensions. Adverse events data were sought from existing safety reviews of biologics. Patient registry studies (of patients taking biologics) and studies of natural history of disease (in patients not taking biologics) were also sought. Eligible studies were of adults with psoriatic arthritis. The treatments of interest were secukinumab and certolizumab pegol with the relevant comparators being etanercept, infliximab, adalimumab, golimumab, ustekinumab, apremilast and placebo.

Fourteen databases were searched for relevant studies up to April 2016. Clinical effectiveness data from RCTs were synthesised using Bayesian network meta-analysis (NMA) methods to formally investigate the relative efficacy of secukinumab and certolizumab pegol compared with the other active comparators. Analyses were conducted on four outcomes PsARC, HAQ conditional on PsARC response, PASI and ACR. Results from other studies were summarised narratively.

Methods of cost-effectiveness review

A systematic review was undertaken to identify published evidence on the cost-effectiveness of certolizumab pegol (CZP) and secukinumab (SEC) in PsA. This also includes the company submissions from Novartis (SEC) and UCB (CZP). The systematic review also includes a broader assessment of published decision-analytic models for relevant comparators infliximab [INF], etanercept [ETN], adalimumab [ADA], golimumab [GOL] and ustekinumab [UST]. The differences in the model structures and assumptions used across the studies were examined to identify any important differences in approaches and areas of remaining uncertainty.

Methods of economic modelling

A de novo decision analytic model was developed to estimate the cost-effectiveness of SEC and CZP compared to other relevant comparators including ETN, INF, ADA, GOL, UST and best supportive care (BSC) for the treatment of adult PsA. A different set of comparators are defined according to each subpopulation of interest. The cost effectiveness model takes the form of a lifetime (40 year) Markov cohort model, developed using R programing language. Outcomes are expressed using quality adjusted life years (QALYs). The parameters of the model were obtained from published literature, manufacturers' reported data and the results of the evidence synthesis.

Although the model shares a number of important similarities with the previous York model, several significant changes have also been implemented. These include:

- Incorporation of subsequent biologic treatments following primary lack of response or secondary failure.
- Three subpopulations specified in the NICE scope for this appraisal.
- Three subgroups according to the level of concomitant psoriasis.

Results of clinical effectiveness review

Nineteen eligible RCTs were included in the systematic review of short-term efficacy. Most were well-conducted and judged to have a low overall risk of bias.

Short-term efficacy in pivotal RCTs

Four eligible trials were of secukinumab and one was of certolizumab pegol. Results from the pivotal RCTs of secukinumab and certolizumab pegol demonstrated their short-term efficacy. Both therapies were associated with statistically significant improvements in all key clinical outcomes. At 3 months, patients taking secukinumab were around six times more likely to be ACR 50 responders – an important clinical outcome to patients – than patients taking placebo. Patients taking certolizumab pegol were around three times more likely to be ACR 50 responders than placebo patients. Clinically important improvements in activities of daily living (assessed using HAQ-DI) were also evident for both therapies, particularly in patients who were PsARC responders. Secukinumab and certolizumab

pegol both also significantly improved measures of health-related quality of life and the resolution of enthesitis and dactylitis.

However, when the populations from these two trials were split into subgroups based on previous biologic experience, results for the biologic-experienced subgroups became difficult to interpret. This was due both to the low numbers of placebo patients (and placebo events) and to the differences in placebo response rates across subgroups. A further complication is that the evidence for certolizumab pegol does not include patients who failed to respond to a first anti-TNF. Whilst secukinumab and probably certolizumab pegol are efficacious in both subgroups, it is not possible to make robust conclusions about any difference in efficacy of these drugs across these subgroups.

Subgroup results from psoriatic arthritis patients recruited to trials of patients with quite severe psoriasis suggested secukinumab may be particularly efficacious in treating the psoriasis symptoms of PsA.

Short-term efficacy compared with other therapies from network meta-analyses
The trials identified to inform a comparison of secukinumab and certolizumab pegol with other therapies were performed across a 15 year period and variation in placebo response was evident for some important outcomes: larger placebo response rates were seen in the more recent trials. There was also important variation across trials with regard to patients' previous use of a biologic therapy: subgroups of biologic-experienced patients were only recruited in more recent trials. The NMAs were therefore performed on the biologic-naïve and -experienced subpopulations separately, and included models which adjusted for and explored the different rates of placebo response across trials.

Across all outcomes the NMA results for the biologic-naïve subpopulation indicated that whilst secukinumab and certolizumab pegol were effective, their relative effectiveness compared with etanercept, adalimumab, golimumab and infliximab and with each other, was uncertain: the rankings of treatment varied with outcome and analysis. However, both agents did seem consistently more effective than apremilast. The results indicate that secukinumab and infliximab are the most effective in terms of PASI response.

Only secukinumab and ustekinumab could be included in the analyses of the biologic-experienced subpopulation. The results showed that across all outcomes analysed both secukinumab and ustekinumab were significantly more effective than placebo. Most of the results suggested secukinumab may be better than ustekinumab. However, the patient numbers in this subpopulation were quite low; the results were therefore uncertain (with wide overlapping credible intervals).

Long-term efficacy

Results from open-label trial extension studies which radiographically assessed joint damage indicated that, after two years of treatment, certolizumab pegol effectively reduced disease progression with the benefits appearing similar to those observed in the open-label studies of the other biologics. Fewer result details were available for secukinumab at two years although the results also indicated effective reduction in radiographic disease progression. Meaningful treatment comparisons of longer-term data for other outcomes were difficult to undertake due to the variation in both time points assessed and in methodological approaches used for data analyses [redacted]

Results from other studies

Patient registry studies suggested that although patients benefit from a second or more anti-TNF, the expected benefit from anti-TNFs diminishes after switching, with a reduced chance of response and reduced drug survival. The paucity of observational data on the natural history of psoriatic arthritis meant it was difficult to produce accurate estimates of yearly disease progression rates in patients not taking anti-TNF therapy.

Results from three systematic reviews of adverse events suggested certolizumab pegol was associated with statistically significantly more serious adverse events and serious infections than placebo. Although secukinumab appears to have a favourable safety profile there is still some uncertainty regarding its safety.

Results of Cost-effectiveness evaluation

Cost-effectiveness reported in existing published studies and manufacturer submissions

No previously published cost-effectiveness studies of SEC or CZP for PsA were identified. The companies submitted de novo analyses for SEC (Novartis) and CZP (UCB).

For the broader set of comparators, the systematic search of published literature identified nine studies which met the inclusion criteria for the cost effectiveness review. Of the nine studies, seven UK studies were identified; only one was not directly related to a previous NICE TA. All of these models employed similar model structures to that originally proposed by Rodgers et al for TA199 (the previous 'York model'). The main differences between these models are in relation to the comparators and associated evidence base, which has altered since TA199, rather than in terms of major structural differences. The choice of optimal treatment, ETN, is consistent across the published models.

The manufacturers' models are the only studies which directly assess the decision problem in relation to the new interventions, i.e. the positioning of SEC and CZP across the pathway for PsA (biologic naïve and experienced populations). Both have a similar structure to the previous York model; however there are a number of key differences, including: the comparators included in each of the subpopulations, clinical evidence used and the methods employed in the evidence synthesis, the source of cost data for HAQ and PASI data, the rate of withdrawal for patients who have initial responded to biologic therapy and baseline characteristics in terms of HAQ and particularly PASI scores. Neither submission reports a list price analysis, instead reporting results using confidential PAS prices.

Cost effectiveness results from de novo modelling

The de novo model, which addressed many of the issues of earlier published models, generated ICERs for three subpopulations according to the positon in the pathway of treatment and three subgroups according to severity of psoriasis:

- For subpopulation 1: in the moderate-severe subgroup, the pairwise ICERs for CZP and SEC 300mg compared to BSC are £20,870 and £26,064 per QALY, respectively. In the fully incremental analysis, the ICER for SEC 300mg compared to CZP is £134,783; therefore CZP is likely to be the optimal treatment. In the mild-moderate psoriasis group, the pairwise ICERs for CZP and SEC 150mg compared to BSC are £23,052 and £21,772 per QALY, respectively. In the fully incremental analysis, CZP is dominated by SEC 150mg and therefore SEC 150mg is likely to be the optimal treatment. In the no concomitant psoriasis subgroup, pairwise ICERs for SEC 150mg and CZP compared to BSC are £23,928 and £24,774 per QALY, respectively. In the fully incremental analysis, the ICER for CZP compared to SEC 150mg is £346,785 and therefore SEC 150mg is likely to be the optimal treatment.
    - For subpopulation 2: in the moderate-severe subgroup, the pairwise ICERs for CZP and SEC 300mg compared to BSC are £21,564 and £29,569 per QALY, respectively. In the fully incremental analysis, SEC 300mg is dominated and CZP is extendedly dominated. Of the remaining non-dominated alternatives, ETN is likely to be the optimal treatment, with an ICER of £21,215 compared to GOL. For the mild to moderate psoriasis subgroup, the pairwise ICERs for CZP and SEC 150mg compared to BSC are £24,103 and £22,032 per QALY, respectively. In the fully incremental analysis, CZP and GOL are dominated and ADA is extendedly dominated. Of the remaining non-dominated alternatives, ETN is likely to be the optimal treatment, with an ICER of £23,256 per QALY compared to SEC 150mg. For the no concomitant psoriasis subgroup, the individual pairwise ICERs for CZP and SEC 150mg compared to BSC are £24,103 and £22,032 per QALY, respectively. ETN is likely to

be the optimal treatment in this subgroup with ICER of £23,883 compared to BSC (fully incremental analysis).

- For subpopulation 3: in the moderate-severe subgroup, the individual pairwise ICER for SEC 300mg compared to BSC is £36,013. In the fully incremental analysis, the ICER of UST vs BSC is £21,684 per QALY and the ICER of SEC 300mg is £85,013 per QALY. In the mild-moderate subgroup the pairwise ICER for SEC 300mg compared to BSC is £40,639. In the fully incremental analysis, the ICER of UST vs BSC is £24,510 per QALY and the ICER of SEC 300mg vs UST is £97,713 per QALY. In the no concomitant subgroup the pairwise ICER for SEC 300mg compared to BSC is £44,774. In the fully incremental analysis, the ICER of UST vs BSC is £26,797 per QALY and the ICER of SEC 300mg vs UST is £111,927 per QALY.

The model also explores a number of uncertainties through the use of scenario analysis, and found that:

- The optimal treatment in subpopulation 2 was sensitive to the choice of evidence synthesis model.
- In the contraindicated subgroup (subpopulation 4), UST appears to be the most cost-effective treatment in moderate-severe psoriasis patients (ICER of £19,969 compared to BSC), however in the mild-moderate and no concomitant psoriasis patients SEC 150mg appears to be the most cost-effective treatment (ICERs of £19,349 and £22,334 compared to BSC for the two subgroups respectively)
- In the biologic experienced subgroup including only secondary failures, CZP seems to be cost effective treatment compared to BSC, with ICERs of £16,573, £19,113 and £20,973 for moderate-severe, mild-moderate and no concomitant psoriasis patients respectively.
- The optimal treatment is not sensitive to the use of biosimilar prices for ETN and INF.
- In sub-population 1, the optimal treatment is consistent across the two scenarios for baseline HAQ, base case assumption (1.22) and using a subpopulation specific baseline HAQ.
- In subpopulations 2 and 3, aside from the use of the Poole, et al HAQ costs, the optimal treatment is consistent across all scenarios (subpopulation specific baselines and alternative withdrawal rates).

Discussion

The key strengths of the systematic review are the rigorous methods used and the breadth of the types of study included. The updated York model confers several advantages over current published cost-effectiveness studies, namely the inclusion of the three subpopulations according to the position in the pathway of treatment, the explicit consideration of the severity of concomitant psoriasis and the modelling of subsequent treatments following primary non-response or secondary failure. The York

model also facilitates a more consistent basis for evaluating CZP and SEC by ensuring comparability in methods and inputs.

Conclusions

The network meta-analysis results for the biologic-naïve subpopulation indicated that whilst secukinumab and certolizumab pegol were effective across all outcomes after three months' therapy, their relative effectiveness compared with other biologics and with each other was uncertain. The results of the economic model indicated that certolizumab pegol and secukinumab may be an effective use of NHS resources, depending on the subpopulation based on prior treatments and subgroup according to psoriasis severity. There were a number of limitations to the assessment, mostly driven by data availability issues.

Suggested research priorities

Adequately powered trials are needed to better inform the efficacy of biologics in biologic-experienced populations. Further research is required to better elucidate the impact of biologics on radiographic disease progression and HAQ in the long-term

Study Registration

PROSPERO: CRD42016033357

Funding

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Plain English Summary

Psoriatic arthritis is an inflammatory disease that involves both skin (psoriasis) and joints. It can greatly reduce a person's quality of life and reduce life expectancy. For patients who have severe active psoriatic arthritis that has not responded sufficiently to conventional treatments, NICE currently recommends a number of effective biologic therapies. The purpose of this project was to assess the benefits, harms and the cost-effectiveness of two new biologic therapies - certolizumab pegol and secukinumab, and to compare them with existing therapies.

We identified and analysed all the data from relevant clinical trials. The results showed that both certolizumab pegol and secukinumab are effective therapies. It is not clear which if any of the many biologic therapies is best, though secukinumab seems particularly good at improving psoriasis symptoms.

Economic modelling found that these new biologics can be considered a cost-effective use of NHS resources when compared with the other therapies currently recommended by NICE for treating psoriatic arthritis. Which treatment is most cost-effective depends on which previous treatments a patient has tried and not responded to, the severity of the psoriasis symptoms, and the price of the treatment. Some of the study's results were somewhat limited due to there not being enough relevant clinical trial data available.

2 Background

Description of health problem

Psoriatic arthritis (PsA) is a chronic autoimmune disease closely associated with psoriasis of the skin and nails, but distinct from rheumatoid arthritis: PsA is one of a family of inflammatory arthritis disorders called spondyloarthritis (or spondyloarthropathy), which also includes ankylosing spondylitis.[1] Psoriatic arthritis is closely linked with inflammatory bowel disease, especially the form called Crohn's disease.[2] Although any joint may be affected, psoriatic arthritis typically affects joints in the hands, feet and spine. Its course may be erratic, with flare-ups and remissions but it can cause joint damage if it is not treated. Early diagnosis is important to avoid damage to joints.[3] Arthritis symptoms include inflamed (swollen) stiff and painful joints; psoriasis symptoms include patchy, raised red areas of inflamed skin with scaling.[4]

Psoriatic arthritis has similar symptoms to other forms of arthritis. The difference between psoriatic arthritis and rheumatoid arthritis is that the pattern of joint involvement is commonly asymmetric, and involves the distal interphalangeal joints (in the hands and feet) and nail lesions. The following terms are used to present the patterns of psoriatic arthritis: oligoarthritis (≤ 4 joints, 22% to 37% of patients); polyarthritis (≥ 5 joints, 36% to 41% of patients); arthritis of distal interphalangeal joints (< 20% of patients); spondylitis (7% to 23% of patients); and arthritis mutilans (approximately 4% of patients).[5, 6]Most patients with psoriatic arthritis will have developed psoriasis first (i.e. joint complications occur around ten years after initial diagnosis of psoriasis), although joint involvement appears first in 19% of patients and concurrently with psoriasis in 16% of cases.[7]

Since psoriatic arthritis can affect both skin and joints it can result in significant quality of life impairment, joint deformity and psychosocial disability.[7, 8] A recent survey of patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis found that disease burden in terms of patient- reported outcome measures was similar in PsA and axial spondyloarthritis patients, but significantly lower for the rheumatoid arthritis patients.[9] The physical and psychosocial problems experienced by patients affect their ability to perform paid work and everyday tasks; psoriatic arthritis has a substantial economic impact on the UK healthcare system due to direct healthcare costs as well as indirect costs, such as reduced work capacity.[10]

Patients with psoriatic arthritis have a 60% higher risk of premature mortality than the general population, with cardiovascular disease being the leading cause of death.[11-13] The estimated reduction in life expectancy for patients with PsA is approximately 3 years[14] with a standardised mortality ratio of 1.62. A Canadian outpatient clinic study reported mortality due to cardiovascular disease as being 30% higher in patients with psoriatic arthritis than that in the general population.[12]

Diagnosis

It is difficult to define psoriatic arthritis because there are no precise diagnostic criteria or diagnostic markers.[15] In general, diagnoses are primarily based on patient symptoms and physical examination. In most cases, the Moll and Wright (1973) criteria have been used for diagnosis.[16] There are several classification criteria which have been introduced since Moll and Wright, but none have been widely accepted or validated. In 2006, the multicentre CASPAR study (Classification Criteria for Psoriatic Arthritis) developed new classification criteria which are simple and have both a high sensitivity and a high specificity; they are currently a preferred method to define cases of PsA (See Table 1).[17]

Table 1 The CASPAR criteria

To meet the CASPAR (Classification Criteria for Psoriatic Arthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with 3 points or more from the following five categories:[17]	
1. Evidence of psoriasis	Current psoriasis* defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist. A personal history of psoriasis defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider. A family history of psoriasis defined as a history of psoriasis in a first- or second-degree relative according to patient report.
2. Psoriatic nail dystrophy	Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.
3. Negative test result for rheumatoid factor	A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.
4. Dactylitis	Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.
5. Radiographic evidence of juxta-articular new bone formation	Defined as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

* Current psoriasis is assigned a score of 2; all other features are assigned a score of 1

Epidemiology

The exact prevalence of psoriatic arthritis is unknown, but estimates vary from 0.3% to 1% of the population. The prevalence of psoriatic arthritis in England in 2013 was estimated to be around 53,900 to 161,600 people. Psoriatic arthritis affects men and women equally, unlike rheumatoid arthritis which is more common in women.[18]

Psoriatic arthritis can develop at any time, including childhood,[19] but normally it appears between the ages of 30 and 55 years.[18] Its development is complex process involving both environmental and genetic factors.[20-22] Studies show a stronger genetic or family link to PsA than other autoimmune rheumatic diseases. Around 40% of people who are diagnosed with PsA and psoriasis also have family members affected by the disease.[2]

Measurement of disease

The GRAPPA–OMERACT psoriatic arthritis working group recently updated the core set of domains to be assessed in clinical trials to reflect both patient and physician priorities. The domain set includes musculoskeletal disease activity (which now includes enthesitis, dactylitis, and spine symptoms in addition to peripheral arthritis), skin disease activity, patient global assessment, pain, physical function, health-related quality of life, fatigue and systemic inflammation. Four new items were added to the research agenda: stiffness, independence, treatment burden, and sleep. [23]

Many trials of psoriatic arthritis have used the American College of Rheumatology 20% improvement criteria (ACR 20) as primary outcome; the ACR criteria were however developed to assess rheumatoid arthritis. The other outcome assessment tools which have commonly been used in clinical trials are:

- PsARC, a multi-domain measure which has similarities with ACR criteria but which was developed specifically for psoriatic arthritis
- PASI, to assess psoriasis
- HAQ-DI, to assess function (activities of daily living)
- Various measures of enthesitis, dactylitis and radiographic progression of disease

However, there are issues with some assessment tools:

- HAQ-DI concentrates on physical disability which may not adequately capture disability in patients with predominantly skin disease. Consequently, there is less change in the context of treatment that has a predominant effect on the skin and not the joints.[24]
- PASI has poor sensitivity to change and responsiveness when skin psoriasis is less than 10% body surface area involvement. Furthermore the correlation with quality of life measures is poor [25]. Also it is time-consuming and not practically very feasible in daily clinical practice.
- PsARC determines only relative changes from baseline and over-estimates the number of responders.[26] In general PsARC placebo responses results are higher compared to other composite measures.[27]

Current service provision

If psoriatic arthritis is not treated early the inflammation can affect the whole body which may lead to lasting joint and tissue damage.[2] The clinical management of psoriatic arthritis therefore aims to suppress joint, tendon and ligament inflammation, and to manage the skin symptoms of the disease. Current practice involves early diagnosis and early use of non-steroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular corticosteroid injections. For patients who do not respond to these treatments disease-modifying anti-rheumatic drugs (DMARDs) are then used (most commonly beginning with methotrexate). When conventional DMARDs are ineffective, or not tolerated, biologic

therapies may be used: anti-tumor necrosis factor (anti-TNF) therapies such as etanercept, infliximab, adalimumab and golimumab are approved by NICE. Anti-TNFs have been shown to slow the progression of joint damage when assessed radiographically.[28, 29] Ustekinumab - a different type of biologic therapy to anti-TNFs (being an interleukin-12/23 inhibitor) - is also recommended as a possible treatment, specifically when DMARDs have not worked well enough, providing that treatment with anti-TNFs is not suitable, or the patient has had an anti-TNF before. Apremilast (a phosphodiesterase-4 inhibitor) is not currently approved by NICE.

Current NICE guidance relates to the treatment of patients who have had an inadequate response to 2 or more conventional DMARDs (administered either individually or in combination). Not all patients respond to initial anti-TNF treatment and for some patients the response diminishes over time. One observational study showed that one third of PsA patients had switched to a second anti-TNF due to lack of efficacy and side effects.[30]NICE does not specifically recommend switching anti-TNFs other than the guidance for ustekinumab, and switching decisions may depend on local clinical commissioning group guidelines: in some parts of the country patients are allowed to switch from one anti-TNF to another.

Quite often patients with PsA go undetected and sometimes they are not recognised and diagnosed by dermatologists or GPs. In the UK, rheumatologists manage the majority of patients with PsA but patients with less severe joint disease may be managed by a dermatologist. However, patients with severe problems with joint and skin will tend to be managed by both rheumatologists and dermatologists.

Description of technology under assessment

Certolizumab pegol (Cimzia, UCB Pharma) is a biologic therapy (a monoclonal antibody which targets tumour necrosis factor (TNF)) which is administered subcutaneously. Anti-TNFs target the activation of tumour necrosis factor alpha (TNF-alpha) and subsequently activation of downstream inflammatory processes, and as such have the potential to offer symptom control as well as altering disease progression. Certolizumab pegol in combination with methotrexate has a marketing authorisation in the UK for treating active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. Certolizumab pegol can be given as monotherapy if methotrexate cannot be tolerated or when continued treatment with methotrexate is inappropriate

Secukinumab (Cosentyx, Novartis), which is also administered subcutaneously, is a different type of biologic therapy to certolizumab pegol, being a monoclonal antibody which targets the interleukin 17A (IL-17A) receptor (rather than targeting TNF). Secukinumab, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been

inadequate. Secukinumab also has marketing authorisation from the European Medicines Agency (EMA) for the treatment of ankylosing spondylitis and moderate to severe plaque psoriasis.

3 Definition of decision problem

The decision problem relates to the optimal use of certolizumab pegol and secukinumab within their marketing authorisations for treating active psoriatic arthritis in adults for whom disease-modifying anti-rheumatic drugs have been inadequately effective. Evaluations will be made at the following points in the treatment pathway:

- Patients who have only received one prior non-biological disease modifying anti-rheumatic drug (DMARD)
- Patients whose disease has inadequately responded to at least two DMARDs
- Patients whose disease has inadequately responded to both DMARDs and biological therapies

Previous NICE appraisals

There have been no previous NICE Technology Appraisals (TA) of certolizumab pegol or secukinumab for psoriatic arthritis, though there have been several appraisals of other biologics for psoriatic arthritis: TA199 (etanercept, infliximab and adalimumab), TA220 (golimumab), and TA340 (ustekinumab). Apremilast, which is not a biologic, is not currently recommended by NICE.

A number of key areas of uncertainty and potential limitations of the evidence base were identified from the previous appraisals. These include:

- The lack of direct head-to-head trial evidence evaluating the relative efficacy and safety of the biologics
- Some limitations in the external validity of the trial populations (i.e. the trial populations had some differences from populations seen in routine clinical practice)
- Lack of patient registry data for psoriatic arthritis
- The long-term effectiveness of biologics in controlling disease activity
- The prescription cost of biologics and also the cost of treating psoriasis in different levels of severity
- The progression of Health Assessment Questionnaire (HAQ) score (a measure of patient function) on and off treatment, and the length of time biologics are assumed to be effective
- Long term progression of psoriatic arthritis with and without biologics
- The lack of an optimal outcome measure for psoriatic arthritis
- The rate of treatment withdrawal and the adverse effects associated with the long-term use of biologics
- A lack of evidence on the efficacy and safety of the sequential use of biologics

The assessment would consider and attempt to address these limitations and areas of uncertainty using relevant evidence where available.

Overall aims and objectives of assessment

To determine the clinical- and cost-effectiveness within the NHS of certolizumab pegol and secukinumab within their marketing authorisations for treating active psoriatic arthritis in adults for whom disease-modifying anti-rheumatic drugs have been inadequately effective.

4 Assessment of clinical effectiveness

4.1 Methods for reviewing clinical effectiveness

Search strategy

The literature search aimed to identify all relevant randomised controlled trials (RCTs) of certolizumab pegol and secukinumab and the comparators etanercept, adalimumab, infliximab, golimumab, apremilast and ustekinumab for the treatment of psoriatic arthritis.

The searches for certolizumab pegol and secukinumab for psoriatic arthritis were not restricted by date. However, as etanercept, adalimumab, infliximab, golimumab, apremilast and ustekinumab for psoriatic arthritis had already been subject to previous technology appraisals, update searches were performed based on the search dates of these previous technology appraisals.

The search strategy was developed in MEDLINE (Ovid) and then adapted for use in the other resources searched. The strategy included terms for psoriatic arthritis combined, using the Boolean operator AND, with terms for the eight treatments. No language or geographical limits were applied. A study design search filter to limit retrieval to randomised controlled trials was used where available.

Search strategies were developed by an information specialist with input from the project team. The MEDLINE search strategy was checked by a second information specialist. The searches were carried out during December 2015 and then updated on 28th April 2016 to capture more recent studies.

The following databases were searched: MEDLINE, MEDLINE In-Process, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), 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.

As DARE ceased at the end of March 2015, additional searches for systematic reviews were carried out in MEDLINE and EMBASE to ensure that any relevant systematic reviews were identified.

Full search strategies can be found in Appendix 12.1.

Inclusion criteria

Two reviewers independently screened all titles and abstracts. Full manuscripts of any titles/abstracts that were relevant were obtained where possible and the relevance of each study was assessed by two

reviewers according to the inclusion criteria, described below. Any discrepancies were resolved by involving a third reviewer. Studies available only as abstracts were also included.

Study design

Randomised or quasi-randomised controlled trials were eligible for the review of clinical efficacy and safety. For the eligible interventions (see below), all open-label extension studies of RCTs were included. For the comparators (below), open-label extensions were identified and listed with the main focus being on those studies which reported data relating to the longest duration of follow up available for each individual comparator.

To evaluate the adverse effect profiles of the different biologics the eligible study designs were systematic reviews which cover a range of diseases, and large observational studies in patients with psoriatic arthritis.

Prospective registry studies which include psoriatic arthritis patients receiving biologics were eligible to identify data on treatment adherence, treatment withdrawal, and the rates and efficacy of switching to new biologics (i.e. sequential use). Potentially relevant registry studies were sought and identified with a focus on those deemed to be most clinically relevant and appropriate to the UK setting. This was decided based on examination of study characteristics and discussion with our clinical adviser.

Studies were also sought on the longer-term natural history of psoriatic arthritis in populations which have not taken a biologic therapy.

Interventions

Certolizumab pegol and secukinumab were eligible at their licensed doses (see Table 2). Studies comparing these two treatments with each other were also eligible.

Comparators

The relevant comparators were:

- Placebo
- DMARDs: methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, azathioprine and ciclosporin
- Biologic therapies: adalimumab, etanercept, golimumab, infliximab and ustekinumab, including any licensed biosimilars
- Apremilast
- Best supportive care

Biologics and apremilast may have been used with or without concomitant DMARDs. Only studies which included treatments used at their licensed dose were eligible. Head-to-head trials of the five biologic comparators (and biosimilars) and apremilast were eligible, but were anticipated to be rare. Therefore, to allow comparisons of active treatments via network meta-analysis, the biologic comparators and apremilast could also have been compared with either placebo or with a DMARD.

Participants

For the evaluation of the effectiveness of certolizumab pegol and secukinumab, included studies were of adults with active psoriatic arthritis for whom DMARDs have been inadequately effective.

Outcomes

For certolizumab pegol and secukinumab studies reporting any of the following outcomes were eligible:

- Disease activity, using the following multi-domain measures: PsARC, ACR 20/50/70
- Functional capacity (assessed using HAQ-DI)
- Radiographic assessment of disease progression
- Response of psoriatic skin lesions (assessed using PASI)
- Measures of dactylitis, enthesitis, and tendonitis
- Mortality
- Health-related quality of life (assessed using EQ-5D or SF-36)
- Adverse effects of treatment, focusing on the key adverse events identified from previous studies of biologics: malignancies, serious infections, reactivation of latent tuberculosis, injection site reactions, and withdrawals due to adverse events

RCTs of comparators needed to report at least one of the following: PsARC, ACR 20/50/70, PASI 50/75/90 or HAQ-DI.

For patient registry studies treatment adherence, treatment withdrawal, and the rates and efficacy of switching to new biologics (i.e. sequential use) were the key outcomes of interest, particularly those which were identified as being useful to inform parameters in the economic model.

Data extraction

For secukinumab and certolizumab pegol data were extracted from published papers and abstracts supplemented by data from the manufacturer submissions (when they were not available from other sources). Data were extracted from previous STA or MTA reports for studies of etanercept, infliximab, adalimumab, golimumab, ustekinumab and apremilast. Where missing or further information on the trials of these treatments was needed data were extracted either from the relevant published trial reports or from reviews[31-34]. Some data may have been missing in the original

technology appraisals due to commercial or academic in confidence restrictions; some of these data may have subsequently been published. Data for ustekinumab at the 12 week time point were extracted from the full clinical study reports of PSUMMIT 1 and PSUMMIT 2 which were accessed via the Yale university Open Data Access (YODA) project. For apremilast, although only the PALACE 1 trial has been published, data from the PALACE 2 and PALACE 3 trials were extracted from STA documents on NICE's website. All data for these treatments were extracted by one reviewer and then checked for any transcription errors by a second reviewer.

For the dichotomous responder outcomes (PsARC, ACR 20/50/70, PASI 50/75/90) intention-to-treat baseline denominators (i.e. the number of patients randomised for each trial arm) were used, with patients assumed to be non-responders where data were missing. This explains why there is a small difference in the ADEPT denominators used between this current MTA and the previous MTA and manufacturer submissions (the latter two used the 'modified ITT' data whereby patients had to have received at least one dose of study treatment).

Data on study design, participant characteristics, efficacy outcomes and quality were extracted by one reviewer using a standardised data extraction form and independently checked by a second reviewer for the secukinumab and certolizumab pegol trials. Disagreements were resolved through consensus. For the comparator treatments most of the data were copied (from previous reports) by one reviewer and then checked for any transcription errors by a second reviewer.

Attempts were made, where possible, to contact authors for missing data. Data from studies with multiple publications were extracted and reported as a single study. For the open-label extension studies of comparator treatments, only the data relating to the latest time point were extracted. Data were also extracted from the manufacturer submissions when they were not available from other sources.

Quality assessment

The quality of the RCTs was assessed using a modified version of the Cochrane risk of bias tool, which incorporated an assessment of baseline imbalance.[35] The assessments of baseline imbalance were made based on evidence from a systematic review of predictors of treatment response to anti-TNFs.[36] The review identified several possible such predictors in patients with psoriatic arthritis, although none were identified as being conclusive due to the limited number of studies and the heterogeneity of response measures. We looked at baseline CRP, age, and sex: young age, male sex and high CRP may be predictive of a better response. Risk of bias assessments were performed by one reviewer and checked independently by a second reviewer. Any disagreements were resolved through consensus or by involvement of the third reviewer if necessary. Open-label extension studies were

less formally evaluated based on imputation methods and patients withdrawal criteria used and on the clinical relevance of any treatment stopping/changing rules.

Methods of data synthesis

The study characteristics and quality assessment results were tabulated and summarised narratively. Where possible, the clinical effectiveness data for the PsARC, ACR, PASI and HAQ-DI outcomes were synthesized using Bayesian network meta-analysis methods (see section 5). For other outcomes, or for studies not included in the network meta-analyses, studies were either summarised narratively or pooled using pairwise meta-analysis methods.

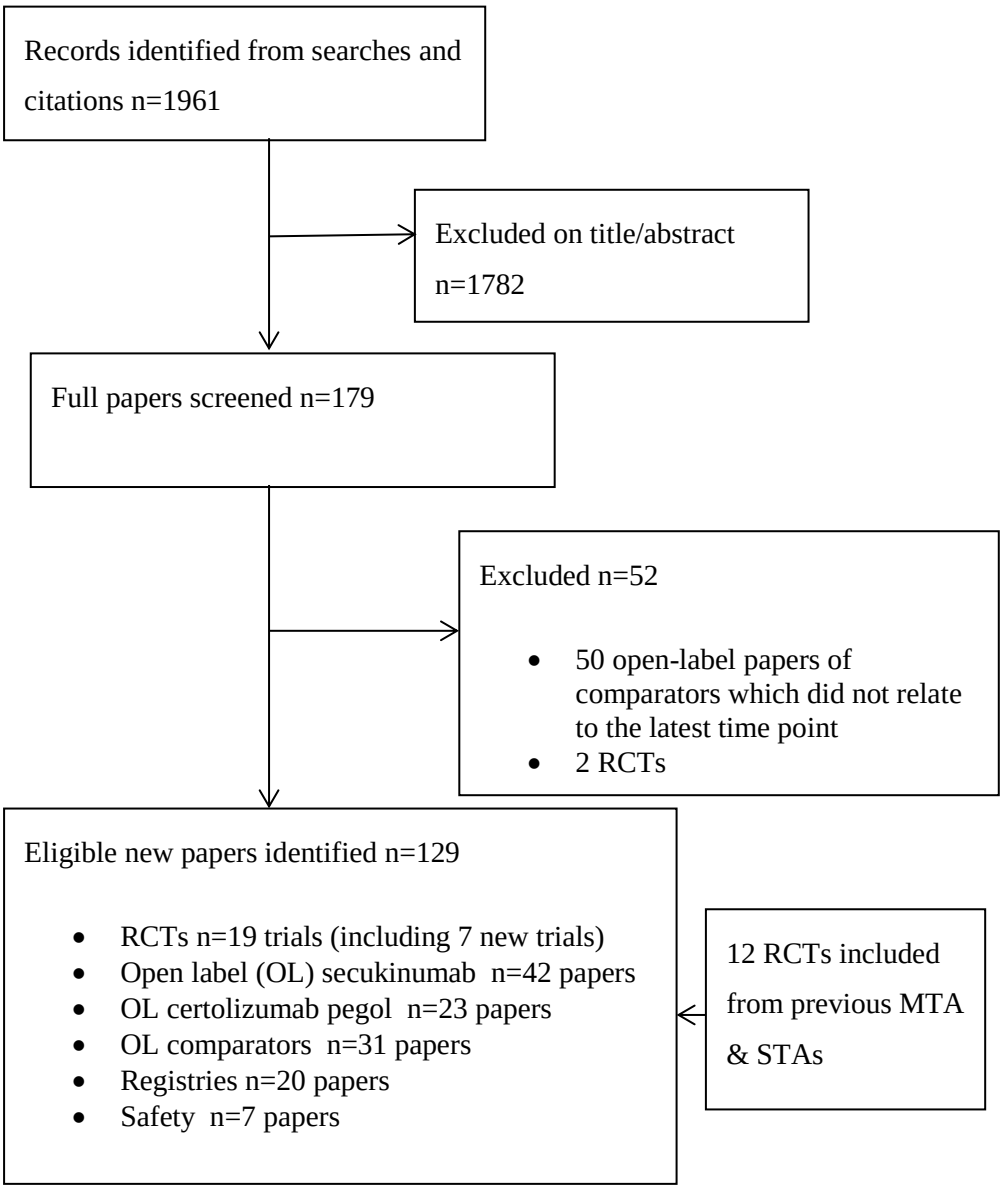
4.2 Quantity and quality of the identified evidence

A total of 1761 records were retrieved from the original December 2015 electronic database searches. The searches were updated on 28th April 2016 with a further 200 records available for screening. After screening titles and abstracts, full copies of 179 papers were assessed for inclusion in the review.

Two RCTs were excluded at the abstract stage for using unlicensed dosages (etanercept 50mg twice weekly[37] and apremilast 20mg and 40mg[38]). Two RCTs were excluded at the full paper stage: one did not report subgroup results for psoriatic arthritis[39] and the other only included patients who were naïve to MTX[40]. The FUTURE 1 trial of secukinumab was excluded from the RCT short-term efficacy review as it used an unlicensed very high loading dose. It was though included as an open-label extension study as the impact of the initial high loading dose would likely be negligible at later time points.[41] Fifty open-label studies of comparator treatments were excluded as they did not relate to the latest (longest) duration of follow up.

Details of the numbers of other eligible full publications or conference abstracts, which relate to open-label studies of the included RCTs and patient registry or safety studies, are presented in Figure 1.

Figure 1 Flow chart showing the number of studies identified and eligible for inclusion



4.3 Characteristics of the RCTs included in the systematic review of short-term efficacy

Of the nineteen included RCTs, 17 were placebo-controlled: one of certolizumab pegol,[42] three of secukinumab (two of which were reported in one publication),[43, 44] one of golimumab,[45] two of infliximab,[46, 47] two of etanercept,[48, 49] three of adalimumab,[50-52] two of ustekinumab,[53, 54] and three of apremilast.[55, 56] The FUTURE 1 trial of secukinumab was excluded from the RCT short-term efficacy review as it used an unlicensed very high loading dose.[41]

Two trials compared active treatments: one compared secukinumab with ustekinumab [57, 58] and one compared infliximab, etanercept and adalimumab.[59]

Most studies were conducted mainly in Europe and North America. All but two[48, 59] were multi-centre trials. Details of the trial durations, different phases and the dosing regimens of the main interventions studied are presented in Table 2. Details of all interventions studied are presented in Table 3. For some trials we excluded individual treatment arms from the systematic review. This may have been due to the doses not being licensed or recommended in the populations studied. Some included trials were excluded from the network meta-analyses due to the populations being different from the other trial populations.

The design of many trials typically included a fully blinded, placebo-controlled phase followed by an 'early escape' cross-over phase (from placebo to an active treatment) for non-responders, then finally cross-over to active treatment for the remaining placebo participants. Non-response in this context related to failure to achieve pre-specified minimum improvements (ranging between 5% and 20%) in tender and swollen joint counts. All the trials using an early escape design ran for 16 weeks before patients were eligible for early escape. Trials then entered open-label extension phases (see section 4.7).

Table 2 Trial durations (include open-label extensions) and dosing regimens of key interventions studied

Main study reference and treatments studied	Eligible licensed dosing regimens (with timings)	Duration of truly randomised and blinded phase (before any treatment cross-over)	Cross-over details	Latest time point with available result data	Anticipated time to response: information from Summary of Product Characteristics (SPC)
FUTURE 2 Secukinumab [43]	150mg subcutaneous injection at weeks 0,1,2 and 3 followed by monthly maintenance dosing from week 4 For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNF inadequate responders, the recommended dose is 300 mg (given as two 150mg injections)	16 weeks	Week 16: Placebo non-responders (not achieving ≥20% improvement from baseline in TJC and SJC) re-randomised to 150mg or 300mg every 4 weeks. Week 24: Placebo responders re-randomised to 150mg or 300mg every 4 weeks.	52 weeks	Clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks
FIXTURE[44] Secukinumab and etanercept	For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNF inadequate responders, the recommended secukinumab dose is 300 mg	12 weeks	At 12 weeks placebo non-responders were re-randomised to secukinumab 150mg or 300mg.	52 weeks	
ERASURE[44] Secukinumab					
CLEAR Secukinumab and Ustekinumab[57 58]	Secukinumab :For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNF inadequate responders, the recommended dose is 300 mg Ustekinumab: 45 mg at week 0, week 4, and every 12 weeks	52 weeks but data currently available only for up to 16 weeks	No cross-overs	52 weeks	
RAPID-PsA Certolizumab pegol[42]	200mg subcutaneous injection Loading dose: 2x200mg at weeks 0,2,4 Maintenance dose: 200mg every 2 weeks Alternative maintenance dose once clinical	16 weeks	Placebo patients failing to achieve a 10% improvement in both TJC and SJC at both weeks 14 and 16 were re-randomised to 200mg or 400mg at week 16 At week 24 the remaining placebo	216 weeks	Clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within

Main study reference and treatments studied	**Eligible licensed dosing regimens (with timings)**	**Duration of truly randomised and blinded phase (before any treatment cross-over)**	**Cross-over details**	**Latest time point with available result data**	**Anticipated time to response: information from Summary of Product Characteristics (SPC)**
	response is confirmed can be considered: 400mg every 4 weeks		patients were re-randomised to 200mg or 400mg		the first 12 weeks of treatment
PALACE 1 PALACE 2 PALACE 3 Apremilast[55, 56, 60]	30 mg twice daily, oral tablets	16 weeks	At week 16, patients without ≥20% reduction in swollen and tender joint counts were required to be re-randomised equally to either apremilast dose if initially randomised to placebo or remained on their initial apremilast dose. At week 24, all remaining placebo-treated patients were switched to apremilast.	104 weeks (PALACE 1)	During pivotal trials the greatest improvement was observed within the first 24 weeks of treatment. If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment should be reconsidered. The patient's response to treatment should be evaluated on a regular basis.
PSUMMIT 1 Ustekinumab[53]	45 mg, subcutaneous injection followed by a 45 mg dose 4 weeks later, and then every 12 weeks.	16 weeks	At week 16, patients with <5% improvement in tender/swollen joint counts entered blinded early escape (placebo to 45 mg, 45 mg to 90 mg, 90 mg to 90 mg) At week 24, all remaining patients in the placebo group received ustekinumab 45 mg, which they continued at week 28 and every 12 weeks thereafter	108 weeks for safety and 100 weeks for efficacy evaluation	Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.
PSUMMIT 2 Ustekinumab[54, 61]	45 mg at week 0, week 4, and every 12 weeks	16 weeks	At week 16, patients with <5% improvement in tender/swollen joint counts entered blinded early escape (placebo to 45 mg, 45 mg to 90 mg, 90 mg to 90 mg) At week 24, all remaining patients in the placebo group received ustekinumab 45 mg.	100 weeks	See above

Main study reference and treatments studied	Eligible licensed dosing regimens (with timings)	Duration of truly randomised and blinded phase (before any treatment cross-over)	Cross-over details	Latest time point with available result data	Anticipated time to response: information from Summary of Product Characteristics (SPC)
GO-REVEAL Golimumab[45]	50 mg once monthly, subcutaneous injection	16 weeks	At week 16, patients with <10% improvement in both tender and swollen joint counts entered blinded early escape (placebo to 50 mg, 50 mg to 100 mg, 100 mg to 100 mg) Open label from week 24 (in which all patients were eligible for golimumab)	256 weeks	Clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period
ADEPT Adalimumab[50]	40mg every other week subcutaneous injection	24 weeks	Open label from 24weeks (in which all patients were eligible for adalimumab)	144 weeks	Clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.
SPIRIT-P1 Adalimumab [62 52]	40mg every other week subcutaneous injection	Not reported	Not reported	Not reported	
Genovese 2007 Adalimumab[51]	40mg every other week subcutaneous injection	12 weeks	Open label from 12 weeks (in which all patients were eligible for adalimumab)	24 weeks	
IMPACT[46] Infliximab	5 mg/kg, intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks.	16 weeks	At week 16 patients initially assigned to receive placebo crossed over to receive infliximab 5 mg/kg	98 weeks	Not reported
IMPACT 2[47] Infliximab	5 mg/kg, intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks.	16 weeks	At week 16 placebo patients with <10% improvement in both tender and swollen joint counts received infliximab 5mg/kg Open label from 24 weeks (in which all	54 weeks	

Main study reference and treatments studied	**Eligible licensed dosing regimens (with timings)**	**Duration of truly randomised and blinded phase (before any treatment cross-over)**	**Cross-over details**	**Latest time point with available result data**	**Anticipated time to response: information from Summary of Product Characteristics (SPC)**
			patients were eligible for infliximab)		
Mease 2004[49] Etanercept	25 mg twice weekly subcutaneous injection	24 weeks	Open label from 24weeks (in which all patients were eligible for etanercept)	104 weeks	Clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.
Mease 2000[48] Etanercept	25 mg twice weekly subcutaneous injection	12 weeks	Open label from 12 weeks (in which all patients were eligible for etanercept)	36 weeks	
Atteno 2010[59] Infliximab Etanercept Adalimumab	INF 5mg/Kg every 6-8 weeks ETA 25mg twice weekly ADA 40mg every other week	52 weeks (blinding not feasible)	No cross-overs	52 weeks	See details for trials of INF, ETA and ADA.

Table 4 describes the population characteristics of the included trials. Where available, this includes subgroup characteristics for patients who had never previously taken a biologic (biologic-naïve populations) and patients who *had* previously taken a biologic (biologic-experienced populations). Biologic-experienced patients were only available for the more recent trials (those of secukinumab, certolizumab pegol, ustekinumab and apremilast); in the earlier trials such patients were not eligible to participate. Trial sample sizes varied, with earlier trials tending to be smaller than more recent trials. Variation in sample size was also evident within treatments: the two trials of etanercept had populations of 60 and 205, and the three trials of adalimumab had populations of 102, 207 and 315. The duration of psoriatic arthritis ranged from 3 to 12 years across trials; the shortest durations (reported as medians) came from the ustekinumab PSUMMIT trials and the longest (reported as means) came from the infliximab IMPACT trial. The duration of psoriasis ranged from 11 to 23 years though these data were not available for the FUTURE 2 secukinumab and RAPID-PsA certolizumab trials. Though not reported in all trials, baseline CRP levels were difficult to interpret as they appear to have slightly skewed distributions with means (range 10 to 31 mg/l) being generally higher than medians (range 7 to 15 mg/l).

Notwithstanding this limited heterogeneity many key patient characteristics were broadly similar across trials including mean ages (which ranged from 45 to 51 years), the proportion of male participants (around 50% for most trials) and tender and swollen joint counts (TJC range 18 to 29, SJC range 9 to 18); an exception was the 3-arm head-to-head trial which had notably lower TJC and SJC.[59] The population in this trial, along with the psoriatic arthritis populations from the large secukinumab psoriasis trials[44] also had markedly higher baseline PASI scores than the other trials (typically around 2 to 3 times higher). The FUTURE 2 secukinumab trial had slightly higher baseline PASI scores than the other trials, most notably in the 150mg treatment arm. The psoriatic arthritis populations from two of the secukinumab psoriasis trials[44] also had lower baseline HAQ-DI scores (range 0.5 to 0.8) than the other trials (range 0.9 to 1.6). In light of these differences the characteristics of the psoriatic arthritis patients in the secukinumab psoriasis trials were not deemed to be similar enough to the other trials to be included in the network meta-analyses. There were three of these psoriasis trials: ERASURE, FIXTURE and CLEAR (baseline data were not available for the psoriatic arthritis patients in CLEAR). To be eligible for the ERASURE, FIXTURE and CLEAR trials patients had to have moderate to severe psoriasis based on PASI>12 and body surface area (BSA) involvement ≥ 10%.**[44]** In the trials only of patients with psoriatic arthritis the proportion of patients with at least moderate psoriasis (i.e. PASI-evaluable patients, defined as BSA covering ≥3%) ranged between 41% and 87%.

In FUTURE 2 (secukinumab) and RAPID-PsA (certolizumab pegol) the biologic-experienced and biologic-naïve subgroups were broadly similar except that the biologic-experienced subgroups tended to have slightly higher TJC and SJC and slightly longer durations of psoriatic arthritis.

Table 3 Treatment doses studied in the review of short-term efficacy

Trial	Trialled treatments and doses (mg)	Doses included in the review	Dose included in the network meta-analysis	Comments
FUTURE 2[43]	SEC 75 SEC 150 SEC 300 Placebo	SEC 150 SEC 300 Placebo	SEC 150 SEC 300 Placebo	75mg not a licensed dose for psoriatic arthritis
ERASURE[44]	SEC 150 SEC 300 Placebo	SEC 300 Placebo	-	The severity of psoriasis seen in the population studied in this trial (>30% BSA involvement) suggests that the 150mg arm results have very limited relevance to clinical practice (as these patients are likely to receive 300mg). Excluded from NMA as baseline PASI and HAQ very different from other trials.
FIXTURE[44]	ETA 50 twice weekly SEC 150 SEC 300 Placebo	SEC 300 Placebo	-	The severity of psoriasis seen in the population studied in this trial (>30% BSA involvement) suggests that the 150mg arm results have very limited relevance to clinical practice (as these patients are likely to receive 300mg). Excluded from NMA as baseline PASI and HAQ very different from other trials. ETA 50mg twice weekly excluded as not a licensed dose in PsA.
CLEAR[57]	SEC 300 UST 45 or 90[a]	SEC 300 UST 45 or 90	-	Baseline characteristics within the subgroup with PsA were not reported therefore it is not clear how severe the psoriasis is within this subgroup. Excluded from NMA based on high mean PASI score in whole trial population.
SPIRIT-P1[52, 62]	IXE 80every 2 weeks IXE 80 every 4 weeks ADA 40 Placebo	ADA 40 Placebo	ADA 40 Placebo	Ixekizumab is not an eligible treatment for this review

Trial	Trialled treatments and doses (mg)	Doses included in the review	Dose included in the network meta-analysis	Comments
RAPID-PsA[42]	CZP 200 every 2 weeks CZP 400 every 4 weeks Placebo	CZP 200 every 2 weeks CZP 400 every 4 weeks Placebo	CZP 200 every 2 weeks CZP 400 every 4 weeks Placebo	
PALACE1[55]	APR 20 APR 30 Placebo	APR 30 Placebo	APR 30 Placebo	20mg not a licensed dose
PALACE2[60]	APR 20 APR 30 Placebo	APR 30 Placebo	APR 30 Placebo	20mg not a licensed dose
PALACE3[60]	APR 20 APR 30 Placebo	APR 30 Placebo	APR 30 Placebo	20mg not a licensed dose
PSUMMIT2[54]	UST 45 UST 90 Placebo	UST 45 Placebo	UST45 Placebo	90mg arm excluded as it was not administered as per license for all patients.
PSUMMIT1[61]	UST 45 UST 90 Placebo	UST 45 Placebo	UST 45 Placebo	90mg excluded as it was not administered as per license.

Trial	Trialled treatments and doses (mg)	Doses included in the review	Dose included in the network meta-analysis	Comments
Atteno (2010) [59]	ETA 25 INF5 mg/kg ADA 40	ETA 25 INF5 mg/kg ADA 40	-	Only 1 year data is available
GO-REVEAL[45]	GOL 50 GOL 100 Placebo	GOL 50 Placebo	GOL 50 Placebo	Excluded 100mg as it was not administered as per license
Genovese (2007)[51]	ADA 40 Placebo	ADA 40 Placebo	ADA 40 Placebo	-
ADEPT[50]	ADA 40 Placebo	ADA 40 Placebo	ADA 40 Placebo	-
IMPACT[46]	INF 5 mg/kg Placebo	INF 5mg/kg Placebo	INF 5mg/kg Placebo	-
IMPACT2[47]	INF5 mg/kg Placebo	INF 5mg/kg Placebo	INF 5mg/kg Placebo	-
Mease (2004)[49]	ETA 25 Placebo	ETA 25 Placebo	ETA 25 Placebo	-
Mease (2000)[48]	ETA 25 Placebo	ETA 25 Placebo	ETA 25 Placebo	-

Trial	Trialled treatments and doses (mg)	Doses included in the review	Dose included in the network meta-analysis	Comments
Trials excluded from the main review of short-term efficacy				
FUTURE 1	SEC 150 Placebo	-	-	Excluded: used unlicensed loading dose. Safety data from MS is eligible though.
PRESTA [37]	ETA 50 twice weekly ETA 50 once weekly	-	-	Excluded on comparator: not a placebo controlled trial and ETA 50mg twice weekly is not a licensed dose
Schett (2012) [38]	APR 20 APR 40 Placebo	-	-	Excluded: did not include licensed dose (APR 30mg)

[a] Dose given as per license - according to patient weight IXE = ixekizumab BSA = Body surface area

Table 4 Baseline population characteristics of the included randomised trials

Trial	Trial Arm	Number randomised	Age Mean (SD)	% Male	Duration of PsA, years Mean (SD)	Duration of psoriasis, years Mean (SD)	CRP mg/l (SD)	TJC Mean (SD)	SJC Mean (SD)	HAQ Mean (SD)	PASI evaluable patients ≥3% BSA (%)	PASI (0-72) Mean (SD)	MTX use at randomisation (%)
FUTURE 2 All patients [43]	150 mg SEC	100	46.5 (11.7)	55	-	-	-	[redacted]	[redacted]	[redacted]	58 (58)	16.2 (14.3)	44
	300mg SEC	100	46.9 (12.6)	51	-	-	-	[redacted]	[redacted]	[redacted]	41 (41)	11.9 (8.4)	44
	Placebo	98	49.9 (12.5)	40	-	-	-	[redacted]	[redacted]	[redacted]	43 (44)	11.6 (8.3)	51
FUTURE 2 Biologic-experienced [43]	SEC For pooled doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUTURE 2 Biologic-naive [43]	SEC For pooled doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERASURE[44a] [63]	300mg SEC	57	46.1 (12.0)	58	-	19.7 (12.7)	-	-	-	0.8 (0.8)	57 (100: subgroup)	21.4 (8.7)	-
	Placebo	68	48.4 (12.4)	63	-	22.6 (13.7)	-	-	-	0.8 (0.6)	68 (100: subgroup	21.3 (10.1)	-
FIXTURE [44a]	300mg SEC	50	47.8 (15.3)	52	-	21.7 (15.3)	-	-	-	0.7 (0.6)	50 (100: subgroup)	25.8 (10.9)	-

Trial	Trial Arm	Number randomised	Age Mean (SD)	% Male	Duration of PsA, years Mean (SD)	Duration of psoriasis, years Mean (SD)	CRP mg/l (SD)	TJC Mean (SD)	SJC Mean (SD)	HAQ Mean (SD)	PASI evaluable patients ≥3% BSA (%)	PASI (0-72) Mean (SD)	MTX use at randomisation (%)
	ETA 100mg /week	44	46.4 (12.0)	57	-	22.6 (13.0)	-	-	-	0.7 (0.6)	44 (100: subgroup)	21.9 (7.5)	-
	Placebo	49	45.7 (11.6)	55	-	20.5 (13.1)	-	-	-	0.5 (0.6)	49 (100: subgroup)	23.7 (8.4)	
CLEAR[a] [57] [58]	SEC 300mg	69	Baseline data not available for subgroup (the 123 patients with psoriatic arthritis)										
	UST	54											
SPIRIT-P1[62] [52]	ADA[e]	101	Baseline data not available (trial reported only in conference abstracts)										
	Placebo	106											
RAPID-PsA All patients[42]	200mg CZP	[redacted]											
	400mg CZP	[redacted]											
	Placebo	[redacted]											
RAPID-PsA Biologic-experienced	Pooled CZP	[redacted]											
	Placebo	[redacted]											
RAPID-PsA Biologic-naïve	Pooled CZP	[redacted]											
	Placebo	[redacted]											

Trial	Trial Arm	Number randomised	Age Mean (SD)	% Male	Duration of PsA, years Mean (SD)	Duration of psoriasis, years Mean (SD)	CRP mg/l (SD)	TJC Mean (SD)	SJC Mean (SD)	HAQ Mean (SD)	PASI evaluable patients ≥3% BSA (%)	PASI (0-72) Mean (SD)	MTX use at randomisation (%)
RAPID-PsA Biologic-experienced (≥3% BSA and PASI>10 at baseline)	Pooled CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAPID-PsA Biologic-naïve (≥3% BSA and PASI>10 at baseline)	Pooled CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PALACE 1[55, 64]	30mg APR	168	51.4 (11.7)	45	8.1 (8.1)	16.50 (12.3)	8.4 (10.2)	23.1 (14.5)	12.8 (7.8)	1.2 (0.6)	82 (49)	9.2 (9.7)	52
	Placebo	168	51.1 (12.1)	52	7.3 (7.1)	15.7 (13.0)	11 (14.4)	23.3 (15.2)	12.8 (8.8)	1.2 (0.6)	68 (41)	9.1 (9.5)	54
PALACE 2[60, 64 56]	APR 30mg	162	50.5 (11.2)	41	6.8 (7.6)	18.7 (14.5)	-	21.8 (16.8)	10.3 (8.1)	1.2 (0.6)	-	7.8 (7.3)	70
	Placebo	159	51.2 (11.0)	47	7.8 (8.3)	17.8 (13.9)	-	18.0 (13.5)	9.2 (6.6)	1.2 (0.6)	-	8.6 (10.0)	59
PALACE 3[60, 64 56]	APR 30mg	167	49.9 (11.4)	47	7.5 (7.6)	17.1 (12.1)	-	20.9 (14.4)	11.6 (8.7)	1.2 (0.6)	-	7.9 (6.3)	50
	Placebo	169	49.5 (11.6)	46	6.8 (6.5)	17.8 (13.3)	-	18.3 (14.9)	11.1 (7.9)	1.2 (0.6)	-	7.6 (7.2)	54
PSUMMIT 2 2014 All patients[54, 61]	45mg UST	103	49.0 (40,56)[b]	47	5.3 (2.3,12.2)[b]	13.3 (5.0,24.4)[b]	13.0 (4.5, 36.3)[b]	22 (15,33)[b]	12 (8,19)[b]	1.4 (0.8,1.9)[b]	80 (78)	8.6 (4.5,18.3)[b]	52
	90mg UST	105	48.0 (41,57)[b]	47	4.5 (1.7,10.3)[b]	11.3 (4.5,21.4)[b]	10.1 (4.8, 19.8)[b]	22 (14,36)[b]	11 (7,17)[b]	1.3 (0.8,1.9)[b]	81 (77)	8.8 (4.5,18.0)[b]	50

Trial	Trial Arm	Number randomised	Age Mean (SD)	% Male	Duration of PsA, years Mean (SD)	Duration of psoriasis, years Mean (SD)	CRP mg/l (SD)	TJC Mean (SD)	SJC Mean (SD)	HAQ Mean (SD)	PASI evaluable patients ≥3% BSA (%)	PASI (0-72) Mean (SD)	MTX use at randomisation (%)
	Placebo	104	48.0 (38.5 - 56.0)[b]	49	5.5 (2.3-12.2)[b]	11.4 (6.0 - 22.0)[b]	8.5 (4.6,22.0)[b]	21 (11-30)[b]	11 (7 -18)[b]	1.3 (0.8-1.8)[b]	80 (77)	7.9 (4.5-16.0)[b]	47
PSUMMIT 2 2014 Biologic-experienced[54, 61]	45mg UST	60	49.0 (39,55)[b]	38	7.3 (4.1,13.7)[b]	15.5 (7.1,24.7)[b]	15.0 (4.9,37.0)[b]	24.0 (16.5,40.5)[b]	14.5 (7.5,20.5)[b]	1.4 (0.8,2.0)[b]	-	-	-
	90mg UST	58	48 (40,56)[b]	38	5.7 (2.5,10.5)[b]	12.6 (7.3,23.4)[b]	10.9 (6.9,26.8)[b]	25.5 (17.0,43.0)[b]	12.5 (7.0,19.0)[b]	1.6 (0.9,1.9)[b]	-	-	-
	Placebo	62	48.5 (37,55)[b]	50	7.1 (4.1,12.5)[b]	12.3 (8.3,22.4)[b]	8.7 (4.2,22.3)[b]	24.0 (12.0,31.0)[b]	11.0 (7.0,17.0)[b]	1.3 (0.8,1.8)[b]	-	-	-
PSUMMIT 1 2013[53, 61]	45mg UST	205	48·0 (39,55)[b]	52	3·4 (1·2–9·2)[b]	12·0 (4·1–22·2)[b]	10·0 (5·9,21·1)[b]	18 (12–28)[b]	10 (7-15)[b]	1.3 (0.8-1.8)[b]	145 (71)	7·1 (3·3-15·3)[b]	48
	90mg UST	204	47.0 (38.5–54.0)[b]	57	4·9 (1·7–8·3)[b]	14·1 (5·4–22·4)[b]	12·3 (6·5,21·7)[b]	20 (12–32)[b]	10 (7-16)[b]	1.3 (0·8-1·6)[b]	149 (73)	8·4 (4·8-14·7)[b]	50
	Placebo	206	48.0 (39,57)[b]	52	3·6 (1·0–9·7)[b]	13·1 (5·3–23·5)[b]	9·6 (6·0,18·6)[b]	22 (13–33)[b]	12 (8-19)[b]	1.3 (0.8-1.8)[b]	146 (71)	8·8 (4·4-14·3)[b]	47
Atteno[59]	ETA	36	49.3 (13.4)	-	-	-	-	13	4	1.2 (0.4)[b]	-	26 (18.5)b	51
	ADA	34	47.5 (11.5)	-	-	-	-	13	5	1.2 (0.3)[b]	-	18 (16.5)b	
	INF	30	48.5 (12.9)	-	-	-	-	12	3	1.5 (0.5)[b]	-	15 (14.8)b	
GO-REVEAL 2009[45]	GOL 50mg	146	45.7 (10.7)	61	7.2 (6.8)	17.7 (11.9)	13 (16)	24.0 (17.1)	14.1 (11.4)	0.98 (0.65)	109 (75)	9.8 (8.6)	49
	Placebo	113	47.0 (10.6)	61	7.6 (7.9)	19.0 (12.9)	13 (16)	21.9 (14.7)	13.4 (9.8)	1.03 (0.55)	79 (70)	8.4 (7.4)	48
Genovese 2007[51]	ADA	51	50.4 (11.0)	57	7.5 (7.0)	18.0 (13.2)	10 (10)	25.3 (18.3)	18.2 (10.9)	0.9 (0.5)	-	-	47

Trial	Trial Arm	Number randomised	Age Mean (SD)	% Male	Duration of PsA, years Mean (SD)	Duration of psoriasis, years Mean (SD)	CRP mg/l (SD)	TJC Mean (SD)	SJC Mean (SD)	HAQ Mean (SD)	PASI evaluable patients ≥3% BSA (%)	PASI (0-72) Mean (SD)	MTX use at randomisation (%)
	Placebo	49	47.7 (11.3)	51	7.2 (7.0)	13.8 (10.7)	16 (17)	29.3 (18.1)	18.4 (12.1)	1.0 (0.7)	-	-	47
ADEPT 2005[50]	ADA	153	48.6 (12.5)	56	9.8 (8.3)	17.2 (12.0)	14 (21)	23.9 (17.3)	14.3 (12.2)	1.0 (0.6)	70 (46)	7.4 (6.0)	51
	Placebo	162	49.2 (11.1)	55	9.2 (8.7)	17.1 (12.6)	14 (17)	25.8 (18.0)	14.3 (11.1)	1.0 (0.7)	70 (43)	8.3 (7.2)	50
IMPACT 2 2005[47]	INF	100	47.1 (12.8)	71	8.4 (7.2)	16.2 (11.0)	19 (21)	24.6 (14.1)	13.9 (7.9)	1.1 (0.6)	83 (83)	11.4 (12.7)	47
	Placebo	100	46.5 (11.3)	51	7.5 (7.8)	16.8 (12.0)	23 (34)	25.1 (13.3)	14.4 (8.9)	1.1 (0.6)	87 (87)	10.2 (9.0)	45
IMPACT 2005[46]	INF	52	45.7 (11.1)	58	11.7 (6.6)	16.9 (10.9)	22 (27)	23.7 (13.7)	14.6 (7.5)	1.2 (0.7)	22 (42)[c]	5.1 (5.9)	46
	Placebo	52	45.2 (9.7)	58	11 (6.6)	19.4 (11.6)	31 (38)	20.4 (12.1)	14.7 (8.2)	1.2 (0.7)	17 (33)[c]	4.2 (5.8)	65
Mease 2004[49]	ETA	101	47.6	57	9.0	18.3	-	20.4 (-)[b]	15.9(-)[b]	1.1(-)[b]	-	-	45
	Placebo	104	47.3	45	9.2	19.7	-	22.1(-)[b]	15.3(-)[b]	1.1(-)[b]	-	-	49
Mease 2000[48]	ETA	30	46.0(30-70)[d]	53	9.0 (1-31)[d]	19.0 (4-53)[d]	14(7-28)[b]	22.5 (11, 32)[b]	14.0 (8, 23)[b]	1.3 (0.9, 1.6)[b]	19 (63)	10.1 (2.3-30.0)[d]	47
	Placebo	30	43.5(24-63)[d]	60	9.5 (1-30)[d]	17.5 (2-43)[d]	12(8-22)[b]	19.0 (10, 39) [b]	14.7 (7, 24)[b]	1.2 (0.8, 1.6)[b]	19 (63)	6.0 (1.5-17.7)[d]	47

[a] Subgroup data for patients with moderate-to-severe psoriasis and psoriatic arthritis
[b] median (25^{th}, 75^{th} percentile; or interquartile range)
[c] Patients with a baseline PASI score ≥2.5
[d] median (range)
BSA Body surface area
[e] main intervention studied was ixekizumab (treatment not eligible for this review)
[β] pooled secukinumab 75mg, 150mg and 300mg doses

All the trials of etanercept, infliximab, adalimumab and golimumab and one ustekinumab trial[53] excluded patients who had previously received an anti-TNF so their populations were comprised entirely of biologic-naïve patients (Table 5). In the remaining trials, where reported, the proportion of biologic-experienced patients ranged from 15% to 58%. Of the trials which allowed recruitment of biologic-experienced patients, the RAPID-PsA trial was more selective than the FUTURE 2, PSUMMIT 2 and PALACE trials: RAPID-PsA was the only trial in which patients with primary failure of a previous anti-TNF were excluded (primary failure was defined as no response within the first 12 weeks of treatment with the anti-TNF); see Appendix 12.2, which details the eligibility criteria for all trials. The results for the RAPID-PsA biologic-experienced subgroup may therefore be somewhat inflated when compared with the other trials reporting results for this subgroup.

The proportion of patients who took concomitant methotrexate ranged from 44 to 70%; most trials allowed concomitant methotrexate although the FIXTURE and ERASURE psoriasis trials did not. The reporting of data on the number of previous DMARDs used was limited, though it appeared that most patients had tried one or two DMARDs.

Table 5 Previous and concomitant treatment details for the included studies

Study	Interventions and dose	Number of prior DMARDS Mean	Percentage of patients with numbers of previous DMARDs	Previous biologic therapy	Concomitant treatments during trial (%)		
					Cortico-steroids	NSAIDs	Methotrexate
FUTURE 2[43]	150 mg SEC	-	-	0=63%, 1=26%, 2-3=11%	23	-	44
	300mg SEC	-	-	0=67%, 1=16%, 2-3=17%	18	-	44
	Placebo	-	-	0=64%, 1=16%, 2-3=19%	21	-	51
ERASURE[a] [44]	300mg SEC	-	-	42% had a prior biologic	-	-	-
	Placebo	-	-	44% had a prior biologic	-	-	-
FIXTURE[a44]	300mg SEC	-	-	22% had a prior biologic	-	-	-
	100 mg ETA per week	-	-	18% had a prior biologic	-	-	-
	Placebo	-	-	18% had a prior biologic	-	-	-
CLEAR[a] [57] [58]	SEC	-	-	-	-	-	-
	UST	-	-	-	-	-	-
SPIRIT-P1 [62] [52]	ADA	No data available (trial reported only in conference abstracts) other than biologic-experienced patients were excluded					
	Placebo						
RAPID-PsA[42]	200mg CZP	-	1=44, ≥2=53	23% had a prior biologic	-	-	64
	400mg CZP	-	1=53, ≥2=45	17% had a prior biologic	-	-	65
	Placebo	-	1=54, ≥2=44	19% had a prior anti-TNF	-	-	62
PALACE 1[55]	30mg APR		2% had never received a DMARD	24% had a prior biologic			52

Study	Interventions and dose	Number of prior DMARDS Mean	Percentage of patients with numbers of previous DMARDs	Previous biologic therapy	Concomitant treatments during trial (%)		
					Cortico-steroids	NSAIDs	Methotrexate
	Placebo		4% had never received a DMARD	24% had a prior anti-TNF			54
PALACE 2[56, 60]	30mg APR		3% had never received a DMARD	14% had a prior biologic			70
	Placebo		1% had never received a DMARD	15% had a prior biologic			59
PALACE 3[56, 60]	30mg APR		All patients had previously received a DMARD	26% had a prior biologic			50
	Placebo		All patients had previously received a DMARD	28% had a prior biologic			54
PSUMMIT 2 2014[54, 61]	45mg UST	-	14% had never received a DMARD	180 (58%) had a prior anti-TNF	20	70	52
	90mg UST	-			15	67	50
	Placebo				13	74	47
PSUMMIT 1 2013[53, 61]	45mg UST	-	20% had never received a DMARD	Biologic-experienced patients excluded	18	76	48
	90mg UST	-			14	74	50
	Placebo	-			16	73	47
Atteno 2010[59]	ETA	-	-	Biologic-experienced patients excluded			51
	ADA	-	-				
	INF	-	-				
GO-REVEAL 2009[45]	50mg GOL	-	0=25, 1-2=69, 2+=6	Biologic-experienced patients excluded	13	75	49
	Placebo	-	0=25, 1-2 =66, 2+=9		17	78	48

Study	Interventions and dose	Number of prior DMARDS Mean	Percentage of patients with numbers of previous DMARDs	Previous biologic therapy	Concomitant treatments during trial (%)		
					Cortico-steroids	NSAIDs	Methotrexate
Genovese 2007[51]	ADA	1.7	All patients had a history of DMARD therapy	Biologic-experienced patients excluded	-	73	47
	Placebo	2.1			-	86	47
ADEPT 2005[50]	ADA	1.5	-	Biologic-experienced patients excluded	-	-	51
	Placebo	1.5	-		-	-	50
IMPACT 2 2005[47]	INF	-	0=17, 1-2=71, 2+=12	Biologic-experienced patients excluded	15	71	47
	Placebo	-	0=24, 1-2=67, 2+=9		10	73	45
IMPACT 2005[46]	INF	-	0=0, 1=52, 2-3=37, 3+=12	Biologic-experienced patients excluded	17	89	46
	Placebo	-	0=2, 1=38, 2-3=48, 3+=12		29	79	65
Mease 2004[49]	ETA	1.6	0=27, 1=40, 2=20	Biologic-experienced patients excluded	19	88	45
	Placebo	1.7	0=21, 1=50, 2=19		15	83	49
Mease 2000[48]	ETA	1.5	-	Biologic-experienced patients excluded	20	67	47
	Placebo	2.0	-		40	77	47

[a] Subgroup data for patients with moderate-to-severe psoriasis and psoriatic arthritis, SEC secukinumab, ETA etanercept, UST ustekinumab, CZP certolizumab pegol, APR apremilast, GOL golimumab, ADA adalimumab, INF infliximab

4.3.1 Risk of bias assessments

Results of the risk of bias assessments are presented in Table 6. All except one[62] [52] of the trials included in the network meta-analyses were judged to have a low overall risk of bias. Only one trial had a high overall risk of bias for all outcomes, which was primarily due to lack of blinding. However, blinding would have been both difficult and impractical as the trial compared infliximab, etanercept and adalimumab.[59] All the other trials were appropriately blinded. Across the trials the randomisation methods were well reported; only the head-to-head trial had unclear judgements for both sequence generation and allocation concealment.[59] The only chance imbalance of note occurred in PSUMMIT 2 where median CRP levels were higher in the 45mg group (13 mg/l) than the placebo group (8.5mg/l). Two of the three secukinumab trials in patients with psoriasis and psoriatic arthritis had overall judgments of unclear risk of bias. This was because psoriatic arthritis subgroup data were being assessed and no details were available on missing outcome data. The IMPACT 2 trial had a high risk of bias for the PASI 75 outcome as LOCF was used for missing data (instead of the more conservative non-responder imputation).

Table 6 Risk of bias judgements for randomised trials (for time points before early-escape cross-over)

Drug and trial		Risk of bias domain							Overall judgement
		Sequence generation	**Allocation concealment**	**Important baseline imbalance**	**Blinding of participants and researchers**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	
Secukinumab FUTURE 2[43]	**Judgement**	Low	Low	Low	Low	Low	Low	Low	**Low**
	Support	IVRS used	IVRS used	15% difference in proportion of males though chance imbalance (based on randomisation methods)	Doses were provided in identical pre-filled syringes	Doses were provided in identical pre-filled syringes	More withdrawals in placebo group but NRI and LOCF were used for missing data	Results reported for all key outcomes	
Secukinumab FIXTURE (subgroup)[44]	**Judgement**	Low	Low	Unclear	Low	Low	Unclear	Low	**Unclear**
	Support	IVRS used	IVRS used	No data on CRP	Adequate blinding (placebo controlled). Double-dummy design used as there was an active comparator arm.	Adequate blinding (placebo controlled). Double-dummy design used as there was an active comparator arm.	Unclear for the PsA subpopulation.	Results reported for all key outcomes	
Secukinumab ERASURE (subgroup)[44]	**Judgement**	Low	Low	Unclear	Low	Low	Unclear	Low	**Unclear**
	Support	IVRS used	IVRS used	No data on CRP	Adequate blinding (placebo controlled)	Adequate blinding (placebo controlled)	Unclear for the PsA subpopulation	Results reported for all key outcomes	
Secukinumab	**Judgement**	Low	Low	Low	Low	Low	Low	Low	**Low**

Drug and trial		Risk of bias domain							Overall judgement
		Sequence generation	**Allocation concealment**	**Important baseline imbalance**	**Blinding of participants and researchers**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	
CLEAR [57, 58]	**Support**	IVRS used	IVRS used	In the psoriasis trial as a whole, demographic and disease characteristics were similar between treatment arms[3]	Treatments looked identical	Treatments looked identical	Drop-outs for the subgroup with PsA were not reported. In the psoriasis trial as a whole, there were no imbalances in drop-outs between groups.	Results reported for key outcomes	
Adalimumab SPIRIT-P1 [62 52]	**Judgement**	Unclear	Unclear	Unclear	Low	Low	Low	Low	**Unclear**
	Support	Randomisation sequence not reported	Not reported	Not reported	Double blind (Subject, Caregiver, Investigator, Outcomes Assessor)	Double blind (Subject, Caregiver, Investigator, Outcomes Assessor)	NRI was used for missing data; continuous data of inadequate responders was excluded after 16week	All main outcomes reported	
Certolizumab pegol RAPID-PsA[42]	**Judgement**	Low	Low	Low	Low	Low	Low	Low	**Low**
	Support	IVRS used	IVRS used	Balanced	Blinded pre-filled syringes were used	Blinded pre-filled syringes were used	[redacted]	Results reported for all key outcomes	
Apremilast PALACE 1[55, 64]	**Judgement**	Low	Low	Low	Low	Low	Low	Low	**Low**
	Support	IVRS used	IVRS used	Balanced	EMA report states that identical tablets and blister cards were used in the	See blinding of participants and researchers cell	NRI and LOCF (for the sensitivity analysis only) were used	All main outcomes reported	

Drug and trial		Risk of bias domain							Overall judgement
		Sequence generation	**Allocation concealment**	**Important baseline imbalance**	**Blinding of participants and researchers**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	
					apremilast psoriasis trials[2]				
PALACE 2[60, 64]	**Judgement**	Low	Low	Unclear	Low	Low	Low	Low	**Low**
	Support	IVRS used	IVRS used	Data not available for individual trials	As for PALACE 1	As for PALACE 1	NRI and LOCF used. Similar withdrawal rates in pooled analysis.	All main outcomes reported	
PALACE 3[60, 64]	**Judgement**	Low	Low	Unclear	Low	Low	Low	Low	**Low**
	Support	IVRS used	IVRS used	Data not available for individual trials	As for PALACE 1	As for PALACE 1	NRI and LOCF used. Similar withdrawal rates in pooled analysis.	All main outcomes reported	
Ustekinumab PSUMMIT 2[54]	**Judgement**	Low	Low	Unclear	Low	Low	Low	Low	**Low**
	Support	IVRS used	IVRS used	Chance imbalance in median CRP (placebo 8.5 vs 45mg 13.0)	Based on details in Craig et al 2013 Ustekinumab STA Table 9[61]	Based on details in Craig et al 2013 Ustekinumab STA Table 9[61]	Low drop-out rate. NRI for ACR and PASI and LOCF for change in HAQ. Otherwise, missing data were not imputed for the rest of the outcomes.	All main outcomes reported	**but important imbalance, likely due to chance**
Ustekinumab PSUMMIT 1[61]	**Judgement**	Low	Low	Low	Low	Low	Low	Low	**Low**
	Support	IVRS used	IVRS used	Balanced	Based on details in Craig et al 2013	Based on details in Craig et al 2013	Low drop-out rate. NRI and LOCF used	All main outcomes reported	

Drug and trial		Risk of bias domain							Overall judgement
		Sequence generation	**Allocation concealment**	**Important baseline imbalance**	**Blinding of participants and researchers**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	
					Ustekinumab STA Table 9[61]	Ustekinumab STA Table 9[61]			
Infliximab vs Etanercept vs adalimumab Atteno et al 2010[59]	**Judgement**	Unclear	Unclear	Unclear	High	High	Unclear	Unclear	**High**
	Support	Study drugs were "randomly given"	Study drugs were "randomly given"	CRP not reported	Head to head trial of treatments with different regimens	Head to head trial of treatments with different regimens	No information on withdrawals nor on imputation methods	No prior registration	
Golimumab GO-REVEAL [45]	**Judgement**	Low	Low	Low	Low	Low	Low	Low	**Low**
	Support	IVRS used	IVRS used	Balanced	Based on text in Craig et al STA full report[65]	Based on text in Craig et al STA full report[65]	Although there was insufficient detail on imputation methods, there were few drop-outs (and balanced across groups).	All main outcomes reported	
Adalimumab Genovese 2007[51]	**Judgement**	Low	Low	Low	Low	Low	Low	Low	**Low**
	Support	Based on Table 10 details in Rodgers et al., 2011	Based on Table 10 details in Rodgers et al., 2011	Balanced	Based on Table 10 details in Rodgers et al., 2011	Based on Table 10 details in Rodgers et al., 2011	NRI and LOCF were used for missing data	Results reported for all key outcomes	
Adalimumab	**Judgement**	Low	Unclear	Low	Low	Low	Low	Low	**Low**

Drug and trial		Risk of bias domain							Overall judgement
		Sequence generation	**Allocation concealment**	**Important baseline imbalance**	**Blinding of participants and researchers**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	
ADEPT [50]	**Support**	Based on Table 10 details in Rodgers et al., 2011	Not reported	Balanced	Based on Table 10 details in Rodgers et al., 2011	Based on Table 10 details in Rodgers et al., 2011	NRI was used for missing data. Also, similar levels of drop-out across groups and similar reasons.	Results reported for all key outcomes	
Infliximab IMPACT 2[47]	**Judgement**	Low	Low	Unclear	Low	Low	High	Low	**High: PASI 75; Low: other outcomes**
	Support	Based on Table 6 details in Rodgers et al., 2011	Based on Table 6 details in Rodgers et al., 2011	20% difference in % males though this will be a chance imbalance (based on randomisation methods)	Based on Table 6 details in Rodgers et al., 2011	Based on Table 6 details in Rodgers et al., 2011	NRI was used for missing PsARC and ACR 20 data. LOCF used for PASI 75. Unclear for HAQ (appears to be LOCF)	Results for all key outcomes reported	
Infliximab IMPACT [46]	**Judgement**	Low	Low	Low	Low	Low	Low	Low	**Low**
	Support	Based on Table 6 details in Rodgers et al., 2011	Based on Table 6 details in Rodgers et al., 2011	Mean CRPs were 31 mg/l for PLA and 22 mg/l for INF[1]	Based on Table 6 details in Rodgers et al., 2011	Based on Table 6 details in Rodgers et al., 2011	Very few drop-outs	Results for all key outcomes reported	**Low**
Etanercept	**Judgement**	Low	Low	Unclear	Low	Low	Low	Low	**Low**

Drug and trial		Risk of bias domain							Overall judgement
		Sequence generation	**Allocation concealment**	**Important baseline imbalance**	**Blinding of participants and researchers**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	
Mease 2004[49]	**Support**	Based on Table 2 details in Rodgers et al., 2011	Based on Table 2 details in Rodgers et al., 2011	12% difference in % males though this will be a chance imbalance (based on randomisation methods)	Based on Table 2 details in Rodgers et al., 2011	Based on Table 2 details in Rodgers et al., 2011	More withdrawals in placebo group; NRI and LOCF were used for missing data	Results reported for all key outcomes	
Etanercept Mease 2000[48]	**Judgement**	Low	Low	Low	Low	Low	Low	Low	**Low**
	Support	Based on Table 2 details in Rodgers et al., 2011	Based on Table 2 details in Rodgers et al., 2011	Balanced	Based on Table 2 details in Rodgers et al., 2011	Based on Table 2 details in Rodgers et al., 2011	Although LOCF was used for missing data (no NRI) there were only 4 drop-outs, all in placebo group.	Results reported for all key outcomes	

[1]Medians of 14.0 mg/land 9.9 mg/l respectively (P 0.15) [2]Assumed to be the same for the placebo-controlled trials in PsA, [3]Baseline characteristics for the PsA subgroup were not reported.

IVRS Interactive voice/web response system, NRI Non-responder imputation, LOCF Last observation carried forward PLA placebo, INF infliximab

4.4 Short-term efficacy of secukinumab

The clinical effectiveness evidence identified for secukinumab consisted of four phase 3 RCTs: FUTURE 2, ERASURE, FIXTURE and CLEAR; the FUTURE trial was of patients with psoriatic arthritis and the ERASURE, FIXTURE and CLEAR trials were trials of patients with psoriasis which reported subgroup data for patients who also had psoriatic arthritis. The FUTURE 2 trial provides the main evidence for secukinumab. FUTURE 1 studied a non-licensed very high loading dose (10 mg/kg) followed by a 150 mg maintenance dose; although this trial was therefore not eligible to contribute data to the review of efficacy of secukinumab, nor to be included in the evidence synthesis, it has been used to provide supportive evidence on secukinumab as, unlike FUTURE 2, it reports data on radiographic progression of joint damage (see section 4.7). FUTURE 2 and ERASURE compared secukinumab 150mg or 300mg with placebo, FIXTURE compared SEC 150mg or 300mg with etanercept (100mg/week) and placebo; and CLEAR compared secukinumab 300mg with ustekinumab 45 or 90mg (dosing was as per license: 45mg in patients weighing ≤100kg and 90mg for patients weighing >100kg).

There are three relevant ongoing trials for which results are not yet available (Table 7).

Table 7 Ongoing trials of secukinumab in patients with active psoriatic arthritis

Trial name and clinicaltrials.gov reference	Purpose of trial
FUTURE 3 NCT01989468	To provide 24 - 52 week efficacy, safety and tolerability data, as well as up to 3-year efficacy, safety and tolerability data in subjects with active Psoriatic Arthritis despite current or previous NSAID, DMARD therapy and/or previous anti-TNF therapy using an autoinjector. Initial data are due to be published in 2016. Estimated primary completion date: January 2018.
FUTURE 4 NCT01752634	To provide 16-week efficacy, safety and tolerability data versus placebo to support the use of secukinumab 150 mg by subcutaneous self-administration with or without a loading regimen and maintenance dosing using pre-filled syringe and to assess efficacy, safety and tolerability up to 2 years in subjects with active PsA despite current or previous NSAID, non-biologic DMARD or biologic anti-TNFα therapy. Recruitment closed (9 patients in the UK) but the study is still active. Estimated primary completion date: December 2017.
FUTURE 5 NCT02404350	To demonstrate efficacy including effect on inhibition of progression of structural damage, safety and tolerability up to 2 years with primary focus at week 24, to support the use of secukinumab pre-filled syringe by subcutaneous self-administration with or without loading regimen in subjects with active Psoriatic Arthritis despite current or previous NSAID, DMARD therapy and/or previous anti-TNF therapy. Patient recruitment began in 2015. Estimated primary completion date: July 2019.

As previously discussed, the baseline characteristics of the ERASURE, FIXTURE and CLEAR subgroup populations were different to the other trials. The patients in these trials had much higher baseline PASI scores and notably lower baseline HAQ-DI scores than the other trials suggesting that these patients had more severe psoriasis and less severe arthritis symptoms (Table 4).

The FUTURE 2 and CLEAR trials were judged to have a low overall risk of bias with unclear risk overall judgements for ERASURE, FIXTURE (Table 6).

4.4.1 FUTURE 2

Table 8 and Table 9 show FUTURE 2 trial results for the key review outcomes for the full trial population across the 12, 16 and 24 week time points. Results for the biologic-naïve and biologic-experienced subgroups are presented in Table 10 and Table 11. The corresponding relative risks for the dichotomous outcomes were calculated by the ERG and are presented in Table 12.

Table 8 PsARC, ACR and HAQ responses in FUTURE 2

Population	Drugs	Time point (weeks)	N	PsARC responders	ACR 20 responders	ACR 50 responders	ACR 70 responders	HAQ change from baseline (SE)
All	Secukinumab 300mg	12	100	[redacted]	57(57%)	30(30%)	-	-
	Secukinumab 150mg		100	[redacted]	56(56%)	32(32%)	-	-
	Placebo		98	[redacted]	25(26%)	5(5%)	-	-
All	Secukinumab 300mg	16	100	69(69%)	57(57%)	30(30%)	-	-
	Secukinumab 150mg		100	72(72%)	60(60%)	32(32%)	-	-
	Placebo		98	41(42%)	18(18%)	5(5%)	-	-
All	Secukinumab 300mg	24	100	[redacted]	54(54%)	35(35%)	20(20%)	-0.56(0.05)
	Secukinumab 150mg		100	[redacted]	51(51%)	35(35%)	21(21%)	-0.48(0.05)
	Placebo		98	[redacted]	15(15%)	7(7%)	1(1%)	-0.31(0.06)

Table 9 PASI response rates in FUTURE 2

Population	Drugs	Time point (weeks)	Patients with psoriasis on at least ≥3% of BSA	PASI 50	PASI 75	PASI 90
All	Secukinumab 300mg	12	41	34(83%)	24(59%)	16(39%)
	Secukinumab 150mg		58	48(83%)	31(53%)	19(33%)
	Placebo		43	5(12%)	2(5%)	2(5%)
All	Secukinumab 300mg	16	41	36(88%)	-	-
	Secukinumab 150mg		58	48(83%)	-	-
	Placebo		43	6(14%)	-	-
All	Secukinumab 300mg	24	41	-	26(63%)	20(49%)
	Secukinumab 150mg		58	-	25(43%)	19(33%)
	Placebo		43	-	7(16%)	4(9%)

Table 10 PsARC and ACR response rates for biologic-naïve and experienced subgroups in FUTURE 2

Population	Drugs	Time point (weeks)	No: randomised	PsARC	ACR 20	ACR 50	ACR 70
Biologic-naïve	Secukinumab 300mg	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-experienced	Secukinumab 300mg	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Biologic-naïve	Secukinumab 300mg	16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-experienced	Secukinumab 300mg	16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-naïve	Secukinumab 300mg	24	67	-	39 (58%)	26 (39%)	15 (22%)
	Secukinumab 150mg		63	-	40 (63%)	28 (44%)	17 (27%)
	Placebo		63	-	10 (16%)	4 (6%)	1(2%)
Biologic-experienced	Secukinumab 300mg	24	33	-	15 (45%)	9 (27%)	5(15%)
	Secukinumab 150mg		37	-	11 (30%)	7 (19%)	4(11%)
	Placebo		35	-	5 (14%)	3 (9%)	0(0%)

Table 11 PASI response rates for biologic-naïve and experienced subgroups in FUTURE 2

Population	Drugs	Time point (weeks)	Patients with psoriasis on at least ≥3% of BSA	PASI 50	PASI 75	PASI 90
Biologic-naïve	Secukinumab 300mg	12	30	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg		36	[redacted]	[redacted]	[redacted]
	placebo		31	[redacted]	[redacted]	[redacted]
Biologic-experienced	Secukinumab 300mg	12	11	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg		22	[redacted]	[redacted]	[redacted]
	placebo		12	[redacted]	[redacted]	[redacted]
Biologic-naïve	Secukinumab 300mg	16	30	-	21(70%)	15(50%)
	Secukinumab 150mg		36	-	23(64%0	16(44%)
	placebo		31	-	3(10%)	3(10%)
Biologic-experienced	Secukinumab 300mg	16	11	-	6(55%)	3(27%)
	Secukinumab 150mg		22	-	10(45%)	6(27%)
	placebo		12	-	0(0%)	0(0%)
Biologic-naïve	Secukinumab 300mg	24	30	-	19 (63%)	16 (53%)
	Secukinumab 150mg		36	-	20 (56%)	14 (39%)
	placebo		31	-	6(19%)	3(10%)
Biologic-experienced	Secukinumab 300mg	24	11	-	7 (64%)	4(36%)
	Secukinumab 150mg		22	-	8 (36%)	5(23%)
	placebo		12	-	1(8%)	1(8%)

Table 12 Relative risks for key dichotomous outcomes in the FUTURE 2 trial: secukinumab 150mg or 300mg versus placebo

Treatment	Time point (weeks)	Population	Relative risk (95% confidence interval)						
			PsARC	ACR 20	ACR 50	ACR 70	PASI 50	PASI 75	PASI 90
Secukinumab 150mg	12	All	1.73 1.31 to 2.29	2.20 1.50 to 3.21	6.27 2.55 to 15.43	NR	7.12 3.10 to 16.36	11.49 2.91 to 45.42	7.04 1.73 to 28.64
	16	All	1.72 1.32 to 2.24	3.27 2.09 to 5.11	6.27 2.55 to 15.43	NR	5.93 2.80 to 12.57	NR	NR
	24	All	[redacted]	3.33 2.01 to 5.51	4.90 2.29 to 10.50	20.58 2.82 to 150.06	NR	2.56 1.26 to 5.55	3.52 1.29 to 9.61
Secukinumab 300mg	12	All	1.81 (1.38 to 2.38)	2.23 1.53 to 3.26	5.88 2.38 to 14.53	NR	7.13 3.09 to 16.45	12.59 3.17 to 49.91	8.39 2.06 to 34.24
	16	All	1.65 (1.26 to 2.16)	3.10 1.98 to 4.87	5.88 2.38 to 14.53	NR	6.29 2.97 to 13.33	NR	NR
	24	All	[redacted]	3.53 2.14 to 5.81	4.90 2.29 to 10.50	19.60 2.68 to 143.24	NR	3.90 1.90 to 7.98	5.24 1.96 to 14.04
Secukinumab 150mg	12	Biologic-naive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	16	Biologic-naive	NR	[redacted]	[redacted]	[redacted]	NR	[redacted]	[redacted]
	24	Biologic-naive	[redacted]	4.00 2.20 to 7.28	7.00 2.61 to 18.80	17.00 2.33 to 123.91	NR	2.87 1.32 to 6.23	4.02 1.27 to 12.70
Secukinumab 300mg	12	Biologic-naive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	16	Biologic-naive	NR	[redacted]	[redacted]	[redacted]	NR	[redacted]	[redacted]
	24	Biologic-naive	[redacted]	3.67 2.01 to 6.71	6.11 2.26 to 16.53	14.10 1.92 to 103.68	NR	3.27 1.52 to 7.06	5.51 1.79 to 17.00
Secukinumab 300mg	12	Biologic-experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Time point (weeks)	Population	Relative risk (95% confidence interval)						
			PsARC	**ACR 20**	**ACR 50**	**ACR 70**	**PASI 50**	**PASI 75**	**PASI 90**
	16	Biologic-experienced	NR	[redacted]	[redacted]	[redacted]	NR	[redacted]	[redacted]
	24	Biologic-experienced	[redacted]	3.18 1.30 to 7.77	3.18 0.62 to 10.75	11.65 0.67 to 202.75	NR	7.64 1.11 to 52.56	4.36 0.57 to 33.32

Results for the 150mg biologic-experienced subgroup not presented as license states that biologic-exced patients should take 300mg

4.4.1.1 Efficacy at 12 to 24 weeks in the full trial population

For the whole trial population, secukinumab was associated with statistically significant improvements in all outcomes at all time points. Patients taking secukinumab were around six times more likely to be ACR50 responders - an outcome of particular clinical importance to patients – than patients taking placebo. An increase in relative risks is apparent when looking across the PsARC, ACR 20, ACR 50 and ACR 70 columns in Table 12. These increases in relative risks are likely to be a consequence of the different placebo rates, with higher rates in the lower threshold outcomes (see the placebo rates in Table 8). The lower threshold outcomes (such as PsARC and ACR 20) appear to under-estimate efficacy because the relative risks tend to be diluted by the high placebo response rates. This association of higher placebo responses with lower relative efficacy was also noted *across* trials by outcome in the evidence synthesis and is discussed in section 5.

FUTURE 2 patients taking secukinumab 150mg or 300mg were also around six to seven times more likely to be PASI 50 responders than patients taking placebo. Efficacy was also demonstrated for the higher PASI thresholds (PASI 75 and PASI 90) with the 300mg group having only slightly higher relative risks than the 150mg group.

All three study arms showed improvements in physical function as assessed using HAQ-DI change from baseline scores; HAQ-DI assesses a patients' ability to perform eight categories of activities of daily living. Patients taking secukinumab had greater reductions in HAQ-DI scores compared with placebo (Table 8). At 24 weeks the difference when compared with placebo (-0.25 units) was statistically significant for 300mg (p=0.004) but the difference of -0.17 units for 150mg did not quite reach statistical significance (p=0.055).[43] The manufacturer also submitted HAQ-DI results based on PsARC responder status (see Table 13). These results show

[redacted]

Table 13 HAQ-DI changes based on PsARC responder status in FUTURE 2

Population	Time point (weeks)	HAQ change in placebo group (SE)		HAQ change in 150mg group (SE)		HAQ change in 300mg group (SE)	
		Responders	Non responders	Responders	Non responders	Responders	Non responders
All	12	[redacted]					
	16	[redacted]					

4.4.1.2 Efficacy in the biologic-naïve and biologic-experienced subgroups

Table 12 also presents relative risks for the subgroups based on patients' previous use of biologics. These subgroup results are difficult to interpret for several reasons. Some of the subgroup sample sizes were particularly small: there were no placebo responders for some outcomes in the biologic-experienced subgroup and the relative risk confidence intervals were therefore extremely wide. The PASI results are effectively based on subgroups (previous biologic status) of a subgroup (patients with psoriasis covering ≥3% of the body). Placebo response rates also differed across subgroups (also see section 4.6). Similar subgroup issues were also seen for certolizumab pegol (see section 4.5.2).

The manufacturer also submitted HAQ-DI results based on PsARC responder status for anti-naïve and experienced population (see Table 14). Again, comparisons between the two subgroups is difficult as [redacted]

Table 14 HAQ-DI changes based on PsARC responder status for biologic-naïve and experienced subgroup in FUTURE 2

Population	Time point (weeks)	HAQ change in placebo group (SE)		HAQ change in 150mg group (SE)		HAQ change in 300mg group (SE)	
		Responders	Non responders	Responders	Non responders	Responders	Non responders
Biologic-naïve	12	[redacted]					
	16						
	24						
Biologic-experienced	12						
	16						
	24						

4.4.1.3 Other efficacy results

Efficacy of secukinumab with or without concomitant methotrexate

Just under half the patients in FUTURE 2 took concomitant methotrexate. In exploratory post-hoc analyses secukinumab was found to be similarly efficacious regardless of whether or not patients were taking concomitant methotrexate.[43] For ACR 50, response rates were statistically significantly higher for the 300mg and 150 mg groups versus placebo for both the concomitant MTX subgroup (p=0.001

and p=0.006 respectively) and the no concomitant MTX subgroup (p=0.007 and p<0.0001 respectively). Similar statistically significant differences were also reported for the ACR 20 and ACR 70 thresholds.[43]

Efficacy of secukinumab in the 1 prior DMARD subgroup

Data were presented in the manufacturer's submission at week 24 for efficacy in the 1 prior DMARD subgroup.

[redacted]

Efficacy in treating dactylitis and enthesitis

At week 24, relative to placebo, secukinumab 150mg and 300mg both statistically significantly improved the resolution of both dactylitis (Leeds Dactylitis Index) and enthesitis (Leeds Enthesitis Index) for secukinumab 300mg and secukinumab 150mg vs placebo respectively (see Table 15).

Table 15 Efficacy in treating dactylitis and enthesitis in FUTURE 2

Outcome	Secukinumab 300mg	Secukinumab 150mg	Placebo
Resolution of dactylitis at week 24	[redacted] p=0.0021	[redacted] p=0.0056	[redacted]
Resolution of enthesitis at week 24	[redacted] p=0.0025	[redacted] p=0.0108	[redacted]
Dactylitis count at week 16, mean change from baseline ±SD	-2.3±4.0	-3.1±4.5	-0.6±2.4
Enthesitis count at week 16, mean change from baseline ±SD	-1.7±1.8	-1.5±2.0	-0.9±2.1

Health-related quality of life

Secukinumab 150 mg and 300 mg were better than placebo for improving EQ-5D overall health state (VAS) up to week 24.

[redacted]

At week 24, there were greater improvements with secukinumab 150 and 300mg in self-reported quality of life and physical functioning compared to placebo as measured by SF36-PCS scores (6.39 and 7.25 vs 1.95 for secukinumab 150 mg and 300 mg vs placebo).

Mortality

No deaths were reported during the trial.

4.4.2 ERASURE and FIXTURE trials

Since the focus of the ERASURE and FIXTURE trials was on patient populations with psoriasis (subgroups of which also had psoriatic arthritis) fewer outcomes were evaluated which were relevant to this assessment. Patients recruited into in the ERASURE and FIXTURE trials had more severe psoriasis but lower baseline HAQ-DI scores than the patients recruited into FUTURE 2 and into the other trials included in the systematic review (see Table 4). The FIXTURE trial was one of the very few identified in the systematic review which compared different biologics (FIXTURE compared secukinumab with etanercept).

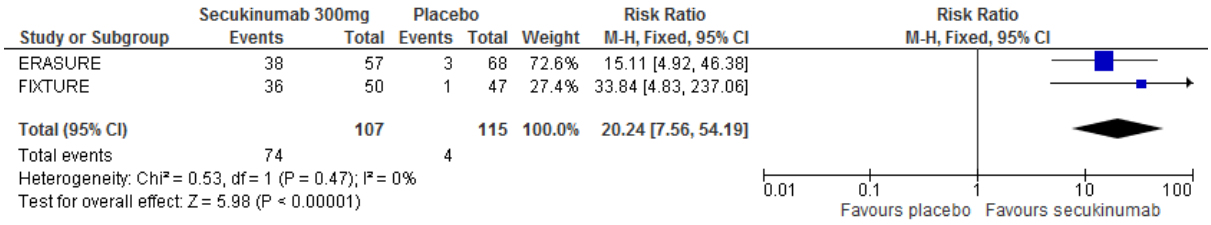
Table 16 and Figure 2 (where data from the two trials have been pooled) illustrate secukinumab's superiority over placebo for the PASI outcomes. In the FIXTURE trial at 12 weeks, secukinumab 300mg was statistically significantly more effective than etanercept 50mg twice weekly in terms of patients achieving a PASI 75 response (RR 1.86, 95% CI 1.24 to 2.81) and a PASI 90 response (RR 2.42, 95% CI 1.20 to 4.88). Changes from baseline in HAQ-DI scores were greater in secukinumab and etanercept treated patients in ERASURE and FIXTURE trials when compared with placebo.

Table 16 Efficacy outcomes in the ERASURE and FIXTURE trials at 12 weeks

Trial	Treatment	Number of PsA patients	PASI 50	PASI 75	PASI 90	HAQ change from baseline[1]
ERASURE	Secukinumab 300mg	57	-	38(67%)	30(53%)	-0.35
	Secukinumab 150mg	46	-	32(70%)	20(43%)	-0.18
	Placebo	68	-	3(4%)	0(0%)	-0.08
FIXTURE	Secukinumab 300mg	50	-	36(72%)	22(44%)	-0.41
	Secukinumab 150mg	49	-	29(59%)	19(39%)	-0.19
	Etanercept 50mg	44	-	17(39%)	8(18%)	-0.29
	Placebo	49	-	1(2%)	1(2%)	0.02

[1]Standard errors not reported

Figure 2 Forest plot of the efficacy of secukinumab 300mg versus placebo for PASI 75 at 12 weeks in PsA patients with moderate to severe psoriasis



4.4.3 CLEAR trial

The CLEAR trial, which compared secukinumab with ustekinumab, was similar to the ERASURE and FIXTURE trials with respect to the population studied (patients with more severe psoriasis than those recruited into FUTURE 2) and the limited data assessed and reported (in CLEAR only PASI 90 and HAQ were reported for the subgroup of patients with psoriatic arthritis).

At 16 weeks, patients treated with secukinumab 300mg had a better PASI 90 response rate than patients receiving ustekinumab 45 or 90mg although the difference was not statistically significant (RR 1.23, 95% CI 0.98 to 1.55; p=0.08). Patients treated with secukinumab 300mg had a greater improvement in HAQ-DI score compared with patients receiving ustekinumab 45 or 90mg (Table 17).

Table 17 Efficacy outcomes in the CLEAR trial at 16 weeks for the subgroup of PsA patients

Treatment	Number of patients	PASI 50	PASI 75	PASI 90	HAQ change from baseline[1]
Secukinumab 300mg	69	-	-	55(80%)	-0.29
Ustekinumab 45-90mg	54	-	-	35(65%)	-0.13

[1]Standard errors not reported

4.4.4 Summary

The results of the FUTURE 2 trial demonstrated the short-term efficacy of secukinumab in treating psoriatic arthritis. When considering the whole trial population secukinumab was associated with statistically and clinically significant improvements in all key outcomes. Patients taking secukinumab were around six times more likely to be ACR 50 responders – a key clinical outcome to patients – than patients taking placebo. Clinically important improvements in activities of daily living (assessed using HAQ-DI) were also evident in patients taking secukinumab, particularly in patients who were PsARC responders. However, when the trial population was split into subgroups based on previous biologic experience, the resulting relative risks for the biologic-experienced subgroup became difficult to interpret. This was due both to the low numbers of placebo patients and to the differences in placebo response rates across subgroups (discussed in section 4.6). Whilst secukinumab is efficacious in both subgroups, it is not possible to make robust conclusions about any difference in efficacy of secukinumab across these subgroups. Similar efficacy across the ACR outcomes was though evident in subgroups of patients based on presence or absence of concomitant methotrexate, although limited data and analyses were available specifically for the 1 prior DMARD group. Treatment with secukinumab resulted in statistically significantly improvements in health-related quality of life measures and in the resolution of both dactylitis and enthesitis.

Results from the trials of patients with more severe psoriasis demonstrated secukinumab's superiority over placebo in terms of psoriasis (PASI) and function (HAQ-DI) outcomes. Secukinumab was also found to be significantly more effective than etanercept for improving psoriasis (assessed using PASI 75 and PASI 90). However, the populations studied in these trials had quite severe psoriasis and less functional impairment (lower baseline HAQ-DI scores) when compared with other trial populations. Their results should not therefore be generalised to more typical psoriatic arthritis populations.

4.5 Short-term efficacy of certolizumab pegol

One eligible RCT of certolizumab pegol was identified; RAPID-PsA[42] compared certolizumab pegol 200mg or 400mg against placebo up to 24 weeks. The trial was dose blinded to 48 weeks and then open-label to 216 weeks. Placebo patients who failed to achieve a 10% improvement from baseline in both swollen and tender joints at week 14 and 16 were re-randomised to active treatment at week 16. At week 24 all the remaining placebo patients were re-randomised to receive 200mg or 400mg of certolizumab pegol. RAPID-PsA was judged to have a low overall risk of bias (Table 6).

Compared to the other psoriatic arthritis trials, the RAPID-PsA trial was more selective in recruiting biologic-experienced patients: patients with primary failure of a previous anti-TNF were excluded (primary failure was defined as no response within the first 12 weeks of treatment with the anti-TNF).

There are no UCB-sponsored ongoing studies of certolizumab pegol in patients with psoriatic arthritis.

Table 18 and Table 19 show RAPID-PsA trial results for the key review outcomes for the full trial population across the 12, 16 and 24 week time points. ACR 20 results, split into subgroups according to the number of previous DMARDs taken by patients, are presented in Table 20. Results for the biologic-naïve and biologic-experienced subgroups are presented in Tables 21 to 24. The corresponding relative risks for the dichotomous outcomes were calculated by the ERG and are presented in Table 25.

Table 18 PsARC, ACR and HAQ responses in RAPID-PsA

Population	Treatment	Time point (weeks)	N	PsARC responders	ACR 20 responders	ACR 50 responders	ACR 70 responders	HAQ change from baseline (SE)
All	200mg every fortnight	12	138	101(73%)	80(58%)	50(36%)	34(25%)	-0.45(0.56)
	400mg once a month		135	89(66%)	70(52%)	44(33%)	17(13%)	-0.39(0.47)
	Placebo		136	52(38%)	33(24%)	15(11%)	4(3%)	-0.16(0.36)
All	200mg every fortnight	16	138	-	78(57%)	-	-	-
	400mg once a month		135	-	73(54%)	-	-	-
	Placebo		136	-	34(25%)	-	-	-
All	200mg every fortnight	24	138	108(78%)	88(64%)	61(44%)	39(28%)	-0.52(0.66)
	400mg once a month		135	104(77%)	76(56%)	54(40%)	32(24%)	-0.43(0.54)
	Placebo		136	45(33%)	32(24%)	17(13%)	6(4%)	-0.17(0.43)

Table 19 PASI response rates in RAPID-PsA

Population	Treatment	Time point (weeks)	Patients with Psoriasis on at least ≥3% BSA	PASI 50	PASI 75	PASI 90
All	200mg every fortnight	12	90	62(69%)	42(47%)	20(22%)
	400mg once a month		76	48(63%)	36(47%)	15(20%)
	Placebo		86	23(27%)	12(14%)	4(5%)
All	200mg every fortnight	24	90	67(74%)	56(62%)	42(47%)
	400mg once a month		76	55(72%)	46(61%)	27(36%)
	Placebo		86	24(28%)	13(15%)	5(6%)

Table 20 RAPID-PsA ACR20 response rates at 12 weeks for subgroups of previous DMARD use

Population	Treatment	N	ACR 20
Previous use of 1 DMARD	200mg every fortnight	61	42(69%)
	400mg once a month	72	42(58%)
	Placebo	74	22(30%)
Previous use of ≥2 DMARDs	200mg every fortnight	73	38(52%)
	400mg once a month	60	28(47%)
	Placebo	60	11(18%)

Table 21 Biologic-naïve and experienced subgroup PsARC, ACR and HAQ results in RAPID-PsA at 12 weeks

Population	Drugs	No: randomised	PsARC	ACR 20	ACR 50	ACR 70	HAQ change from baseline (SE)
Biologic-naive	Certolizumab pegol combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-experienced	Certolizumab pegol combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 22 Biologic-naïve and experienced subgroup PASI response rates in RAPID-PsA at 12 weeks

Population	Drugs	Patients with Psoriasis on at least ≥3% BSA	PASI 50	PASI 75	PASI 90
Biologic-naive	Certolizumab pegol combined	130	80(62%)	56(43%)	25(19%)
	Placebo	66	18(27%)	11(17%)	3(5%)
Biologic-experienced	Certolizumab pegol combined	36	30(83%)	22(61%)	10(28%)
	Placebo	20	5(25%)	1(5%)	1(5%)

Table 23 Biologic-naïve and experienced PsARC, ACR and HAQ subgroup results from RAPID-PsA at 24 weeks

Population	Drugs	Time point (weeks)	No: randomised	PsARC	ACR 20	ACR 50	ACR 70	HAQ change from baseline (SE)
Biologic-naive	Certolizumab pegol combined	24	219	170 (78%)	132 (60%)	91 (42%)	57 (26%)	-0.45(0.6)
	Placebo		110	59 (54%)	29 (26%)	16 (15%)	5 (5%)	-0.2(0.45)
Biologic-experienced	Certolizumab pegol combined	24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 24 Biologic-naïve and experienced PASI subgroup results from RAPID-PsA at 24 weeks

Population	Drugs	Time point (weeks)	Patients with Psoriasis on at least ≥3% BSA	PASI 50	PASI 75	PASI 90
Biologic-naive	Certolizumab pegol combined	24	130	89(68%)	73(56%)	48(37%)
	Placebo		66	20(30%)	13(20%)	5(8%)
Biologic-experienced	Certolizumab pegol combined	24	36	33(92%)	29(81%)	21(58%)
	Placebo		20	4(20%)	0(0%)	0(0%)

Table 25 Relative risks for key outcomes in the RAPID-PsA trial: Certolizumab pegol 200mg or 400mg versus placebo

Dose	Week	Population	Relative risk (95% confidence interval)						
			PsARC	ACR 20	ACR 50	ACR 70	PASI 50	PASI 75	PASI 90
200mg every fortnight	12	All	1.91 (1.51 to 2.42)	2.39 (1.72 to 3.32)	3.29 (1.94 to 5.56)	8.38 (3.06 to 12.39)	2.58 (1.77 to 3.75)	3.34 (1.89 to 5.91)	4.78 (1.70 to 13.41)
	16	All	NR	2.26 (1.63 to 3.13)	NR	NR	NR	NR	NR
	24	All	2.37 (1.83 to 3.05)	2.71 (1.95 to 3.76)	3.54 (2.18 to 5.73)	6.41 (2.80 to 14.64)	2.67 (1.86 to 3.83)	4.12 (2.43 to 6.97)	8.03 (3.33 to 19.33)
400mg once a month	12	All	1.72 (1.35 to 2.20)	2.14 (1.52 to 3.00)	2.96 (1.73 to 5.05)	4.28 (1.48 to 12.39)	2.36 (1.60 to 3.49)	3.39 (1.91 to 6.04)	4.24 (1.47 to 12.23)
	16	All	NR	2.16 (1.55 to 3.01)	NR	NR	NR	NR	NR
	24	All	2.33 (1.80 to 3.01)	2.39 (1.71 to 3.35)	3.20 (1.96 to 5.23)	5.37 (2.32 to 12.43)	2.59 (1.80 to 3.74)	4.00 (2.35 to 6.82)	6.11 (2.48 to 15.07)
Combined arms	12	Naive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	24	Naive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combined arms	12	Experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	24	Experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.5.1 Efficacy at 12 to 24 weeks in the RAPID PsA full trial population

For the full trial population the relative risks in Table 25 are for comparisons of the different certolizumab regimens (200mg every 2 weeks or 400mg every 4 weeks) with placebo, across the 12, 16 and 24 week time points and across the PsARC, ACR and PASI outcomes. For the subgroup analyses (based on previous biologic status) combined data from the two certolizumab pegol arms were used to calculate relative risks.

For the full trial population, when compared with placebo, certolizumab pegol was associated with statistically significant improvements in all outcomes at all time points (for which data were available). Patients taking certolizumab pegol were around three times more likely to be ACR50 responders than patients taking placebo. Similar to the pattern seen with the secukinumab FUTURE 2 results, an increase in relative risks is apparent as the outcome thresholds (for achieving a response) increase across the PsARC, ACR and PASI columns (see Table 25). Again these increases are likely to be a consequence of the different placebo rates, with higher rates of placebo response in the lower threshold outcomes.

RAPID-PsA patients taking certolizumab pegol were around two-and-a-half times more likely to be PASI 50 responders than patients taking placebo. Efficacy was also demonstrated in the results for the higher PASI thresholds. Improvements in physical function, as assessed using HAQ-DI change from baseline scores, were also seen with the difference being reported as being statistically significant ($p<0.001$) at 24 weeks.[42] The manufacturer also submitted HAQ-DI results based on PsARC responder status (see Table 26)

[redacted]

Table 26 RAPID-PsA trial HAQ-DI changes from baseline based on PsARC responder status

Population	Time point (weeks)	Change in placebo group (SD)		Change in 200mg group (SD)		Change in 400mg group (SD)	
		Responders	Non responders	Responders	Non responders	Responders	Non responders
All	12	[redacted]					
	24	[redacted]					

4.5.2 Efficacy in the biologic-naïve and biologic-experienced subgroups

Table 25 presents relative risks for subgroups based on patients' previous use of biologics. When comparing results for all outcomes across subgroups the efficacy of certolizumab pegol *appears* somewhat better in the biologic-experienced subgroup than in the biologic-naïve subgroup; this trial evidence is contrary to evidence from large patient registries, which suggest there may be decreased effectiveness with each new anti-TNF taken (see section 4.8.1). The differences between subgroups observed in RAPID-PsA are likely to have been influenced by two factors. Firstly, there is a problem

with sample size with low numbers of placebo patients and placebo responders in the biologic-experienced subgroup. There is therefore much uncertainty about these estimates which is reflected in the very wide confidence intervals. Secondly there is a notable difference in placebo response rates between the two subgroups (

Table 21, and section 4.6). Furthermore, as detailed previously in section 4.3, the RAPID-PsA trial excluded patients with primary failure of a previous biologic so the subgroups were not as different as they could have been (other trials did not exclude primary failures).

The manufacturer also submitted HAQ-DI results based on PsARC responder status for anti-naïve and experienced population (see Table 27).

[redacted]

Table 27 HAQ-DI changes based on PsARC responder status for biologic-naïve and experienced subgroup in RAPID-PsA

Population	Time point (weeks)	HAQ change in placebo group (SD)		HAQ change in 200mg group (SD)		HAQ change in 400mg group (SD)	
		Responders	Non responders	Responders	Non responders	Responders	Non responders
Biologic-naïve	12	[redacted]					
	24						
Biologic-experienced	12						
	24						

4.5.3 Other efficacy results

Efficacy of certolizumab pegol with or without concomitant methotrexate

Results were not reported for subgroups based specifically on methotrexate use, although results were reported based on concomitant use of a DMARD (which was mostly methotrexate). Concomitant DMARD use did not seem to affect ACR 20 (57% with vs 50% without) or PsARC (68% with vs 73% without) response rates to certolizumab pegol (combined dose) at week 12.[42]

Efficacy of certolizumab pegol in the 1 prior DMARD subgroup

When compared with placebo at weeks 12 and 24 certolizumab pegol was associated with statistically significantly better ACR20 response rates ($p<0.001$); 207 patients who had had 1 prior DMARD were included in the analysis.[42] Data in the manufacturer's submission showed that

[redacted]

[redacted]

Efficacy in treating dactylitis and enthesitis

At week 24, patients treated with certolizumab pegol achieved statistically significant improvements in dactylitis (assessed using the Leeds Dactylitis Index) when compared to placebo; statistically significant results were also seen for enthesitis, as assessed using the Leeds Enthesitis Index (Table 28).

Table 28 Efficacy in treating dactylitis and enthesitis in RAPID-PsA

Treatment	Outcome, mean change from baseline at week 24	
	Dactylitis count ±SD	Enthesitis count ±SD
Certolizumab pegol 200mg	-40.7±34.6 p≤0.003	-2±1.8 p<0.001
Certolizumab pegol 400mg	-53.5±69.1 p<0.001	-1.8±1.9 p≤0.003
Placebo	-22.0±46.9	-1.1±1.8

Health-related quality of life

At week 12, EQ-5D VAS scores were higher in certolizumab pegol treated groups [redacted]

Also at week 24, there was a significant improvements with pooled certolizumab pegol in all domains of the SF-36, including both the physical [redacted] and mental components [redacted] regardless of the dose regimen and prior TNF inhibitor status.

[redacted]

Mortality

Two deaths were reported during the 24 weeks. One was in the 200mg group and one was in the 400mg group; trial investigators considered both deaths to be unrelated to study medication.

4.5.4 Summary

The results of the RAPID-PsA trial demonstrated the short-term efficacy of certolizumab pegol in treating psoriatic arthritis. When considering the full trial population certolizumab pegol was associated with statistically significant improvements in all key outcomes. When the trial population was split into subgroups based on previous biologic experience, the results became difficult to compare (as was seen for FUTURE 2). The low numbers of placebo patients in the biologic-

experienced subgroup coupled with higher placebo response rates in the biologic-naïve subgroup meant it was not possible to make reliable conclusions about the difference in the efficacy of certolizumab pegol across these subgroups. Furthermore, patients with primary failure of a previous biologic were excluded from RAPID-PsA so estimates of efficacy may have been slightly inflated when comparisons are made with other trials which recruited biologic-experienced patients (e.g. FUTURE 2 and PSUMMIT 2). Similar efficacy across the ACR and PsARC outcomes was seen in subgroups of patients based on presence or absence of a concomitant DMARD and [redacted] Treatment with certolizumab pegol resulted in statistically significantly improvements in health-related quality of life measures and in the resolution of both dactylitis and enthesitis.

4.6 Evaluating the secukinumab and certolizumab pegol trial results in comparison to other treatments

In order to more fully evaluate the clinical efficacy of secukinumab and certolizumab pegol the trial results of these two newer biologics need to be compared with each other and with the results of the older biologics (and apremilast). However, this is not straightforward for two reasons. Firstly, there is variation across trials with respect to previous biologic use:

- The populations recruited to clinical trials have changed over time, with earlier trials excluding biologic-experienced patients and later trials including such patients.
- The RAPID-PsA trial was more selective than the FUTURE 2, PSUMMIT 2 and PALACE trials in recruiting its biologic-experienced patients: only in RAPID-PsA were patients with primary failure of a previous biologic excluded (see section 4.3).

Secondly, placebo response rates have increased markedly over time across the trials included in this review. This issue is key when interpreting relative risks because, although relative risks are easy to interpret clinically, their ceilings (maximum values) are limited by baseline response rates. For example, in FUTURE 2 the placebo response rate for PsARC was [redacted] in the biologic-naïve subgroup. This high rate meant that the maximum possible relative risk would be [redacted]; this maximum result is lower than some of the *actual* relative risks for other biologics presented in Table 29, which compares unadjusted relative risks across the trials in the network meta-analyses. Comparisons between treatments using odds ratios and which adjust for the varying placebo rates were therefore necessary (see section 5).

Examination of the trial baseline characteristics across trials offers no clear reason as to why placebo response rates in biologic trials have increased over time. The PsARC placebo response rates increased most markedly from 2013 onwards, starting with the PSUMMIT trials. One theory is the possibility of increasing patient and clinician expectations over time i.e. more caution and lower expectations when the first biologics were trialled, and more confidence about the likely benefits in more recent trials. Subjective patient- and clinician-reported outcomes such as PsARC and ACR may be prone to such expectation effects. This theory might also explain why, within trials, higher placebo response rates are observed in the biologic-naïve subgroups when compared with biologic-experienced subgroups, where treatment expectations might be lower. Coupled with this is the trend - beginning with the PSUMMIT trials – for increases in the number of active treatment arms offered in trials: typically there was one active arm in the early trials and two or more active arms in more recent trials (e.g. the FUTURE 2 secukinumab trial had three active treatment arms: 75mg, 150mg and 300mg). Patients in the more recent trials might therefore also be more confident and optimistic about the likelihood that they are receiving an active treatment.

Ideally the different treatments would be compared in head-to-head trials. However, only one trial identified in the systematic review compared two or more biologics directly in a psoriatic arthritis population. The Atteno (2010) trial compared infliximab, etanercept and adalimumab.[59]It reported that patients on infliximab and adalimumab showed the greatest improvement in terms of PASI (statistically significantly better than etanercept), while patients on etanercept showed the greatest improvement in TJC (statistically significantly better than infliximab and adalimumab) and HAQ-DI (statistically significantly better than adalimumab). However, the reliability of this study's results are limited somewhat by its small size (100 patients were randomised in total). This trial also did not report its methods clearly (see Table 6) and was rated as having a high risk of bias (though blinding would be difficult to achieve in such a trial). Finally, by reporting results only at the 52 week time point the results of this trial could not be included in our network meta-analyses.

Table 29 Unadjusted relative risks (compared with placebo) across the trials included in the evidence synthesis

Trial name	Treatment	Time point (weeks)	Population	Relative risk (95% confidence interval)						
				PsARC	ACR 20	ACR 50	ACR 70	PASI 50	PASI 75	PASI 90
FUTURE 2	Secukinumab 300mg	12	All	[redacted]	2.23 1.53 to 3.26	[redacted]	NR	7.13 3.09 to 16.45	12.59 3.17 to 49.91	8.39 2.06 to 34.24
	Secukinumab 150mg	12	All	[redacted]	2.20 1.50 to 3.21	[redacted]	NR	7.12 3.10 to 16.36	11.49 2.91 to 45.42	7.04 1.73 to 28.64
	Secukinumab 300mg	12	Biologic-naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.20 1.15 to 25.40
	Secukinumab 150mg	12	Biologic-naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.60 1.37 to 22.91
	Secukinumab 300mg	12	Biologic-experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.78 0.59 to 162.47
	Secukinumab 150mg	12	Biologic-experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7.22 0.44 to 117.84
SPIRIT-P1	Adalimumab	12	All	NR	1.65 1.18 to 2.32	6.30 2.54 to 15.59	38.82 2.37 to 635.80	NR	5.21 2.50 to 10.85	14.78 2.01 to 108.77
RAPID-PsA	Certolizumab pegol 200mg	12	All	[redacted]	2.39 1.72 to 3.32	3.29 1.94 to 5.56	8.38 3.06 to 22.97	2.58 1.77 to 3.75	3.34 1.89 to 5.91	4.78 1.70 to 13.41
	Certolizumab pegol 400mg	12	All	[redacted]	2.14 1.52 to 3.00	2.96 1.73 to 5.05	4.28 1.48 to 12.39	2.36 1.60 to 3.49	3.39 1.91 to 6.04	4.24 1.47 to 12.23
	Certolizumab pegol combined	12	Biologic-naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.56 0.77 to 40.30
	Certolizumab pegol combined	12	Biologic-experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.70 2.01 to 11.01
PALACE 1	Apremilast	16	All	1.56 1.17 to 2.07	2.00 1.39 to 2.89	2.70 1.35 to 5.40	3.50 0.74 to 16.60	2.71 1.50 to 4.91	4.98 1.53 to 16.18	NR
PALACE 2	Apremilast	16	All	1.44 1.10 to 1.90	1.70 1.15 to 5.52	2.09 0.93 to 4.69	1.96 0.18 to 21.43	3.17 1.69 to 5.96	8.17 1.95 to 34.14	NR
PALACE 3	Apremilast	16	All	1.94 1.46 to 2.58	2.22 1.54 to 3.20	1.81 0.97 to 3.35	1.52 0.44 to 5.28	1.71 1.10 to 2.64	2.83 1.26 to 6.35	NR
PSUMMIT 2	Ustekinumab 45mg	12	Biologic-naïve	NR	2.08 1.01 to 4.28	1.63 0.42 to 6.39	2.93 0.32 to 27.06	NR	14.17 2.00 to 100.35	NR

Trial name	Treatment	Time point (weeks)	Population	Relative risk (95% confidence interval)						
				PsARC	ACR 20	ACR 50	ACR 70	PASI 50	PASI 75	PASI 90
PSUMMIT 2	Ustekinumab 45mg	24	Biologic-naïve	1.47 0.92 to 2.34	1.87 1.08 to 3.26	2.93 0.85 to 10.08	1.95 0.38 to 10.10	NR	5.83 1.93 to 17.67	NR
	Ustekinumab 45mg	12	Biologic-experienced	NR	2.64 1.33 to 5.23	9.30 1.21 to 71.19	9.30 0.51 to 169.03	NR	15.91 2.18 to 116.14	NR
	Ustekinumab 45mg	24	Biologic-experienced	2.13 1.32 to 3.44	2.53 1.27 to 5.03	2.33 0.76 to 7.15	3.10 0.33 to 28.98	NR	22.73 3.18 to 162.50	NR
	Ustekinumab 45mg	12	All	1.65 1.18 to 2.31	2.38 1.44 to 3.91	3.53 1.20 to 10.38	7.07 0.89 to 56.44	7.29 3.52 to 15.07	15.50 3.84 to 62.60	16.00 2.17 to 117.80
	Ustekinumab 45mg	24	All	1.80 1.28 to 2.52	2.16 1.39 to 3.36	2.60 1.13 to 5.95	2.36 0.63 to 8.86	NR	10.25 3.85 to 27.28	NR
PSUMMIT 1	Ustekinumab 45mg	12	Biologic-naïve	1.62 1.31 to 2.01	1.94 1.43 to 2.64	3.47 1.83 to 6.60	2.68 0.72 to 9.96	NR	4.34 2.48 to 7.58	NR
	Ustekinumab 45mg	24	Biologic-naïve	1.50 1.21 to 1.86	1.86 1.38 to 2.50	2.85 1.72 to 4.70	5.02 1.96 to 12.87	2.89 2.06 to 4.05	5.22 3.22 to 8.47	NR
GO-REVEAL	Golimumab 50mg	14	All (biologic-naïve)	3.45 2.39 to 4.99	5.73 3.10 to 10.57	17.03 4.22 to 68.75	13.93 1.89 to 102.80	6.52 3.16 to 13.47	15.94 3.98 to 63.84	32.67 2.01 to 530.63
Genovese 2007	Adalimumab	12	All (biologic-naïve)	1.86 1.10 to 3.13	2.50 1.21 to 5.15	13.00 1.77 to 95.73	15.00 0.88 to 255.86	NR	NR	NR
ADEPT	Adalimumab	12	All (biologic-naïve)	2.37 1.77 to 3.16	4.05 2.71 to 6.06	9.53 4.22 to 21.51	31.76 4.39 to 230.09	5.00 2.77 to 9.03	11.33 3.65 to 35.17	43.00 2.66 to 695.98
IMPACT 2	Infliximab	14	All (biologic-naïve)	2.85 2.03 to 4.01	5.27 2.95 to 9.44	12.00 3.82 to 37.70	15.00 2.02 to 111.42	8.91 4.57 to 17.38	27.78 6.99 to 110.35	72.31 4.50 to 1160.52
IMPACT	Infliximab	16	All (biologic-naïve)	3.55 2.05 to 6.13	6.80 2.89 to 16.01	49.00 3.06 to 784.91	31.00 1.90 to 504.77	33.00 2.15 to 505.75	22.73 1.46 to 353.35	12.47 0.77 to 201.07
Mease 2004	Etanercept	12	All (biologic-naïve)	2.35 1.72 to 3.21	3.86 2.39 to 6.23	9.78 3.62 to 26.41	23.68 1.41 to 396.59	NR	NR	NR
Mease 2000	Etanercept	12	All (biologic-naïve)	3.71 1.91 to 7.21	5.50 2.15 to 14.04	15.00 2.11 to 106.49	9.00 0.51 to 160.07	2.00 0.72 to 5.54	11.00 0.65 to 185.70	NR

4.7 Long-term effectiveness

4.7.1 Open-label extension studies

Long-term efficacy of secukinumab

The Novartis submission to NICE for the appraisal in 2016 reported long-term data for both FUTURE 1 (to 104 weeks) and FUTURE 2 (to 52 weeks). Although FUTURE 1 was not eligible for the systematic review of efficacy because it initiated the randomized phase of the study with a non-licensed high loading dose (10 mg/kg), it did use a 150 mg maintenance dose and so can be considered to provide useful long-term data. Importantly, this trial reported radiographic efficacy outcomes (at 2 years); FUTURE 2 did not report radiographic efficacy outcomes.

FUTURE 2

Of the FUTURE 2 patients originally randomised to secukinumab 150mg or 300mg by week 52, 22 (11%) had withdrawn for any reason, 10 of which withdrew due to an adverse event or loss of efficacy. In FUTURE 2, most of the dichotomous data reported in the submission used non-responder imputations for missing data; a mixed-effects repeated-measures model was used for continuous outcomes. There were no stopping rules up to week 52, so non-responding patients could keep taking secukinumab allowing the possibility of achievement of much later responses than would be viable in the NHS. For time points *after* week 52 the protocol stated that subjects who are deemed not to be benefiting from the study treatment based upon lack of improvement or worsening of their symptoms should discontinue the study. However, results for post-week 52 time points are not yet available. Results for key review outcomes at week 52 are presented in Table 30. They suggest that secukinumab continues to be an effective treatment for psoriatic arthritis at this later time point.

Table 30 Efficacy results for FUTURE 2 at 52 weeks

Outcome	Secukinumab 300mg	Secukinumab 150mg
ACR response, N	**100**	**100**
% ACR 20	64	39
% ACR 50	44	41
% ACR 70	24	20
PASI response (≥3 BSA), N	**41**	**58**
% PASI 75	73	57
% PASI 90	56	43
PsARC response, N	**100**	**100**
% PsARC response	[redacted]	[redacted]
HAQ-DI, N	**100**	**100**
Mean (SD)	-0.56 (0.05)	-0.47 (0.05)
SF-36, N	**100**	**100**
Mean (SD)	[redacted]	[redacted]

Longer-term efficacy in FUTURE 2 patients who were responders at 16 weeks

In the NHS patients will typically be allowed 16 weeks to achieve a response, after which secukinumab may be stopped in non-responding patients. The assessment group requested results specifically for patients who are responders at 16 weeks to inform what happens to this group of patients in the longer-term. The results (Figure 3 and Figure 4) indicate that for the lower threshold outcomes - such as ACR 20 and PASI 50 - response rates remain high from week 16 to week 52. As the outcome thresholds increase, response rates become more variable over time and there is generally a greater decrease in response rates compared to the lower threshold outcomes. Around 70% of patients on 150mg still achieve an ACR 50 response at week 52, and around 55% still achieve an ACR70 (Figure 3); the corresponding results for PASI 75 and PASI 90 are around 85% and around 70% respectively (Figure 4).

Figure 3 Long-term response rates in FUTURE 2 secukinumab patients who were ACR20 (A), ACR40 (B) or ACR70 (C) responders at 16 weeks

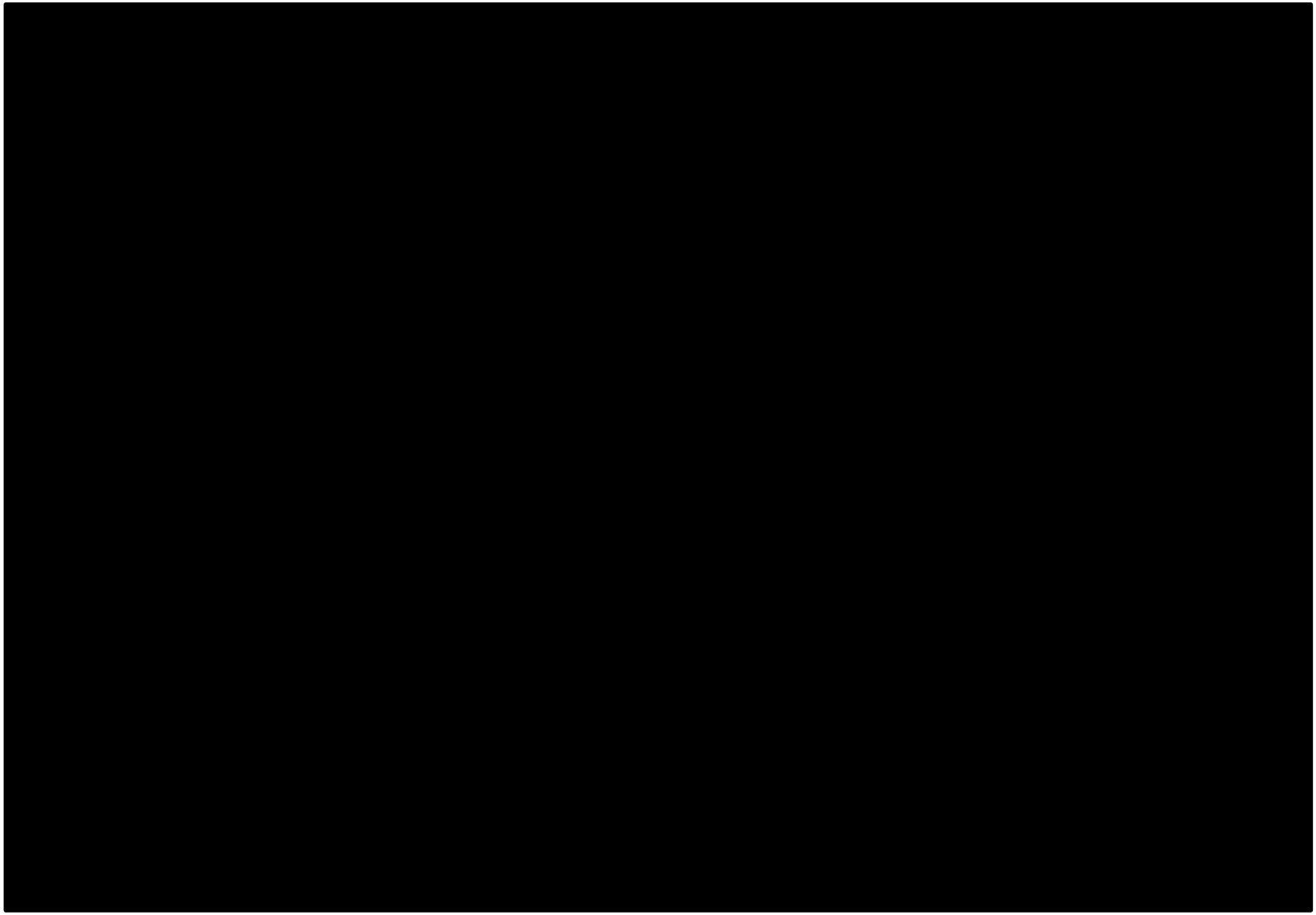
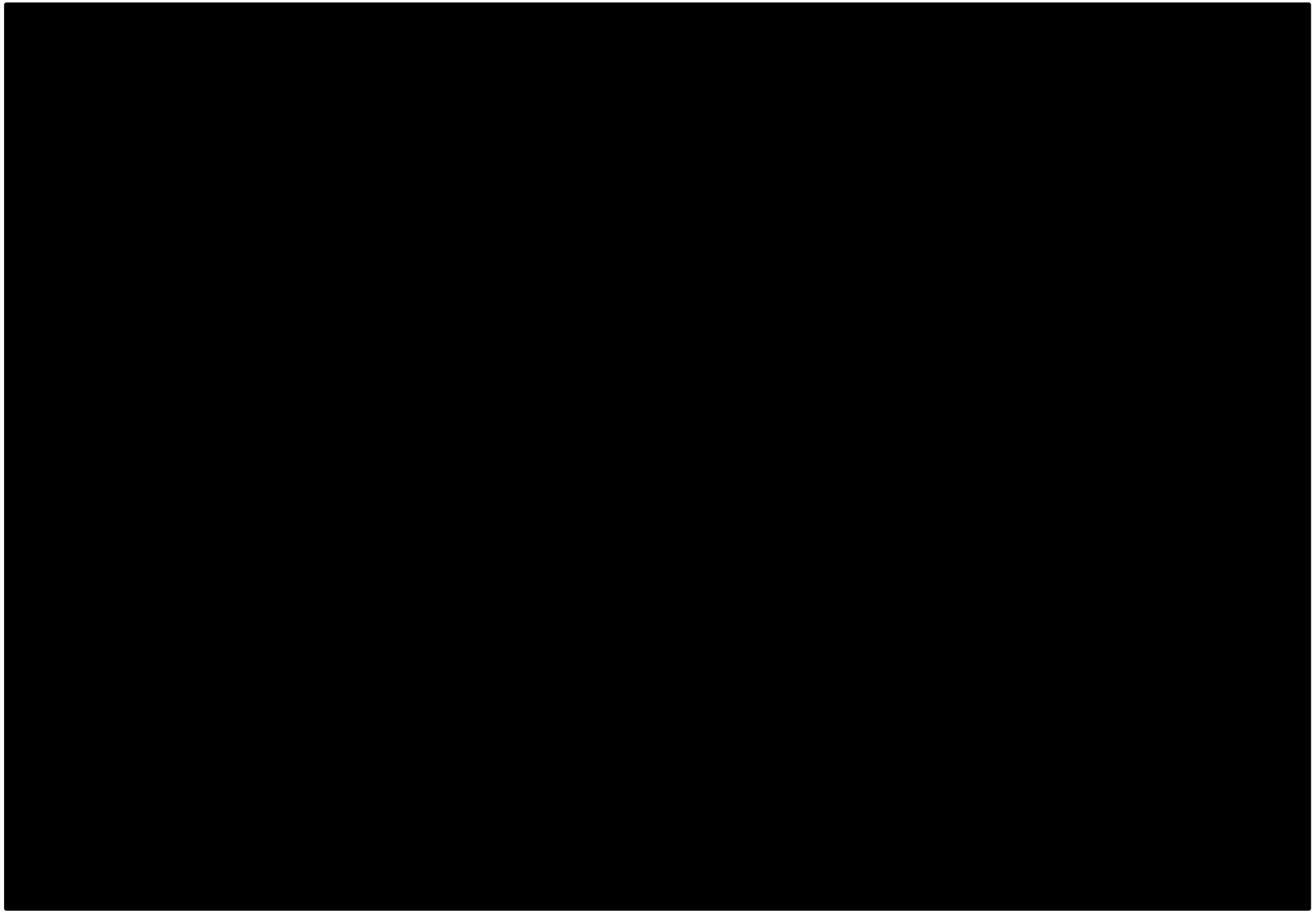


Figure 4 Long-term response rates in FUTURE 2 secukinumab patients who were PASI50 (A), PASI75 (B) or PASI 90 responders at 16 weeks



FUTURE 1

In FUTURE 1 patients originally randomised to secukinumab 75mg or 150mg or placebo, 15% had withdrawn at week 52 for any reason, of which 6% were due to an adverse event or loss of efficacy.[41] At week 104 79% of patients remained in the study. Here, we report only on the long term efficacy of secukinumab 150mg. Results at 52 weeks are similar to those seen in FUTURE 2; observed data were also available at 2 years (Table 31).

Table 31 Efficacy results for FUTURE 1 at 52 weeks and 104 weeks

	Secukinumab 150mg at 52 weeks	Secukinumab 150mg at 104 weeks*
ACR response, N	**202**	**153**
% ACR 20	60	74
% ACR 50	43	46
% ACR 70	24	28
PASI response (≥3 BSA), N	**108**	**82**
% PASI 75	77	83
% PASI 90	60	70
Dactylitis (LDI), N	**104**	**-**
% resolution of dactylitis	32	-
Enthesitis (LEI), N	**126**	-
% resolution of enthesitis	34	-
HAQ-DI, N	**202**	**153**
Mean (SE)	-0.41(0.04)	-0.42 (-)
SF-36, N	**202**	**152**
mean (SE)	5.89(0.54)	5.94(-)

*observed data, SF-36: short form-36

Radiographic progression of joint damage

In FUTURE 1 at week 52 the observed population comprised 189 of the 202 patients randomised to 150mg; this group had a mean Sharp/van der Heijde change from baseline score of 0.37. At 104 weeks 85% of patients treated with secukinumab 150mg had no radiographic progression - defined as a change in Sharp/van der Heijde score of ≤0.5 - between baseline and week 104. This result was based on the observed population; no further details were presented and the sample size was not stated.

Long-term efficacy of certolizumab pegol

The UCB submission reported long-term efficacy data for the RAPID-PsA trial at time points up to around 4 years (216 weeks). By week 96, 20% of the 273 patients originally randomised to certolizumab had withdrawn from the study; 13.5% of the total cohort had withdrawn due to either an adverse event or loss of efficacy. Non-responder imputations were used for dichotomous outcomes and LOCF used for most of the continuous outcomes (except for radiographic progression).

At week 96 the ACR 20, 50 and 70 response rates were 64%, 50%, and 35% respectively,[67] and were [redacted]). PASI 75 and 90 response rates were 53% and 44% at week 96;[67] and [redacted].

[redacted]. The improvement in HAQ-DI from baseline was maintained [redacted] Efficacy results for the overall population together with the biologic-naïve and experienced subgroups are presented in [redacted].

Table 32 Long-term efficacy results for Rapid-PsA trial at 216 weeks

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

[redacted]

Longer-term efficacy in patients who were responders at 12 weeks

In the NHS patients will typically be allowed 12 weeks to achieve a response, after which certolizumab pegol may be stopped in non-responding patients. The assessment group requested

results specifically for patients who are responders at 12 weeks to inform what happens to this group of patients in the longer-term. The response rates at one year are similar to those seen with secukinumab. Later results show that, across outcomes, around two-thirds (of responders at 12 weeks) remain responders at four years (Figure 5 and Figure 6).

Figure 5 Long-term response rates in RAPID-PsA certolizumab patients who were ACR20 (A), ACR40 (B) or ACR70 (C) responders at 12 weeks

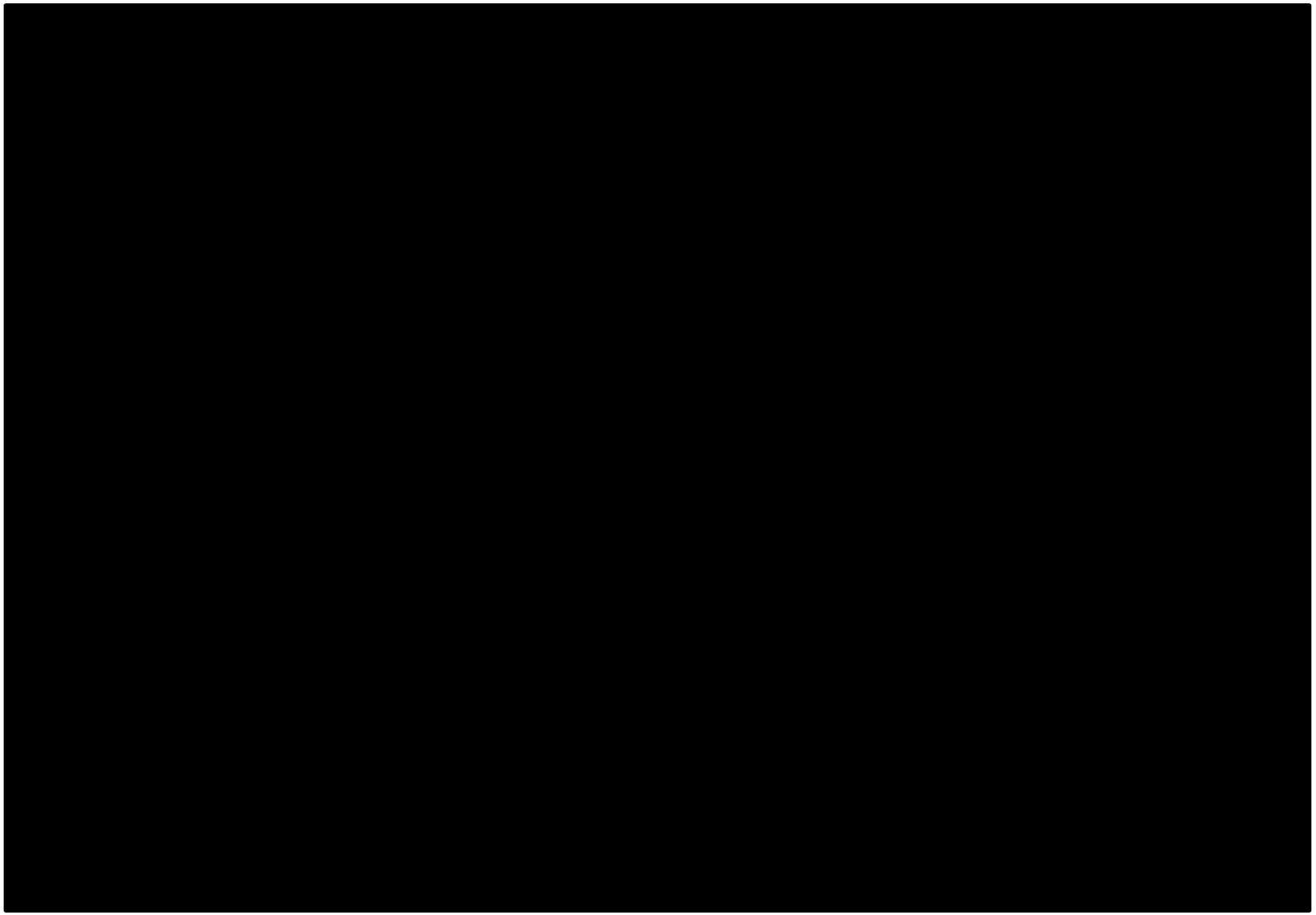
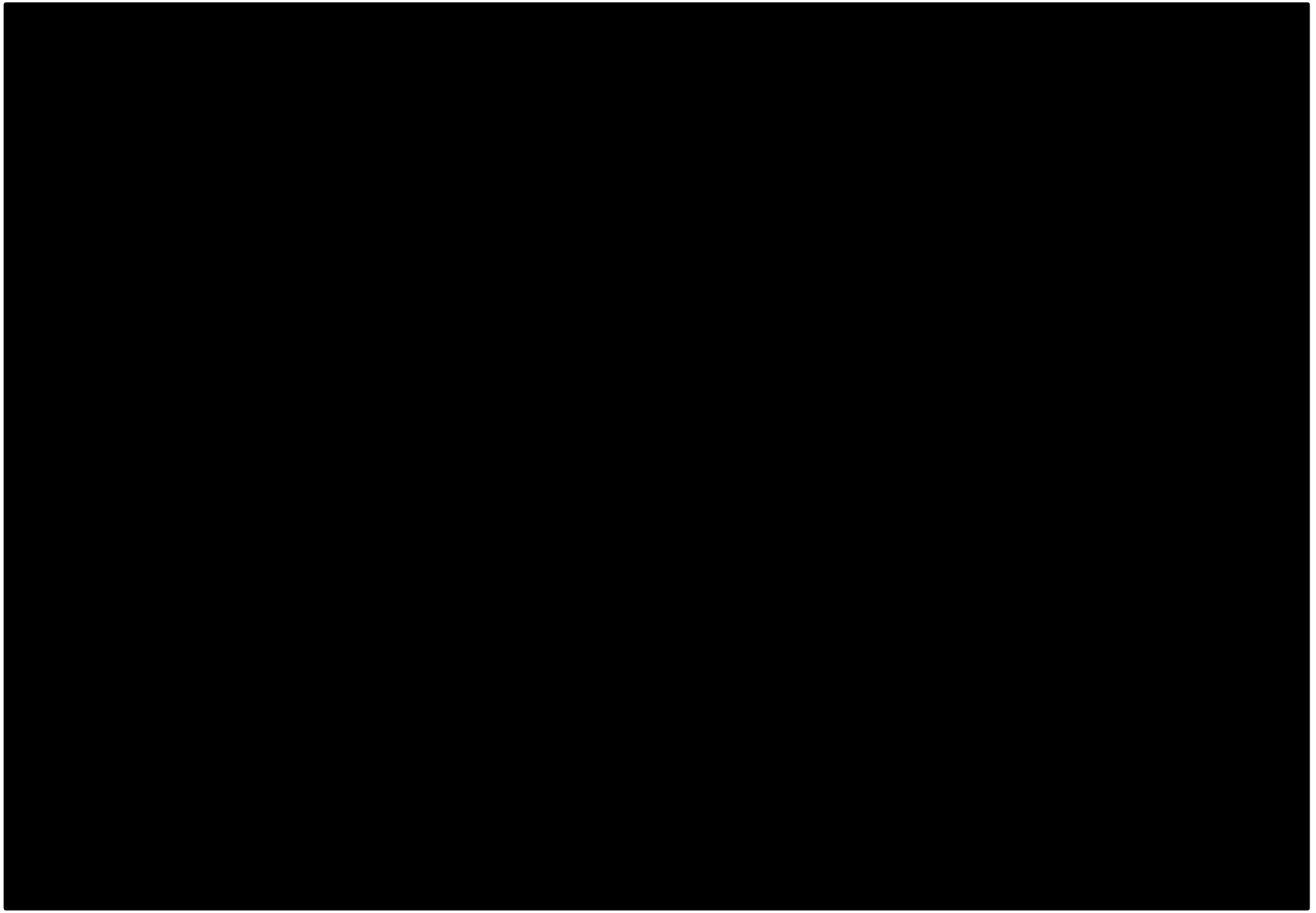


Figure 6 Long-term response rates in RAPID-PsA certolizumab patients who werePASI50 (A), PASI75 (B) or PASI90 (C) responders at 12 weeks



Radiographic progression of joint damage

At week 96, the modified Total Sharp Score (mTSS) non-progressor rate (non-progression defined as mTSS change from baseline ≤0.5 points) was 87%. This was based on observed data for the combined certolizumab pegol groups: 218 of the 273 randomised. For patients randomised to certolizumab pegol (combined group) the mean level of progression was 0.14 (SE 0.09) which is below the 0.5 non-progression cut-off. Subgroup analyses indicated that patients (randomised to certolizumab pegol) with a baseline mTSS of >3.5 had slightly greater radiographic progression at week 96 than patients with a baseline mTSS of ≤3.5: 0.24 (SE 0.19) for mTSS >3.5 vs 0.07 (SE 0.04) for mTSS ≤3.5.

Efficacy of other therapies

Methods and result details relating to the latest time point for which long-term data were available for golimumab, etanercept, adalimumab, infliximab, ustekinumab and apremilast are presented in Table 33.

The GO-REVEAL (golimumab) study reported results at 5 years using the originally randomised intention-to-treat groups.[68] Across the groups the proportion of responders ranged from 63 to 70% for ACR 20; 43 to 51% for ACR 50 and 61 to 72% for PASI 75. Mean changes from baseline in modified SHS score ranged from 0.1 to 0.3 units. Clinically important improvements in HAQ (a decrease of ≥ 0.3) were seen for 52 to 58% of randomised patients. The use of concomitant methotrexate at baseline did not affect ACR 20 or PASI 75 but did appear to reduce radiographic progression when a comparison was made with patients who did not use concomitant methotrexate at baseline. Although some method details were not totally clear, it appeared that the data imputations used were not conservative enough. For example, it seems that LOCF was used for patients who stopped treatment due to an adverse event (so a patient responding well to treatment but who discontinued treatment early in the study due to an adverse event was counted as a responder at 5 years). Also, it was unclear whether there were any stopping rules - such as how long non-responders were allowed to remain on treatment - which raise further uncertainties about the study's applicability to clinical practice.

The follow up for the Mease 2004 etanercept trial[49] extended to 2 years and consisted of three phases: the 24 week initial randomised phase, an optional 24 week maintenance therapy phase (according to randomised assignment), and a 48 week open-label phase. Most results were given as percentages and it was not totally clear what the denominator was for particular results. Several results were only presented as graphs. Very limited data were provided on reasons for withdrawal from the study and HAQ results were not reported. The ACR response results were similar to those seen in GO-REVEAL (at 5 years) although the proportions of PASI 75 responders were markedly lower.

The ADEPT adalimumab trial was extended to 2.75 years for radiographic progression outcomes and 2 years for other outcomes.[69] The ACR 50 results were similar to those seen for the etanercept and

golimumab open-label studies. PASI 75 results were only presented in a graph; the response was around 60% (n=128), which is similar to the GO-REVEAL PASI 75 result at 5 years. Non-responders could increase their dose from 40mg every other week (the recommended dose) to 40mg weekly; this occurred in 54 (19%) patients. The use of LOCF imputation for missing data for the ACR, PASI and PsARC outcomes is different (potentially much less conservative) from the imputations used in the placebo-controlled phase, where non-responder imputations were used. This is likely to have inflated the response rates in the open-label phase. The results for HAQ remained very stable throughout the 2 years. These open-label HAQ results are similar to the placebo-controlled fully-blinded 24 week phase where HAQ remained the same between week 12 and week 24 in both the adalimumab and the placebo groups.

The ustekinumab PSUMMIT 1 trial was extended to 108 weeks with efficacy data evaluated at 100 weeks.[70, 71] The change from baseline SHS radiographic progression scores varied across the three treatment groups. Change from baseline HAQ results ranged between -0.36 to -0.45, which were similar to the adalimumab study results around.

The infliximab IMPACT trial was extended to 98 weeks.[72] The data for all patients were summarised as one group (as for the adalimumab open-label study). At 98 weeks 46% and 34% were ACR 20 and ACR 50 responders respectively. The mean change in modified SHS score was 1.2 which is similar to the results in the ustekinumab PSUMMIT 1 study. However, the result was based on 41% of the initial 104 patients. The authors also acknowledged that the 2 year radiographic progression result may have reflected nonlinear progression of damage, with more damage occurring in earlier disease stages. Mean changes from baseline were not available for HAQ.

For apremilast the PALACE 1 trial was extended to 2 years.[56, 73] There were no separate results for the patients at 104 weeks who were in the placebo group at the beginning of the trial. For the 30mg group, at 2 years 40% of patients were ACR 20 responders and 30% were PASI 75 responders. The HAQ result may be an overestimate as it was based on data from patients remaining in the study at 2 years (i.e. observed data). No data were reported on any radiographic progression outcomes.

Table 33 Open-label extension studies of other therapies for psoriatic arthritis

<table>
<tr><th>Original trial name with relevant OL references; Treatment and dose; Latest time point[a]</th><th>Number of patients</th><th>Analysis and imputation methods used by the study authors</th><th>Main results
(ITT data extracted where possible)</th><th>Key withdrawal data</th></tr>
<tr><td>GO-REVEAL[68, 74]

Golimumab 50mg or 100mg (at investigator's discretion)

5 years</td><td>Of 405 randomised (113 placebo, 146 50mg, 146 100mg) 279 were (69%) still on treatment at 5 years</td><td>It appeared that LOCF was used except for: lack of efficacy discontinuations, where NRI was used and; radiographic scores where observed data were used (n=267)</td><td>At 5 years:
<table>
<tr><th></th><th>Modified SHS score[b]</th><th>HAQ</th><th>ACR 20</th><th>ACR 50</th><th>PASI 75[c]</th></tr>
<tr><td>Placebo/ GOL 50mg</td><td>0.3 (3.8)</td><td>0.7 (0.6)</td><td>71/113 (63%)</td><td>49/113 (43%)</td><td>48/79 (61%)</td></tr>
<tr><td>50mg</td><td>0.3 (4.2)</td><td>0.6 (0.6)</td><td>96/146 (66%)</td><td>70/146 (48%)</td><td>67/109 (61%)</td></tr>
<tr><td>100mg</td><td>0.1 (2.7)</td><td>0.6 (0.6)</td><td>102/146 (70%)</td><td>74/146 (51%)</td><td>78/108 (72%)</td></tr>
</table></td><td>126/405 (31%) stopped treatment: 50 due to an AE and 23 due to lack of efficacy</td></tr>
<tr><td>Mease 2004[75]

Etanercept 25mg twice weekly

Up to 2 years</td><td>Of 205 randomised (104 placebo, 101 ETA) 169 took part in the extended study</td><td>Analyses were based on observed populations. All analyses were performed on the subset of patients who had radiograph data for the 2 year assessment (n=141; 70 PLA/ETA, 71 ETA)</td><td>At up to 2 years:
<table>
<tr><th></th><th>Modified Sharp score[b]</th><th>PsARC</th><th>ACR 20</th><th>ACR 50</th><th>PASI 75[c]</th></tr>
<tr><td>Placebo /ETA</td><td>0.5</td><td>~80%</td><td>63%</td><td>49%</td><td rowspan="2">~38% of 102 patients</td></tr>
<tr><td>ETA</td><td>-0.38</td><td>~80%</td><td>64%</td><td>44%</td></tr>
</table></td><td>44/205 (21%) stopped treatment: 14 in RCT phase, 9 in maintenance phase and 21 in open-label phase. 3 patients withdrew from OL phase due to an AE</td></tr>
<tr><td>ADEPT[69]

Adalimumab 40mg every other week; patients without ≥20% improvement in TJC and SJC after 12 weeks of OL could increase to 40mg per week

2 years; 2.75 years for radiographic data</td><td>Of 313 randomised (162 placebo, 151 ADA) 289 completed 24 week RCT of which 285 chose to enrol in the extended study</td><td>Most analyses based on a modified ITT population (any patients who had received a dose in either study phase, n=298) with LOCF imputation.</td><td>At 2 years (2.75 years for modified Sharp score):
<table>
<tr><th></th><th>Modified Sharp score[b]</th><th>HAQ[b]</th><th>PsARC</th><th>ACR 20</th><th>ACR 50</th></tr>
<tr><td>Placebo /ADA</td><td>0.9 (6.4) n=128</td><td rowspan="2">-0.3 (0.5)</td><td rowspan="2">188/298 (63%)</td><td rowspan="2">161/298 (54%)</td><td rowspan="2">127/298 (43%)</td></tr>
<tr><td>ADA</td><td>0.5 (4.2) n=115</td></tr>
</table></td><td>44 of 285 stopped treatment in the OL phase: 10 due to AEs; 12 due to lack of efficacy</td></tr>
</table>

<table>
<tr><th>Original trial name with relevant OL references; Treatment and dose; Latest time point[a]</th><th>Number of patients</th><th>Analysis and imputation methods used by the study authors</th><th>Main results
(ITT data extracted where possible)</th><th>Key withdrawal data</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>IMPACT[72]

Infliximab 5 mg/kg

Up to 2 years</td><td>104 patients took part in the RCT. 78 out of the 87 patients who completed the first year continued to enrol in the extended 2 year study</td><td>Analyses were based on the 78 patients who entered year 2 (analysed as one group).</td><td>At 98 weeks,<table><tr><th></th><th>Modified SHS score[b]</th><th>PsARC</th><th>ACR 20</th><th>ACR 50</th><th>PASI 75[d]</th></tr><tr><td>Placebo /INF</td><td rowspan="2">1.2 (8.7), n=43</td><td rowspan="2">52/104 (50%)</td><td rowspan="2">48/104 (46%)</td><td rowspan="2">35/104 (34%)</td><td rowspan="2">64% (n=unclear)</td></tr><tr><td>INF</td></tr></table></td><td>26 patients withdrew over the 2 years. 12 due to AEs; 3 due to lack of efficacy</td></tr>
<tr><td>PSUMMIT 1[70, 71]

Ustekinumab 45 mg or 90mg every 12 weeks

100 weeks</td><td>615 randomised: 206 placebo, 205 UST 45mg and 204 UST 90mg
598 received at least one dose of ustekinumab</td><td>Analyses were based on ITT populations using LOCF and NRI for most analyses.
Missing radiographic data between week 52 and week 100 were imputed using linear extrapolation (if data were available for 2 time points) otherwise the median change in the total scores from all patients within the methotrexate stratification was used.</td><td>At 100 weeks:<table><tr><th></th><th>Total SHS score[b]</th><th>HAQ[b]</th><th>ACR 20</th><th>ACR 50</th><th>PASI 75[c]</th></tr><tr><td>Placebo /UST 45mg</td><td>2.3 (12.6) n=189</td><td>-0.36 (0.51)</td><td>111/206 (54%)</td><td>66/206 (32%)</td><td>78/136 (57%)</td></tr><tr><td>45mg</td><td>1.0 (3.8)</td><td>-0.36 (0.56)</td><td>101/205 (49%)</td><td>69/205 (34%)</td><td>87/145 (60%)</td></tr><tr><td>90mg</td><td>1.2 (5.1)</td><td>-0.45 (0.6)</td><td>112/204 (55%)</td><td>81/204 (40%)</td><td>92/149 (62%)</td></tr></table></td><td>By week 88 (last dose), 125 patients (20.3%) had discontinued treatment. 31 due to an AE; 40 due to lack of efficacy</td></tr>
<tr><td>PALACE 1[56 73]
Apremilast 30 mg twice daily, oral tablets;
2 years</td><td>504 patients were randomised (168 placebo, 168 APR 20mg, 168 APR 30mg. 101 patients received 30mg continuously for 2</td><td>Analyses were based on the observed population for the extension period</td><td>At 104 weeks:<table><tr><th></th><th>HAQ[b]</th><th>ACR 20</th><th>PASI 75[c]</th></tr><tr><td>APR 30mg</td><td>-0.43 n=101</td><td>(67/168) 40%</td><td>(21/71) 29.6%</td></tr></table></td><td>8.2% discontinued treatment due to AEs between weeks 0 to 52 and 1.5% between weeks 53 to 104.</td></tr>
</table>

Original trial name with relevant OL references; Treatment and dose; Latest time point[a]	**Number of patients**	**Analysis and imputation methods used by the study authors**	**Main results (ITT data extracted where possible)**	**Key withdrawal data**
	years (observed population)			

Standard deviations in brackets, OL open-label, LOCF Last observation carried forward, NRI Non-responder imputation, SHS Sharp/van der Heijde, [a] with published results [b]change from RCT baseline, [c] in patients with ≥3% body surface area involvement, [d] Patients with a baseline PASI score ≥2.5

Summary

The uncontrolled nature of open-label extension studies means it is often very difficult to determine the magnitude of effects which can be ascribed only to active treatment; results should generally be viewed with much more caution than the results of the earlier randomised controlled study phases. Furthermore, it is not straightforward to compare long-term results across different treatments due to the variation in outcomes and time points reported. There is also variation in the methodological approaches used for analyses and for imputing missing data. Additionally, most studies did not report whether there were any treatment stopping rules and it is likely that the decisions made regarding continuation of treatment were not reflective of those used in the NHS, limiting the applicability of many of these results. For example, in the open-label ADEPT study non-responders after 12 weeks had their dose doubled – the opposite of what would be expected in practice (where treatment with adalimumab would have been stopped).

With these caveats in mind, the results relating specifically to those patients who were responders at 12 or 16 weeks appear to be the most clinically relevant and useful (for the dichotomous outcomes), although such data were only available for certolizumab pegol and secukinumab [redacted]

The available data on disease progression based on radiographic assessments of joint damage indicate that, after two years of treatment, certolizumab pegol effectively reduces disease progression with results being similar to those observed in the open-label studies of the other anti-TNFs. For secukinumab, fewer result details were available at two years although the results also indicated effective reduction in radiographic disease progression.

For long-term HAQ results, missing data were often imputed using last observation carried forward, which is not the most conservative of approaches for this outcome. Notwithstanding this, the results suggest that HAQ gains remain stable in psoriatic arthritis patients treated with biologics. Two year open-label HAQ results from ADEPT were similar to the placebo-controlled fully-blinded 24 week phase where HAQ remained the same between week 12 and week 24 in both the adalimumab and the placebo groups. This stability of HAQ over time was also seen in the open-label studies of certolizumab pegol (data up to four years) and secukinumab (data to one year).

Withdrawals rates due to adverse events or loss of efficacy were low in both FUTURE 2 (5% at 52 weeks) and RAPID-PsA (around 10% at 52 weeks).

4.8 Review of anti-TNF patient registry studies

4.8.1 Drug survival and anti-TNF switching

The database of references which resulted from the searches for RCTs was also screened to identify registries containing psoriatic arthritis patients and their publication output. The results of this search were supplemented by separate searches for the output of the identified patient registries reporting information on their psoriatic arthritis cohorts. A library of 165 potentially relevant studies was assembled and screened fully, from which there were 12 studies reporting data on drug survival and switching of anti-TNF treatments. The populations of all 12 studies were defined as having clinically diagnosed psoriatic arthritis. These studies are presented in Table 34.

These studies were all retrospective analyses of prospective patient registers from primarily European countries (10 studies), along with one Australian study and another from the USA. The majority of patients in each of the registries had been treated with etanercept, adalimumab, or infliximab; two of the studies named other anti-TNFα treatments golimumab and certolizumab pegol, but neither had sufficient data to provide individual drug survival information for these.

Drug survival was reported in a number of ways: as the number of patients remaining on treatment as a given time point; the proportion of patients remaining on treatment at each time point; or as the median duration patients remained on treatment.

Treatment withdrawal rates in patients who had switched anti-TNFs were reported in three studies.[76-78] The Danish DANBIO registry [76] reported up to three sequential anti-TNFs, with 548 patients who had switched treatment once, and 189 patients who had switched treatment twice. The UK's BSRBR[77] patient register also reported drug survival rates for their population of 178 one-time switchers over two years, while the 95 switchers in the Norwegian NOR-DMARD[78] register were followed for 3 years.

For the first course of anti-TNF treatment, the proportion of patients remaining on treatment where reported ranged from 60% to 88% at one year, 57% to 81% at two years, and 55% to 73% at three years. Three studies reported 1st anti-TNF drug survival rates for 5 years or more, these were the BSRBR study[79] in which 47% of patients were still on the initial anti-TNF treatment at 5 years, and the Swedish SSATG[80] registry with 5 year survival at around 40%. Another Swedish registry, ARTIS[81]**,** reported 6 year 1st anti-TNF drug survival of 37% and 8 year survival of 32%.

Median 1st anti-TNF survival time across all anti-TNFs was reported as 2.5 to 2.9 years..[82,83] One study reported this separately by anti-TNF: etanercept 2.62 yrs; adalimumab 4.21 yrs; and infliximab 1.92 yrs.[84]

In patients who switched anti-TNF, drug survival was consistently lower than in those who did not. DANBIO [76] had the largest population of switchers; the median drug survival for a first anti-TNF was 2.2 years (95% CI 1.9-2.5), whereas median drug survival for a second anti-TNF was 1.3 years (95% CI 1.0-1.6) (n=548) and was 1.1 years (95% CI 0.7-1.5) (n=189) for those on a third anti-TNF.

There is some evidence suggesting drug survival varies between types of anti-TNF; both the Australian ARAD registry and the BSRBR study report rates for individual therapies, and both indicate that adalimumab and etanercept have considerably higher survival rates than infliximab. Two studies reported the impact of concomitant methotrexate or other DMARD.[80, 82] One reported a small increase in drug survival at one year, from 65% to 80% but this effect was diminished at 3 years (from 55% to 60%) and 5 years (from 37.5% to 40%.[80] The other study reported that median drug survival time for anti-TNFα monotherapy was 30.8 months, compared with 32.4 months for combination therapy (anti-TNF + MTX or DMARD).[82]

Reasons for discontinuation of treatment varied widely between studies due in part to the inconsistency of observation period duration. Across all registries, between 20-35% of patients withdrew from treatment due to lack of efficacy, and generally a smaller proportion due to adverse events. Frequency of adverse events was linked to the types of anti-TNF used and whether patients received concomitant methotrexate; which generally reduced AE frequency where MTX subgroups were analysed.

Only one study reported an analysis of response rates; this was based on the 3 month response rates from the NORMARD registry (n= 439). [85] A retrospective comparison of response rates in switchers and non-switchers found that switchers had a lower response rate to the 1st anti-TNF: for ACR 50 30.5% compared to 40%. In addition, the response to the 2nd anti-TNF was lower than to the 1st: 22.5% (compared with 30.5% though this was not statistically significant). The same pattern was seen for ACR20 and 70, and for the latter the difference reached statistical significance.

In summary, across all relevant studies, those who switched treatment had a shorter median drug survival time, also showing a continuously smaller proportion of patients remaining on each subsequent treatment option. This may reflect a lack of improvement in treatment response after switching biologic; however, there is limited direct data on the effect of sequential treatments upon relevant outcome measures. The proportion of patients withdrawing from treatment due to lack of effect also seems to increase with the number of times a patient switches anti-TNF therapy. The

registry data suggests that whilst patients can benefit from a second or more anti-TNF, the expected benefit from anti-TNFs diminishes after switching, with a reduced chance of response and reduced drug survival.

Table 34 Registry studies reporting data on anti-TNF drug survival and switching

Publication	Registry name	N (follow-up)	Population	Anti-TNFs included	Drug survival data	Reason for discontinuation
Carmona *et al.* [86]	Spanish Society of Rheumatology Registry for Adverse Events of Biological Therapies in Rheumatic Diseases (BIOBADASER)	570 (5 years) 963.6 pt yrs	PsA	Etanercept Adalimumab Infliximab	As a proportion, anti-TNFα survival was 0.88 [CI 0.84-0.90] at 1 yr; 0.81[CI 0.77-0.84] at 2 yrs and 0.73 [CI 0.67-0.78] at 3 yrs.	Not split by diagnosis
Chen *et al.*[84]	Australian Rheumatology Association Database (ARAD)	286 (10 years)	PsA	Etanercept Adalimumab Infliximab	Median survival time Etanercept (N=110) 2.62 yrs [CI 1.10-4.45] Adalimumab (N=144) 4.21 yrs Infliximab (N=23) 1.92 yrs [CI 0.96-2.88]	**Any LoE AE** E: 41% 20.5% 8% A: 35% 17.7% 11.5% I: 70% 29.6% 11.1%
Fagerli *et al.*[85]	Norwegian Antirheumatic Drug Register (NOR-DMARD)	439 (3 years) 547 pt yrs	PsA	Etanercept Adalimumab Infliximab Golimumab Certolizumab	Proportion of non-switchers (N=344) remaining on first anti-TNFα after 1 year was 0.83; at 3 years was 0.71. 1 year survival for all patients on 1st anti-TNFα was 0.74. Proportion of those who switched to a different anti-TNFα (N=95) remaining on 2nd treatment for 1 year was 0.56; 3 year survival was 0.36.	**NR**

Response rate (%) at 3 months

	Non-switchers 1st	Switchers 1st	2nd	P value switchers 1st vs 2nd
ACR 20	64.4	45.8		NS
ACR 50	40.0	30.5	22.5	NS
ACR 70	32.2	23.7	12.5	0.04

Fagerli *et al*.[79]	British Society of Rheumatologists Biologics Register (BSRBR)	666 (5 years)	PsA	Etanercept Adalimumab Infliximab	After 5 years 46.8% of patients were still on initial anti-TNFα.	**LoE** **AE** 35.3% 28.8% Other/missing: 35.9%
Glintborg *et al.*[83]	DANBIO – Danish Rheumatologic Database	764 (9 years) 2135 pt years	PsA	Etanercept Adalimumab Infliximab	Proportion of cohort remaining on same anti-TNFα after 1 year was 0.70, and 0.57 at 2 years. Median drug survival was 2.9 years	**LoE** **AE** 23% 12%
Glintborg *et al.*[76]	DANBIO – Danish Rheumatologic Database	1422; 548 switchers (10 years)	PsA	Etanercept Adalimumab Infliximab Golimumab Certolizumab Other non-anti-TNF biologics	Median survival time on first course of treatment was 2.2 years [CI 1.9-2.5]. Second course [N=548] drug survival was 1.3 years [CI 1.0-1.6]. Third course (N=189) median survival was 1.1 years [CI 0.7-1.5]. Median drug survival of first anti-TNFα among switchers was 0.7 years [CI 0.6-0.8].	**Any** **LoE** **AE** 1st: 56% 26% 16% 2nd: 55% 28% 15% 3rd: 55% 33% 14%
Glintborg *et al.*[87]	DANBIO and ICEBIO (Iceland)	462 (<10 years) 1185 pt yrs	PsA (Patients on Infliximab)	Infliximab (variable dose)	1 year drug survival for infliximab was 59.5% across both registers. Dose did not affect drug survival or treatment response.	**LoE** **AE** 25% 29%
Iannone *et al.*[88]	Italian Group for the Study of Early Arthritis (GISEA)	328 (2 years)	PsA	Etanercept Adalimumab Infliximab	2 year overall drug survival was 0.67.	**NR**

Kristensen *et al.*[80]	South Swedish Arthritis Treatment Group (SSATG)	261 (7 years)	PsA	Etanercept Adalimumab Infliximab	Kaplan Meier graph estimates drug survival was: Anti-TNFα only: 1yr: 0.65; 3yr: 0.55; 5yr: 0.375 Anti-TNFα + MTX: 1yr: 0.8; 3yr: 0.6; 5yr: 0.4	Risk of AE lower with concomitant MTX
Mease *et* al.[82]	Consortium of Rheumatology Researchers of North America (CORRONA)	497 (7 years)	PsA	Etanercept Adalimumab Infliximab	Median drug survival time for anti-TNFα monotherapy was 30.8 months, and 32.4 months for combination therapy (anti-TNF + MTX or DMARD).	**NR**
Saad *et al.*[77]	British Society of Rheumatologists Biologics Register (BSRBR)	566 (3 years)	PsA	Etanercept Adalimumab Infliximab	Drug survival: 1yr / 2yr / 3yr Total 1st anti-TNFα: 0.82 / 0.70 / 0.59 Etanercept (N=316): 0.86 / 0.79 / 0.65 Adalimumab (N=88): 0.91 / 0.70 / 0.66 Infliximab (N=162): 0.71 / 0.52 / 0.43 Switchers (N=178): 0.74 / 0.66 / -	**As % of total** **LoE** 9.5% **AE** 10%
Simard *et al.*[81]	Swedish Biologics Register (ARTIS)	1417 (9 years)	PsA	**NR**	Kaplan Meier graph estimates survival of first anti-TNFα was 0.75 at 1 yr; 0.63 at 2 yrs; 0.5 at 4 yrs; 0.37 at 6 yrs and 0.32 at 8 yrs.	**LoE** 9.4% **AE** 8.2% Within 1 year of treatment initiation

Pt years = patient years, LoE = lack of efficacy, AE = adverse event

4.8.2 Effect of anti-TNFs on radiographic progression and HAQ score

Four patient registry studies were identified that provided longitudinal data on the effect of anti-TNFs on HAQ scores, one of which also reported on radiographic progression, these are presented in Table 35.

One study reported on radiographic progression; a comparison of anti-TNF and methotrexate found an inhibitive effect of anti-TNF on radiographic progression over four years of observation. Radiographic progression was measured in terms of newly forming erosions and change in a modified Steinbrocker score (mSS); radiographic progression according to both measures was significantly more prevalent in the methotrexate group at each follow-up assessment.

Four studies reported on disease progression in terms of HAQ score for between 6 months and 5 years at varying frequency. Eder *et al*[89] compared HAQ score change in 70 patients treated with methotrexate with 65 on an anti-TNF, finding no significant difference in HAQ score between the groups at the two assessments made up to four years from baseline. HAQ score was measured in 658 patients receiving anti-TNFs for 5 years in the largest cohort [83] (DANBIO). Baseline mean HAQ score was 1.0, decreasing to 0.3 by 3 years, and increasing to 0.5 at 5 years. This suggests sustained long term improvement of functional status during anti-TNF treatment, though the number of patients at each time point after the 6 month assessment decreased significantly. Therefore, the trend of improving HAQ observed in this study is potentially due to a higher attrition of patients with greater functional impairment skewing the data. The third study on HAQ change is from the NOR-DMARD register[85], showing an improvement in HAQ score from 0.7 at baseline to 0.39 at 3 months, and 0.38 at 6 months. This study also found no significant difference in HAQ response in patients receiving methotrexate compared to those on biologics alone. The BSRBR[90] study followed an initial cohort of 562 patients on biologics for 18 months, this group of patients appears to have more advanced disease (12 years since onset) and poorer functional status than those in the other included studies, with a median baseline HAQ of 1.88 (95% CI 1.38-2.25). There is a 0.63 point decrease in HAQ score between baseline and 6 months of treatment, representing what the authors describe as a clinically important improvement, median HAQ then increases to and remains at 1.38 (95% CI 0.63-2.00) at both the 12 month and 18 month assessments. Disease duration at the time of treatment initiation is over twice as long in the BSRBR study as in two of the aforementioned studies on HAQ, showing that significant improvements in functional status is achievable using anti-TNF therapy in advanced cases of PsA.

Treatment with anti-TNFs appears to yield significant improvement in radiographic progression and long term HAQ score change in patient registry studies, though it is not clear to what extent treatment is responsible for the reduction in mean cohort HAQ over time. Estimation of HAQ change using

measures more robust to attrition bias or profiling those lost to follow-up based on disease severity would have given a truer representation of HAQ change in these cohorts. The paucity of radiographic data in these registry studies is perhaps surprising given the significance of radiographic damage as a measure of disease progression and treatment effects. This lack of published data may be because few of these registries were set up to record PsA-specific outcomes, and there has historically been little consensus on a method for objectively taking and scoring joint radiographs in this disease. It may be that HAQ was usually preferred as an acceptable and standardised proxy for assessing bone erosion, and as a patient-reported outcome measure, can be cheaply and routinely recorded without the need for specialist assessment.

Table 35 Registries reporting the effects of anti-TNF treatment on HAQ and radiographic progression

Publication	Study description	Findings
Eder *et al.* [89]	Up to 4 years of radiographic progression in 65 patients treated with anti-TNFα compared with 70 patients treated with methotrexate alone in the University of Toronto cohort. Only patients with bone erosions at baseline were included.	At the first assessment after baseline (1-2 years): Methotrexate group: 68% developed a new erosion in at least one joint, 80% of patients exhibited radiographic progression. Anti-TNFα group: 56.4% had a new eroded joint and 58.9% had radiographic progression. At the 2-4 year assessment: Methotrexate group: 84% developed a new erosion, 88% had radiographic progression. Anti-TNFα group: 75% had a new eroded joint and 61% with radiographic progression. **HAQ Score** Anti-TNFα Methotrexate Baseline 0.9 ±0.7 0.7 ±0.7 1-2 yr 0.6 ±0.6 0.6 ±0.6 3-4 yr 0.6 ±0.6 0.7 ±0.7
Fagerli *et al.*[85]	Analysis of the effect of methotrexate co-medication in 440 PsA patients in the NOR-DMARD register.	The study found no difference in treatment response between those on anti-TNFα monotherapy and those with concomitant MTX. Mean cohort HAQ was recorded as 0.7 at baseline, 0.39 at 3 months, and 0.38 at 6 months. Mean change from baseline at 3 months = 0.31.
Glintborg *et al.* [83]	Analysis of long term anti-TNF treatment response data from DANBIO Danish patient register (N=658) Measured HAQ over 5 years.	**HAQ score** **N patients** Baseline 1.0 658 2 weeks 0.75 275 6 weeks 0.6 366 6 months 0.6 406 1 year 0.4 318 2 years 0.4 229 3 years 0.3 127 4 years 0.3 104 5 years 0.5 45
Glintborg *et al* [76]	DANBIO – Danish Rheumatologic Database (n=1422; 548 switchers) (10 years) PsA (Etanercept Adalimumab Infliximab Golimumab Certolizumab Other non-anti-TNF biologics	**HAQ (median) (IQR)** Anti-TNF 0 mth 3 mths 6 mths 1st(n=1422) 1 (0.5-1.5) 0.6 (0.1-1.1) 0.6 (0.1-1.0) 2nd (n=548) 1.1 (0.6-1.6) 0.9 (0.4-1.5) 0.9 (0.4-1.4) 3rd (n=189) 1.4 (0.9- 1.0 (0.6-1.5) 1.3 (0.5-

			2.9)	1.6)
Saad *et al.*[90]	Evaluation of the effect of anti-TNF therapies on quality of life and functional status in the BSRBR cohort of 596 PsA patients.		HAQ score, median (IQR)	N patients
		Baseline	1.88 (1.38-2.25)	562
		6 months	1.25 (0.63-1.88)	424
		12 months	1.38 (0.63-2.00)	382
		18 months	1.38 (0.63-2.00)	344

4.9 Review of the natural history of psoriatic arthritis: registry & cohort study data

A total of four publications analysing patterns of natural disease progression in registries or long-term cohort data were found and are shown in Table 36. These were reviewed in order to gain an understanding of the manner in which disease progresses in patients who do not receive anti-TNF therapy, despite being eligible for treatment. Due to the now ubiquitous nature of anti-TNFs and only recent recognition of PsA as a separate and distinct form of arthritis, information on the long-term uncontrolled progression of the disease is scarce. Two of the studies found in the literature search were different analyses of the same dataset derived from the NOAR registry, one was a 2 year prospective cohort study, and the other a retrospective analysis of a Canadian single-site patient registry.

The studies explore changes in functional disability in terms of HAQ score and bone erosion as measures of disease activity and progression over time. There is a great deal of variability between the three cohorts under observation in terms of both baseline characteristics and patterns of disease. It should be noted that disease classification of the NOAR cohort[91, 92] was performed retrospectively and both studies analysing the 79 patients emphasise that they are unlikely to be representative of psoriatic arthritis patients, preferring instead to refer to them as having polyarthritis plus psoriasis. The Morgan *et al.*[92] study analysed change in median cohort HAQ score over 5 years in 79 patients, finding an increase of 0.125 HAQ units over the observation period; indicating a small increase of 0.025 in HAQ score every year. The patients in this analysis may or may not have been treated with DMARDs over this period, the analysis in Rodgers *et al*. includes only those patients who had previously received two or more DMARDs at each time point, finding an annual HAQ score change of -0.060 per year over the first two years (n=24), and an annual increase of 0.077 HAQ units over years 3 to 5 (n=52). This represents a faster progression of disease than that found in the Morgan study, but is inconsistent and derived from a small cohort of varying size.

A prospective cohort study of progression in early arthritis carried out by Kane *et al*.[91] found that HAQ score changed from 0.71 at baseline to 0.4 at 1 year and remained as such until the end of the two year observation period, representing a decrease of 0.31 HAQ units. This decrease is likely

explained by increase in uptake of DMARDs, 12% of patients were receiving DMARD treatment at baseline, compared to 59% at 1 year and 56% at 2 years. This was the only study that recorded radiographic progression, finding consistent increases across all measures between baseline and 2 years, despite the simultaneous drop in HAQ score. Sharp erosion score increased from 1.2 at baseline to 3 at two years, demonstrating how HAQ score change may not reflect progressive radiographic damage, particularly during early disease.

The study by Husted *et al*.[93] was the longest and largest study of natural history of PsA, with 341 patients included and observed for up to 10 years. This study showed several patterns of disease progression existed within the patient population, rather than a universal consistent deterioration over time. Patients were assigned to one of three disability states based on their HAQ score, these were as follows: 'No disability' (HAQ<0.5), 'moderate disability' (HAQ 0.5-1.5), and severe disability (HAQ 1.51-3.0). Transition of patients between groups was recorded over the course of the observation period to ascertain the direction of change in their symptoms. 46% remained in the same disability group over the course of the study, with 28% of these in the no disability state, 12% in the moderate state, and 6% in the severely disabled state. 26.7% made a single transition between disability groups, reflecting steady improvement or deterioration, and 27.3% experienced two or more transitions between disability states. Though this methodology may reveal broad patterns of disease progression, it appears to be insensitive to change within groups and weights HAQ change near thresholds more highly, e.g. a patient with a baseline HAQ at the lower end of a Markov group can experience a significant worsening of their disability without progressing into the next group. Mean HAQ change between consecutive assessments was 0.55(±0.32) for those moving from a lower to a higher state, and -0.57(±0.36) for those moving to a lower state, with assessments being on average 1.29 years apart. In those patients who did not move between groups, the mean HAQ score change was -0.002(±0.215). A more complete picture of patterns of disease progression would have been possible had there been more Markov states, the mean HAQ change for the majority of patients at any one time was effectively zero, but this may conceal significant within-group changes in either direction. Greater age was associated with a slower improvement in HAQ score in those in the moderate and severe disability groups, and disability worsened slower in males than in females. Time since PsA diagnosis was related to more frequent transition between disability states, and there was no association found between PASI score and transition between disability states. In summary, this study indicates that functional disability (HAQ) in PsA is generally stable over time in the majority of patients, but there are groups who exhibit patterns of more rapidly worsening or improving symptoms at certain periods, with some who experience fluctuating deterioration and improvement over time.

Due to the paucity of observational data on natural history of PsA, it is difficult to produce accurate estimates of yearly disease progression rates without anti-TNF therapy. None of the included studies

can claim to provide accurate long-term estimates on uncontrolled disease progression, it is clear from the largest cohort that functional disability deteriorates over time, but the course of HAQ progression is not constant or predictable. Therefore it is unclear whether an average rate of HAQ change is a useful statistic, as this change is neither constant nor generalisable to the patient population. Kane *et al*. does show that despite reductions in functional disability in early-stage disease under DMARD therapy, radiographic progression continues to occur, which theoretically will ultimately result in worsening disability in the long-term; however, due to the lack of large and long term observational studies, HAQ change over time in uncontrolled PsA is yet to be properly measured.

Table 36 Registries reporting on natural history of psoriatic arthritis

Publication	Study description	Population characteristics	Findings
Husted *et al.* [93]	Analysed long-term change in physical function in psoriatic arthritis patients enrolled in the University of Toronto PsA cohort. Patients were assigned to one of three disability states depending on physical function and transition between states was recorded over time. 341 patients observed for up to 10 years.	Anti-TNF naïve PsA patients N male 201 N female 140 Age (mean) 45.9 yrs Duration of PsA (mean) 10.6 yrs PASI (mean) 7.1 ±9.7 Baseline HAQ 0.69 ±0.67	Patients adhered to one of three longitudinal patterns: 46% remained stable - 28% of patients remained in the 'no disability' state (HAQ <0.5) 12% 'moderate' (0.5-1.5), and 6% in 'severe disability' (1.51-3) throughout the study. 26.7% made a single change to a lower or higher disability group, reflecting steady improvement or deterioration, and 27.3% experienced 2 or more transitions between states of disability. Mean time between assessments was 1.29 years. Mean change in HAQ between consecutive assessments in deteriorating patients was +0.55, and was -0.57 in improving patients. Greater age was related to slower improvement of HAQ in the moderate and severe disability groups. Decline in disability was slower in males than in females, and time since diagnosis was related to more frequent transition between disability states. No association was found between PASI score and transition between disability states.
Kane *et al.*[91]	Analysis of 2 year prospective study of 129 PsA patients at St. Vincent's University Hospital Early Arthritis Clinic, Dublin.	Anti-TNF naïve PsA patients Median PsA symptom duration was 9.9 months and mean age at presentation was 41.2 yrs. Baseline HAQ score was 0.71. 12% of patients were on DMARDS and 11% on corticosteroids.	The proportion of patients on DMARDs increased to 59% at 1 yr assessment, and was 56% at 2 yrs, mean HAQ score decreased from 0.71 to 0.4 at both 1 and 2 yr assessments, measures of joint swelling also decreased. DMARD-free remission at 1 and 2 years was 12% and 11% respectively. Measures of radiographic progression all increased from baseline to 2 yrs, mean Sharp erosion score increased from 1.2 (SD 2.9) at baseline to 3 (SD 5.2) at 2 years.
Morgan *et* al. [92]	Analysis of HAQ score change over five years in 79 patients with inflammatory arthritis plus psoriasis in the Norfolk Arthritis Register (NOAR) dataset.	Patients with inflammatory polyarthritis plus psoriasis. N male 36 N female 43 Age (median) 51.2 Baseline HAQ 0.625	After 5 years, median cohort HAQ score had increased from 0.625 to 0.75. 54% of the patients had used DMARDs over the observational period.

		(0.25-1.375) DMARD use 16.5%	
Rodgers *et al.*[94]	Analysis of HAQ score change over five years in the NOAR dataset using inclusion criteria specific to eligibility for treatment with biologics (uncontrolled and have tried two or more DMARDs).	Included in the analysis were patients with inflammatory polyarthritis plus psoriasis, 3+ tender joints and 3+ swollen joints, and previous use of two or more DMARDs.	Patients meeting the eligibility criteria at baseline (N=27) had a HAQ score of 1.55 and for the first two years this changed by -0.060 units per year. Between year three to five, HAQ changed by +0.077 units per year in those meeting the eligibility criteria (N=52).

4.10 Review of adverse effects of certolizumab pegol, secukinumab and comparators

4.10.1 Randomised trials of certolizumab pegol or secukinumab for psoriatic arthritis

Secukinumab: FUTURE 2

During the 16-week placebo-controlled period, adverse events were reported in 54% and 58% of patients in the pooled secukinumab and placebo groups, respectively. The most frequently reported adverse events up to 16 weeks in any secukinumab group (vs placebo) were upper respiratory tract infection ([redacted] vs 7%), nasopharyngitis ([redacted] vs 8%), headache ([redacted] vs 4%), nausea ([redacted] vs 4%), diarrhoea ([redacted] vs 3%) and urinary tract infection [redacted] vs 4%). Rates of infections and infestations were similar across treatment groups (27% on any secukinumab dose versus 31% placebo) and no cases of active tuberculosis were reported.

The majority of adverse events that occurred up to week 16 were mild ([redacted] of adverse events on any secukinumab dose and [redacted] on placebo) and moderate ([redacted] of adverse events on any secukinumab dose and [redacted] on placebo) in severity. Severe adverse events were reported in five patients (1.7% of pooled secukinumab population) compared to none on placebo. Around 3% of patients in the secukinumab groups reported non-fatal SAEs compared to 2% on placebo. More patients on placebo discontinued study treatment due to an adverse event compared to the pooled secukinumab group [redacted]

Certolizumab pegol: RAPID-PsA

During the 24 week period, the incidence of drug-related adverse events was 26% in the pooled certolizumab pegol group and 27% in the placebo group and were mostly mild intensity (51% pooled certolizumab pegol versus 54% placebo) or moderate intensity (30% pooled certolizumab pegol versus 36% placebo). The incidence of serious adverse events was 6.6% in the pooled certolizumab pegol group and 4.4% in the placebo group. The incidence of SAEs was 5.8% in the CZP 200 mg group and 9.6% in the CZP 400 mg group.

[redacted]

[redacted]. The most common serious adverse events were infections [redacted]

4.10.2 Open-label extensions of RCTs of certolizumab pegol and secukinumab

Secukinumab

FUTURE 2

By the 52 week time point, the most common adverse events experienced in patients receiving 150mg were infection and infestations (79 cases per 100 patient-years), upper respiratory tract infection (18 per 100 patient-years) and nasopharyngitis (14 per 100 patient-years). The rate of discontinuation due to adverse events in patients who received at least one dose of secukinumab 150mg was 2%. No deaths were reported.

FUTURE 1

At week 104 79% of patients remained in the open-label extension study. Infections and infestations were the most common adverse event reported occurring at a rate of 68 per 100 patient-years. Malignant or unspecified tumours occurred at a rate of 0.3 per 100-patient years and major adverse cardiac event rates occurred at a rate of 0.7 per 100 patient-years. No cases of active tuberculosis or suicide were reported. At week 52 the rate of discontinuation due to adverse events was 3.9%.

Pooled safety analysis of plaque psoriasis and psoriatic arthritis trials

A conference abstract reported a pooled safety analysis for seven phase III secukinumab trials; five plaque psoriasis trials (ERASURE, FIXTURE, SCULPTURE, FEATURE, JUNCTURE) and two psoriatic arthritis trials (FUTURE 1 and FUTURE 2).[95] All trials except FUTURE 2 contributed data up to (at least) 52 weeks; FUTURE had data up to 24 weeks. A total of 3,928 patients received at least one dose of secukinumab (3,225 patient-years of exposure; mean exposure 299.8 days for secukinumab and 105.7 days for placebo). Exposure-adjusted incidence rates per 100 patient-years for secukinumab and placebo respectively were: 241 and 329 for adverse events; 8 and 10 for serious adverse events and 93 and 94 for infections/infestations. Around 3% of patients treated with secukinumab discontinued treatment due to an adverse event. Nasopharyngitis and upper respiratory tract infections were the most commonly reported events.

Four deaths occurred in patients treated with secukinumab (one intracranial haemorrhage; one cardio-respiratory arrest; one alcohol intoxication and one of unknown cause); all the deaths were deemed unrelated to the secukinumab according to the investigators. There were two (0.05%) cases of suicidality with secukinumab; one attempted suicide and one case of suicidal ideation.

Certolizumab pegol: Rapid-PSA

In the open label extension study, 393 patients had been exposed to certolizumab pegol by week 96 (total exposure: 606 patient-years). At week 96 the incidence of overall treatment-emergent adverse events was 87.8% (345/393 patients; 330 per 100 patient-years). For SAEs the rate was 17% (67 patients; 14.5 per 100 patient-years). Around 4% of patients reported a serious infection (16 cases; 3.3 per 100 patient-years) and 14.2% of patients reported an upper respiratory tract infection (56 patients; 13.7per 100 patient years) with no cases of active tuberculosis. Malignancies were reported in 1% of patients (4 patients; 0.7per 100 patient-years).

By 96 weeks, 9.2% of patients had experienced an adverse event leading to withdrawal and 6 patients (1.5%) had experienced an adverse event leading to death (2 cardiac disorders, 1 sudden death, 1 case of breast cancer, 1 case of sepsis and 1 lymphoma). According to the investigator, both cardiac events were not considered to be related to the study medication.

4.10.3 Reviews of safety outcomes for other biologics

Six relevant reviews of adverse events were identified from the searches. The key results for three of these reviews[94, 96, 97] have been summarised in a recently published HTA report of a multiple technology appraisal of anti-TNFs for ankylosing spondylitis and non-radiographic axial spondyloarthritis.[98]

The Cochrane systematic review and network meta-analysis of adverse events of nine biologics in adults with any disease (except HIV/AIDS) used data from 160 RCTs (n=48,676) and 46 open-label extension studies (n=11,954).[96] The most frequently studied disease in the included trials was rheumatoid arthritis. When compared with control treatments only infliximab and certolizumab pegol were statistically significantly associated with adverse events. Infliximab had higher rates of total adverse events (number needed to harm 13, 95% CrI 8 to 505) and withdrawals because of adverse events (number needed to harm 10, 95% CrI 5 to 30). Certolizumab pegol had higher rates of serious infections (number needed to harm 12, 95% CrI 4 to 79) and serious adverse events (number needed to harm 18, 95% CrI 9 to 162). An individual patient data meta-analysis (n=22,904 from 74 RCTs) examining short-term cancer risk associated with etanercept, infliximab and adalimumab found no increase in risk of cancers excluding non-melanoma skin cancer (relative risk 0.99, 95% CI 0.61 to 1.68) when considering all three anti-TNFs together.[97] However, a doubling in the risk of non-melanoma skin cancer was found, with 332 events per 100,000 person years in the control group and 655 events per 100,000 person years in the anti-TNF group (HR 2.02, 95% CI 1.11 to 3.95). NICE TA199 included a review of studies (including both randomised and non-randomised studies) of the adverse effects of etanercept, infliximab and adalimumab. The rates of serious adverse events covered a broadly similar range across the three anti-TNFs. However, all estimates were derived from a highly

heterogeneous group of studies in terms of patients, study design and treatment regimens so reliable estimates of the relative rate of serious adverse events for each anti-TNF could not be made.[94]

Of the three more recent reviews identified,[99-101] two were reported only as conference abstracts.[99, 100] A Danish guideline panel performed a network meta-analysis of serious adverse events from 87 RCTs (n=27,333) of biologics for inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis and spondylarthritis).[99] The conference abstract reported the odds of a serious adverse event to be statistically significantly higher for certolizuamb pegol compared with placebo (OR 1.6, 95% CI 1.19 to 2.16). Treatment with certolizumab pegol was also statistically significantly more likely to result in serious adverse events compared with golimumab (OR 2.02, 95% CI 1.26 to 3.25) etanercept (OR 1.70, 95% CI 1.15 to 2.51) and adalimumab (OR 1.44, 95% CI 1.02 to 2.02). The other conference abstract reported a 2014 systematic review and meta-analysis on the safety profile of certolizumab pegol in patients with an immune-mediated inflammatory disease.[100] The review identified 18 RCTs with 6992 participants; the results, presented in Table 37, also highlight the increased risk of serious adverse events associated with certolizumab pegol (compared to 'control'), particularly the risk of infectious SAEs.

Table 37 Results of a meta-analysis of safety outcomes for certolizumab pegol

Type of event	Risk ratio versus control (95% CI)
Overall AEs	1.07 (1.03 to 1.10)
Overall SAEs	1.58 (1.31 to 1.92)
Overall ADRs	1.20 (1.05 to 1.38)
Infectious SAEs	2.14 (1.34 to 3.43)
Injection site reactions	2.01 (0.95 to 4.29)
Neoplasms	1.18 (0.59 to 2.39)
Tuberculosis	2.90 (0.73 to 11.43)
Withdrawals due to AEs	1.19 (0.96 to 1.47)
Fatal AEs	2.08 (0.83 to 5.17)
Infectious AEs	1.21 (1.09 to 1.34)
Upper respiratory tract infections	1.33 (1.15 to 1.53)

A review published in 2012 examined the safety of anti-TNFs for treating psoriasis and psoriatic arthritis and focussed mainly on data from European patient registries of biologics used across a range of diseases (mostly rheumatoid arthritis).[101] It was (at least) partly funded by Pfizer, the manufacturer of etanercept and it did not appear to be systematic in its methods of selection, critical appraisal, and synthesis of the included studies. It concluded that the safety profile of the monoclonal antibodies (infliximab and adalimumab) seems generally less favourable than that of etanercept, particularly in terms of infections, cancer and hepatotoxicity. The conclusion for infections appeared largely to be based on a BSRBR analysis specifically on lower respiratory tract infections, even though a previous

BSRBR study reported no difference in the risk of infection between adalimumab, etanercept and infliximab.[102]The conclusion for cancer appeared to be based on an analysis of a small number (38) of lymphomas in a case-control study derived from the French RATIO registry (the data were collected between 2004 and 2006).[103] The conclusion for hepatotoxicity was based on a very small number of case reports.

4.10.4 Recent large observational studies

One recent observational study on the safety of biologics in patients with psoriatic arthritis was identified. It was an Israeli retrospective cohort study based on a health services database which reported on 3128 patients between 2002 and 2013. The study examined the association between traditional DMARDs or anti-TNFs and herpes zoster (shingles). There were 182 cases of herpes zoster in 20,096 person years. The risk of herpes zoster significantly increased in patients treated with a combination of an anti-TNF with a traditional DMARD, but did not increase significantly with each of these types of therapy alone.[104]

4.10.5 Summary

Safety assessments of new treatments can sometimes be limited in systematic reviews of RCTs due to the small number of trials and relatively short follow up durations for which data are available. Where available, safety data from trials relating to the same treatment for other indications are therefore sometimes evaluated. For this review, more data from trials of other patient populations were available for certolizumab pegol than for secukinumab. The results from three systematic reviews (which looked specifically at adverse events) suggested that certolizumab pegol was associated with statistically significantly more serious adverse events and serious infections when compared with placebo. Secukinumab was not included in these systematic reviews of adverse events, probably due to the limited availability of data at the time. Although secukinumab appears to have a favourable safety profile, the fairly small number of trials for which data are currently available means there is still some uncertainty regarding its safety.

5 Evidence synthesis: Relative efficacy of treatments

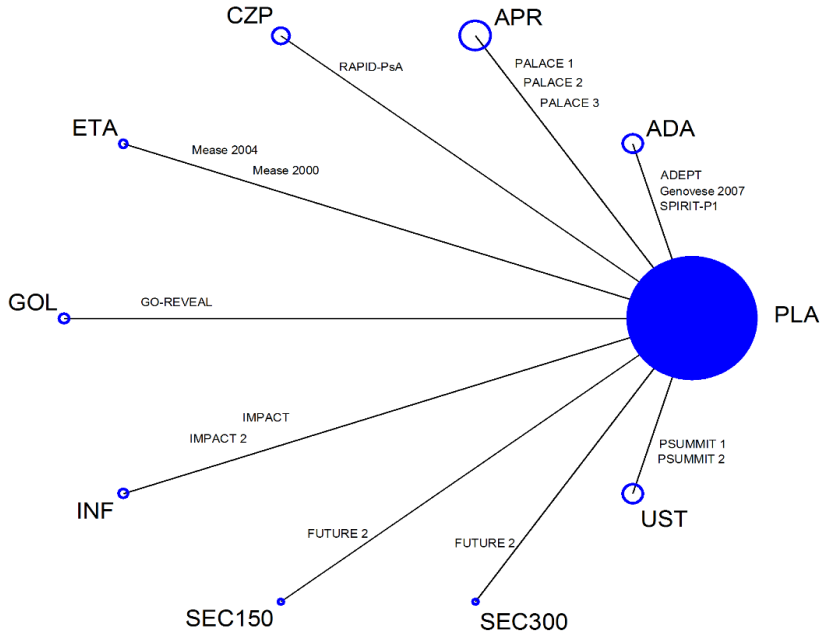
The effectiveness of secukinumab and certolizumab pegol have been summarised in section 4. Results for the main outcomes ACR, PsARC, PASI, HAQ, and HAQ conditional on PsARC for all the comparator agents (etanercept, adalimumab, infliximab, golimumab, ustekinumab and apremilast) have also been presented. These data indicate that all these agents demonstrate statistically significant clinical efficacy in PsA. In order to determine the relative efficacy of these agents it would be ideal to have the results from good quality adequately powered RCTs comparing active treatments with one another. However, as the evidence base is made up almost entirely of comparisons with placebo only, statistical methods for making indirect comparisons – network meta-analysis (NMA) should be considered. NMA enables the comparison of multiple treatments using both direct comparisons of interventions within randomised controlled trials and indirect comparisons across trials based on a common comparator.[105] As suggested by the term, NMA needs a 'network of evidence' to be established between all of the interventions of interest. The drugs being evaluated here all have a common comparator: placebo. It is this common comparator that allows the network between secukinumab, certolizumab pegol and all the active comparators to be established and to provide information on the benefits of these agents relative to placebo and each other. The relevant comparators included on the evidence-base are presented in Table 38 and the basic network diagram in Figure 7.

Table 38 List of comparators included in evidence synthesis

Treatments, description	Treatments, abbreviation	Class of therapy
Secukinumab 150 mg	SEC150	Anti-ILs
Secukinumab 300mg	SEC300	Anti-ILs
Certolizumab pegol	CZP	Anti-TNF
Ustekinumab: 45mg	UST	Anti-ILs
Golimumab: 50mg	GOL	Anti-TNF
Adalimumab: 40 mg	ADA	Anti-TNF
Infliximab: 5mg mg/kg	INF	Anti-TNF
Etanercept: 25mg	ETA	Anti-TNF
Apremilast: 30mg	APR	APR

ILs Interleukins

Figure 7: Network of evidence (not outcome or subgroup specific)



ADA=adalimumab 40 mg; APR=apremilast 30mg; CZP=certolizumab pegol; ETA=etanercept 25mg; GOL=golimumab 50mg; INF=infliximab 5mg mg/kg; PLA=placebo; SEC150= secukinumab 150 mg; SEC300=secukinumab 300mg; UST=ustekinumab 45mg

Four separate outcomes were considered. Three outcomes were included in the NMA to inform the economic model: PsARC response, change of HAQ score conditional on PsARC response, PASI 50, 75 and 90 responses. In addition, ACR 20, 50 and 70 responses were analysed as ACR is the primary outcome in most of the included trials. Trials with data suitable for the NMA are identified in Table 39. Data from the 12 week time point were used where available, otherwise data relating to the closest time point after 12 weeks were used (normally 14 or 16 weeks). Not all trials provided data for all of the outcomes analysed.

Framework of analyses

The evidence synthesis was undertaken using WinBUGS (version 1.4.3). WinBUGS is a Bayesian analysis software tool that, through the use of Markov Chain Monte Carlo, evaluates posterior distributions for the parameters of interest given likelihood functions derived from data and prior probabilities (uninformative priors were used throughout). There were few individual studies on each treatment, therefore fixed-effect models were used across studies in all analyses. Parameter estimates for all functional parameters were reported from the models. These differ by outcome, and further details are presented in the subsections below. Treatment effects were expressed in relation to placebo. Due to the sparse evidence imposing a high level of uncertainty over estimates of functional parameters, point estimates are medians throughout. Some models assumed exchangeability across treatments within a class, that is, different treatments of the same class were assumed to be similar,

rather than equal. Within such models we reported the relative effectiveness estimates for each treatment (called shrunken estimates) rather than the class means, allowing us to represent any residual differences across treatments.

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. Checking for consistency in the current network was not possible due to the lack of trials which directly compare active agents. Our examination of the study details and patient characteristics (see section 4.3) identified that the trials of the newer agents (secukinumab, certolizumab, ustekinumab, and apremilast) included biologic experienced patients as well as biologic naïve patients. Given that it is evident from large observational data sets (section 4.8) that efficacy response rates in biologic-experienced patients are lower than in biologic-naïve patients it was not considered appropriate to conduct an 'all patients' NMA for any outcome, but to analyse biologic-naïve and -experienced patients separately. Therefore, separate analyses (separate networks) for treatment naïve and treatment experienced patients were constructed for each of the four outcomes: one each for PsARC, HAQ conditional on PsARC, PASI 50/75/90, and ACR 20/ 50/70 responses. A summary of the trials reporting data on each of these outcomes is presented in Table 39. It should be noted that, the NICE scope for the present appraisal subdivides biologic-naïve patients into those who have failed one conventional DMARD and those who have failed two conventional DMARDs. However, sufficient data were not available for these further levels of subgroup analysis.

Table 39 Evidence on PsARC, HAQ conditional on PsARC, PASI and ACR by trial

			PsARC			HAQ score conditional on PsARC			PASI 50, 75 and 90			ACR 20, 50, and 70		
Trial	**Year**	**Active treatment**	**naïve**	**exp**	**Time point weeks**	**naïve**	**exp**	**Time point weeks**	**naïve**	**exp**	**Time point weeks**	**naïve**	**exp**	**Time point weeks**
FUTURE 2	2015	SEC	Y	Y	12	Y	Y	12	Y	Y	12	Y	Y	12
RAPID-PsA	2014	CZP	Y	Y*	12	Y	Y*	12	Y	Y*	12	Y	Y*	12
PSUMMIT 1	2013	UST	Y		24	Y**		24	Y		12	Y		12
PSUMMIT 2	2014	UST	Y	Y	24		Y	24	Y	Y	12	Y		12
GO-REVEAL	2009	GOL	Y		14	Y		14	Y		14	Y		14
Genovese 2007	2007	ADA	Y		12	Y		12				Y		12
ADEPT	2005	ADA	Y		12	Y		12	Y		12	Y		12
IMPACT 2	2005	INF	Y		14	Y		14	Y		14	Y		14
IMPACT	2005	INF	Y		16	Y		16	Y		16	Y		16
Mease 2004	2004	ETA	Y		12	Y		12				Y		12
Mease 2000	2000	ETA	Y		12				Y		12	Y		12
PALACE 1	2014	APR	Y		16	Y		16	Y		16	Y		16
PALACE 2	2014	APR	Y		16	Y		16	Y		16	Y		16
PALACE 3	2014	APR	Y		16	Y		16	Y		16	Y		16
SPIRIT-P1	2015	ADA							Y		12	Y		12

*Certolizumab treatment experienced data not included in the NMA as the definition of treatment experienced patients in this trial was different from that in other trial (see Section 4.3); ** pooled data

As discussed in section 4.6 another important difference between the included trials is the observed results in the placebo arms, particularly for PsARC (Table 40), PASI outcomes (Table 50) and ACR (Table 56). Our investigations on trial designs and patient characteristics did not identify any clear reasons for such differences, other than that placebo response rates appear to have increased over time. This observation (termed 'placebo creep') has been made in several other areas of clinical research and its impact on indirect treatment comparisons discussed.[106] In the current review, across all trials the PsARC placebo response rates are high, but are much higher in more recently conducted trials, and this has implications when interpreting unadjusted effect estimates. This is because the ceilings (maximum values) of relative risks are limited by baseline response rates. For example, in FUTURE 2 the placebo response rate for PsARC in the biologic naïve subgroup was [redacted] which meant that the maximum possible relative risk would be [redacted]; this maximum result is lower than some of the actual relative risks for other biologics (see Table 40). Higher placebo rates therefore appear to dilute effect estimates somewhat. This is also demonstrated by the examining the relative risks moving up the ACR outcome thresholds from ACR20 to ACR70 which generally increase (see Table 29). However, it is not clear exactly how these varying placebo rates will affect treatment effects when calculated using odds ratios. The evidence synthesis - which was based on odds ratios -

therefore explored a potential relationship between baseline risk and relative effectiveness. The NMA explored scenarios where a meta-regression on baseline risk (i.e. placebo response) was implemented for PsARC, PASI and ACR outcomes, which imposes an interaction effect between baseline risk and relative effectiveness.[107] Further details of these analyses are presented below. Given HAQ scores are modelled conditional on PsARC response such an interaction effect was deemed to be less relevant, and a meta-regression model was not implemented on HAQ.

5.2 PsARC response

5.2.1 Subpopulation: Biologic naïve

5.2.1.1 Data

For the biologic-naïve population, trial specific PsARC response data were available from 14 trials for nine active treatments (SEC150, SEC300, CZP, UST, GOL, ADA, INF, ETA, APR) and all treatments were compared with placebo (Table 40).

The nine active treatments were categorised into three classes i.e. anti-TNFs, anti-interleukins (ILs) and apremilast. Outcome data for golimumab, infliximab, and apremilast at 14-16 weeks, and ustekinumab at 24 week were included in the analysis and assumed equivalent to outcomes at 12 weeks. The inclusion of the 24 week PsARC data for ustekinumab was based on an assumption that they fairly reflected the 12 week results (subgroup results for PsARC at 12 weeks in PSUMMIT 2 were not available, though 12 week data for the full population were available); this issue is discussed further in Appendix 12.3.2. The trial specific data included in the PsARC response analysis are presented in Table 40.

Table 40 Summary of trial specific data in the biologic naïve subpopulation for PsARC response

Trial, Year	T, treatment arm	PsARC response, TREAT			PsARC response, PLA			ORs			RRs		
		r	N	%	r	N	%	ORs	95% CI		RRs	95% CI	
FUTURE 2, 2015	SEC300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**3.19**	1.80	5.66	**1.59**	1.17	2.15
FUTURE 2, 2015	SEC150	[redacted]	[redacted]	[redacted]				**3.17**	1.77	5.67	**1.59**	1.17	2.16
RAPID-PsA, 2014	CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2.98**	2.00	4.44	**1.61**	1.28	2.04
PSUMMIT 1, 2013	UST	115	205	56%	77	206	37%	**2.14**	1.51	3.03	**1.50**	1.21	1.86
PSUMMIT 2, 2014	UST	24	43	56%	16	42	38%	**2.05**	0.96	4.40	**1.47**	0.92	2.34
GO-REVEAL, 2009	GOL	107	146	73%	24	113	21%	**10.17**	6.13	16.88	**3.45**	2.39	4.99
Genovese 2007, 2007	ADA	26	51	51%	14	51	27%	**2.75**	1.29	5.86	**1.86**	1.10	3.13
ADEPT, 2005	ADA	94	153	61%	42	162	26%	**4.55**	2.97	6.97	**2.37**	1.77	3.16
IMPACT 2, 2005	INF	77	100	77%	27	100	27%	**9.05**	5.39	15.20	**2.85**	2.03	4.01
IMPACT, 2005	INF	39	52	75%	11	52	21%	**11.18**	5.17	24.19	**3.55**	2.05	6.13
Mease 2004	ETA	73	101	72%	32	104	31%	**5.87**	3.57	9.65	**2.35**	1.72	3.21
Mease 2000	ETA	26	30	87%	7	30	23%	**21.36**	8.05	56.68	**3.71**	1.91	7.21
PALACE 1, 2014	APR	78	168	46%	50	168	30%	**2.05**	1.35	3.10	**1.56**	1.17	2.07
PALACE 2, 2014	APR	78	162	48%	53	159	33%	**1.86**	1.23	2.80	**1.44**	1.10	1.90
PALACE 3, 2014	APR	88	167	53%	46	169	27%	**2.98**	1.97	4.51	**1.94**	1.46	2.58

r = number of PsARC responders; N = number randomised

The NMA implemented separate models for the pooling of treatment effects and of placebo responses. We first implemented a model with independent treatment effects across treatments. Then a number of alternative models were implemented to explore the possibility of placebo response, and within this, whether there was similarity between treatment effects for treatments of the same class.

Exploring placebo response as a treatment effect modifier

The trial specific data shows that higher placebo rates are associated with lower relative effectiveness estimates. Our investigations regarding trial designs and patient characteristics did not identify a clear reason for such differences although placebo response rates appear to have increased over time. Investigation of the effect of placebo response as a treatment effect modifier identified two trials, Mease 2000 (etanercept) and Genovese 2007 (adalimumab), as contributing most to the placebo effect (see Appendix 12.3.3.1 for details). Thus exclusion of these trials was anticipated to result in a much less pronounced placebo effect. Sensitivity analyses excluding both the Mease 2000 and Genovese 2007 trials were performed. It should be noted that the source of any relationship between placebo response and treatment effect is unclear the reader should interpret the results carefully and with caution.

Exploring treatment effects as class:

In the context of an adjusted model for placebo response, we explored the possibility of there being class effects. Three different class groupings were considered: all treatments as a single class; all biologics as a class with apremilast separate; and to reflect the pharmacology, anti-TNFs grouped, ILs grouped and apremilast separate. Additionally, for the latter two groupings, we explored two within-class assumptions: assuming treatments within a class to have equal effectiveness and, alternatively, that treatments within a class have similar (exchangeable) effectiveness. Fixed effects across studies were assumed for all models. We have not considered models assuming exchangeability between classes.

Summary of all treatment effect models explored:

All models implemented for the evidence synthesis of PsARC response are presented in Table 41. The models are numbered for ease of reference. Details the models are presented in Appendix 12.3.3.1.

Table 41 Key assumptions of models implemented for the evidence synthesis of PsARC response

Sets of analysis	Study	Treatments	Meta-regression	Class
A1	FE	independent	No baseline adjustment	No class effect
B1	FE	independent	Common interaction term with log odds of response in placebo arm	No class effect
C1	FE	Equal|class	Common interaction term with log odds of response in placebo arm	independent class effect class = {all treatments}
C2	FE	Equal|class, remaining treatments independent*		independent class effect class = APR independent; {all remaining biologics}
C3	FE	Equal|class, remaining treatments independent*		independent class effect class = {Anti-TNFs, ILs}; APR independent
D1	FE	Exchangeable|class, remaining treatments independent*	Common interaction term with log odds of response in placebo arm	independent class effect class = APR independent; {all other biologics}
D2	FE	Exchangeable|class, remaining treatments independent*		independent class effect class = {Anti-TNFs, ILs}; APR independent

*APR independent; FE-fixed effect

Model A1 considers the effectiveness of treatments are independent of each other. Model B1 considers the relative effectiveness of the alternative treatments as independent from each other, but that all depend on the response in the placebo arm. Models C1, C2 and C3 consider the treatments as equal in terms of their effectiveness within class, but dependent on the effect of the placebo arm. Model D1 and D2 assume the treatments to have a similar, but not equal effectiveness and dependent on the effect of the placebo arm; this model introduces more flexibility than assuming treatment effects to be equal (models C2 and C3), but does not fully assume treatments to differ as in model A1. It allows that there are differences between the effectiveness of treatments that we may not be able to explain but that we should consider.

As stated earlier, sensitivity analysis around the adjustment for placebo response were performed: sets of analyses (model A1, B1, C1, C2, C3, D1 and D2) were conducted for PsARC response excluding the Mease 2000 and Genovese 2007 trials.

5.2.1.2 NMA Results

Treatment effect models

Table 42 presents results of the treatment effects of PsARC response on the log odds scale. Results are presented for all the alternative models with measures of goodness of fit. There were no issues with convergence. More detailed results of the models, A1, B1, C1, C2, C3, D1 and D2 are presented in Appendix 12.3.3.2 (ORs as well as log odds, together with means, medians, and 95% credible intervals are presented).

Table 42 NMA Results of PsARC response: log odds ratios (median) of treatments analysed (including Genovese 2007 and Mease 2000 studies) in biologic naïve subpopulation

Meta-reg		no		yes		yes		yes		yes		yes		yes	
treatments		ind		ind		=|class		=|class		=|class		~|class **		~|class **	
class		no		no		{all}		{APR, other}		{Il,TNF, APR}		{APR, other}		{Ils,TNFs,APR}	
	Log Odds PLA	**A1**	r	**B1**	r	**C1**	r	**C2**	r	**C3**	r	**D1**	r	**D2**	r
SEC300	-0.16	1.178	5	2.110	1							1.844	3	1.833	3
SEC150	-0.16	1.175	6	2.104	2					1.285	2	1.839	4	1.822	4
UST	-0.51	0.758	9	1.187	7							1.197	8	1.174	8
CZP	-0.28	1.094	7	1.837	5	1.278	1	1.565	1			1.722	5	1.716	5
GOL	-1.32	2.339	1	1.619	6							1.692	6	1.712	6
ADA	-1.02	1.401	4	1.081	8					1.648	1	1.201	7	1.201	7
INF	-1.15	2.296	2	1.870	4							1.853	2	1.875	1
ETA	-0.99	2.043	3	1.917	3							1.856	1	1.872	2
APR	-0.85	0.813	8	0.765	9			0.756	2	0.779	3	0.769	9	0.771	9
Beta (mean)		-		-1.471		-0.498		-1.692		-1.061		-1.264		-1.225	
Residual deviance*		29.9		27.2		59.24		46.8		47.5		27.8		27.9	
DIC		193.1		190.5		148.0		203.8		199.1		190.0		190.3	

r – ranking of treatments according to point estimates; *compared to 27 data points; ** shrunken estimates; ind – independent treatment effect; =|class – equal class effect; ~| - exchangeable class effect

The placebo response adjusted model B1 fits well compared with the unadjusted model A1 (smaller DIC and residual deviance) but not significantly so, as the difference in DIC is less than 5 points.[108]Also the results (rankings) generated by Model B1 are very different from the observed trial results. Models D1 and D2 also fit well compared with the unadjusted model A1 (smaller DIC and residual deviance) but again not significantly so. As models D1 and D2 show similar DIC and residual deviance, all three models fit the existing data equally well. Model C1 does not fit well with the existing data: although it resulted in a smaller DIC, it showed a much increased residual deviance.

Model C2 and C3 also do not fit well with the existing data, resulting in higher residual deviance and DIC.

The interaction term (beta) is always negative in all models which means higher placebo response rates in trials are associated with bigger treatment effects for the same treatment, demonstrating that adjustment for heterogeneity in the placebo responses across trials was required. The interaction term varies between models; a more negative interaction term reflects a stronger association. Amongst the well-fitting models including an interaction term (B1, D1 and D2), the more negative interaction term is observed in model B1 The interaction terms are similar between model D1 and D2.

The results of the sensitivity analyses are presented in Appendix 12.3.3.2. Excluding Genovese 2007 and Mease 2000 studies from the analysis affects the treatment effects resulting in changes in the ranking of the treatment effects. As expected, the interaction term (beta) is less negative in model B1 after excluding the Genovese 2007 and Mease 2000 trials from the analysis: reduced to -1.149 from -1.471. However, the interaction term (beta) is still negative which means these two trials have a limited impact on the estimation of association of placebo response rates and treatment effects. For Models D1 and D2 the changes in estimated beta are minimal. Reflecting previous analyses Models C1, C2 and C3 do not fit well with the data.

Preferred models

The unadjusted model A1 fits the data as well as any of the other models and generates results that reflect the observed results.

Considering the placebo adjusted models, it must be borne in mind that without any clear rationale for the placebo effect, the results must be interpreted with caution. The results (rankings) generated by Model B1 are very different from the observed trial results. Regarding possible class effects, the analyses found that an assumption of equal class effect for the treatments does not produced a better-fitting model (models C1, C2, C3) than assuming independent treatment effects (models A1, B1) or similar treatment effects (models D1, D2). There was a little difference in goodness of fit statistics (DIC and residual deviance) between models D1 and D2, and we consider the exchangeable class effect model (D2) which utilised two classes (anti-interleukins and anti-TNFs) with apremilast separate, to be most clinically plausible.

Excluding the Genovese 2007 and Mease 2000 trials had an impact on results in the independent treatment model, but had a minimum impact on the interaction terms in the preferred class effect model. Therefore, these two trials were not excluded from our preferred analysis.

Hence, we consider models A1 and D2 including Genovese 2007 and Mease 2000 to be our preferred models for the economic model in Section 6. A comparison of these analyses with those presented in

the company submissions (Novartis and UCB) and those in the previous MTA (Rodgers et al. 2010) is presented in Appendix 12.3.3.4.

Table 43 presents the probability and odds ratios for PSARC response from these preferred models.

Table 43 NMA results: Probability of PsARC response and odds ratios by treatments in the biologic naïve subpopulation

	Not adjusted for placebo response, independent treatment (Model A1)		**Adjusted for placebo response, class effects assumed * (Model D2)**	
	Probability	**OR**	**Probability**	**OR**
treatments	**Median (95% CrI)**	**Median (95% CrI)**	**Median (95% CrI)**	**Median (95% CrI)**
PLA	0.31 (0.26 to 0.36)		0.31 (0.26 to 0.36)	
SEC300	0.59 (0.40 to 0.76)	3.25 (1.56 to 6.89)	0.73 (0.57 to 0.86)	6.25 (3.15 to 13.31)
SEC150	0.59 (0.40 to 0.76)	3.24 (1.54 to 6.96)	0.73 (0.57 to 0.86)	6.18 (3.10 to 13.30)
UST	0.49 (0.38 to 0.60)	2.13 (1.49 to 3.07)	0.59 (0.48 to 0.70)	3.24 (2.25 to 4.86)
CZP	0.57 (0.44 to 0.69)	2.99 (1.88 to 4.81)	0.71 (0.60 to 0.81)	5.56 (3.59 to 9.11)
GOL	0.82 (0.71 to 0.90)	10.37 (5.87 to 18.98)	0.71 (0.58 to 0.81)	5.54 (3.23 to 9.06)
ADA	0.64 (0.53 to 0.75)	4.06 (2.70 to 6.21)	0.60 (0.49 to 0.69)	3.33 (2.30 to 4.70)
INF	0.81 (0.71 to 0.89)	9.93 (5.91 to 17.06)	0.74 (0.63 to 0.83)	6.52 (4.18 to 10.04)
ETA	0.77 (0.65 to 0.86)	7.71 (4.53 to 13.58)	0.74 (0.64 to 0.82)	6.50 (4.38 to 9.85)
APR	0.50 (0.41 to 0.59)	2.26 (1.73 to 2.94)	0.49 (0.41 to 0.57)	2.16 (1.76 to 2.64)

*shrunken estimates presented here

The NMA that does not adjust for placebo response finds that secukinumab is more effective than certolizumab, and both are more effective than ustekinumab and apremilast, but both are somewhat less effective than all comparator anti-TNFs. After adjusting for the unexplained increase in placebo rates seen in more recent trials (and hence of newer agents), and under a class effect that allows for exchangeability for treatments within each class, the probability of response with secukinumab remains slightly higher than certolizumab pegol and both remain more effective than ustekinumab and apremilast, but now their probability of response is similar to, or only slightly less than that of the anti-TNF comparators.

These results indicate that whilst secukinumab and certolizumab are effective in terms of the PsARC outcome, the relative effectiveness of these biologics compared with etanercept, adalimumab, golimumab, ustekinumab and infliximab and with each other, is uncertain. Both agents do seem to be more effective than apremilast.

5.2.2 Subpopulation: Biologic experienced

For the biologic experienced population, trial specific PsARC response data were available from three trials for three active treatments (SEC300, CZP, UST), all compared with placebo. However, the data from the certolizumab pegol trial were not included in the analysis as the RAPID-PsA trial excluded primary failures of a prior anti-TNF (i.e. no response within the first 12 weeks of treatment) from being recruited in its biologic experienced population and so is not comparable with the other two trials. The data included in the NMA for treatment experienced patients are presented in Table 44.

Table 44 Summary of trial specific data in the biologic-experienced subpopulation for PsARC response outcome

Name	**T, treatment arm**	**PsARC response, TREAT**			**PsARC response, PLA**			**ORs**			**RRs**		
		r	N	(%)	r	N	(%)	ORs	95% CI		RRs	95% CI	
FUTURE 2	SEC300	[redacted]						5.75	2.38	13.89	2.44	1.38	4.31
PSUMMIT 2	UST	33	60	(55)	16	62	(26)	3.51	1.75	7.04	2.13	1.32	3.44

r = number of PsARC responders; N = number randomised

The NMA conducted for the synthesis of data in the biologic experienced population is equal to that implemented in the treatment naïve population: treatment effects are assumed to be independent and the model assumed fixed effects across trials. Due to the sparse data, no adjustment for placebo response rate was made in this subgroup analysis. Results of the analysis are presented in the Table 45. The result shows that the probability of a PsARC response is higher with secukinumab than ustekinumab, but the credible intervals overlap with each other and the difference is likely to be insignificant. The results are comparable to the observed data (compare Table 44 and Table 45).

Table 45 NMA Results of PsARC response: probability of PsARC response, odds ratios and treatment effects on log scale in biologic experienced subpopulation

Treatments	Probability of PsARC response	Odds ratios	Treatment effects (Log odds)
	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)
PLA	0.266 (0.19 to 0.36)		-1.013 (-1.48 to -0.58)
SEC300	0.686 (0.41 to 0.88)	6.033 (2.15 to 18.39)	1.797 (0.77 to 2.91)
UST	0.566 (0.35 to 0.76)	3.559 (1.68 to 7.76)	1.279 (0.53 to 2.07)
Residual deviance*	4.07		
DIC	24.62		

*Compared 4 data points

5.3 HAQ changes conditional on PsARC response/non-response

5.3.1 Subpopulation: Biologic naïve

5.3.1.1 Data

For the biologic naïve population HAQ changes conditional on PsARC responses were available for nine active treatments (SEC150, SEC300, CZP, UST, GOL, ADA, INF, ETA, APR from 13 trials (Table 39). The data for HAQ change conditional on PsARC response are presented in Table 46.

Table 46 HAQ changes conditional on PsARC response and non-response by trials and treatments in biologic naïve subpopulation – observed data

Trial	Treatments	HAQ changes conditional on PsARC response in treatment arm		HAQ changes conditional on PsARC response in placebo arm		HAQ changes conditional on PsARC non-response in treatment arm		HAQ changes conditional on PsARC non-response in placebo arm	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
FUTURE 2	SEC150	[redacted]							
FUTURE 2	SEC300	[redacted]							
RAPID-PsA	CZP	[redacted]		[redacted]		[redacted]		[redacted]	
PSUMMIT1+PSUMMIT2	UST	-0.487	0.05	-0.260	0.04	-0.097	0.05	-0.001	0.03
GO-REVEAL	GOL	-0.424	0.07	-0.286	0.05	-0.049	0.06	0.023	0.02
ADEPT	ADA	-0.500	0.05	-0.313	0.08	-0.120	0.05	0.026	0.04
Genovese 2007	ADA	-0.423	0.08	-0.177	0.06	-0.150	0.09	-0.057	0.05
IMPACT 2	INF	-0.580	0.06	-0.160	0.10	-0.110	0.06	0.070	0.04
IMPACT	INF	-0.650	0.09	-0.270	0.14	-0.200	0.09	0.020	0.05
Mease 2004	ETA	-0.635	0.06	-0.258	0.01	-0.196	0.07	-0.002	0.04
PALACE 1	APR	-0.460	0.05	-0.320	0.07	-0.070	0.05	0.000	0.04
PALACE 2	APR	-0.330	0.06	-0.220	0.07	-0.120	0.05	0.010	0.04
PALACE 3	APR	-0.290	0.05	-0.250	0.06	-0.080	0.05	0.000	0.03

SE=standard error

Outcome data for golimumab and infliximab at 14-16 weeks, and ustekinumab at 24 weeks were included in the analysis and assumed equivalent to outcomes at 12 weeks. The rationale for the inclusion of the 24 week data for ustekinumab is discussed in Appendix 12.3.2. The observed data indicate that HAQ changes conditional on PsARC response do vary by treatment ranging between [redacted] (SEC300, FUTURE 2) and -0.290 (APR, PALACE 3). The observed HAQ changes conditional on PsARC non-response in treatments range between [redacted] (SEC150, FUTURE 2) and -0.049 (GOL, GO-REVEAL).

For the placebo arms the observed HAQ changes conditional on PsARC response and non-response differ between trials (ranging between [redacted] (FUTURE 2) and -0.160 (IMPACT 2) for response, and [redacted] (RAPID-PsA) to 0.070 (IMPACT 2) for non-response).

The observed HAQ changes conditional on PsARC response and non-response with treatments are greater than placebo in all trials.

5.3.1.2 Methods

We consider three models to estimate the HAQ changes conditional on PsARC responder or non-responder status. A detailed description of the model and underlying assumptions are presented in Appendix 12.3.4.1. The model E1 considers treatments independent and fixed effect across studies. Models E2 and E3 apply a class effect comprising three groups: anti-TNFs, ILs, and apremilast. This class effect reflects the best fitting class effect model for PsARC (see section 5.2.1.2). The model E2 assumes that the treatments are similar within class (exchangeable) and fixed effect across studies; and model E3 considers that the treatments are equal within class and fixed effect across studies.

5.3.1.3 NMA Results

The results are presented as absolute changes in HAQ in relation to baseline (Table 47). More detailed results are presented in Appendix 12.3.4.2.

Table 47 NMA Results of HAQ changes (median) conditional on PsARC response/non-response in the biologic naïve subpopulation

treatments	independent treatment		Exchangeable|class {ILs,TNFs,APR}		Equal|class {ILs,TNFs, APR}								
studies	FE		FE		FE								
	E1		**E2****		**E3**								
	PsARC response	PsARC non-response	PsARC response	PsARC non-response	PsARC response	PsARC non-response	PsARC resp vs. non-rep						
							E1	r	**E2****	r	**E3**	r
Placebo	-0.26		-0.26		-0.25		-0.26	10	-0.26	10	-0.25	4
SEC150	-0.39	-0.08	-0.44	-0.09			-0.31	8	-0.35	8		
SEC300	-0.55	-0.05	-0.51	-0.08	-0.47	-0.08	-0.49	1	-0.43	3	-0.39	1
UST	-0.49	-0.10	-0.48	-0.09			-0.39	4	-0.39	4		
CZP	-0.43	-0.07	-0.47	-0.12			-0.36	6	-0.35	7		
GOL	-0.44	-0.06	-0.49	-0.11	-0.52	-0.13	-0.38	5	-0.37	5	-0.39	1
ADA	-0.49	-0.13	-0.50	-0.13			-0.36	7	-0.37	6		
INF	-0.66	-0.20	-0.60	-0.14			-0.46	2	-0.46	1		
ETA	-0.64	-0.20	-0.59	-0.14			-0.44	3	-0.45	2		
APR	-0.36	-0.09	-0.36	-0.09	-0.36	-0.09	-0.27	9	-0.27	9	-0.27	3
DIC	-126.0		-133.0		-131.4							

r – ranking of treatments according to point estimates; **shrunken estimates; FE-fixed effect

The model fit statistics (DIC) indicate that neither class effect model (E2 or E3) is a better fit for the data than the unadjusted, independent treatments model (E1). The fit of both of the class effect models were similar, but the one that allowed exchangeability within classes (E2) was considered to be the most clinically plausible. For the purposes of the economic model in Section 6, Models E1 and E2 were the preferred models.

The results from the two preferred models are similar. The results from the unadjusted independent treatment effects model found that significant reductions in mean HAQ score were achieved with response to all nine treatments and response to placebo. However, patients who responded to placebo achieved a lower level of improvement in the HAQ score than those who responded to active treatment and furthermore, the improvement in response to placebo is below the minimally important difference for PsA of –0.35.[66]

The median conditional on response HAQ change was highest with infliximab and etanercept, followed by secukinumab 300 mg, but secukinumab 150 and certolizumab pegol were worse than all treatments except for apremilast.

5.3.2 Subpopulation: Biologic experienced

For the biologic experienced population HAQ changes conditional on PsARC responses were available for three active treatments (SEC300, CZP, UST) from 3 trials. However, the data from the certolizumab pegol trial were not included in the analysis as the biologic experienced population in

the RAPID-PsA trial is not comparable with the other two trials (see section 5.2.2). The data included in the NMA for treatment experienced patients are presented in Table 48.

Table 48 HAQ changes conditional on PsARC response and non-response by trials and treatments – biologic experienced subpopulation – observed data

Trial	Treatment	HAQ changes conditional on PsARC response in treatment arm		HAQ changes conditional on PsARC response in placebo arm		HAQ changes conditional on PsARC non-response in treatment arm		HAQ changes conditional on PsARC non-response in placebo arm	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
FUTURE 2	SEC300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSUMMIT2	UST	-0.315	0.11	-0.146	0.09	0.007	0.13	0.010	0.05

SE=Standard error

Outcomes data at 24 week were included in the analysis and assumed equivalent to outcomes at 12 weeks (see Appendix 12.3.2). The observed data indicate that, as in the treatment naïve subgroup, HAQ changes conditional on PsARC response do vary by treatments. The observed HAQ changes conditional on PsARC response and non-response in placebo arms differ between trials. The observed HAQ changes conditional on PsARC response and non-response with treatments are greater than placebo in all trials.

The NMA conducted for the synthesis of data in the biologic experienced population is equal to that implemented in the treatment naïve population: treatment effects are assumed to be independent and the model assumed fixed effects across trials. No class effect assumption was made for this subgroup analysis. The results are presented as absolute changes in HAQ in relation to baseline (Table 49). These results are generally comparable with the observed estimates from the primary studies.

Table 49 NMA Results of evidence synthesis of HAQ changes conditional on PsARC response/non-response in biologic experienced subpopulation

	HAQ changes in PsARC response in relation to PNR				HAQ changes in PsARC non response in relation to PNR			
	mean	median	95% CrI		mean	median	95% CrI	
Placebo/baseline effect	-0.134	-0.134	-0.288	0.021				
SEC300	-0.385	-0.385	-0.624	-0.145	-0.431	-0.430	-0.880	0.014
UST	-0.320	-0.320	-0.552	-0.086	0.003	0.002	-0.269	0.274
DIC	-8.10							

The results from the independent treatment effects model found that significant reductions in mean HAQ score were achieved with response to secukinumab and ustekinumab and response to placebo. As for the biologic-naïve patients, those who responded to placebo achieved a lower level of

improvement in the HAQ score than those who responded to active treatments and furthermore the improvement in responders to placebo is below the below the minimally important difference for PsA of –0.35.[66]

5.4 PASI response

5.4.1 Subpopulation: Biologic naïve

5.4.1.1 Data

For the biologic naïve population, PASI response data were available for nine active treatments (SEC150, SEC300, CZP, UST, GOL, ADA, INF, ETA, APR) from 13 trials (Table 2). A brief summary of PASI responses in different trials are presented in Table 50. Outcomes at 14 and 16 weeks were included in the analysis and assumed equivalent to outcomes at 12 weeks. Data from the 12 week time point were used for the two PSUMMIT trials. Not all patients who were randomised to trials were eligible for the PASI evaluation and the proportion of PASI evaluable patients differed between trials, ranging between 42% and 84% in treatment arms and 31% and 87% in placebo arms. All trials reported PASI50 and PASI75 except PSUMMIT 2 and SPIRIT-P1 trials which did not report PASI50. A few trials did not report PASI90 (i.e. PALACE trials, RAPID-PsA, Mease 2000 and PSUMMIT 2).

Table 50 Summary of trial specific data in biologic naïve subpopulation for PASI response outcome

Trial name	Treatments	PASI evaluated N (%) of patients' randomised in treatment		PASI responses in treatment arm						PASI evaluated N (%) of patients' randomised in placebo		PASI responses in placebo arm					
				PASI50		PASI75		PASI90				PASI50		PASI75		PASI90	
				N	%	N	%	N	%			N	%	N	%	N	%
FUTURE 2	2,SEC300	[redacted]															
FUTURE 2	3,SEC150	[redacted]															
RAPID-PsA	4,CZP	[redacted]															
PSUMMIT 1	5,UST	145	(71)	89	(61)	56	(39)	28	(19)	146	(71)	31	(21)	13	(9)	6	(4)
GO-REVEAL	6,GOL	109	(75)	63	(58)	44	(40)	22	(20)	79	(70)	7	(9)	2	(3)	0	(0)
ADEPT	7,ADA	69	(45)	50	(72)	34	(49)	21	(30)	69	(43)	10	(14)	3	(4)	0	(0)
IMPACT 2	8,INF	83	(83)	68	(82)	53	(64)	34	(41)	87	(87)	8	(9)	2	(2)	0	(0)
IMPACT	8,INF	22	(42)	22	(100)	15	(68)	8	(36)	16	(31)	0	(0)	0	(0)	0	(0)
Mease 2000	9,ETA	19	(63)	8	(42)	5	(26)	NA		19	(63)	4	(21)	0	(0)	NA	
PALACE 1	10,APR	82	(49)	36	(44)	18	(22)	NA		68	(40)	11	(16)	3	(4)	NA	
PALACE 2	10,APR	77	(48)	33	(43)	17	(22)	NA		74	(47)	10	(14)	2	(3)	NA	
PALACE 3	10,APR	90	(54)	38	(42)	20	(22)	NA		89	(53)	22	(25)	7	(8)	NA	
SPIRIT-P1	7,ADA	68	(67)	NA		23	(34)	15	(22)	67	(63)	NA		5	(7)	1	(1)
PSUMMIT 2	5,UST	36	(84)	NA		17	(47)	NA		30	(71)	NA		1	(3)	NA	

5.4.1.2 Methods

The 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[109]: the single model included all categories of PASI and generated a single effect estimate for each treatment and also probabilities of achieving PASI 50, 75 and 90.

Reflecting the analyses on PsARC, alternative assumptions were tested in two analyses. The first assumed independent treatment effects and did not include any meta-regression for placebo effects (Model F1). As the number of trials to inform each treatment effect was small, a fixed effect model was used. In a second analysis, we explored the impact on treatment effects of adjusting for placebo responses i.e. baseline effects (meta-regression model). As can be seen from Table 50 there were large differences between trials for PASI responses in placebo arms, ranging between zero and 27% (0% in IMPACT and 27% RAPID-PsA). The IMPACT trial had a very small sample size and reported zero response in the placebo arm and 100% response in the treatment arm which lead to very extreme values for placebo adjustment. Therefore, the IMPACT trial could not be included in the meta-regression analysis. Unlike the analysis for PsARC, for PASI, we did not assume a class effect as the

evidence from individual trials does not support such an assumption. Table 51 presents the key assumptions for the models implemented for PASI response. The detailed model assumptions are presented in Appendix 12.3.5.1.

Table 51 Summary of models implemented for evidence synthesis of PASI response

Sets of analyses	Study	Treatment	Meta-regression	Thresholds, i.e. Cut-offs	Baseline effect for meta-regression
F1	FE	Independent	No baseline adjustment	FE	-
G1	FE	Independent	No baseline adjustment	FE	-
G2	FE	Independent	Common interaction term with baseline effect	FE	Adjusted with trial specific baseline effects

FE-fixed effect

Model F1 considers that treatments are independent to each other and assumed fixed effects on cut-offs/ thresholds. Model G1 considers the same assumption as model F1, but the IMPACT trial was excluded from the analysis. Model G2 assumes treatments are independent to each other, but treatment effects are adjusted with the trial specific baseline effects assuming a common interaction term (beta).

5.4.1.3 NMA Results

Table 52 presents the results of the treatment effects for PASI responses estimated from the three models with measures of goodness of fit. There were no issues with convergence.

Table 52 NMA Results of PASI response: treatment effects (median) on probit scale in the biologic naïve subpopulation

Meta-reg treatments	no independent		no independent		yes independent	
Cut-offs	FE		FE		FE	
	F1	**r**	**G1**	**r**	**G2**	**r**
PLA	1.024	-	0.983	-	1.015	-
SEC300	-1.936	2	-1.932	2	-1.864	1
SEC150	-1.870	3	-1.865	3	-1.798	2
CZP	-0.875	7	-0.873	7	-1.424	4
UST	-1.134	6	-1.131	6	-1.342	6
GOL	-1.645	4	-1.635	4	-1.141	7
ADA	-1.477	5	-1.476	5	-1.422	5
INF	-2.412	1	-2.276	1	-1.798	2
ETA	-0.798	8	-0.797	8	-0.849	8
APR	-0.749	9	-0.748	9	-0.815	9
Beta	--		--		-1.310	
Residual deviance	76.6*		62.5[$]		58.4[$]	
DIC	318.9		297.2		293.7	
	[*]Compared 65 data points		[$]Compared 61 data points			

r-– ranking of treatments according to point estimates; FE-fixed effect

The results of models G1 and F1 are similar except for a small effect on the estimate of effect for infliximab; therefore model F1 is the preferred unadjusted model as it does not exclude a trial. In Model G2, DIC and residual deviance are lower than model G1, indicating that model fits well with the existing data and the data supports the assumption of adjustment with baseline effects.

Table 53 shows the probability of achieving PASI 50/75/90 from the preferred treatment unadjusted and adjusted model in biologic naïve population.

Table 53 NMA Results of PASI response: probability of achieving PASI50/75/90 in the biologic-naïve subpopulation

	Independent treatment, unadjusted for placebo response (Model F1)			Independent treatment, adjusted for placebo response (Model G2)		
	PASI50	**PASI75**	**PASI90**	**PASI50**	**PASI75**	**PASI90**
	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)
PLA	0.153 (0.13 to 0.18)	0.054 (0.04 to 0.07)	0.015 (0.01 to 0.02)	0.155 (0.12 to 0.19)	0.055 (0.04 to 0.07)	0.016 (0.01 to 0.02)
SEC300	0.819 (0.61 to 0.94)	0.627 (0.38 to 0.84)	0.405 (0.19 to 0.67)	0.801 (0.62 to 0.91)	0.604 (0.40 to 0.78)	0.384 (0.21 to 0.58)
SEC150	0.801 (0.59 to 0.93)	0.603 (0.36 to 0.82)	0.380 (0.18 to 0.63)	0.783 (0.60 to 0.90)	0.579 (0.38 to 0.75)	0.359 (0.19 to 0.54)
CZP	0.441 (0.31 to 0.59)	0.231 (0.14 to 0.36)	0.097 (0.05 to 0.18)	0.657 (0.50 to 0.82)	0.429 (0.29 to 0.63)	0.231 (0.13 to 0.41)
UST	0.544 (0.44 to 0.65)	0.317 (0.23 to 0.42)	0.149 (0.09 to 0.22)	0.627 (0.52 to 0.74)	0.398 (0.30 to 0.52)	0.207 (0.14 to 0.31)
GOL	0.732 (0.58 to 0.86)	0.514 (0.35 to 0.68)	0.297 (0.17 to 0.47)	0.548 (0.36 to 0.70)	0.322 (0.17 to 0.48)	0.154 (0.07 to 0.27)
ADA	0.675 (0.55 to 0.78)	0.448 (0.32 to 0.58)	0.242 (0.15 to 0.36)	0.657 (0.54 to 0.76)	0.429 (0.32 to 0.55)	0.231 (0.15 to 0.33)
INF	0.918 (0.84 to 0.96)	0.789 (0.67 to 0.88)	0.593 (0.44 to 0.73)	0.782 (0.61 to 0.88)	0.578 (0.39 to 0.73)	0.358 (0.20 to 0.52)
ETA	0.411 (0.15 to 0.72)	0.209 (0.05 to 0.50)	0.084 (0.01 to 0.29)	0.434 (0.20 to 0.69)	0.227 (0.08 to 0.47)	0.095 (0.02 to 0.26)
APR	0.391 (0.31 to 0.49)	0.195 (0.14 to 0.27)	0.077 (0.05 to 0.12)	0.420 (0.33 to 0.52)	0.216 (0.16 to 0.30)	0.090 (0.06 to 0.14)

The results of the unadjusted NMA for PASI as a single outcome or as separate categorical variables, show that all treatments are more effective than placebo. The difference between treatments is uncertain, with wide credible intervals that mostly overlap with each other. The results show that patients taking infliximab have the highest probability of achieving PASI 50, 75 and 90 responses. However, after adjustment for placebo, secukinumab 300 mg has the highest probability of response. The probabilities for certolizumab changed between the models, but in both it appears to be less efficacious than all other treatments excepting apremilast and etanercept in achieving PASI responses. The estimated probabilities from the analysis reflect fairly closely those from the primary studies indicating the model fits the data well.

5.4.2 Subpopulation: Biologic experienced

For the biologic experienced population, trial specific PASI response data were available for three active treatments (SEC300, CZP, UST) from three trials, but as for the other outcomes, the data from the certolizumab pegol trial were not included in the analysis as the biologic experienced population in the RAPID-PsA trial is not comparable with the other two trials (see 5.2.2). The data included in the NMA for the treatment experienced patients are presented in Table 54.

Table 54 Summary of trial specific data in the biologic experienced subpopulation for PASI response outcome

Trial name	Treatments	PASI evaluated N (%) of patients' randomised to treatment	PASI responses in treatment arm						PASI evaluated N (%) of patients' randomised to placebo	PASI responses in placebo arm				
			PASI50		PASI75		PASI90			PASI50		PASI75		PASI90	
			N	%	N	%	N	%		N	%	N	%	N	%
FUTURE 2	2,SEC300	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	
PSUMMIT 2	3,UST	44	(73)	NA	14	(32)	NA		50	(81)	NA	1	(2)	NA	

In the FUTURE 2 trial, only a small proportion of patients were eligible for the PASI evaluations, only 33% in treatment arm and 34% in placebo arm. The small sample size and associated lack of events in this placebo arm increase uncertainty in the analysis.

A NMA under the same specification as used in model F1 (independent treatments unadjusted biologic naive analysis) biologic naive. Due to the sparse data, no adjustment was undertaken for this subgroup analysis. Results of the analysis are presented in the Table 55.

Table 55 NMA Results of PASI response: probability of achieving PASI50/75/90 and treatment effects in the biologic experienced subpopulation

	Treatment effect on probit scale Median (95% CrI)	Probability		
		PASI50 Median (95% CrI)	PASI75 Median (95% CrI)	PASI90 Median (95% CrI)
PLA	1.354 (0.59 to 2.19)	0.088 (0.01 to 0.28)	0.012 (0.00 to 0.06)	0.002 (0.00 to 0.02)
SEC300	-2.509 (-4.01 to -1.23)	0.875 (0.46 to 1.00)	0.598 (0.23 to 0.89)	0.365 (0.08 to 0.75)
UST	-1.659 (-2.73 to -0.83)	0.628 (0.29 to 0.89)	0.279 (0.07 to 0.61)	0.120 (0.01 to 0.42)
PASI50	-			
PASI75	0.870 (0.28 to 1.84)			
PASI90	1.484 (0.70 to 2.56)			
Residual deviance*	5.99			
DIC	26.75			

*Compared 6 data points

The result shows that the probability of achieving PASI response in all categories is much higher in secukinumab than ustekinumab, although the estimates are highly uncertain, with wide credible intervals that overlap with each other. The results are fairly comparable to observed data.

5.5 ACR response

5.5.1 Subpopulation: Biologic naïve

5.5.1.1 Data

For the biologic naïve population, evidence on ACR response was available for nine active treatments (SEC150, SEC300, UST, CZP, GOL, ADA, INF, ETA, APR) from 15 trials. A brief summary of ACR responses in different trials are presented in Table 56. Outcomes at 14 and 16 weeks were included in the analysis and assumed equivalent to outcomes at 12 weeks. All 15 trials reported all three categories of ACR response (20/50/70).

Table 56 Summary of trial specific data in biologic naïve subpopulation for ACR response outcome

Trial name	Treatments	ACR responses in treatment arm							ACR responses in placebo arm					
		N	ACR20		ACR50		ACR70		N	ACR20		ACR50		ACR70	
			r	(%)	r	(%)	r	(%)		r	(%)	r	(%)	r	(%)
FUTURE 2	SEC300														
FUTURE 2	SEC150														
PSUMMIT 1	UST	205	85	(41)	38	(19)	8	(4)	206	44	(21)	11	(5)	3	(1)
PSUMMIT 2	UST	43	17	(40)	5	(12)	3	(7)	42	8	(19)	3	(7)	1	(2)
RAPID-PsA	CZP														
GO-REVEAL	GOL	146	74	(51)	44	(30)	18	(12)	113	10	(9)	2	(2)	1	(1)
Genovese 2007	ADA	51	20	(39)	13	(25)	7	(14)	51	8	(16)	1	(2)	0	(0)
ADEPT	ADA	153	88	(58)	54	(35)	30	(20)	162	23	(14)	6	(4)	1	(1)
SPIRIT-P1	ADA	101	52	(51)	30	(30)	18	(18)	106	33	(31)	5	(5)	0	(0)
IMPACT 2	INF	100	58	(58)	36	(36)	15	(15)	100	11	(11)	3	(3)	1	(1)
IMPACT	INF	52	34	(65)	24	(46)	15	(29)	52	5	(10)	0	(0)	0	(0)
Mease 2004	ETA	101	60	(59)	38	(38)	11	(11)	104	16	(15)	4	(4)	0	(0)
Mease 2000	ETA	30	22	(73)	15	(50)	4	(13)	30	4	(13)	1	(3)	0	(0)
PALACE 1	APR	168	64	(38)	27	(16)	7	(4)	168	32	(19)	10	(6)	2	(1)
PALACE 2	APR	162	52	(32)	17	(10)	2	(1)	159	30	(19)	8	(5)	1	(1)
PALACE 3	APR	167	68	(41)	25	(15)	6	(4)	169	31	(18)	14	(8)	4	(2)

r=number of ACR response; N=number randomised

5.5.1.2 Methods

As ACR is, like PASI, a categorical variable (ACR 20, 50, and 70), the NMA for ACR utilised a similar framework of analysis to that used to estimate the probability of PASI responses: all categories of ACR were within a single model which generated a single effect estimate for each treatment and also probabilities of achieving ACR 20, 50, and 70.

Analogously to the analyses on PsARC, sets of alternative analyses were conducted for ACR response outcomes. We explored the effect of differences in trial specific placebo responses on treatment effect by undertaking a meta-regression. In the context of an adjusted model for placebo response, we explored the possibility of there being class effects. Three different class groupings were considered: all treatments as a single class; all biologics as a class with apremilast separate; and to reflect the pharmacology, anti-TNFs grouped, ILs grouped and apremilast separate. Additionally we explored two within-class assumptions: assuming treatments within a class to have equal effectiveness and, alternatively, those treatments within a class have similar (exchangeable) effectiveness. Fixed-effects across studies were assumed for all models. We have not considered models assuming exchangeability between classes.

Summary of all treatment effect models explored:

All models implemented for the evidence synthesis of ACR response are presented in Table 41. Detailed coding of the models is presented in Appendix 12.3.6.1.

Table 57 Key assumptions of models implemented for evidence synthesis of ACR response

Sets of analysis	Study	Treatments	Meta-regression	Class
H1	FE	independent	No baseline adjustment	No class effect
I1	FE	independent	Common interaction term with baseline effect	No class effect
J1	FE	Equal|class	Common interaction term with baseline effect	independent class effect class = {all treatments}
J2	FE	Equal|class, remaining treatments independent*		independent class effect class = APR independent; {all remaining biologics}
J3	FE	Equal|class, remaining treatments independent*		independent class effect class = {Anti-TNFs, ILs}; APR independent
K1	FE	Exchangeable|class, remaining treatments independent*	Common interaction term with baseline effect	independent class effect class = APR independent; {all other biologics}
K2	FE	Exchangeable|class, remaining treatments independent*		independent class effect class = {Anti-TNFs, ILs}; APR independent

*APR independent; FE-fixed effect

Model H1 considers the treatments are independent of each other. Model I1 considers the relative effectiveness of the alternative treatments as independent from each other, but that all depend on the response in the placebo arm. Model J1 considers the treatments as equal in terms of their effectiveness, but dependent on the effect of the placebo arm. Model J2 and J3 consider the treatments as equal in terms of their effectiveness within class, but dependent on the effect of the placebo arm. Model K1 and K2 assume the treatments to have a similar, but not equal effectiveness and dependent on the effect of the placebo arm.

5.5.1.3 NMA Results

Table 58 presents the results of the treatment effects for ACR responses estimated from the seven models with measures of goodness of fit. There were no issues with convergence.

Table 58 NMA Results of ACR response: treatment effects (median) on probit scale in biologic naïve subpopulation

Meta-reg	no		yes		yes		yes		yes		yes		yes	
treatments	ind		ind		=|class {all}		=|class {APR,other }		=|class {ILs,TNFs, APR}		~|class ** (APR, other)		~|class ** (ILs, TNFs, APR)	
Cut-offs	FE		FE		FE		FE		FE		FE		FE	
	H1	**r**	**I1**	**r**	**J1**	**r**	**J2**	**r**	**J3**	**r**	**K1**	**r**	**K2**	**r**
PLA	0.952		0.961		0.882		0.966		0.966		0.963		0.961	
SEC300	-0.914	6	-1.397	2							-1.274	2	-1.236	3
SEC150	-0.932	5	-1.415	1			-1.094	1	-1.095	1	-1.283	1	-1.246	2
UST	-0.570	8	-0.722	8							-0.750	8	-0.732	8
CZP	-0.811	7	-1.265	3	-0.830	1					-1.193	5	-1.176	5
GOL	-1.429	2	-0.918	7							-1.010	7	-1.040	7
ADA	-1.072	4	-1.126	6					-0.609	2	-1.121	6	-1.124	6
INF	-1.617	1	-1.212	5							-1.246	3	-1.269	1
ETA	-1.362	3	-1.214	4							-1.215	4	-1.228	4
APR	-0.509	9	-0.592	9			-0.610	2	-0.014	3	-0.581	9	-0.576	9
Beta (mean)			-1.276		1.327		-1.627		-1.621		-1.099		-1.018	
Residual deviance*	120.0		119.1		156.1		148.3		148.3		120.0		120.4	
DIC	482.22		480.94		511.66		503.43		503.37		480.90		481.1	

r – ranking of active treatments according to point estimates; *compared to 92 data points; ** shrunken estimates; ind – independent treatment effect; =|class – equal class effect; ~| - exchangeable class effect; FE-fixed effect

The placebo response adjusted model I1 fits well compared with the unadjusted model H1 (smaller DIC and residual deviance), but not significantly so. Also the results (rankings) generated by Model I1 are very different from the observed trial results. Model J1, J2 and J3 do not fit well with the existing data resulting in significantly higher residual deviance and DIC. Both models K1 and K2 fit as well as the unadjusted model H1 (similar DIC and residual deviance).

Among all the placebo response adjusted models, models I1, K1 and K2 show similar DIC and residual deviance, which means that these three models fit the existing data equally well, though not significantly better than the unadjusted model.

The interaction term (beta) is negative in all models which means higher placebo response rates in trials are associated with higher treatment effects, demonstrating that adjustment for heterogeneity in the placebo responses across trials was required. The interaction term varies between models but is similar between model K1 and K2.

5.5.1.4 Preferred models

The unadjusted model H1 fits the data as well as any of the other models and generates results that reflect the observed results. Considering the placebo adjusted models, Model I1 generated results (rankings) which do not reflect well the observed trial results. Using an assumption of equal class effect for the treatments does not produced a better-fitting model (model J1, J2, J3) than assuming independent treatment effects (model H1, I1) or similar (exchangeable) treatment effects (model K1, K2). In addition, there was a little difference in goodness of fit statistics (DIC and residual deviance) between models K1 and K2, and we consider the exchangeable class effect model which utilised two classes (anti-interleukins and anti-TNFs), with apremilast separate to be most clinically plausible. Hence, our preferred models to be implemented in the economic model in Section 6 are models H1 and K2.

Table 59 presents the probabilities of achieving ACR20/50/70 responses in biologic naïve population from the preferred models: H1 and K2.

Table 59 NMA Results of ACR response: probability of achieving ACR20/50/70 in biologic naïve subpopulation

	Not adjusted for placebo response, independent treatment (Model H1)			Adjusted for placebo response, class effects assumed * (Model K2)		
	ACR20	**ACR50**	**ACR70**	**ACR20**	**ACR50**	**ACR70**
	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)
PLA	0.17 (0.15, 0.19)	0.05 (0.04, 0.06)	0.01 (0.01, 0.02)	0.17 (0.15, 0.19)	0.05 (0.04, 0.06)	0.01 (0.01, 0.02)
SEC300	0.49 (0.33, 0.64)	0.24 (0.14, 0.38)	0.09 (0.04, 0.18)	0.61 (0.46, 0.75)	0.35 (0.22, 0.50)	0.16 (0.08, 0.27)
SEC150	0.49 (0.34, 0.65)	0.25 (0.14, 0.39)	0.10 (0.04, 0.19)	0.61 (0.46, 0.75)	0.35 (0.22, 0.51)	0.16 (0.08, 0.27)
UST	0.35 (0.27, 0.44)	0.15 (0.10, 0.21)	0.05 (0.03, 0.08)	0.41 (0.34, 0.49)	0.19 (0.14, 0.25)	0.07 (0.04, 0.10)
CZP	0.44 (0.34, 0.55)	0.21 (0.14, 0.30)	0.08 (0.04, 0.13)	0.58 (0.49, 0.69)	0.33 (0.24, 0.43)	0.14 (0.09, 0.22)
GOL	0.68 (0.55, 0.80)	0.43 (0.30, 0.57)	0.21 (0.12, 0.33)	0.53 (0.40, 0.66)	0.28 (0.18, 0.40)	0.11 (0.06, 0.19)
ADA	0.55 (0.47, 0.62)	0.29 (0.23, 0.36)	0.12 (0.09, 0.17)	0.56 (0.50, 0.63)	0.31 (0.26, 0.37)	0.13 (0.10, 0.17)
INF	0.75 (0.65, 0.83)	0.50 (0.39, 0.62)	0.27 (0.18, 0.38)	0.62 (0.51, 0.72)	0.36 (0.26, 0.47)	0.17 (0.10, 0.24)
ETA	0.66 (0.55, 0.76)	0.40 (0.29, 0.52)	0.19 (0.12, 0.29)	0.61 (0.51, 0.69)	0.35 (0.27, 0.43)	0.16 (0.11, 0.21)
APR	0.33 (0.27, 0.39)	0.13 (0.10, 0.17)	0.04 (0.03, 0.06)	0.35 (0.30, 0.41)	0.15 (0.12, 0.19)	0.05 (0.03, 0.07)

*probabilities estimated from the shrunken estimates

The results of the unadjusted NMA for ACR as a single outcome or as separate categorical variables, show that all treatments are more effective than placebo. The difference between treatments is uncertain, with wide credible intervals that mostly overlap with each other. The results show that patients taking infliximab have the highest probability of achieving ACR 20, 50 and 70 responses. The probabilities for secukinumab are lower than those for infliximab, etanercept, golimumab, and adalimumab. After adjustment for placebo, the probabilities for secukinumab 300 mg and 150 mg increase and are very similar to those for infliximab. The probabilities of achieving ACR 20, 50 and 70 responses with certolizumab increased between the models: in the unadjusted model the probabilities were higher only than those for apremilast and ustekinumab, but after adjustment they were also higher than those for golimumab, adalimumab and ustekinumab.

5.5.2 Subpopulation: Biologic experienced

For the biologic experienced population, trial specific ACR response data were available for three active treatments (SEC300, CZP, UST) from three trials, but as for the other outcomes, the data from the certolizumab pegol trial were not included in the analysis as the biologic experienced population in the RAPID-PsA trial is not comparable with the other two trials. The data included in the NMA for treatment experienced patients are presented in Table 60.

Table 60 Summary of trial specific data in biologic experienced subpopulation for ACR response outcome

Trial name	Treatments	ACR responses in treatment arm						ACR responses in placebo arm					
		N	ACR20		ACR50		ACR70		N	ACR20		ACR50		ACR70	
			r	%	r	%	r	%		r	%	r	%	r	%
FUTURE 2	2,SEC300	[redacted]													
PSUMMIT 2	3,UST	60	23	(38)	9	(15)	4	(7)	62	9	(15)	1	(2)	0	(0)

The NMA model was similar to model H1: independent treatment effects biologic-naive. Due to the lack of data, no adjustment was undertaken for this subgroup analysis.

Results of the analysis are presented in the Table 61. The result shows that the probabilities of achieving ACR response in all categories are slightly higher in ustekinumab than secukinumab, although the differences are insignificant. The results are fairly comparable to the observed data (compare Table 60 and Table 61).

Table 61 NMA Results of ACR response: probability of achieving ACR20/50/70 and treatment effects in biologic experienced subpopulation

	Treatment effect on probit scale Median (95% CrI)	Probability		
		ACR20 Median (95% CrI)	ACR50 Median (95% CrI)	ACR70 Median (95% CrI)
PLA	1.06 (0.76, 1.38)	0.14 (0.08, 0.22)	0.03 (0.01, 0.06)	0.01 (0.00, 0.02)
SEC300	-0.71 (-1.36, -0.08)	0.36 (0.19, 0.57)	0.11 (0.04, 0.25)	0.03 (0.01, 0.11)
UST	-0.85 (-1.34, -0.37)	0.42 (0.26, 0.59)	0.14 (0.06, 0.27)	0.05 (0.01, 0.12)
ACR20	-			
ACR50	0.85 (0.62, 1.13)			
ACR70	1.47 (1.10, 1.92)			
Residual deviance*	11.33			
DIC	45.85			

*Compared 11 data points

5.6 Summary of findings of relative efficacy from NMA

The NMA was conducted to formally investigate the relative efficacy of secukinumab and certolizumab pegol and the other active comparators. Analyses were conducted on four outcomes

PsARC, HAQ conditional on PsARC response, PASI and ACR. Analyses were not run for the full trial populations due to heterogeneity across trials, but were instead performed separately for the biologic-naive and -experienced subgroups. The rate of placebo response was identified as a source of heterogeneity within the biologic-naive population networks; this was explored and a preferred adjusted model was identified. Unadjusted and adjusted results were presented for each outcome.

Biologic-naive patients

In terms of PsARC response the results indicated that whilst secukinumab and certolizumab pegol are effective, the relative effectiveness of these biologics compared with etanercept, adalimumab, golimumab and infliximab and with each other, is uncertain, though both agents do seem to be more effective than apremilast.

In terms of HAQ conditional on PsARC response the results from the preferred adjusted model were similar to the independent treatment effect analysis. The results from the unadjusted independent treatment effects model found that significant reductions in mean HAQ score were achieved with response to all nine treatments and response to placebo, though the improvement in response to placebo is below the minimum clinically significant threshold for PsA of –0.35.[66] The median HAQ change was highest with infliximab and etanercept, followed by secukinumab 300 mg, but secukinumab 150 mg and certolizumab pegol were worse than all treatments except for apremilast.

The results of the unadjusted NMA for PASI as a single outcome or as separate categorical variables, indicated that all treatments were more effective than placebo. The difference between treatments was uncertain, with wide credible intervals that mostly overlap with each other. The results showed that patients treated with infliximab have the highest probability of achieving PASI 50, 75 and 90 responses. However, after adjustment for placebo, secukinumab 300 mg has the highest probability of response. The probabilities for certolizumab pegol changed between the models, but in both it appears to be less efficacious than all other treatments except apremilast and etanercept in achieving PASI responses.

Similarly for ACR responses, differences between treatments were uncertain, with wide credible intervals that mostly overlapped with each other. The unadjusted results suggested that patients taking secukinumab or certolizumab pegol had lower probabilities of response than those for infliximab, etanercept, golimumab, and adalimumab. After adjustment for placebo response, the probabilities of response for both secukinumab and certolizumab pegol increased; those for secukinumab were very similar to those for infliximab.

Biologic-experienced patients

Only secukinumab and ustekinumab could be included in these analyses. The results showed that across all outcomes analysed both secukinumab and ustekinumab were significantly more effective than placebo. Most of the results suggested secukinumab may be better than ustekinumab, though the results were uncertain with wide overlapping credible intervals.

6 Assessment of existing cost-effectiveness evidence

The purpose of this section is to review the existing evidence on the cost-effectiveness of certolizumab pegol (CZP) and secukinumab (SEC) within their marketing authorisations for treating active psoriatic arthritis in adults for whom disease-modifying anti-rheumatic drugs have been inadequately effective. The review includes published cost-effectiveness studies and the company submissions from Novartis (SEC) and UCB (CZP). The review also includes a broader assessment of published decision-analytic models for relevant comparators. The differences in the model structures and assumptions used across the studies are examined to identify any important differences in approaches and areas of remaining uncertainty. The findings from the review also provide the basis for the development of a new decision-analytic model reported in Section 7.

6.1 Methods

To identify published economic evidence for CZP and SEC, a broad range of studies were considered for inclusion in the assessment of cost-effectiveness, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included.

A broader review of economic evidence for the comparator treatments (infliximab [INF], etanercept [ETN], adalimumab [ADA], golimumab [GOL] and ustekinumab [UST]) was also undertaken. The objective was to summarise the modelling approaches and assumptions employed in previous studies and to identify any important differences that may have arisen since the previous MTA (TA199[94]). Since the focus of the broader review related to modelling approaches and assumptions, only decision analytic modelling studies were included. The broader review also provides an important basis to identify common areas and potential differences between the approaches previously used for the comparator treatments and those employed by UCB and Novartis for the specific technologies being considered in this appraisal. The broader review also helped inform the conceptualisation of the de-novo model presented in Section 7.

The following databases were searched for relevant published literature: Cochrane Controlled Trials Register (CCTR), EMBASE, Health Economic Evaluations Databases (HEED), MEDLINE, National Research Register (NRR), NHS Economic Evaluation Database (NHS EED), PsycINFO, and Science Citation Index. Full details of the main search strategy for this review are presented in 12.4. The searches for CZP and SEC for psoriatic arthritis were not restricted by date. The searches for the broader comparator review was date restricted to identify studies published since the previous MTA report for ADA, ETN and INF (TA199[94]). Additional hand-searching of related TAs (TA 199[94],

220[110] and 340[61]) was also undertaken. Two reviewers assessed all obtained titles and abstracts for inclusion, with any discrepancies resolved by discussion. .

In addition, Novartis and UCB submitted evidence on the cost-effectiveness of CZP and SEC. These submissions were reviewed and the approaches and findings compared with those found in the review of previously published studies. The quality of the cost-effectiveness studies for CZP and SEC was also assessed according to a checklist updated from that developed by Drummond.[111]

6.2 Results

6.2.1 Identified published studies

No previously published cost-effectiveness studies of SEC for PsA were identified. Two conference abstracts were identified evaluating the cost effectiveness of CZP for PsA in Greece and Romania.[112, 113] Further details were not provided on request from the corresponding authors and so these abstracts were subsequently excluded from further consideration. Given the lack of previously published studies, only the company submissions are considered for SEC and CZP.

The systematic search of published literature identified nine studies which met the inclusion criteria for the cost effectiveness review for the broader set of comparators. From the nine studies, seven UK studies were identified. Three of the UK studies were reports from the independent Assessment Group(AG)/Evidence Review Group (ERG) for the previous NICE appraisals of: ETN, INF and ADA (TA 199[94], GOL (TA220[110]) and UST (TA340[61]). A further three studies were the subsequent journal publications based on the reports for TA199[114], TA220[115] and TA340.[116] The final UK study identified was a more recent study which aimed to update the systematic review, synthesis and model previously conducted as part of TA199. This study was funded by Pfizer.[31]

Of the two non-UK studies, one evaluated the cost effectiveness of UST for PsA in Russia[117] and the other evaluated the cost effectiveness of a mixture of biologic treatments to treat moderate to severe PsA in Germany.[118] Both of these studies were only available as conference abstracts. Further details were not provided on request from the authors and hence these two studies were excluded from the review.

6.2.2 Review of the existing published cost-effectiveness studies

The review starts with an overview of the seven UK studies identified in relation to the broader set of comparators and then considers the *de-novo* analyses submitted by the companies for SEC and CZP.

6.2.2.1 Summary of published studies for comparator treatments

Of the seven published studies included in the broader review of comparators, six of these were directly related to three previous NICE TAs: TA199, TA220 and TA340. All of these publications employed a similar modelling approach to that originally proposed by Rodgers et al for TA199

(hereafter referred to as the 'York model'). The only study identified which was not directly related to a previous NICE TA was Cawson et al.[31] This study also used a very similar approach to the previous York model. Hence the main differences between these studies lies in relation to the comparators and associated evidence base which have altered since TA199, rather than in terms of major structural differences. Since the provenance of the modelling approach used in all these studies can be related back to the York model, only the latter is described in full in the following section. The key differences in the other published studies are subsequently summarised.

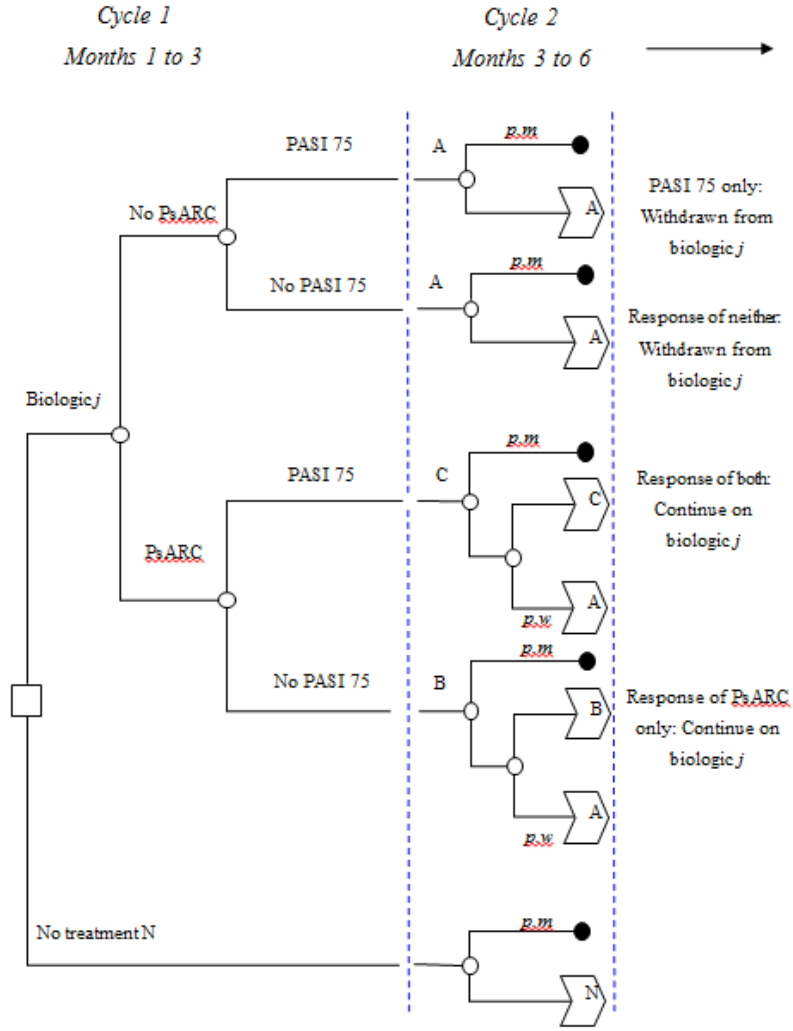
6.2.2.2 Summary of the York model (TA199)

The York model is a cohort Markov model (see Figure 8), built using the R software package. The model was developed to estimate the costs and QALYs of three biologics (ETN, INF or ADA) over a lifetime horizon (40 years) compared with palliative care alone. The model adopts the perspective of the UK National Health Service and personal social services (NHS & PSS). The price year assumed for costs is 2008/2009 and the annual discount rate is 3.5%[119] for both costs and QALYs.

The model structure is based on an understanding of the disease process and how this should be modelled to determine cost-effectiveness.[120] The model is based on a two part structure:

- initial-response period (short-term model used to determine initial response rate and treatment continuation decision)
- post-response period (longer-term model used to characterise natural history of disease [i.e. without biologics] and impact of biologics while on therapy and when therapy is stopped).

Figure 8 Schematic of the York model



Patients receiving biologics and who meet the response criteria during the initial-response period, continue on their biologic treatment in the post-response period. Biologics are withdrawn in non-responders and these patients are assumed to move onto palliative care alone. Changes in HAQ and PASI are used to quantitatively model the short- and longer-term cost and quality of life implications (estimated using QALYs) of the use of biologics versus palliative care alone.

Initial (primary) response to the drug is defined using PsARC for joints and PASI 75 for psoriasis, based on BSR[121] and BAD[122] guidelines. Since two response variables are considered (PsARC and PASI), there are four possible outcomes in the initial-response period: (i) skin response only, (ii) joints response only, (iii) response of both and (iii) response of neither. In the base case analysis, only joint (PsARC) response is used to determine treatment continuation. Alternative response rules are

explored in separate scenarios: skin (PASI 75) response only, and response for both measures (PsARC and PASI 75).

The time point for the assessment of response is assumed to occur at 'around 3-months' or between 12 and 16 weeks. Although differences in the recommended time points for assessing initial response were identified by the authors based on the licenses and between guideline-making bodies, a common time point was subsequently assumed. This was justified based on the authors' conclusions that there appeared a lack of a clinically meaningful difference in the biologics' response rates for joint disease or psoriasis between approximately 12 weeks and 24 weeks.

In the decision model, the change in HAQ compared with baseline is conditional on whether a PsARC response was achieved and the specific biologic treatment received. During the initial 3-month response period, the model assumes that patients on biologics have some improvement in HAQ even if they do not reach the PsARC threshold. Patients who do not achieve the required level of response during the first 3 months are withdrawn from therapy, and are assumed to follow the same HAQ trajectory after withdrawal as patients who had palliative care only.

The model assumes that patients who achieve a PASI 75 response will gain at least a 75% improvement in psoriasis compared with baseline PASI. Patients who do not achieve a PASI 75 response will also have some proportionate gain in PASI while they continue taking a biologic, though this will be less than a 75% improvement. The distribution of PASI scores observed in the trials was reflected within the model by utilising the PASI50, PASI75 and PASI 90 data to determine the change in PASI score for PASI 75 responders and non-responders.

Following an initial response to biologic therapy, the model assumed that patients maintain the initial improvement in HAQ for the remaining period of time on that therapy. This assumption was justified based on evidence from an elicitation exercise with clinical experts and supported by data on HAQ and HRQoL from biologics registers and radiographic information supplied by manufacturers' of biologics. It was also assumed that patients maintain the improvement in PASI while on biologic therapy.

The model assumes that no patients withdraw due to adverse events in the first 3 months. The authors noted that since responses in the RCTs are reported on an ITT basis, including withdrawal during the first 3 months would constitute double counting. The model includes an ongoing risk of withdrawal from biologic therapy over the longer term due to lack of continuing efficacy ('secondary non-response'), adverse events or other reasons. The rate of withdrawal after 3 months is assumed to be independent of the HAQ and PASI score, to be independent of whether the initial response was for both psoriasis and arthritis or just arthritis and to be constant over time.

On withdrawal of a biologic treatment, it is assumed that mean PASI returns to its initial score at baseline (rebound equal to initial gain). The authors acknowledged that there was more uncertainty about change in HAQ associated with withdrawal (rebound). In the base-case analysis it is assumed that rebound is equal to initial gain. Other scenarios (rebound less than initial gain and rebound equal to natural history) were explored using sensitivity analyses.

6.2.2.3 Patients characteristics in the York model

Table 62 shows the baseline characteristics used in the York model. Patients were assumed to fulfil the BSR guidelines and criteria specified for commencing biologics i.e. that their PsA has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination.

The model cohort is assumed to be 47 years old at the start of the model, with at least 7 years since diagnosis of PsA, based on the average characteristics of participants in the included RCTs. The mean baseline HAQ at the start of the model is assumed to be 1.05 and patients are assumed to have mild-to-moderate psoriasis with a PASI score of 7.5, based on the average HAQ and PASI baseline score in the RCTs. The mean body weight is assumed to be between 60-80kg based on the mean adult weight of the general population for men and women.

Table 62 Baseline patients characteristics used in the York model

Age (SD)	47
Weight (SD)	60-80kg
Baseline HAQ	1.05
Baseline PASI	7.5

Alternative subgroups were explored in scenario analyses based on different baseline HAQ and PASI scores:

- An alternative, more severe HAQ of 1.8, which is the mean HAQ of patients entering the BSR biologics register (BSRBR).[77]
- No skin involvement, with a PASI score of zero (personal communication was cited stating that 50% of patients with PsA starting biologics in clinical practice would have mild or no skin involvement)
- Moderate to severe psoriasis, with a PASI score of 12.5 (personal communication was cited stating that 25% of patients with PsA starting biologics in clinical practice would have a baseline PASI>10).

6.2.2.4 Choice of intervention and comparators in the York model

INF, ETN, ADA and palliative care were included, reflecting the licensed biologic treatments available when TA199 was conducted. Palliative care was assumed to represent conventional care without biologic treatment.

6.2.2.5 Sequencing of treatments in the York model

In the base case analysis, patients who are withdrawn from treatment (primary non-response or secondary withdrawal) were assumed to receive palliative care alone. A separate exploratory scenario assessed the cost-effectiveness of a further biologic treatment used as a second line of therapy (biologic experienced), if the first biologic is withdrawn. This scenario considered two subgroups: failure of first biologic because of adverse events and failure because of efficacy.

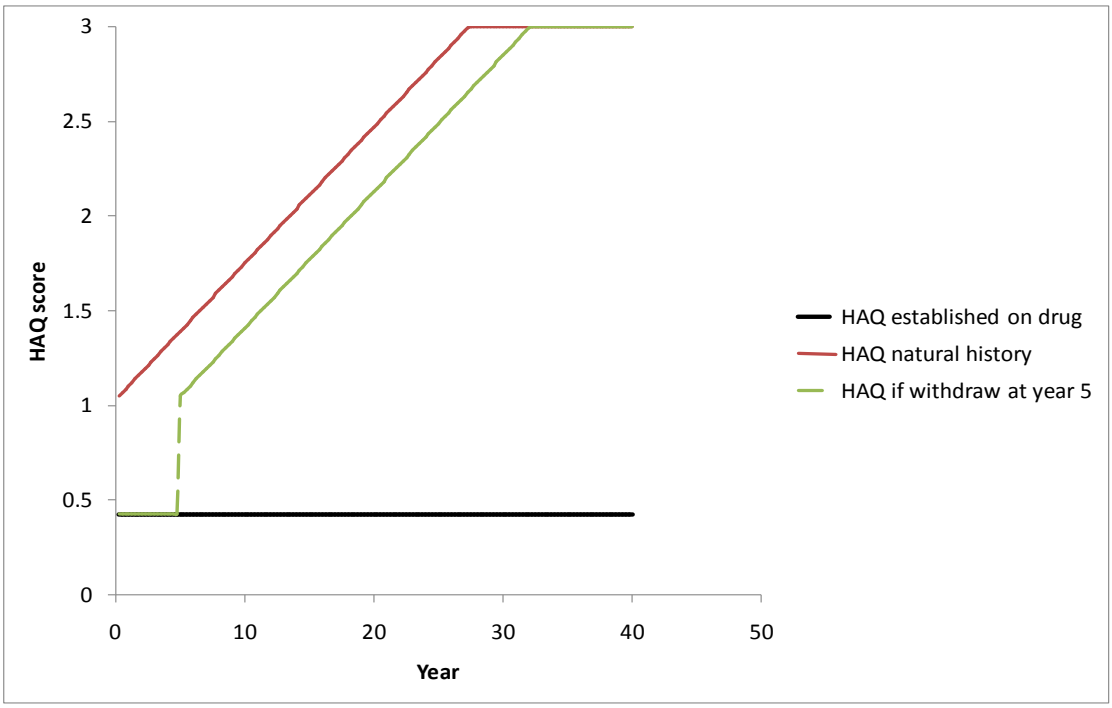
In the absence of RCT data on these subgroups, treatment response and withdrawal rates for these subgroups were estimated from observational data for RA patients from the BSR register. For a patient that failed first line therapy due to lack of efficacy, the risk of failing the second-line therapy due to lack of efficacy increases by 2.7 (95% CI 2.1-3.4). If a patient fails first line therapy because of an adverse event, then the risk of failing the second-line therapy for adverse events increases by 2.3 (1.9-2.9).

6.2.2.6 Natural history of PsA in the York model

PsA is a progressive disease and untreated PsA patients may have persistent inflammation and progressive joint damage (see Section 2). This was reflected in the York model by applying a constant rate of HAQ increase to patients receiving palliative care alone (Figure 9). The increase in HAQ was applied to characterise the natural history of HAQ (i.e. without biologic treatment) and was estimated as 0.018 in a three-month cycle, based on data from NOAR registry. Figure 9 graphically shows how the HAQ progression assumptions (on and off treatment) were applied in the York model.

For the psoriasis component of PsA, it was assumed that PASI does not worsen over time (off treatment), which was stated to be consistent with clinical evidence.

Figure 9 Illustration of the progression of arthritis for a patient successfully maintained on biologic, a patient without biologic and a patient who withdraws at 5 years, implemented in the York model



6.2.2.7 Sources and synthesis of effectiveness data in the York model

The effectiveness of the alternative treatments was estimated using a network meta-analysis (NMA). The network of evidence was based on six trials that have a common comparator (placebo). Three different synthesis models were specified to allow relevant outcomes for the economic model to be synthesised: PsARC response at 12-16 weeks; change in HAQ score conditional on a PsARC response; and the probability of achieving PASI 50, 75 and 90 responses.

In the decision model, the change in HAQ compared with baseline is conditional on PsARC response status. It is uncertain whether the change in HAQ is the same for all PsARC treatment responders, or depends on the particular biologic treatment received. In the base-case, the change in HAQ depended on PsARC response and the individual biologic treatment, while alternative scenarios (i.e. HAQ change the same for all PsARC responders) were assessed within the sensitivity analysis.

A placebo or expectation effect, which is the improvement reported for patients in the placebo arms of the RCT, is uncertain and may not be reproducible in clinical practice. In the base-case, the mean change in HAQ across the placebo arms of the RCTs was discounted from the change in HAQ for patients using biologics. This was applied in the decision model by taking away the change in HAQ in the placebo arm, weighted by the PsARC response in that arm, from the HAQ change in the treatment arm. A similar adjustment is made for the expected change in PASI score. An alternative scenario was

conducted assuming that the response rate to treatment in the RCTs is fully generalisable to general practice, and therefore no adjustment for placebo/expectancy effects is made.

Data on time to withdrawal from first biologic were separately synthesised using a meta-analysis of five European registry studies, one of which was the UK BSRBR registry[77]. The estimated annual probability of withdrawing from the biologic treatment after the first cycle is 0.165, therefore, patients who achieve an initial PsARC response will on average remain on biologic drugs for just over 6 years in the model (1/0.165 = 6.06 years). This was assumed to be identical for all biologics.

The base-case model uses a published estimate of the additional mortality risk in PsA (Wong et al[12]).

6.2.2.8 Sources of utility data used in the York model

QALYs were determined by estimating health utilities as a function of HAQ and PASI. The York model used an equation based on an ordinary least-squares regression of patient level data from one of the companies (Wyeth) submitting evidence for TA199. It was stated that similar results were obtained from separate trials across each of the three companies, indicating that the relationship between HAQ, PASI and utility appears stable across independent clinical trials. The equation below shows the algorithm used in the base case analysis of the York model:

$$Expected\ utility = 0.897 - 0.298 * HAQ - 0.004 * PASI$$

6.2.2.9 Summary of resource utilisation and costs data used in the York model

The acquisition costs of the drugs and their administration and monitoring were obtained from BSR guidelines for the use of biologics and national prices and tariffs. The base-case assumes that vial sharing is not permitted for infliximab and therefore separate scenarios regarding the use of three or four vials per patient were considered according to different weight assumptions.

Health care costs increase with severity of both arthritis and psoriasis. Health state costs associated with HAQ were derived from data from a UK-based study by Kobelt et al[123], including 916 patients with RA with between 5 and 9 years follow up. Direct health-care resources were collected prospectively for all patients for hospitalisations, surgical interventions and RA medications. Based on this study, Bansback et al[124]separately applied a linear regression model to estimate the relationship between HAQ score and resource use (equation shown below). The regression estimates were subsequently reduced by 15% to account for expenditure on DMARDs and to avoid double counting with other drug acquisition costs which were separately estimated.

Direct cost per 3-month period = 342 + 103.5 x HAQ

Since the Kobelt study only includes RA patients, separate costs were estimated for treating mild-to-moderate psoriasis in patients who do not use biologics, or who do not respond to biologics, from NHS unit costs of phototherapy and a UK RCT. For patients with moderate or severe psoriasis, costs were obtained from a Dutch RCT and adjusted to UK price levels (Hartman et al[125]). These costs were assigned to patients based on whether a PASI 75 response was achieved or not (Table 63).

Table 63 Psoriasis (PASI) costs applied in the York model

	Mild to moderate psoriasis 3-month cost	Moderate to severe psoriasis 3-month cost
On anti-TNFα with PASI-75 response	£16	£16
On anti-TNFα without PASI-75 response	£198	£566
Not on anti-TNFα therapy	£198	£566

6.2.2.10 Cost-effectiveness results from the York model

The summary results from the York model are those which are reported in the FAD document for TA199. The results of the base-case model reported that INF was the most effective strategy taking into account both joint and skin effects (QALYs = 7.3), followed by ETN (QALYs = 7.0) and ADA (QALYs = 6.6). In terms of costs, INF was the most costly treatment (£88,442) followed by ETN (£74,841) and ADA (£68,638). The ICER for ETN compared with palliative care was £17,853 per QALY. The ICER for INF compared with ETN was around £44,326 per QALY. ADA was extendedly dominated. Of the three biologic therapies, ETN had the highest probability of being cost-effective at a threshold between £20,000 (probability = 44%) and £30,000 (probability = 48%) per QALY.

The results of subgroup analysis showed that biologics appear slightly less cost-effective if the baseline HAQ is 1.8 (high), although the ICER for ETN remained below £20,000 per QALY. In patients with negligible baseline psoriasis (i.e. PASI = 0), ETN was the most cost-effective strategy with an ICER of £18,512 per QALY compared with palliative care. The ICER of INF versus ETN increased to £64,744 per QALY and ADA remained extendedly dominated. However, for a cohort in which baseline PASI was moderate to severe (PASI of 12.5 rather than 7.5), ADA was no longer extendedly dominated. The ICER of ADA versus palliative care was £16,310 per QALY. The ICER

of ETN versus ADA was £19,319 per QALY and the ICER of INF versus ETN was £27,778 per QALY.

In the scenario considering the cost-effectiveness of biologics, used as a second course of therapy after a first biologic has failed for PsA patients with mild-to-moderate skin disease, the incremental cost-effectiveness ratios depend on which drug was used as first-line therapy, and is therefore ineligible for use as second-line. For patients failing ETN, ADA has an ICER of less than £20,000 and INF is around £25,000 per QALY. The ICERs were reported to be broadly similar for people whose psoriatic arthritis failed to respond to first-line therapy because of adverse effects and those whose disease failed first-line therapy because of inefficacy.

6.2.2.11 Summary of key differences in modelling approaches from other published studies

As described in Section 6.2.2.1, following the development of the York model for TA199[94], three further models were developed comparing different sets of interventions. The model developed for TA220[65] compared ETN, INF, ADA, GOL and palliative care in a biologic naïve population. The model developed for TA340[61] compared ETN, INF, ADA, GOL, UST and palliative care in biologic naïve and biologic experienced populations. The model developed by Cawson, et al[31] compared ETN, INF, ADA, GOL and palliative care in a biologic naïve population.

The model structure used in each of the three models is broadly the same as the York model. There were some minor variations in the duration of the response period, in particular extending this up to 24 weeks in TA220 to reflect the longer response period for UST in line with its license, but generally all models have a similar underlying structure and use PsARC as the main response measure.

One key difference between the models concerns the different sets of interventions which have been compared. The sequence of published studies closely follows the licensing of additional tumour necrosis factor (TNF) alpha inhibitors after TA199 (GOL) and new biologic alternatives (UST). As a result, the scope of each study has been extended to include these additional DMARDs (individually or in combination, in line with BSR guidelines). However, since one of the RCTs for UST included patients with and without prior exposure to TNF alpha inhibitors, the decision problem for TA340 was subsequently broadened to reflect these different populations. For the TNF alpha inhibitor-exposed (experienced) population, UST was compared with conventional management only, because at the time of the submission there were no RCTs of TNF alpha inhibitors in this population. Analyses were based on clinical effectiveness evidence from the TNF alpha inhibitor-exposed subpopulation of the PSUMMIT 2 trial.

As new interventions have been included, subsequent modelling studies have been based on revised NMAs incorporating new RCT evidence for the interventions being assessed in each appraisal (GOL

in TA220 and UST in TA340). However, the synthesis approaches and methodologies applied across the studies remains consistent with that applied in the York model. The only exception to this is the comparison of UST versus conventional care in the TNF alpha inhibitor-exposed subpopulation which was based on subgroup results from the PSUMMIT 2 trial. For this subpopulation an NMA was not considered feasible due to the lack of RCT evidence for the comparator treatments.

The main approaches to estimating longer term costs and QALYs employ similar methodologies and assumptions across the studies identified. The main difference in relation to costs concerns the link to PASI. Estimates of PASI costs applied in the GOL and UST appraisals (TA220 and TA340) were derived from a clinician survey and used to estimate the expected difference in cost per additional point change in PASI score. This contrasts with the approach used in the York model which distinguished costs on the basis of PASI 75 response. Although different utility algorithms have been applied in each of the models (TA220 and TA340 used patient level data from each company's respective trials), these have reported similar coefficients for HAQ and PASI to those applied in the York model. All studies have also routinely reported results based on the utility estimates used in the York model in separate scenarios.

With the exception of TA220 (GOL), all models have used the same assumptions and data sources to model the natural history and progression of PsA (i.e. assuming a constant PASI score and a linear increase [worsening] of HAQ over time). In TA220 (GOL) the annual rate of change per year was derived from alternative source, the Leeds NESPAR study. However the estimate is broadly similar to the estimate applied in the York model and other published models (0.0719 per year compared to 0.077 per year in the York model). All published studies have used the same estimate (16.5% per annum) concerning longer term withdrawal of biologic treatment due to lack of efficacy.

6.2.2.12 Comparison of cost effectiveness results from published models

Given the different interventions and effectiveness data utilised in each of the models, it is not surprising that each generates different costs and QALYs, resulting in different ICERs for the various options being compared (see Table 64). However, there appeared a number of findings which were consistent across the separate studies. Consistently, ETN appeared to represent the most cost effective strategy based on fully incremental ICER calculations, with an ICER ranging between £16,426 and £17,853 per additional QALY versus palliative (i.e. conventional) care. In addition, INF was reported to be the most effective and costly strategy with the exception of TA220, where INF was reported to have the same effectiveness as ETN. There appeared greater variation across the studies in terms of the ICERs reported for INF versus palliative care, ranging between £20,789 and £40,943 per QALY across than reported for other strategies. These differences appear largely due to differences in assumptions related to dosing for INF based on body weight. In all fully incremental comparisons,

treatments other than ETN and INF were reported to be either dominated or extendedly dominated. The majority of studies reported that the ICER for INF versus ETN (the next less effective and non-dominated strategy) ranged between £44,326 and £268,107 per QALY. In contrast, INF was reported to be dominated by ETN in TA220 (i.e. same effectiveness but higher cost).

TA340 included a separate analysis of a biologic experienced population for UST. In this analysis UST was reported to be cost-effective compared to BSC (ICER around £25,000) in the biologic experienced/ineligible population. UST was subsequently approved by NICE for this population, highlighting the importance of considering the impact of broader treatment pathways for PsA for future studies.

Analysis of subgroups, according to psoriasis involvement, has been consistently done via deterministic sensitivity analysis in TA199, TA220 and TA340, specifying a negligible or more severe PASI score.

Table 64 Summary of cost-effectiveness results from the published studies and NICE TAs

TA 199 **Rodgers et al**[94] **Bojke, et al**[114]	**TA 220** **Cummins et al**[126] **Yang et al**[115]	**TA 340** **Craig, et al**[61] **O'Connor et al**[116]	**Cawson, et al**[31]
Only fully incremental ICERs presented. The ICER of ETN compared with palliative care = £17,853 and the ICER of INF compared with ETN = £44,326 per QALY. ADA is extendedly dominated. Of the three biologic therapies, ETN has the highest probability of being cost-effective at a threshold between £20,000 and £30,000 per QALY.	Pairwise ICERs presented versus palliative care and fully incremental comparisons presented. <u>Pairwise ICERs versus palliative care (Company corrected)</u> ADA = £18,824 GOL=£19,993 ETN = £17,177 INF = £23,578 <u>Fully incremental ICERs</u> ETN versus palliative care = £17,177 per QALY. ADA and GOL extendedly dominated. INF dominated by ETN.	Pairwise ICERs presented versus palliative care and fully incremental comparisons presented. Separate analyses presented for TNF-alpha inhibitor naïve and experienced populations. ERG alternative model estimates presented below including UST Patient Access Scheme (PAS). <u>Pairwise ICERs versus palliative care – naïve (ERG alternative model including UST PAS)</u> UST = £21,857 ADA = £29,915 ETN = £17,809 GOL = £19,213 INF = £40,943 <u>Fully incremental ICERs – naïve (ERG alternative model including UST PAS)</u> ETN versus palliative care = £17,809 per QALY. INF versus ETN = £268,107 per QALY. UST and GOL dominated. ADA extendedly dominated. <u>Experienced patients (ERG alternative model including UST PAS)</u> UST versus palliative care	Pairwise ICERs presented versus palliative care and fully incremental comparisons presented. <u>Pairwise ICERs versus palliative care</u> ADA=£17,222 GOL=£17,435 ETN=£16,426 INF=£20,789 <u>Fully incremental ICERs</u> ETN versus palliative care = £16,426 per QALY. INF versus ETN = £62,527 per QALY. GOL dominated. ADA extendedly dominated.

		= £25,393 per QALY.	

*ICERs reported for TA199, 220 and 340 based on the preferred assumptions of the committee from FAD documents

6.2.3 Critique of company submissions

Two de-novo economic models were submitted by the companies (Novartis and UCB), as part of this technology appraisal. The main features of the models are summarised in Table 65 below and critiqued in the sections following this. Quality assessment checklists for the two submissions are presented in Appendix 12.6.

Table 65 Summary of the Novartis and UCB models

	Novartis submission	**UCB submission**
Comparators	These are specified according to the subpopulations considered: 1. Biologic naïve (One prior DMARD): SEC 150mg, Standard of Care (SoC; MTX 25 mg per week) 2. Biologic naïve (Two or more prior DMARDs): SEC 150mg, CZP, ADA, ETN, INF, GOL and SoC 3. Biologic experienced: SEC 300mg, CZP, UST and SoC	These are specified according to the subpopulations considered: 1. Biologic naïve (One prior DMARD): CZP, cDMARD 2. Biologic naïve (One or more prior DMARDs): CZP, SEC 150mg, ADA, ETN, INF, GOL and SoC 3. Biologic experienced: CZP, SEC 300mg, UST and a mix of treatments defined as MTX other cDMARDs and palliation (anti rheumatics)
Model structure	Short-term (3-month) decision-tree, leading into a long-term (40 year) Markov cohort model. Response at 3 months defined using both PsARC and PASI 75. Responders enter the maintenance phase and can switch to SoC due to death or withdrawal from treatment. Disease progression, through PASI and HAQ, are linked to costs and utilities. For patients on treatment, HAQ and PASI scores remain constant from 12 weeks. For patients that withdraw from treatment, PASI and HAQ both rebounds back to the baseline value in the cycle after stopping active treatment. Patients on SoC experienced a linear increase in their HAQ score of 0.018 for each cycle.	Cohort Markov model. Three periods: 1) short-term, in which the initial response to treatment is determined (12 or 24 weeks depending on the treatment 2) treatment continuation (up to 36 weeks post initial response), 3) long term period (50 years). PsARC is used to determine response. Responders enter the maintenance phase and can switch to another treatment due to loss of efficacy due or for other reasons. Initial non-responders switch to the next line of treatment immediately after the initial period. Disease progression, through PASI and HAQ, are linked to costs and utilities. For patients on treatment, HAQ and PASI scores remain constant. For patients that withdraw from treatment, PASI rebounds back to the baseline value in the cycle after stopping active treatment, but HAQ rebounds to a worse position. Patients on SoC experienced a linear increase in their HAQ score of 0.018 for each cycle.
Sequencing	Not addressed in the base case analysis. Included as a scenario in which patients move to a subsequent "basket" of biologics before switching to SoC. This was applied only in the anti TNF naïve population.	Full sequence model of biologics followed by the mix of palliation, the sequence differs based on the subpopulation, ranging from one line to three lines of treatments. Switching can only occur in the first four years, after which patients remain on treatment indefinitely, accounting for mortality.
Patient inputs	Homogenous cohort using average characteristics from FUTURE2 trial: Baseline HAQ = [redacted] Baseline PASI = [redacted]	Homogenous cohort using average characteristics from RAPID-PsA trial. Biologic naïve (One prior DMARD: Baseline HAQ = [redacted] Baseline PASI = [redacted]

	These baseline values were applied to each of the 3 subpopulations	<u>Biologic naïve (One or more prior DMARDs</u> For anti TNF naïve pop baseline HAQ = 1.29 Baseline PASI = 11.58 <u>Biologic experienced</u> Baseline HAQ = 1.37 Baseline PASI = [redacted]
Sources of effectiveness evidence and synthesis	See Section 6.2.3.4 and Appendix 12.7	See Section 6.2.3.4 and Appendix 12.7
Sources of cost data	MIMs 2016 and BNF 2015 for acquisition costs and doses required for treatments. PSSRU 2015 and NHS reference costs 2014-2015 for administration and monitoring costs. Health state costs were estimated based on Kobelt et al.	MIMs 2016 and BNF 2015 for acquisition costs and doses required for treatments. PSSRU 2015 and NHS reference costs 2014-2015 for administration and monitoring costs. Health state costs were estimated based on Poole et al.
Utilities	Algorithm derived from patient-level data of FUTURE2 in which utility is a function of HAQ, PASI, Age, gender and anti-TNF response state. The algorithm from the York model was also applied in a scenario analysis	Algorithm derived from patient-level data of RAPID-PsA in which utility is a function of HAQ and PASI. The algorithm from the York model was also applied in a scenario analysis

6.2.3.1 Model structure and assumptions

The two company models have a similar structure to the York model, reflecting both the initial short term (response period) and long-term (maintenance) phases (see Figure 10 and Figure **11**). Within the short term response period, treatment response is assessed within a decision tree in the Novartis submission, and within a Markov cohort model in the UCB submission. Both submissions characterise the long term phase (modelled via changes in HAQ and PASI) using a Markov cohort model. This longer term phase is 40 years in the Novartis model and 50 years in the UCB model. Both models are built in MS Excel.

Figure 10 Overview of the UCB model structure

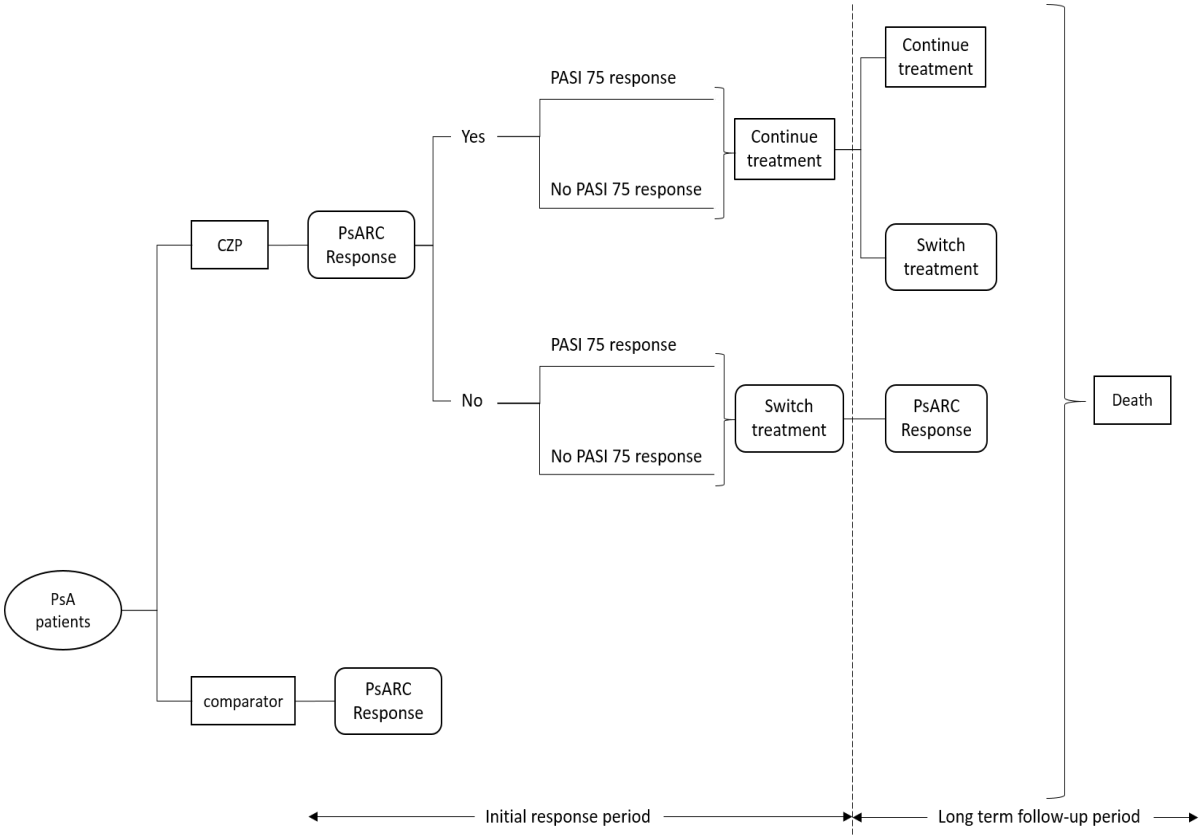
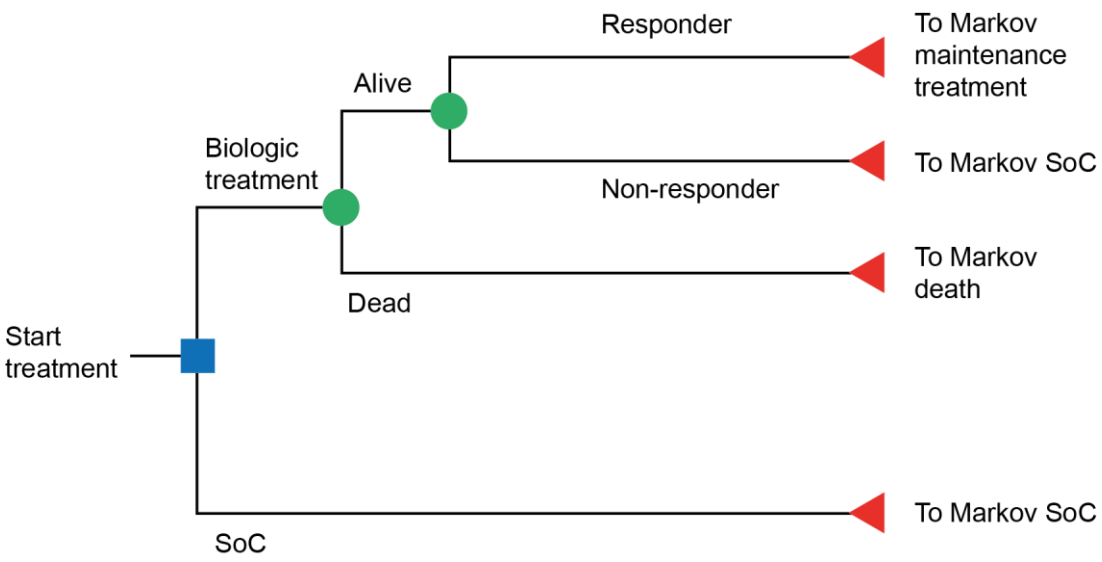
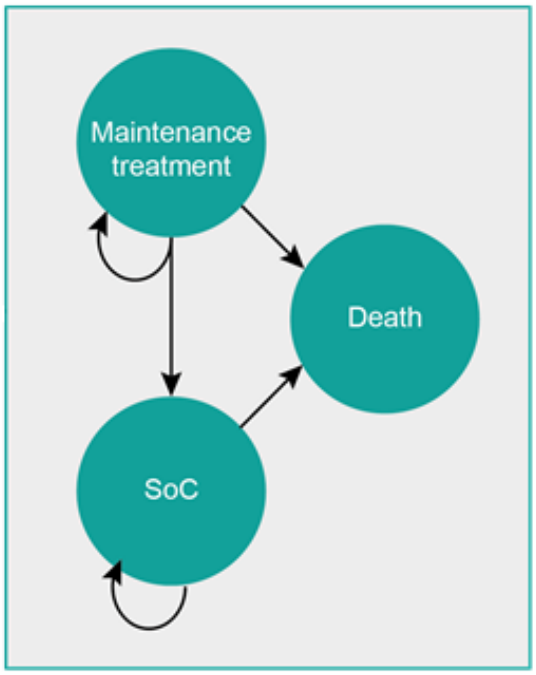


Figure 11 Overview of Novartis model structure

a) Decision tree structure



b) Markov model structure (base case)



Although both submissions share a similar underlying structure there are important differences in the base case approaches of each company in terms of the definition and timing of the response assessment:

- In the UCB base case model, response is defined in terms of PsARC alone. The base case also assumes that PsARC response is assessed at 24 weeks both for CZP and for all other comparators. The use of 24 weeks contrasts with previously published studies reviewed for the comparator treatments which have consistently assumed this assessment would occur at around 3 months (12-16 weeks). The main exception in previous studies has been for UST where a 24 week time point

has been used in accordance with its marketing authorisation. The justification provided by UCB for choosing a common time point of 24 weeks for all treatments was based on the EULAR Treat to Target (2013) recommendations, which state that a maximum of 6 months is recommended for reaching the treatment target. However, the submission from UCB also notes that that the same recommendations also advise that therapy should be adapted earlier than 6 months if no significant reduction in disease activity is observed. The UCB submission does not explicitly discuss the proportion of patients in whom their therapy would be adapted earlier than the 24 week time point, nor is there any discussion of the potential biases that could arise by assuming that therapy is only adapted after 24 weeks. However, a separate scenario where the initial response was assessed at 12 weeks both for CZP and for other comparators (including UST) was explored as part of a scenario analysis. Patients are then further stratified according to PASI75 response or not. This stratification is not assumed in the base case to alter the decision to continue treatment but allows alternative cost and utility assumptions to be applied according to PsARC response status.

- In the Novartis model, patients are defined as responders if both a PsARC and PASI 75 response are achieved at 12 weeks (or 24 weeks for UST). The model also includes additional scenarios were either PASI or PsARC only are used to determine a patient's initial response. Although the company notes that the SEC SmPC recommends a 16 week assessment point, a 12 week time point is assumed for SEC based on consistency with BSR/BHPR guidelines and previous NICE appraisals.

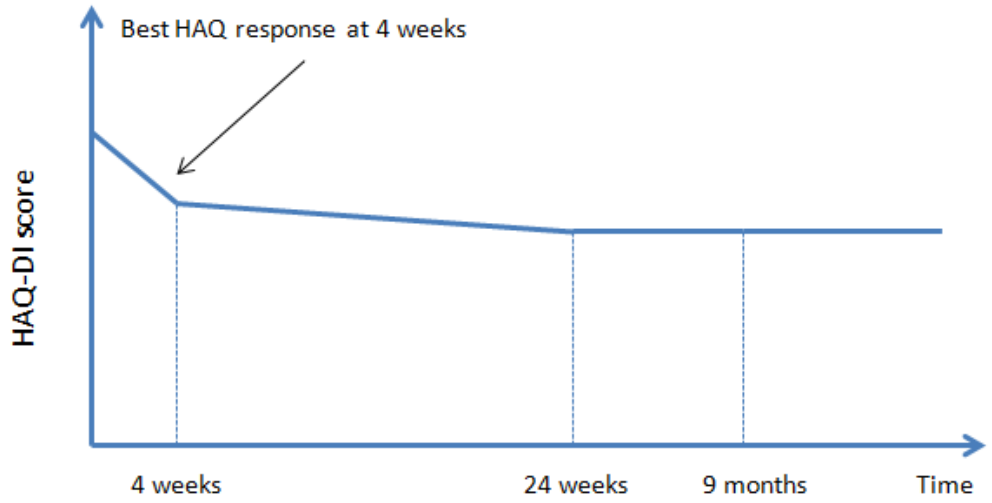
In both models, HAQ changes are based on a treatment-specific rate of change conditional upon PsARC response status. However, important differences were evident between the companies, in the approaches and assumptions applied in their respective models:

- In the UCB model, HAQ change for CZP is based on the week 4 data from the RAPID-PsA trial. UCB justify this assumption on the basis that the RAPID-PSA showed minimal further change in HAQ between weeks 4 and 24. In the absence of HAQ data over time for the other comparators, a similar assumption was made for the comparators. An alternative assumption was explored as part of a scenario analysis where the highest rate of change (or 'best') HAQ change for the comparators is achieved only at 24 weeks. These assumptions are applied in the UCB model to the treatment response period (24 weeks in the base case). Beyond 24 weeks, it is also assumed that there is continued improvement in HAQ up to week 36 post initial response. UCB justify this additional period of HAQ improvement based on continued improvement over this period observed in the RAPID-PSA trial. In the absence of data, a similar assumption is applied to all the comparators. After 36 weeks it is assumed that HAQ remains constant for patients for the remainder of the period on treatment. **Figure 12**

illustrates the separate intervals over which different assumptions are applied for patients responding to biological treatment in the UCB submission.

- In the Novartis model, HAQ change data was derived directly from data reported during the 12-16 week time period included in their main NMA and was assumed to remain constant from 12 weeks onwards for patients who remained on treatment. This approach is consistent with the assumption made in the previous York model.

Figure 12 Illustration of HAQ-DI change for patients responding to biologic treatment in the UCB model



In both models the change in PASI score is derived from the distribution of PASI responses. The approaches followed by each company are consistent with the approach and assumptions of the York model.

The two submissions also account for the correlation between PASI75 and PsARC using a similar method to the York model. However, both companies source data on the correlation coefficients from their own trial data as opposed to the data used within the York model.

Both submissions also incorporate an adjustment to HAQ and PASI scores in order to account for a possible 'placebo' or 'expectation' effects in order to generalise the treatment effects from the RCTs to routine practice. The methods of adjustment follow the same approach as the York model, by reducing the change in HAQ for biologics by the weighted average of change in HAQ for PsARC responders and non-responders across the SoC arm. A similar approach is followed for PASI. Consequently, SoC patients were not assumed to experience any HAQ or PASI improvement in the models.

The Novartis model assumes that when a treatment is withdrawn, patients rebound to their baseline HAQ (i.e. rebound equal to gain) and their HAQ continues to deteriorate in line with the natural history of HAQ (i.e. a constant monthly rate of HAQ deterioration). In contrast, the UCB submission assumes that the HAQ trajectory of patients switching to a subsequent treatment initially rebounds to a higher (i.e. worse) HAQ value than the original baseline.

The two submissions include a gender-specific multiplier effect for PsA mortality. The Novartis submission applied the relative risks reported in Wong et al[12] (1.65 and 1.59 for men and women respectively) to life tables from the general population. The impact of these multiplier effects was assessed by removing the effects in a scenario analysis. In the UCB submission a standardised mortality ratio of 1.36 was applied for males and females.[14] This represents an updated analysis of the cohort from Wong, et al.

6.2.3.1 Intervention and comparators

According to BSR guidelines, biologic treatments should be considered for patients with active PsA who have inadequately responded to two previous cDMARDs.[121] However, in accordance with the NICE scope and the licenses for SEC and CZP, the two submissions have addressed three different subpopulations, including the one prior non-biologic DMARD population. The 3 subpopulations specified in the NICE scope are:

Subpopulation 1 (Biologic naïve - 1 prior DMARD): People who have received 1 prior non-biologic DMARD.

Subpopulation 2 (Biologic naïve - 2 or more prior DMARDs): People whose disease has not responded adequately to at least 2 prior non-biologic DMARDs.

Subpopulation 3 (Biologic experienced or contraindicated): People whose disease has not responded adequately to non-biologic DMARDs and not adequately responded to biological therapies (including ETN, ADA, INF and GOL) or for whom biologic therapies are contraindicated.

There are two areas where the company submissions appear to deviate from the specified NICE scope. Firstly, subpopulation 2 is subsequently defined by UCB as all-biologic naïve people. Hence, subpopulation 2 is presented by UCB as an expansion of subpopulation 1 (i.e. representing 1 or more prior DMARDs). In contrast, the Novartis submission specifies subpopulation 2 in accordance with the NICE scope (i.e. inadequate response to at least 2 DMARDs). Secondly, both companies focus on the biologic experienced population for subpopulation 3. Hence neither company separately considers people who are contraindicated to biologic therapies (including ETN, ADA, INF and GOL).

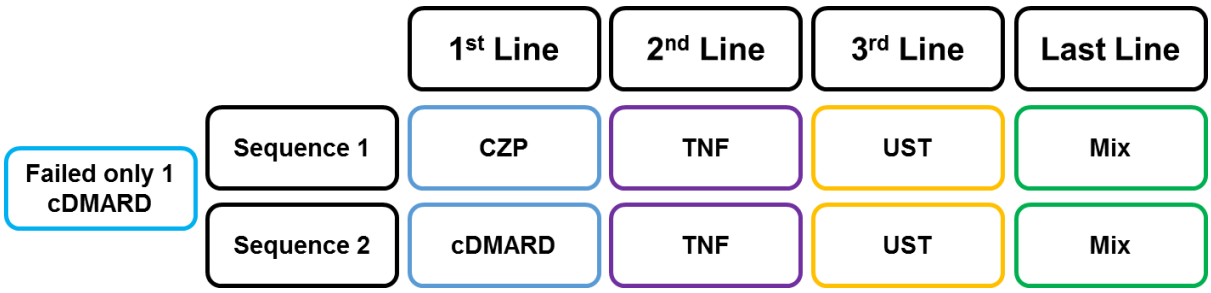
The interventions and comparators in both submissions are specified separately for each of the three subpopulations. Conceptually there are important differences between the submissions in terms of the scope of the models and the approaches used to model the interventions and comparators:

- The UCB model has been developed to assess the cost-effectiveness of the interventions in the context of a treatment pathway and hence explicitly considers subsequent treatment lines by modelling separate sequences. The length and composition of the sequences differs across each of the three subpopulations.
- The base-case model from Novartis for each subpopulation focuses on each specific point in the pathway (i.e. the point that a decision to initiate a new intervention would be made for each subpopulation) and does not attempt to formally model the sequences of subsequent treatments. Instead, the impact of further treatment and associated sequences is explored as part of a separate scenario and is presented as an exploratory analysis. Novartis justify this approach given the limitations in the data available to model sequencing of treatments and the lack of formal guidelines concerning the order in which biologics should be used sequentially.

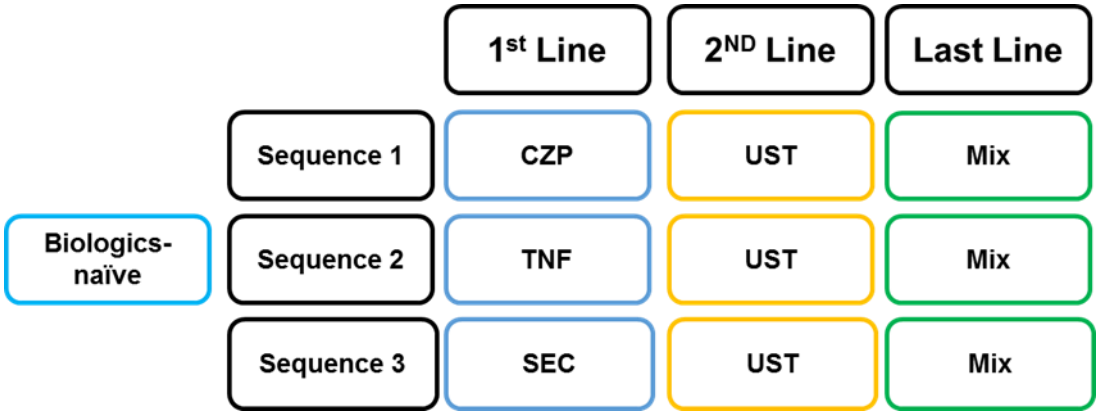
The interventions and comparators in each subpopulation are summarised in Figure 13 (UCB) and Figure 14 (Novartis). The figures illustrate the different approaches employed by the companies and the focus on the entire pathway (sequences and different lines) in the UCB submission compared to the approach used by Novartis in their base-case.

Figure 13 Interventions and comparators according to subpopulations (UCB)

a) Subpopulation 1: *(Biologic naïve - 1 prior DMARD)*



b) Subpopulation 2: *(All biologic naïve - 1 or more prior DMARDs)*



c) Subpopulation 3: *(Biologic experienced)*

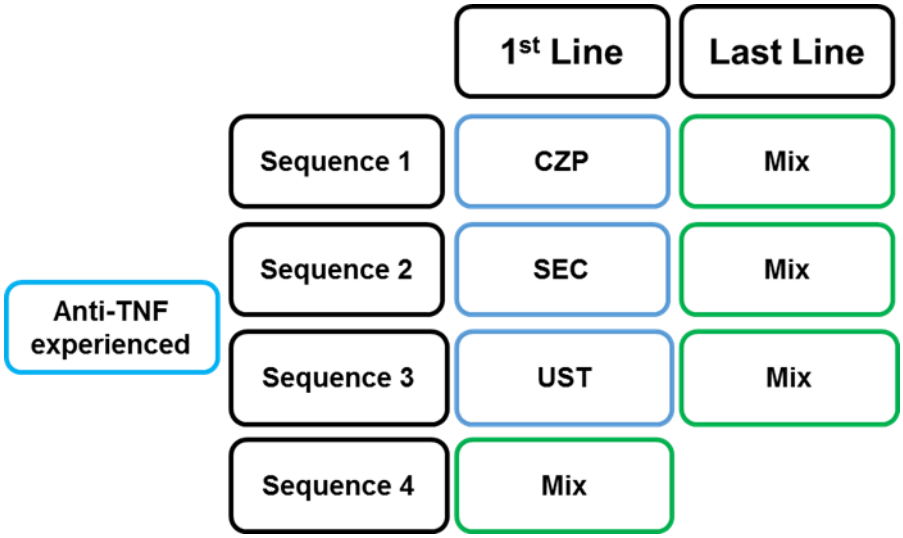
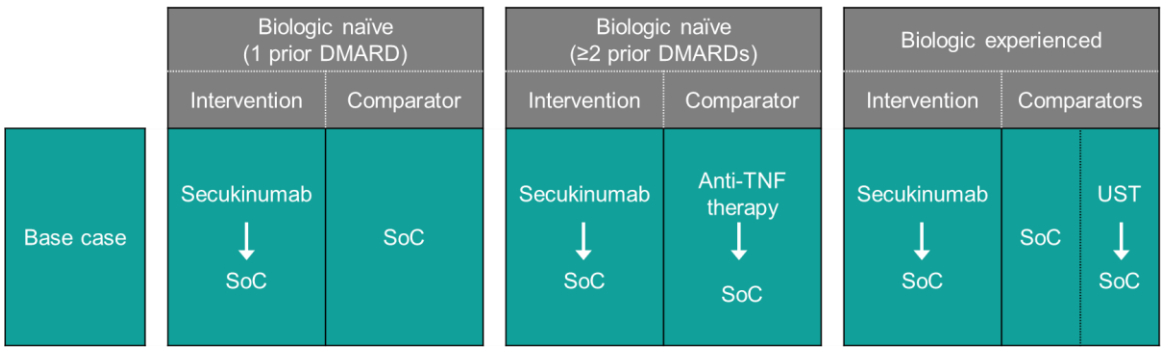


Figure 14 Interventions and comparators according to subpopulations (Novartis)



Subpopulation 1: Biologic naïve - 1 prior DMARD

In the UCB model, two sequences are compared in subpopulation 1:

- Sequence 1: 1st line (CZP) ->2nd line (TNF)->3rd line (UST)->Last line (Mix)
- Sequence 2: 1st line (cDMARD) ->2nd line (TNF)->3rd line (UST)->Last line (Mix)

The sequences differ in terms of the 1st line therapy (CZP or cDMARDs) and the subsequent lines of therapies (up to 3 further lines) in both sequences are assumed to be identical. Primary and secondary failures to 1st line therapy are assumed to move onto a 2nd line treatment comprising a mixture of four TNF alpha inhibitors (ETN, INF, ADA, and GOL). The mixture of the four TNF alpha inhibitors is modelled assuming an equal market share (25%) and costs and outcomes are estimated as the weighted sum. Following failure of the mixture of TNFs, patients are assumed to move onto UST as a 3rd line treatment before moving onto the last line (Mix). The last line (Mix) is defined as a mixture of cDMARDs (base case: methotrexate = 58.8%, leflunomide = 1.5%, sulfasalazine, 2.9% methotrexate sodium) and palliation (34.6%).

The UCB submission states that, while SEC is also a relevant comparator in this subpopulation (i.e. a 3rd sequence starting with SEC), the lack of published clinical evidence specifically on the 1 prior DMARD subpopulation precluded SEC from being formally included.

In the Novartis model, the intervention assessed in subpopulation 1 is SEC 150mg and the comparator is SoC (defined as 100% use of methotrexate, dose 25mg per week). Similarly the lack of published clinical evidence specifically on the 1 prior DMARD subpopulation precluded CZP from being formally included in the Novartis submission. Following primary or secondary treatment failure of SEC, patients are assumed to move to SoC (methotrexate) without further biologic treatment.

Although SEC 300mg is the licensed dose for biologic-naïve patients with concomitant moderate to severe psoriasis, Novartis stated three reasons why the 300mg dose was included for biologic-naïve patients (subpopulation 1 and 2):

1. The use of SEC 300mg for moderate to severe psoriasis is already recommended based on a separate appraisal in this indication.
2. No comparator data for biologic-naïve PSA patients with concomitant moderate to severe psoriasis were reported to be available.
3. The subgroup of biologic-naïve patients with concomitant moderate to severe psoriasis in FUTURE 2 was too small to appropriately inform model inputs.

Subpopulation 2: Biologic naïve – (1 or more prior DMARDs – UCB; 2 or more prior DMARDs – Novartis)

In the UCB model, three main sequences are compared in subpopulation 2:

- Sequence 1: 1st line (CZP) ->2nd line (UST)->Last line (Mix)
- Sequence 2: 1st line (TNF) ->2nd line (UST)->Last line (Mix)
- Sequence 3: 1st line (SEC) ->2nd line (UST)->Last line (Mix)

The sequences start with CZP, other TNF alpha inhibitors (ETN, INF, ADA and GOL) or SEC. In contrast to subpopulation 1, the four other TNF alpha inhibitors are evaluated as alternative 1st line treatments. Hence, Sequence 2 actually comprises 4 separate sequences with ETN, INF, ADA or GOL specified as the 1st line treatment. The 6 sequences assessed in subpopulation 2 are thus:

- Sequence 1: 1st line (CZP) ->2nd line (UST)->Last line (Mix)
- Sequence 2: 1st line (ETN) ->2nd line (UST)->Last line (Mix)
- Sequence 3: 1st line (INF) ->2nd line (UST)->Last line (Mix)
- Sequence 4: 1st line (ADA) ->2nd line (UST)->Last line (Mix)
- Sequence 5: 1st line (GOL) ->2nd line (UST)->Last line (Mix)
- Sequence 6: 1st line (SEC) ->2nd line (UST)->Last line (Mix)

Primary and secondary failures to 1st line treatment are assumed to subsequently move onto UST before moving onto 'Mix' (similarly defined as in subpopulation 1as a mixture of cDMARDs and palliation).

The UCB model does not separately model the 150mg and 300mg doses of SEC for subpopulation 2. Instead, a single SEC sequence is modelled based on a weighted approach according to prevalence of moderate-severe plaque psoriasis in subpopulation 2 and assuming 53.7% of patients would have a PASI over 10 at baseline. The proportion used as the basis for weighting is referenced to an academic on confidence study and no further details are reported. The weighting is only discussed in the context of costing and hence it is unclear whether the efficacy estimates for SEC were similarly weighted or not.

In the Novartis model, the treatment assessed in subpopulation 2 is SEC 150mg and five TNF-alpha inhibitors (CZP and ETN, INF, ADA, GOL) are included as individual comparators. Primary and secondary failures are assumed to subsequently move onto standard of care (SoC) without biologic therapy (100% use of methotrexate, dose 25mg per week).

The Novartis submission also considers a separate scenario (exploratory analysis) for subpopulation 2 in which it is assumed that patients can move onto a mixed biologic therapy, prior to moving to SoC.

The mixed biologic treatment therapy comprises a mix of all biologics other than that received at first-line. This mixed strategy is assigned a weighted average efficacy, costs, and AE incidence rates. The weights assumed are not formally specified but appear to be based on a similar approach to UCB (i.e. assuming each has an equal market share). Two scenarios were considered in which either the same first-line efficacy is assumed for the mixed biologic therapy or a 20% decline in efficacy for HAQ, PsARC and PASI response while on second-line therapy.

Available biosimilars for ETN and INF are also included in the two submissions as part of separate scenario analyses.

Subpopulation 3: Biologic experienced
In the UCB model, four sequences are compared in subpopulation 3:

- Sequence 1: 1st line (CZP) ->Last line (Mix)
- Sequence 2: 1st line (SEC 300mg) ->Last line (Mix)
- Sequence 3: 1st line (UST) -->Last line (Mix)
- Sequence 4: 1st line (Mix)

In common with the other subpopulations, the sequences for subpopulation 3 differ in terms of the 1st line therapy (CZP, SEC 300mg, UST or Mix) and the subsequent line of therapy (Mix – comprising a mixture of cDMARDs and palliative care) is assumed to be identical. The SEC sequence is modelled based on the 300mg dose in accordance with the licensed dose for biologic experienced patients.

In the Novartis model, the intervention assessed in subpopulation 3 is SEC 300mg and UST and SOC are included as separate comparators. The Novartis submission does not discuss why CZP is not included as a separate comparator for subpopulation 3. Following primary or secondary treatment failure of SEC or UST, patients are assumed to move to SoC without further biologic treatment (i.e. methotrexate).

6.2.3.2 Patient characteristics

The UCB submission uses the RAPID-PsA trial and specifies different baseline characteristics for the three sub populations. In the Novartis submission, baseline characteristics were reported to be similar across subgroups in the FUTURE 2 trial and hence the same values were assigned to all patient characteristics apart from PASI.

Table 66 and Table 67 reports the values applied in the two company models. The subpopulations are broadly similar in terms of age and weight; however there are some differences in terms of baseline

HAQ and PASI assumed across the separate models. The UCB submission applies an increasing baseline mean HAQ score across subpopulations 1 to 3, which contrasts with the same HAQ score applied across the three subpopulations in the Novartis submission. There appears more variation in the baseline PASI scores between the submissions with mean PASI scores assumed to be greater than 10 and less than 10 respectively in the UCB and Novartis submissions for each of the subpopulations.

Table 66 Baseline characteristics in subpopulations 1-3 (UCB)

	Subpopulation 1	Subpopulation 2	Subpopulation 3
Age (SD)	[redacted]	47	49
% Female	[redacted]	55.6%	53.8%
Weight kg, mean (SD)	[redacted]	84 (18)	87 (20)
HAQ, mean	[redacted]	1.29	1.37
PASI, mean	[redacted]	11.58	12.04

Table 67 Baseline characteristics in subpopulations 1-3 (Novartis)

	Subpopulation 1	Subpopulation 2	Subpopulation 3
Age (SD)	47.96	47.96	47.96
% Female	51.6%	51.6%	51.6%
Weight kg, mean (SD)	87.11 (19.66)	87.11 (19.66)	87.11 (19.66)
HAQ, mean	[redacted]	[redacted]	[redacted]
PASI, mean	[redacted]	[redacted]	[redacted]

The differences in the mean PASI scores appear an important source of variation between the two submissions. By assuming a mean PASI of >10, the UCB base case results relate to an 'average' PsA patient with concomitant moderate to severe psoriasis (i.e. ≥3% of BSA and PASI >10). In contrast, the Novartis base case results relate to an 'average' PsA patient with concomitant mild to moderate psoriasis (≥3% of BSA and PASI ≤10). These differences are likely to have an impact on subsequent costs and outcomes, most importantly in terms of the appropriate dosing and costs assumed for SEC (i.e. 150mg or 300mg depending on the presence and severity of concomitant psoriasis) in the naïve subpopulations (i.e. subpopulations 1 and 2).

The UCB submission presents separate deterministic sensitivity analyses based on different PASI scores. These sensitivity analyses were presented for two alternative baseline PASI scores (0 and 12.5). These sensitivity analyses essentially reflect separate subgroups without concomitant psoriasis (mean PASI=0) and a subgroup with concomitant moderate to severe psoriasis (mean PASI = 12.5). The Novartis model does not present separate subgroup results or sensitivity analyses in relation to the baseline PASI score.

Given that PASI is directly observable and because the severity of concomitant psoriasis means that different SEC dosages are appropriate for the separate subgroups (i.e. SEC 150mg for naïve patients

without concomitant psoriasis or with concomitant mild to moderate psoriasis and SEC 300mg for experienced patients and for naïve patients with concomitant moderate to severe psoriasis), it would appear more appropriate for both companies to have more explicitly three specific subgroups within each of the subpopulations as opposed to assuming a single 'average' PsA patient or cohort. These three subgroups are:

1) PsA without concomitant psoriasis.

2) PsA with concomitant mild to moderate psoriasis (≥3% of BSA and PASI ≤10).

3) PsA with concomitant moderate to severe psoriasis (≥3% of BSA and PASI >10).

6.2.3.3 Withdrawal from treatment and the natural history of PsA

Following treatment failure and withdrawal, the Novartis assumes that patients will revert back to the original baseline HAQ and PASI scores, which is consistent with the 'rebound equal to gain' approach previously applied in the York model. In contrast, the UCB submission assumes that the HAQ trajectory of patients switching to a subsequent treatment initially rebounds to a higher (i.e. worse) HAQ value than the original baseline. The value assumed for rebound is equal to the baseline value plus the HAQ change for the previous treatment's PsARC non-responders. Furthermore, when switching from the second to the third line treatment this rebound increases further, representing the baseline plus the previous two treatments' change in HAQ for non-PsARC responders. For example, in a treatment sequence addressing subpopulation 1, the baseline HAQ is assumed to be [redacted]; upon switching to the second line treatment, this initially increases to [redacted] and increases further to [redacted] and [redacted]. The UCB submission does not include any discussion or justification for this approach.

The natural progression of PsA (i.e. in the absence of biologic treatments), in terms of increasing HAQ score, is reflected in both models using the approach adopted in the York model. The two models assume that HAQ score linearly increases over time by 0.018 every three months until it reaches the maximum, 3. This increasing HAQ score is applied in conventional treatment arms of both models and to patients who subsequently move onto conventional (i.e. non-biologic) treatment.

Both the UCB and Novartis models consider the possibility that patients who initially respond to treatment may subsequently withdraw from treatment in the longer term model. Based on safety and tolerability data from the FUTURE 1 and 2 trials (see Section 4), the Novartis submission derived the discontinuation rates for patients receiving SEC 150 and 300mg. This was [redacted] and [redacted] for the first year and [redacted] and [redacted] for subsequent years (applied until the end of the model). These values were used for all comparators in the base case and alternative values were examined in sensitivity analysis, where withdrawal rate values were derived from different trials (Table 68 shows these values).

Table 68 Discontinuation rates applied in sensitivity analysis (Novartis)

Annual discontinuation rate	SEC 150	SEC 300	CZP	ETN	ADA	INF	GOL	UST
Year 1	[redacted]	[redacted]	15.1%	15.6%	15.0%	13.9%	29.5%	26.1%
Year 2+	[redacted]	[redacted]	15.1%	15.6%	15.0%	8.5%	29.5%	11.3%

The UCB model assumes an annual discontinuation rate of 16.5% for all biologic treatments. This figure is consistent with the assumption and data used to inform the York model. A further assumption was also included in the UCB model such that if a patient continued on a therapy for at least 48 months there would be no risk of longer term withdrawal beyond this time point. This assumption was justified due to the lack of data reporting long term withdrawal rates.

6.2.3.4 Sources and synthesis of effectiveness

The main clinical outcomes included in the company models were PsARC and PASI (50, 75 and 90) response and HAQ changes conditional upon PsARC response. The sources and assumptions of the effectiveness evidence used in the base case of each of the economic models are summarised in detail in Appendix 12.7. A brief overview is provided below specifically focused on the relationship between the meta-analyses undertaken by each company and the specific inputs and assumptions applied to each subpopulation within the economic models.

Subpopulation 1: Biologic naïve - 1 prior DMARD

For the biologic naïve (1 prior DMARD) subpopulation, both companies used the results from post-hoc subgroup analyses of the naïve subgroup (1 prior DMARD) from either RAPID-PSA (UCB) or FUTURE 2 (Novartis) to inform PsARC and PASI responses and conditional HAQ scores.

Subpopulation 2: Biologic naïve – (1 or more prior DMARDs – UCB; 2 or more prior DMARDs – Novartis)

PsARC and PASI responses were derived directly from the estimates of the separate NMAs undertaken by each company. The populations used for subpopulation for each NMA differed. The UCB estimates were derived from a NMA based on trials (or relevant subgroups) of only biologic naïve patients. In the absence of subgroup data for SEC for biologic naïve patients, UCB included a separate assumption that the effectiveness of SEC [redacted]. In contrast, Novartis used the results from their NMA based on the overall population (i.e. including both naïve and experienced patients for some trials) results for all treatments.

A variety of different sources and assumptions were used to inform HAQ change scores, including results from the NMA, external published estimates and assumptions.

Subpopulation 3: Biologic experienced

There were important differences in the approaches and assumptions used by each company for subpopulation 3. The UCB model included PsARC and PASI response estimates for CZP and SoC directly from a subgroup of biologic experienced patients from RAPID-PSA and then applied separate assumptions for SEC 300mg and UST. In contrast, Novartis assumed a common reduction in the efficacy of biologic-experienced patients based on a comparison between biologic naïve and experienced subgroups in the FUTURE 2 trial. The efficacy reductions were subsequently applied to the all population NMA. The following reductions were applied:

- PsARC reduced by [redacted]%
- PASI 50-74 reduced by [redacted]%
- PASI 75-89 reduced by [redacted]%
- PASI 90-99 reduced by [redacted]%

For HAQ change scores, the UCB model derived data for CZP and SoC directly from the biologic experienced subgroup of RAPID-PSA and used separate assumptions for UST and SEC 300mg. Novartis assumed the same change scores as applied to subpopulation 2.

6.2.3.5 Sources of utility data

The two submissions present separate utility algorithms derived from patient data in the FUTURE2 (Novartis) and RAPID-PsA (UCB) trials. These algorithms are estimated to determine the independent contribution of HAQ and PASI scores to health utilities.

Table 69 shows the parameters used in each submission, alongside the values used in the York model. The Novartis algorithm, in addition to HAQ and PASI, also includes age, gender and the baseline utility as explanatory variables, together with the response status for anti-TNF treatment. This implies that a different algorithm was defined according to PsARC response status. The algorithm also accounts for the decline in utility over time by including age as a covariate. Both submissions also used the algorithm adopted by the York model within a separate scenario analysis. The UCB and York algorithms are broadly consistent, however the Novartis algorithm predicts a much smaller coefficient for HAQ score (-0.172 as opposed to -0.298 in the York algorithm and -0.258 in the UCB model). This implies that a much smaller utility decrement for a point increase in HAQ.

Table 69 Utility algorithms used in the company submissions

Parameter	Novartis	UCB	York model

	FUTURE 2 (SE)	**RAPID-PsA (SE)**	
Intercept	[redacted]	[redacted]	0.897 (0.006)
HAQ score	[redacted]	[redacted]	-0.298 (0.006)
PASI total score	[redacted]	[redacted]	-0.004 (0.0003)
EQ-5D coefficient	[redacted]	n/a	n/a
Anti-TNF therapy status (Anti-TNF naïve was used as the reference for anti-TNF therapy status)			
Inadequate responder	[redacted]	n/a	n/a
Gender (Female was used as the reference)			
Male	[redacted]	n/a	n/a
Age (years)	[redacted]	n/a	n/a

6.2.3.6 Summary of resource utilisation and costs data

In both models, resource use and costs were categorised in terms of drug acquisition, administration and monitoring and associated health state costs (i.e. according to HAQ and PASI scores). In both models, it was assumed that DMARDs were used concomitantly with all biologic treatments (58% using MTX in the UCB model and 100% using MTX in the Novartis model). Adverse event costs were only included in the Novartis model

Drug acquisition costs

Both models estimated the acquisition costs for CZP based on the PAS scheme currently under approval. There were differences in the approaches and costs used by the companies for SEC. In the Novartis model the acquisition costs for SEC 150mg and 300mg were based on the PAS scheme for SEC. The Novartis model also only evaluated the 300 mg dose for the biologic experienced subpopulation and the 150mg dose for subpopulations 1 and 2 for reasons previously outlined. In the UCB model the acquisition costs for SEC were based on the list prices and a weighted cost was estimated for subpopulations 1 and 2 based on the 150mg and 300mg doses, based on the proportion of patients assumed to have concomitant moderate to severe psoriasis.

Both companies used national list prices (BNF and MIMS) for other comparators and incorporated existing PAS schemes for UST and GOL. Both companies used a similar approach to estimating

acquisition costs for INF by assuming a normal distribution of weights to determine the required number of vials based on patient level data in the FUTURE2 (mean 87.11kg, SD 19.66kg) and RAPID-PsA (mean 84.34kg, SD 18.77kg) trials. The drug acquisition costs for biosimilars in both submissions were sourced from MIMS (2016) and were approximately 90% of the price of the originator product.

Drug administration and monitoring costs

In terms of drug administration costs, the Novartis model assumed a half-day inpatient visit for each infusion for INF (£326.46). For all other (subcutaneously administered) biologics, resource use associated with administration was based on a single ½ hour session with a specialist community nurse in the first 3-month period in order to train patients in self-administration (£37.50). No administration costs were assumed for MTX.

In contrast, the UCB model assumed a cost of £159 for each infusion for INF based on the cost of delivering a simple Parenteral Chemotherapy (1st attendance). For all other (subcutaneously administered) biologics and MTX, the UCB model assumed a cost of £43 based on the cost of a 1-hour nurse visit at a GP practice.

Although the two submissions included the same laboratory tests for monitoring PsA patients, there were differences in the costs that are applied for these. In the UCB submission, monitoring costs were defined as laboratory tests and estimated at £117.6 for the first 3 months and £21 for the subsequent 3 months. The monitoring costs for biologics, applied in Novartis model were lower, £79 for the first 3 months and £4.20 for the subsequent 3 months.

Adverse events

Only the Novartis submission included the resource costs of adverse events. These comprised the costs of TB reactivation (£3,054) and other serious infections (£1,527) based on the approach used for a separate NICE appraisal for ankylosing spondylitis (TA383).

HAQ and PASI costs

In the Novartis submission, HAQ and PASI costs were estimated using the same approach as the York model (uprated to 2016 costs). Table 70 shows the inputs used by Novartis and the previous estimates used in the York model.

Table 70 HAQ and PASI costs applied in the Novartis model

Input	York model	Novartis model	Unit
Intercept	£233	£255.78	Per 3 months
Cost per HAQ change	£103	£113.07	Per 1-unit change per 3 months
Health states			
Uncontrolled psoriasis (PASI <75)	£198	£217.36	Per 3 months
Controlled psoriasis (PASI >75)	£16	£17.56	Per 3 months

In the UCB submission, health state costs for HAQ and PASI were derived from a separate study by Poole et al.[127] The Poole study utilised data from a sample of PsA patients from the BSRBR to develop a multivariate model estimating disease severity from parameters routinely available in primary care data. The multivariate model was subsequently applied to routine data from The Health Improvement Network (THIN) to link to treatment and resource costs. These costs include costs of drugs, contacts with a general practitioner and other health care professionals, tests, hospital outpatient attendances, and inpatient admissions. The relationship between disease severity and costs, based on HAQ, was then estimated using a generalised linear model (GLM). Table 71 shows the coefficients from the GLM. Annual costs applied in the model were estimated using the following regression:

Annual costs = Exp (Intercept + HAQ-DI coefficient * HAQ-DI score + Age coefficient * Age + Interaction coefficient * HAQ-DI score * Age).

Table 71 HAQ and PASI costs applied in the UCB model

	Mean	SE
Intercept	3.537	0.010
HAQ coefficient	2.048	0.006
Age coefficient	0.026	0.000
Interaction coefficient, for interaction between HAQ-DI and age	−0.012	0.000

An adjustment was applied in the UCB model to avoid double counting prescription costs which accounted for 38% of the total costs in the Poole study. Hence, HAQ costs were assumed to be 62% of the total costs. The final costs were then uprated to 2015 values.

The UCB submission stated that since the costs from Poole included all medical resource use for PsA patients, adding additional PASI related costs would result in double counting. Consequently, PASI-related costs were not included in the model base case. A sensitivity analysis including PASI-related costs was undertaken based on the method used in York model with costs uprated to 2015 values.

6.2.4 Cost effectiveness results from the company submissions

6.2.4.1 Subpopulation 1: Biologic naïve - 1 prior DMARD

The base case (deterministic) results for subpopulation 1 are reported in Table 72 (UCB model) and Table 73 (Novartis model). The UCB model reports an ICER of £23,666 per QALY based on the comparison of sequence starting with CZP compared to a separate sequence starting with cDMARDs. The Novartis model reports an ICER of £12,189 per QALY based on a comparison for SEC 150 vs SoC. Neither company included both CZP and SEC as relevant comparators in this subpopulation and hence direct comparisons of CZP and SEC are not possible in this subpopulation.

There appear to be large differences in the total costs and QALYs reported for the comparator treatment across the separate models. This may be partly explained by the different model time horizons (50 years in the UCB model and 40 years in the Novartis model), the inclusion of subsequent lines of biologic therapy and the different sources of cost data for HAQ and PASI. The UCB submission reports higher incremental costs and QALYs for CZP relative to the comparator treatment, compared to the results presented for SEC 150mg in the Novartis submission.

Table 72 Base case results for subpopulation 1 (Biologic naïve - 1 prior DMARD) – UCB submission

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
cDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	-
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£23,666

Table 73 Base case results for subpopulation 1 (Biologic naïve - 1 prior DMARD) – Novartis submission

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-
SEC 150mg	[redacted]	[redacted]	[redacted]	[redacted]	£12,189

6.2.4.2 Subpopulation 2: Biologic naïve – (1 or more prior DMARDs – UCB; 2 or more prior DMARDs – Novartis)

The base case (deterministic) results for subpopulation 2 are reported in Table 74 (UCB model) and Table 75 (Novartis model). The UCB model reports that CZP dominates all the other treatments including SEC. In contrast, the Novartis model reports that SEC 150mg dominates all the other treatments with the exception of SoC (less costly and less effective than SEC 150mg) and INF (more costly and more effective than SEC 150). The ICER of SEC 150mg vs SoC is reported in the Novartis submission to be £10,549 per QALY and the ICER of INF vs SEC 150mg is £220,558 per QALY.

Since both companies included both CZP and SEC as relevant comparators in this subpopulation, a direct comparison between the submissions is possible for subpopulation 2. Both companies report their own treatment to be the most cost-effective treatment at conventional cost-effectiveness thresholds and both report that their specific treatment dominates the other. The contrasting conclusions could arise from several important differences previously noted, including: (i) different NMA approaches (i.e. the use of 24 week data by UCB in the base case vs 12-16 week data from Novartis); different acquisition costs and dosages assumed for SEC (weighted estimate for SEC based on list price costs of SEC 150mg and SEC 300mg in the UCB submission vs PAS price for SEC 150mg assumed in the Novartis submission); inclusion of subsequent lines of biologic therapy in the UCB submission; different sources of cost data for HAQ and PASI and different model horizons.

Since the UCB model did not present comparisons against a strategy of no biologic therapy, it is difficult to determine the external validity of the results presented for the comparator treatments. In contrast the Novartis submission presents both fully incremental ICERs and pairwise ICERs vs SoC. The presentation of the pairwise ICERs vs SoC provides an important basis to consider issues of cross-validation based on the consistency of the findings for the comparator treatments and those reported from the broader comparator review presented earlier in the section. It is notable that the ICERs reported for the comparator treatments (ADA, ETN, GOL ad INF) in the Novartis submission appear higher (i.e. less favourable) than reported in previous studies. Indeed, none of these comparator treatments would appear to be cost-effective vs SoC at conventional cost-effectiveness thresholds. The reason for this difference and implications in terms of external validity are not discussed in the Novartis submission.

Table 74 UCB base case ICER results for subpopulation 2 (Biologic naïve - 1 or more prior DMARDs)

Treatments	Total costs	Total QALYs	Incremental costs vs next least costly intervention	Incremental QALYs vs next least costly intervention	ICER vs next least costly intervention
CZP	[redacted]	[redacted]	[redacted]	[redacted]	-
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
SEC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
INF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 75 Novartis base case ICER results for subpopulation 2 (Biologic naïve - 2 or more prior DMARDs)

Treatments	Total costs	Total QALYs	Incremental costs versus SoC	Incremental QALYs versus SoC	ICER vs. SoC (QALYs)	ICER vs. next least costly intervention
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
SEC 150mg	[redacted]	[redacted]	[redacted]	[redacted]	£10,549	£10,549
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£28,432	Dominated by SEC
ETN	[redacted]	[redacted]	[redacted]	[redacted]	£31,280	Dominated by SEC
GOL	[redacted]	[redacted]	[redacted]	[redacted]	£33,802	Dominated by SEC
ETN	[redacted]	[redacted]	[redacted]	[redacted]	£32,706	Dominated by SEC
INF	[redacted]	[redacted]	[redacted]	[redacted]	£53,223	£220,558

6.2.4.3 Subpopulation 3: Biologic experienced

The base case (deterministic) results for subpopulation 3 are reported in Table 76 (UCB model) and Table 77 (Novartis model). The UCB model reports that CZP dominates UST and SEC 300mg. The least costly and least effective, non-dominated treatment in the UCB model is Mix (i.e. a mixture of cDMARDs and palliative care). The ICER of CZP vs Mix is reported to be £8,894 per QALY. In

contrast, the Novartis model reports that SEC 300mg extendedly dominates CZP and UST. The ICER of SEC 300 vs SoC is reported to be £27,562 per QALY.

Similar to the conclusions reported for subpopulation 2, both companies report their own treatment to be the most cost-effective treatment at conventional cost-effectiveness thresholds and both report that their specific treatment either dominates (UCB model) or extendedly dominates (Novartis model) the other.

The Novartis submission again presents both fully incremental ICERs and pairwise ICERs vs SoC for subpopulation 3. Although pairwise comparisons vs the non-biologic comparator (Mix) are not presented in the UCB submission, these can be estimated for UST vs Mix from the data reported in their ICER results table. As with subpopulation 2, there provide an opportunity to consider issues of cross-validation in terms of the consistency of findings for one of the comparator treatments (UST) considered in the broader review. The ICER for UST vs SoC is reported to be £37,228 per QALY in the Novartis submission, indicating that UST is not cost-effective compared to SoC at conventional cost-effectiveness thresholds. Again, this appears inconsistent with previous studies reporting the cost-effectiveness of UST in a biologic experienced population and the reasons and possible implications in terms of external validity are not discussed in the Novartis submission. One possible explanation is the different approaches used in the Novartis submission for the experienced population (i.e. applying a common reduction in the efficacy rate to all treatments based on a comparison between the biologic-naïve and biologic-experienced subgroups based on FUTURE 2 data as opposed to using the actual subgroup data reported for UST). The pairwise ICER for UST vs Mix estimated from the results presented in the UCB results table result in an ICER of £28,068 per QALY. This appears reasonably consistent with the ICER reported in TA340 for UST (£25,393 per QALY).

Table 76 UCB base case ICER results for subpopulation 3 (Biologic experienced)

Treatments	Total costs (£)	Total QALYs	Incremental costs vs next least costly alternative (£)	Incremental QALYs vs next least costly intervention	ICER vs next least costly intervention (£)
Mix	[redacted]	[redacted]	[redacted]	[redacted]	-
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£8,894
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by CZP
SEC 300mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by CZP

Table 77 Novartis base case ICER results for subpopulation 3 (Biologic experienced)

Treatments	Total costs	Total QALYs	Incremental costs versus SoC	Incremental QALYs versus SoC	ICER vs. SoC (QALYs)	ICER vs. next least costly intervention
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£29,538	Extendedly dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£37,228	Extendedly dominated
SEC 300	[redacted]	[redacted]	[redacted]	[redacted]	£27,562	£27,562

6.3 Relevance of submitted cost-effectiveness evidence for NICE decision-making: summary and motivation for de novo model

The company submissions are the only studies which directly assess the decision problem in relation to the new interventions, i.e. the positioning of these treatments within the pathway for PsA (biologic naïve and experienced populations). While the studies in relation to the broader comparators are helpful in terms of highlighting similarities and possible differences between the approaches being applied by the separate companies and those previously used for previous TA appraisals, they are not directly relevant to the evaluation of SEC and CZP.

In general the structure and approaches of both models were similar in many key respects to the York model conducted for TA199 (ETN, ADA and INF). The main differences were:

- The timing of the initial response period which was assumed to be 24 weeks in the UCB submission and 3 months (i.e. 12-16 weeks) assumed in both the Novartis submission (with the exception of UST) and the York model. The justification provided by Novartis for assuming 3 months for the initial response period was to ensure consistency with previous NICE appraisals and BSR/BHPR guidelines and to maximise the data included in the NMA. UCB justified the 24 week period based on EULAR (2011) guidelines, although results were also reported as part of separate sensitivity analysis assuming a 3 month response period.
- The definition of response differed in the Novartis base case (PsARC and PASI) compared to the use of PsARC only in the base case approaches used by both UCB and the previous York model. The Novartis submission presented a separate sensitivity analysis assuming that response was assessed just using PsARC and this reported only minor differences from their base case.
- The focus on sequences and the incorporation of subsequent lines of treatments in the UCB base case as opposed to presenting this as a separate exploratory scenario (Novartis and York models).
- Assumptions concerning HAQ improvement in responding patients. In common with the York model, the Novartis model assumed that the HAQ gain reported at 3 months was the maximum

reduction achieved on treatment and assumed no further change (i.e. increase or decrease) beyond this period for patients while they remained on this treatment. In contrast the UCB model employed different assumptions during the initial 9 month treatment i.e. that the highest rate of change is obtained at 4 weeks but that further improvements in HAQ are possible during a period of 9 months for a responding patient who remains on treatment. After 9 months, the UCB model assumed no further change beyond this period for patients while they remained on this treatment.

- Assumptions related to the rebound effect on HAQ following treatment withdrawal. The UCB submission assumes that the HAQ trajectory of patients switching to the next treatment rebounds to a worse position than their original baseline HAQ score. Both the Novartis and York models assume that patients rebound back to their original baseline HAQ score.
- The inclusion of additional subpopulations (subpopulations 1 and 3) in the Novartis and UCB submissions, based on the broader scope for the appraisal of SEC and CZP compared to the scope of TA199.
- Differences in the source of cost data for HAQ and PASI data. The Novartis submission estimates costs associated with HAQ and PASI based on the same sources and assumptions previously used in the York model. In contrast, the UCB submission based costs on a separate study by Poole et al and justified this on the basis that the PsA population included was more appropriate than deriving costs based on a RA population and employing separate assumptions for PASI costs.
- Differences in the rate of withdrawal for patients who have initial responded to biologic therapy. Although UCB assumed the same annual withdrawal rate as the York model (16.5% per annum), the UCB submission only applied this to the first 4 years of a treatment. Thereafter it was assumed that no patient would withdraw. This assumption was justified by UCB based on the lack of longer term evidence reported for withdrawal. Novartis utilise withdrawal data form their trial population (FUTURE2) and applied a [redacted] per annum rate for the first year and [redacted] for subsequent years.
- Differences in the baseline characteristics in terms of HAQ and particularly PASI scores. By assuming a mean PASI of >10, the UCB base case results relate to an 'average' PsA patient with concomitant moderate to severe psoriasis (i.e. ≥3% of BSA and PASI >10). In contrast, the Novartis base case results relate to an 'average' PsA patient with concomitant mild to moderate psoriasis (≥3% of BSA and PASI ≤10) similar to the base case in the York model. Both the UCB and York model also presented separate sensitivity analyses based on different PASI scores which reflected subgroups of PsA patients without concomitant psoriasis and with concomitant moderate to severe psoriasis. Separate sensitivity and scenario analyses were not presented in the Novartis submission.
- Differences in the model time horizon. This was assumed to be 40 years in the Novartis and York models and 50 years in the UCB model.

As highlighted in the results section, drawing robust conclusions from the results reported from the separate companies are challenging given the differences noted in the approaches and data sources employed. Comparisons in subpopulation 1 are not possible since neither company included the other treatment in their comparisons. The difficulty of comparing results across subpopulations 2 are further hampered by the different assumptions made concerning the dosage of SEC included and in both subpopulations 2 and 3 based on the use of list prices for SEC in the UCB submission and PAS prices in the Novartis submission.

Assessments of cross-validity were possible for subpopulations 2 and 3 based on the Novartis results presented for comparator treatment and those reported in previous studies. The results from the Novartis model did not appear consistent with the cost-effectiveness reported for the comparator treatment assessed in previous NICE TAs (TA199, 220 and 340). A discussion of possible reasons for this difference was not provided in the Novartis submission. An assessment of cross-validity was only possible in terms of subpopulation 3 for the UCB submission. Here the reported ICER appeared reasonably consistent for the main comparator treatment (UST) and the ICER reported in the previous NICE TA (TA340).

Given the different approaches and assumptions employed by the companies, there remains considerable uncertainty regarding both the cost-effectiveness of SEC and CZP in each of the subpopulations and potential implications for the NHS. These differences make it challenging to draw robust conclusions from the current submissions, particularly given the contradictory findings reported for several of the subpopulations in terms of the relative cost-effectiveness of SEC and CZP. Furthermore, neither company incorporated the full range of interventions and comparators as stated in the NICE scope across all three subpopulations. The following section describes the development of a de novo model which attempts to address several areas of remaining uncertainty and to apply a consistent basis for evaluating the cost-effectiveness of the full range of interventions and comparators as stated in the NICE scope across all three subpopulations

7 Independent economic assessment

7.1 Introduction

The review of published models, and the company submissions, show that the underlying structure used to model the cost-effectiveness of treatments for PsA, has remained largely unaltered since the previous York model for TA199.[94] Despite the similarity observed across studies in terms of the model structure, important differences were identified in terms of associated assumptions and data sources. None of these can be considered unequivocally superior to the others; however there are a number of issues with each of the currently available models (see Section 6.3).

In terms of the previous York model, this does not consider all of the subpopulations defined in the NICE scope for this assessment. Currently available guidance, issued by NICE on the use of biologics in PsA[128], recommends that patients try two cDMARDs over a six months period before they can be considered for biologic treatment in accordance with current BSR guidelines. However, as defined in the NICE scope for this appraisal, three subpopulations need to be considered:

- *Subpopulation 1 (Biologic naïve - 1 prior DMARD)*
- *Subpopulation 2 (Biologic naïve - 2 or more prior DMARDs)*
- *Subpopulation 3 (Biologic experienced or contraindicated)*

The two company submissions consider these three of the subpopulations in their economic models; however neither includes the full range of relevant treatments for all of the subpopulations and neither specifically considers patients contraindicated to existing biologic treatments.

In modelling the cost-effectiveness of available treatments, it is also important to consider the possibility that patients may switch to another active treatment, following primary failure (non-response) or secondary withdrawal (initial response with later withdrawal due to adverse event or loss of efficacy). Therefore, a key objective of the de novo model is to assess the cost-effectiveness of SEC and CZP for PsA within possible sequences of available treatments.

7.2 Methods

7.2.1 Overview

A decision analytic model was developed to estimate the cost-effectiveness of SEC and CZP compared to other relevant comparators including ETN, INF, ADA, GOL, UST and best supportive care (BSC) for the treatment of adult PsA. BSC is defined as a mix of cDMARDs and palliative care (see Section 7.2.4). A different set of comparators are defined according to each subpopulation of interest (see Section 7.2.3).

The cost effectiveness model takes the form of a Markov cohort model with 3-monthly cycles, developed using R programing language (see Appendix 12.8 for the full model code). A lifetime horizon (40-years) is assumed. A half cycle correction was not applied as the cycle length is three months, which is relatively short, and therefore half cycle correction is unlikely to be required.[111]

Although the model shares a number of important similarities with the previous York model, several significant changes have also been implemented. These include:

- The base case model attempts to replicate 'real world' clinical practice, in terms of incorporating subsequent biologic treatments following primary lack of response or secondary failure. Ignoring these subsequent treatment lines and/or assuming patients move directly onto BSC following failure of an initial biologic treatment could result in overly optimistic estimates of cost-effectiveness of new (and more effective) interventions. This may arise because the consequences of treatment failure are likely to be over stated compared to 'real world' clinical practice since additional treatment options remain which are more cost-effective than BSC alone. Although exploratory scenarios were considered in the previous York model in relation to treatment sequences, the formal inclusion of further lines of treatment within the base model necessitated significant amendments to the previous R code.
- The model now includes the three-subpopulations specified in the NICE scope for this appraisal.
- Rather than presenting a single base case reflecting an 'average' PsA patient, heterogeneity in terms of baseline PASI is now formally addressed by presenting results for three distinct subgroups within each subpopulation: (i) PsA without concomitant psoriasis; (ii) PsA with concomitant mild to moderate psoriasis (≥3% of BSA and PASI ≤10) and (iii) PsA with concomitant moderate to severe psoriasis (≥3% of BSA and PASI >10). Differences in baseline PASI were previously considered in the previous York model as part of a sensitivity analysis. However, since the decision problem differs across the specific subgroups due to the different licensed dosages of SEC, it was considered more appropriate to model these subgroups separately.

Outcomes are expressed using quality adjusted life years (QALYs).[129] The QALY provides a summary measure combining estimates of the remaining length of life (life-years) and its associated quality. QALYs are derived from health related utilities by multiplying a utility value (quality of life) by the time spent with this utility (length of life). Utility values are generated from the main clinical outcomes of the disease, HAQ reflecting the arthritis component and PASI representing the psoriasis element (see Section 7.2.8). These clinical scores (HAQ = 0 to 3 and PASI = 0 to 72) represent the health states of the model and are also associated with healthcare resource use and costs (see Section 7.2.9.5).

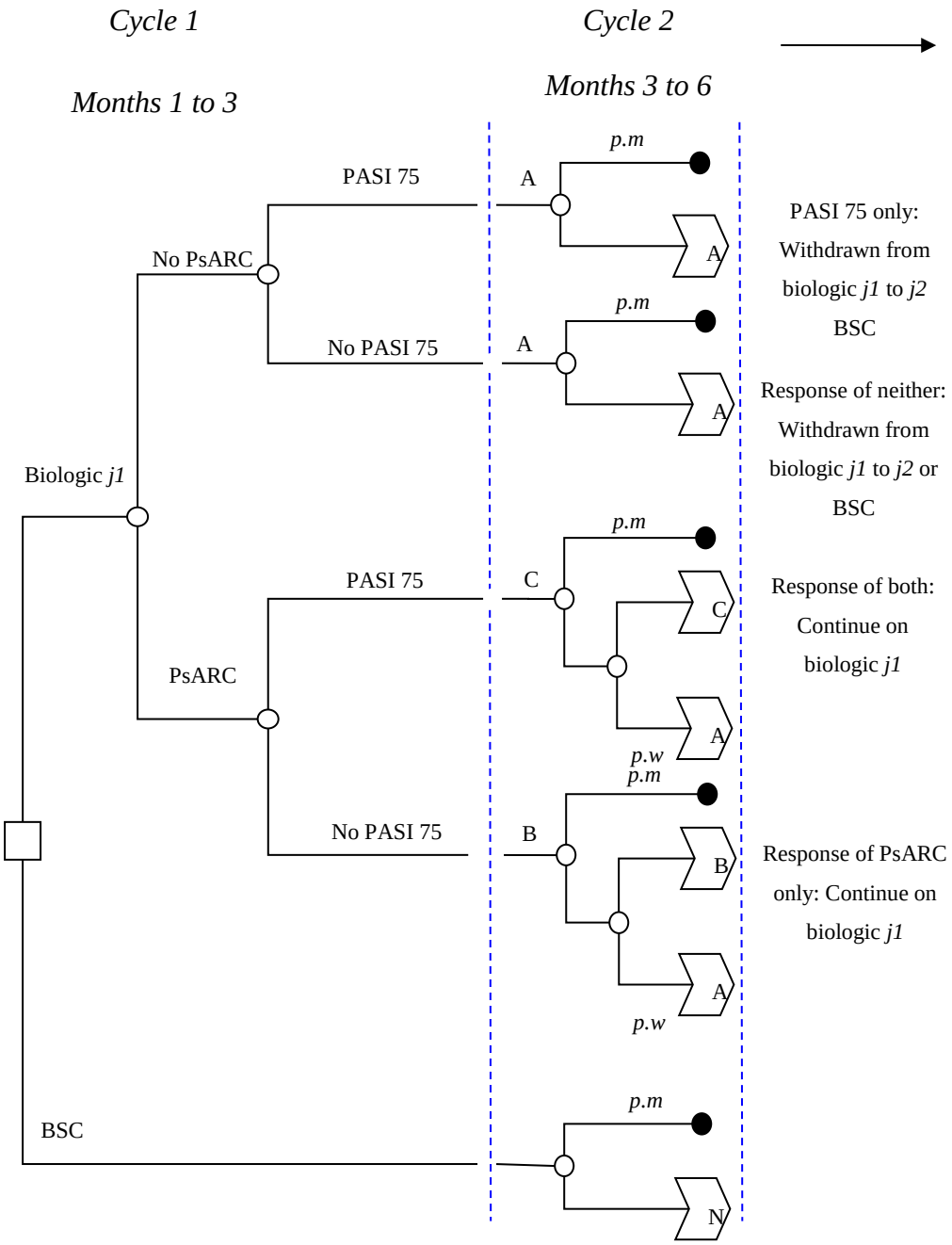
The parameters of the model were obtained from published literature, data reported in the company submissions and the results of the evidence synthesis in Section 5. The model adopts an NHS & PSS perspective. A price year of 2016 is assumed and a 3.5% annual discount rate is applied to costs and QALYs.[119]

7.2.2 Model structure and assumptions

Figure 15 illustrates the model structure. The structure remains largely unchanged since the previous York model (see Figure 8). However, in the updated York model, patients who withdraw from an initial treatment during cycle 1 due to a lack of response or adverse events (or later cycles for patients who initially respond) are assumed eligible to receive further treatments prior to moving to BSC. The subsequent treatment lines are defined separately for each of the three subpopulations (see Section 7.2.4).

Patients enter the model and receive one of the treatments or BSC, relevant to each particular subgroup. Patients remain on treatment for three months (13 weeks), after which if they respond, defined using PsARC criteria, they continue on the treatment; otherwise they move to BSC or another biologic treatment, if the sequence allows.

Figure 15 Overview of the model structure



Key: A – Withdrawn from biologic *j1* to *j2* or BSC. B – Continue on biologic *j1* with response of arthritis but not of psoriasis. C – Continue on biologic *j* with response of both arthritis and psoriasis. N – No treatment.

P.m – Probability of mortality (any cause).

P.w – Probability of withdrawal from biologic after first 3 months.

PsARC response data reported in the clinical trials (see Section 4), dichotomise patients into two groups: responders and non-responders (due to lack of efficacy or adverse events). In accordance with current BSR guidelines (and to ensure consistency with previous NICE TAs), only PsARC response is used to determine continuation on treatment. PsARC responders/ non responders are further stratified according to PASI response status, to provide a more granular assessment of utilities and costs. PsARC and PsARC responses are assumed to be correlated. For consistency, the same correlation co-efficient (0.4) applied in the previous York model in assumed. This value is also assumed to apply across all subpopulations, subgroups and individual treatments.

PASI changes observed in the clinical trials are categorised according to the proportion of patients that achieve at least 50%, 75% and 90% improvement in their baseline PASI (PASI50, PASI75 and PASI90 respectively). The calculation of the expected improvement in PASI for PASI 75 responders and non-responders is equivalent to the approach used in the previous York model.[94] That is, the new model also assumes that patients who achieve a PASI 75 response will gain at least a 75% improvement in psoriasis compared with baseline PASI, with some achieving a 90% improvement. Similarly patients who do not achieve a PASI 75 response may achieve PASI 50.

Functional capability, in terms of the arthritis component of the disease, is measured using HAQ. A relationship between PsARC response and HAQ score is explicitly considered in the current model. The change in baseline HAQ score is assumed to be conditional on PsARC response status. To ensure that the treatment effect is reproducible in the clinical practice, an adjustment for the placebo or expectation effect is applied within the new model. This adjustment follows the same methods employed in the previous York model.

An individual's HAQ and PASI score determine health state costs (in addition to treatment related costs) and QALYs; hence the model tracks these clinical scores over time. The new model employs "tunnel" states[130] to reflect how long patients stay in a particular health state (HAQ and PASI score) and when they move (switch to another treatment) (see Section 7.2.4). The ability to build multidimensional arrays, facilitated through the use of R, enables this functionality and the inclusion of subsequent lines of treatments, either after the initial response period or during the longer-term period.

After the treatment response period, responders are subject to an ongoing risk of withdrawal from treatment due to lack of efficacy or the presence of adverse events (modelled together as an overall risk of withdrawal). HAQ and PASI scores again change according to the second line treatment received and associated response status. It is assumed that PsARC responders continuing on treatment after the initial 3 month response period maintain their improvement in HAQ and PASI scores until subsequent withdrawal (i.e. no progression in HAQ and PASI scores). Once patients withdraw from

treatment to BSC, or to another biologic treatment, their HAQ and PASI scores rebound to their baseline values (see Section 7.2.5).

A summary of data inputs used in the model is given in Table 78. These are described in detail in the relevant sections that follow. The effectiveness data utilised in the model is shown separately in Table 79 in Section 7.2.6. The variable names in both tables follow those used in the R code, reported in Appendix 12.8.

Table 78 Summary of data inputs for the York model

Description	Variable name	Mean	SE	Source / appendix
Gender male =1, female = 0	Male	1		
Baseline HAQ	HAQ0	1.22		Mean of RCTs (Section 4)
Baseline age	Age	47		Mean of RCTs (Section 4)
Model time horizon cycles	num_cycles	160		Clinical opinion
Cycle length, year	Cl	0.25		
Discount rate (per year)	r	0.035		UK treasury
Utility function intercept	h0	0.897	0.006	Rodgers et al
Change in utility for 1 unit change in HAQ	h1	-0.298	0.006	
Change in utility for 1 unit change in PASI	h2	-0.004	0.0003	
Interaction term HAQ PASI	h3	0	10xE-5	
Change in HAQ while on treatment per 3 month period	HAQ1.d	0		Rodgers et al
Change in HAQ while not on treatment per 3 month period	HAQ1.w	0.018	0.007	Rodgers et al
Rebound in HAQ upon withdrawal (compared to HAQ at baseline) (Zero means 'rebound equal to initial gain')	loss.w	0		Assumption
Intercept of regression of log-mortality versus age in men	ln.R.g.m	-10.25	0.046	Gompertz parameters parameterising life table data for England & Wales
Intercept of regression of log-mortality versus age in women	ln.R.g.f	-11.10	0.046	
Change in log-mortality with additional year of age in men over 40 years	a.g.m	0.094	0.0006	
Change in log-mortality with additional year of age in women over 40 years	a.g.f	0.101	0.0006	
Standardised mortality ratio for PsA vs general population	SMRmen SMRwomen	1.36		Ali et al (2007)
Log withdrawal rate from biologics per year	ln.long.yr	-1.823	0.2044	Rodgers et al
Correlation between PASI 75 and PsARC	rho.new	0.4	0.1	ADEPT trial

7.2.3 Patients characteristics

As discussed in Section 7.2.1, the NICE scope for this appraisal specified three specific subpopulations of interest, reflecting the various stages of the treatment pathway for adult PsA. These three subpopulations are subsequently referred to as:

- Subpopulation 1: Biologic naïve, one previous cDMARD
- Subpopulation 2: Biologic naïve, ≥ two previous cDMARDs
- Subpopulation 3: Biologic experienced

Within subpopulation 3, the availability of evidence relating to CZP, necessitates the specification of a further scenario analysis to address the subgroup of patients who have previously responded to biologic treatment (primary responders), but who have subsequently withdrawn due to loss of efficacy or an adverse event.

In addition, in the NICE scope for this appraisal, a further population (subpopulation 4) contraindicated to TNF-alpha inhibitors (including ETN, ADA, INF and GOL) was also considered for SEC. CZP was not considered within the contraindicated population on the basis that patients contraindicated to other TNF-alpha inhibitors would likely also be contraindicated to CZP (a new TNF-alpha inhibitor).

In the updated York model, separate versions of the model are specified representing each of the three main subpopulations. In the base case of each of these models, the baseline age is assumed to be 47 and mean baseline HAQ is 1.22. These values represent the average baseline characteristics from the included trials (see Section 4). Baseline weight is required for administration of INF, however not all trials report these values. Here the weight distribution reported in the RAPID-PsA trials (see Section 7.2.9.1) is used.

As discussed in Section 6, it is also important to consider the impact of differences in baseline characteristics, in terms of HAQ and particularly PASI scores, and the impact that these differences have on cost-effectiveness and the choice of optimal treatment. This is a particular issue in terms of the severity of concomitant psoriasis, as SEC 300mg, as opposed to the standard dose of SEC 150mg is approved in patients with more severe psoriasis. To explore the impact of severity of the psoriasis component of the disease on cost-effectiveness, separate analyses are presented according to three concomitant psoriasis subgroups. Clinical opinion suggests that about 50% of patients that receive biologic treatment, have mild or minimal concomitant psoriasis (less than 3% body surface area (BSA) or a PASI score of less than 2.5), 25% have mild-to-moderate concomitant psoriasis (a baseline PASI score between 2.5 and 10), and 25% have moderate-to-severe concomitant psoriasis (a PASI

score greater than 10) [122]. These definitions have been used as the basis for the three concomitant psoriasis subgroups formally considered here:

- no concomitant psoriasis, with a baseline PASI score of 0);
- mild to moderate concomitant psoriasis, with a baseline PASI score of 7.3 (the same value used in the previous York model)
- moderate to severe concomitant psoriasis, with a baseline PASI score of 12.5 (the same value used as part of a separate sensitivity analysis presented in the previous York model).

In the absence of effectiveness data reported for these subgroups, an assumption is made that treatments are similarly effective (in relative terms) for each subgroup within the separate subpopulations. Hence, the differences in cost-effectiveness for these subgroups and driven entirely by the different baseline PASI scores and the subsequent impact on costs and outcomes of these differences.

Baseline HAQ scores are assumed the same across the separate subpopulations and PASI subgroups. Differences in baseline HAQ scores were considered in a separate sensitivity analysis based on estimates reported in the UCB submission.

7.2.4 Choice of intervention and comparators

- In subpopulation 1, only SEC, CZP and BSC are included in accordance with the NICE scope. Based on the license of SEC, SEC 150mg is included for the no concomitant PASI and mild to moderate PASI subgroups in the naïve populations and SEC 300mg for the severe psoriasis subgroup.
- In subpopulation 2, SEC, CZP and other TNF-alpha inhibitors (ETN, INF, ADA and GOL) are considered to be relevant treatment alternatives in accordance with the NICE scope. Although BSC is not formally stated to be a relevant comparator in the NICE scope, it is included within the model as a separate comparator this subpopulation to assist in subsequent validation. That is, the inclusion of BSC enables an assessment of cross-validity compared to previously published studies for the broader set of comparators (ETN, INF, ADA and GOL). Again, in accordance with the license of SEC, SEC 150mg is evaluated for the no concomitant PASI and mild to moderate PASI subgroups in the naïve populations and SEC 300mg for the severe psoriasis subgroup.
- In subpopulation 3, SEC 300mg, CZP, UST and BSC are regarded as relevant treatment alternatives in accordance with the NICE scope. As previously stated, since the data available for CZP only informs a subgroup of subpopulation 3, a separate analysis is conducted for CZP compared to BSC (see Section 7.2.3).

- In the additional contraindicated subpopulation (subpopulation 4), SEC, UST and BSC are regarded as relevant treatment alternatives. An assumption is made for this subpopulation that patients contraindicated to TNF alpha inhibitors are biologic naïve and hence the effectiveness data is derived from this population. In reality it is recognised that contraindications (e.g. infection, TB activation) after a TNF alpha inhibitor has been tried. However, for simplicity this analysis assumes patients are biologic naïve. Hence, in accordance with the license of SEC, SEC 150mg is evaluated for the no concomitant PASI and mild to moderate PASI subgroups in the naïve populations and SEC 300mg for the severe psoriasis subgroup.

In accordance with the NICE scope for this appraisal, apremilast was not included as a comparator in any of the subpopulations, as at the time this report was completed it had not been approved for use in adult PsA by NICE.

A key element of updating the previous York economic model is the formal incorporation of subsequent lines of therapy assumed within the base case. Specifically, the updated model allows for patients to move (switch) to a second treatment rather than BSC, due to primary non-response or secondary failure of treatment. The model also allows third and fourth line treatments. This functionality is enabled in the R by including tunnel states to track the HAQ and PASI scores of patients who switch therapy. Tunnel states are generated for every cycle in the model (160 cycles). Further tunnel states are generated within this structure where patients can switch to a 3rd and 4th treatment. This significantly increases the size of the Markov structure compared to the previous York model.

The length of the treatment sequence depends on the subpopulation: subpopulation 1 (biologic naïve one previous cDMARD) are eligible to receive three lines of treatment, before moving to BSC; subpopulation 2 (biologic naïve ≥ 2 previous cDMARDs) are eligible to receive two lines of treatment, before moving to BSC; and subpopulation 3 (biologic experienced) are eligible to receive one treatment, before moving to BSC. Subpopulation 4 is assumed to be equivalent to subpopulation 3 in terms of sequencing, the only difference being the use of SEC 150mg as opposed to SEC 300mg

The sequences of treatments are shown in Figure 16, Figure 17 and Figure 18 for the main subpopulations 1, 2 and 3 respectively. Only the biologic naïve populations are eligible to receive further active treatments once they have failed on their initial treatment.

- In subpopulation 1, patients may be eligible to receive further biologics. ETN is assumed to be the next biologic treatment as part of the overall sequence, on the basis that is it the lowest cost currently approved biologic and because it was consistently reported to be more cost effective

than other TNFs in previously published studies. Following failure of ETN, patients are assumed to receive UST before moving onto BSC.

- In subpopulation 2, patients are assumed to subsequently receive UST (approved in the biologic experienced population) before moving onto BSC.
- Patients in subpopulation 3 are assumed to move to BSC after failure of SEC 300mg, UST or CZP (secondary failures only).

Figure 16 Treatment sequences in subpopulation 1

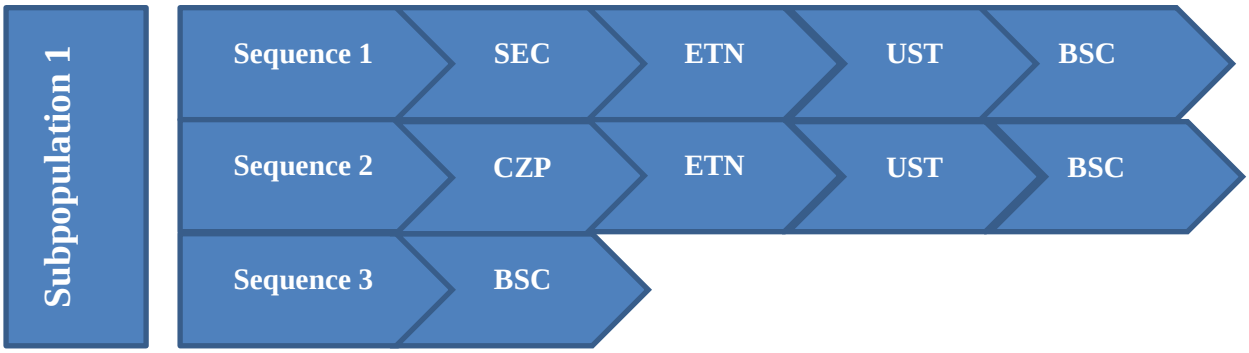


Figure 17 Treatment sequences in subpopulation 2

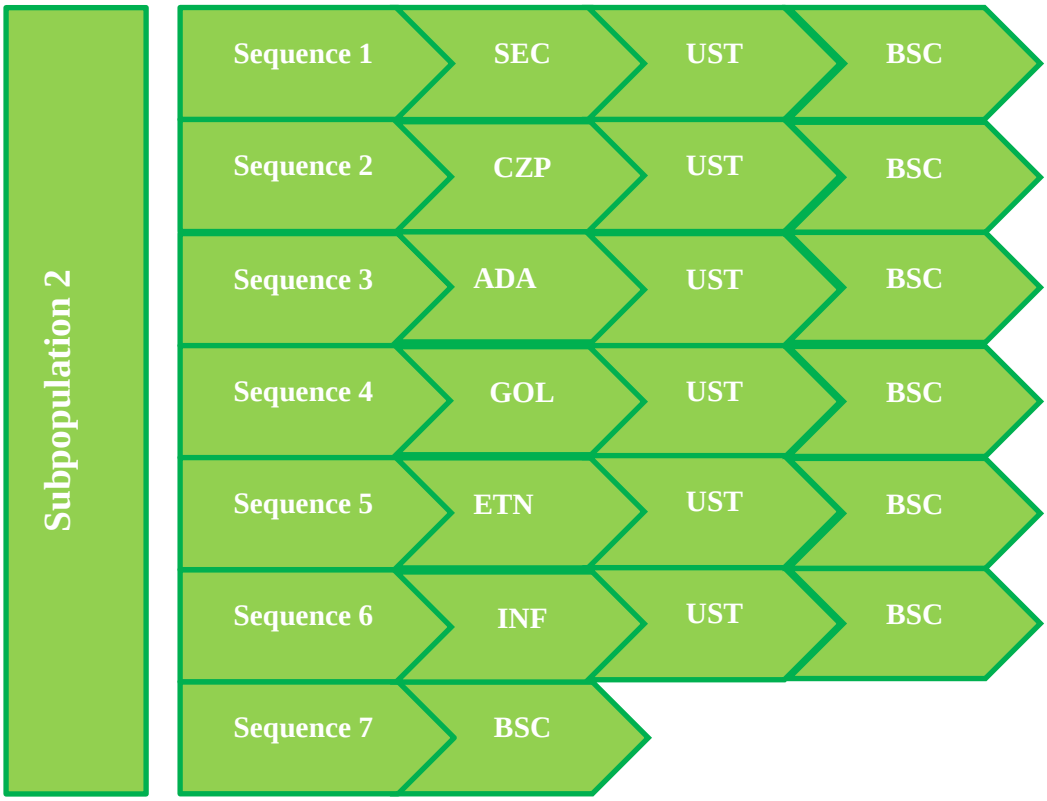
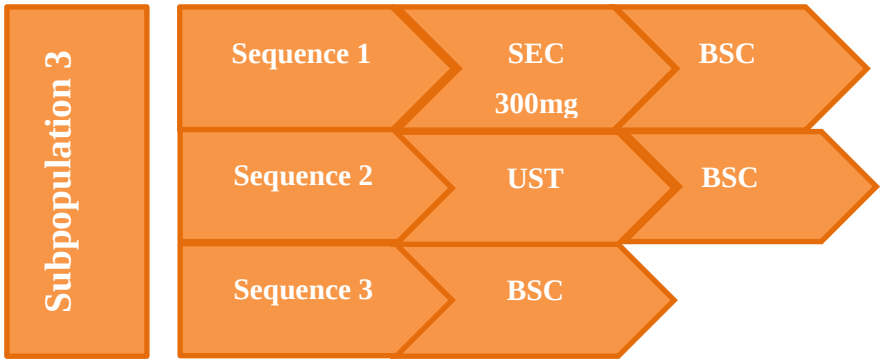


Figure 18 Treatment sequences in subpopulation 3



ETN and INF are available as the originator products or biosimilars. The originator product of ETN is Enbrel and the biosimilar version is Benepali (SB4, Biogen Idec Limited). The originator product of INF is Remicade (Janssen/MSD) and the biosmilar versions are Inflextra (Hospira), Remsima (Napp Pharmaceuticals) and SB2 (Samsung Bioepsis Co). In each of the base case scenarios, the list prices for the originator products of ETN and INF are assumed. A separate analysis is presented using the prices of the biosimilar products (see Appendix 12.12). The biosimilar analysis is restricted to subpopulation 2. In this separate analysis the biosimilars versions are assumed to be equivalent to the originator products in terms of effectiveness.

7.2.5 Withdrawal from treatment and the natural history of PsA

As the psoriasis element of PsA is not progressive, it is assumed that PASI score does not increase over time for patients receiving BSC. The arthritis element of PsA is assumed to be progressive, consistent with the clinical evidence (see Section 4). Therefore, for patients not receiving biologic therapies, HAQ score is assumed to worsen over time reflecting the decrease in functional capability as the arthritis component of the disease progresses. In the absence of a more appropriate alternative identified in the review of long-term open label (Section 4.7.1) and registry data (Section 4.8), the rate determined in the previous York model, derived from the NOAR register, was utilised in the updated York model. This rate of 0.018 per 3-month cycle is assumed to be constant over time. Figure 12, in Section 6.2.2.6, shows the trajectory of HAQ over time, for patients receiving BSC alone (in red).

For PsARC responders, there is a risk of withdrawal following the first cycle of the model (3 months). This risk is due to adverse events and loss of efficacy. Based on the previous York model, this probability is estimated from a meta-analysis of registry data from several countries to be -1.823 (SE 0.2044) on the log scale, or *exp* $(-1.823 + 0.5*0.2044^2) = 0.165$ per year. This probability of withdrawal (0.165 per year) is assumed to be independent of HAQ and PASI score in the model, relevant for all comparators and is constant over time. Alternative scenarios were specified according to those reported in the company submissions (see Section 7.2.10).

Following withdrawal, the 'rebound' of HAQ and PASI is assumed to be equivalent to the gain. This assumption is consistent with the previous York model (see the green line in Figure 12, Section 6.2.2.6). The rebound effect is assumed to happen immediately following withdrawal.

7.2.6 Sources of effectiveness data

The effectiveness data applied in the economic model is derived from the NMA, reported separately in Section 5. Three outcomes were included in the NMA to inform the economic model: 1) PsARC response, 2) change in HAQ score conditional on PsARC response and 3) PASI 50, 75 and 90 responses.

The NMA implemented separate models for the pooling of treatment effects and placebo responses. A number of alternative models were implemented to explore the possibility of placebo response determining the effectiveness of alternative treatments, and also whether there was similarity between treatment effects for treatments of the same class. These are discussed in detail in Section 5. The following sections specify the approaches used in the economic model for each of the three outcomes.

7.2.6.1 PsARC response

Section 5 details the data available for PsARC response, for each of the comparators. The NMA implemented seven alternative models for PsARC response in the naïve populations (see Table 41). Due to data limitations, these could only be specified for all biologic naïve patients (i.e. not separately for subpopulations 1and 2). Of these seven models, two were considered to be the preferred models on the basis of model fit, goodness of fit statistics and clinical plausibility. These are:

1) Model A1: No baseline adjustment. Assumes that the treatments are independent (fixed effect), and therefore utilises the baseline and treatment effects as observed in the trial.
2) Model D2: A meta-regression on baseline risk (placebo response). Treatments within a class have similar (exchangeable) effectiveness and depend on the effect of the placebo arm. Shrunken estimates are reported to account for the differences between treatments. The Genovese 2007 and Mease 2000 trials are included.

Results for the two preferred PsARC models, in the naïve population, are presented in Table 43. These show the median probabilities and ORs.

For the biologic experienced population (subpopulation 3), it was not possible to conduct a meta-regression due to data limitations; therefore only independent analysis estimates are available for this subpopulation (model A1). As discussed in Section 7.2.3, the data from the RAPID-PsA trial (CZP) were not included in the analysis. Results for the biologic experienced population are presented in Table 45. These show the median probabilities and ORs.

7.2.6.2 HAQ conditional on PsARC response

Given HAQ scores are modelled conditional on PsARC response, modelling an interaction effect between baseline and treatment effect was deemed to be less relevant, and a meta-regression model was not implemented on HAQ (see 5.3). Instead three models are implemented in the biologic naïve populations (see 5.3.1), two of which model a class effect for treatments. Again, due to data limitations, these could only be specified for all biologic naïve patients. Of these three models, two were considered to be the preferred models on the basis of model fit, goodness of fit statistics and clinical plausibility. These are:

1) Model E1: No baseline adjustment. Assumes that the treatments are independent (fixed effect), and therefore utilises the baseline and treatment effects as observed in the trial.
2) Model E2: No baseline adjustment. A class effect is applied comprising three groups: anti-TNFs, ILs, and apremilast. Treatments are similar within class (exchangeable) and fixed effect across studies.

Results for the two preferred HAQ change models, in the naïve population, are presented in Table 47. These show the absolute median changes (with a more negative number representing a larger HAQ improvement).

For the biologic experienced population (subpopulation 3), it was not possible to determine a class effect; therefore only independent analysis estimates are available for this subpopulation (model E1). As discussed in Section 5.3, the data from the RAPID-PsA trial (CZP) were not included in the analysis. Results for the biologic experienced population are presented in Table 49. These show the absolute median/mean HAQ changes.

7.2.6.3 PASI 50, 75 and 90 responses

Section 5 details the data available for PASI response, for each of the comparators. The NMA 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. For the economic model this was used to determine the probabilities of achieving PASI 50, 75 and 90.

The NMA implemented three alternative models for PASI response in the naïve populations (see Table 51). Due to data limitations, these could only be specified for all biologic naïve patients. Of these three models, two were considered to be the preferred models on the basis of model fit, goodness of fit statistics and clinical plausibility. These are:

1) Model F1: No baseline adjustment. Assumes that treatments are independent and fixed effect on cut-offs/ thresholds.

2) Model G2: Common interaction term with baseline effect. Assumes treatments are independent, but treatment effects are adjusted with the trial specific baseline effects assuming a common interaction term.

Results for the two preferred PASI response models, in the naïve population, are presented in Table 53. These show the median probabilities for PASI 50, 75 and 90.

For the biologic experienced population (subpopulation 3), it was not possible to determine a class effect; therefore only independent analysis estimates are available for this subpopulation (model F1). As discussed in Section 5.4, the data from the RAPID-PsA trial (CZP) were not included in the analysis. Results for the biologic experienced population are presented in Table 55. These show the median/mean probabilities and ORs.

7.2.6.4 Combinations of evidence synthesis estimates utilised in the economic model

As discussed in the sections above, results are available for two alternative evidence synthesis models, for each of the three outcomes (PsARC response, change in HAQ score conditional on PsARC response and PASI 50, 75 and 90 responses). The economic model utilises two combinations of these results for PsARC response, HAQ conditional on PsARC response and PASI response. These are:

- Independent analysis: PsARC response (Model A1), HAQ conditional on PsARC response (Model E1), and PASI response (Model F1)
- Meta-regression: PsARC response (Model D2), HAQ conditional on PsARC response (Model E2), and PASI response (Model G2)

Table 79 presents the effectiveness data used in the updated York model. The clinical effectiveness results reported in Section 5 are, on the whole, reported as medians. The economic model instead utilises the means from the NMA. The means represent the most appropriate values for the economic model in order to inform a decision regarding the expected cost-effectiveness of competing treatments.

Table 79 Effectiveness data utilised in the economic model

Placebo responses for biologic naïve population: Treatment effects from independent analysis			
Probability of PsARC response	p.psarc.plac2	0.3073	Section 4
Change in HAQ given a PsARC response	HAQ.resp.plac2	-0.2629	
Probability of PASI 50 response	p.pasi.50.plac2	0.153	
Probability of PASI 75 response	p.pasi.75.plac2	0.054	
Probability of PASI 90 response	p.pasi.90.plac2	0.015	
Placebo responses for biologic naïve population: Treatment effects from meta-regression			
Probability of PsARC response	p.psarc.plac2	0.3073	Section 4

Change in HAQ given a PsARC response	HAQ.resp.plac2	-0.2579	
Probability of PASI 50 response	p.pasi.50.plac2	0.155	
Probability of PASI 75 response	p.pasi.75.plac2	0.055	
Probability of PASI 90 response	p.pasi.90.plac2	0.016	
Placebo responses for biologic experienced population: Treatment effects from independent analysis			
Probability of PsARC response	p.psarc.plac3	0.268	Section 4
Change in HAQ given a PsARC response	HAQ.resp.plac3	-0.134	
Probability of PASI 50 response	p.pasi.50.plac3	0.103	
Probability of PASI 75 response	p.pasi.75.plac3	0.012	
Probability of PASI 90 response	p.pasi.90.plac3	0.004	

Treatments' input data for biologic naïve population: Treatment effects from independent analysis

Description	Variable name	ETN	INF	ADA	GOL	CZP	SEC 150mg	SEC 300mg
Probability of PsARC response	psarc2	0.77	0.8114	0.6421	0.8168	0.5697	0.5849	0.5870
Change in HAQ in first 3 months given no PsARC response	HAQ.noresp2	-0.20	-0.1966	-0.1344	-0.0634	-0.0683	-0.0825	-0.0535
Change in HAQ in first 3 months given PsARC response	HAQ.resp2	-0.6407	-0.66	-0.4889	-0.4385	-0.4284	-0.3947	-0.5472
Probability of PASI 50 response	p.pasi.50_2	0.411	0.918	0.675	0.732	0.441	0.801	0.819
Probability of PASI 75 response	pasi75_2	0.209	0.789	0.448	0.514	0.231	0.603	0.627
Probability of PASI 90 response	p.pasi.90_2	0.084	0.593	0.242	0.297	0.097	0.380	0.405

Treatments' input data for biologic naïve population: Treatment effects from meta-regression

Description	Variable name	ETN	INF	ADA	GOL	CZP	SEC 150mg	SEC 300mg
Probability of PsARC response	psarc2	0.74	0.74	0.60	0.71	0.71	0.73	0.73
Change in HAQ in first 3 months given no PsARC response	HAQ.noresp2	-0.15	-0.15	-0.13	-0.11	-0.12	-0.09	-0.08
Change in HAQ in first 3 months given PsARC response	HAQ.resp2	-0.59	-0.60	-0.50	-0.48	-0.47	-0.43	-0.51
Probability of PASI 50 response	p.pasi.50_2	0.43	0.77	0.66	0.54	0.66	0.77	0.79
Probability of PASI 75 response	pasi75_2	0.24	0.57	0.43	0.32	0.44	0.57	0.60
Probability of PASI 90 response	p.pasi.90_2	0.11	0.36	0.23	0.16	0.24	0.36	0.39

Treatments' input data for biologic experienced population: Treatment effects from independent analysis

Description	Variable name	CZP	SEC 300MG	UST
Probability of PsARC response	Psarc3	[redacted]	0.674	0.562
Change in HAQ in first 3 months given no PsARC response	HAQ.noresp3	[redacted]	-0.4295	0.0015
Change in HAQ in first 3 months given PsARC response	HAQ.resp3	[redacted]	-0.3838	-0.32
Probability of PASI 50 response	p.pasi.50_3	0.56	0.875	0.628
Probability of PASI 75	pasi75_3	0.41	0.598	0.279
Probability of PASI 90 response	p.pasi.90_3	0.19	0.365	0.12

7.2.6.5 Correlation between PsARC and PASI responses

Although treatment continuation is determined by PsARC response, the model needs to consider the proportion of those who achieve PASI75 together with PsARC, as this cohort has different PASI score, hence incur different costs and QALYs (see Section 7.2.9.5). Based on previous published models and the company submissions, a positive correlation between the two main responses in the model, PsARC and PASI75, is included in the base case model. The correlation co-efficient value used in the model is (0.4), taken from the analysis conducted as part of the previous York model.

Table 80 shows the effect of treatment, in terms of PsARC and PASI75 response probabilities, utilising the results from the evidence synthesis model performing independent analysis. The positive correlation columns account for the correlation between these two outcomes to generate the proportion of patients achieving joint only and joint plus skin improvement together. The no correlation columns assume independence between the two responses (no correlation co-efficient applied). The no correlation columns are only shown for illustration here, as these values are not employed in the updated York model. Assuming a positive correlation between PsARC and PASI (the assumption in the updated York model), ETN has the highest probability of a joint only response and INF the lowest probability of a joint only response. For both a joint and skin response, INF has the highest probability and CZP the lowest probability.

Table 80 Probabilities of PsARC and PASI 75 responses at 3 months: Independent analysis

Treatment	Evidence synthesis		Positive correlation		No Correlation	
	PsARC	PASI75	Joints only	Joints & skin	Joints only	Joints & skin
ETN	0.770	0.227	0.525	0.245	0.595	0.175
INF	0.811	0.785	0.110	0.701	0.175	0.637
ADA	0.642	0.449	0.259	0.384	0.354	0.288
GOL	0.817	0.514	0.320	0.497	0.397	0.420
CZP	0.570	0.236	0.351	0.218	0.435	0.134
SEC 150MG	0.585	0.600	0.138	0.447	0.234	0.351
SEC 300MG	0.587	0.623	0.126	0.461	0.221	0.366
UST*	0.486	0.319	0.238	0.248	0.331	0.155

* Values for UST refer to 6 months

Table 81 also shows the effect of treatment, in terms of PsARC and PASI75 response probabilities but instead utilises the evidence synthesis outcomes based on meta-regression. There are some differences between the independent probabilities and the meta-regression probabilities, reflecting the adjustments made to the relative effectiveness of treatments using class effect shrunken estimates in the meta-regression, as opposed to relative treatments effects as observed in the trials in the independent analysis (see Section 5). Assuming a positive correlation between PsARC and PASI, again ETN has the highest probability of a joint only response; however SEC 300mg has the lowest probability of a joint only response. For both a joint and skin response, SEC 300mg has the highest probability and ETN the lowest probability.

Table 81 Probabilities of PsARC and PASI 75 responses at 3 months: Meta-regression, shrunken estimates

Treatment	The evidence synthesis outcome		Positive correlation		No Correlation	
	PsARC	PASI75	Joints only	Joints & skin	Joints only	Joints & skin
ETN	0.740	0.238	0.489	0.251	0.564	0.176
INF	0.740	0.573	0.229	0.511	0.316	0.424
ADA	0.594	0.430	0.241	0.353	0.338	0.256
GOL	0.706	0.323	0.393	0.313	0.478	0.228
CZP	0.710	0.436	0.310	0.399	0.400	0.309
SEC 150mg	0.728	0.575	0.222	0.507	0.309	0.419
SEC 300mg	0.730	0.600	0.205	0.525	0.292	0.438
UST*	0.589	0.401	0.256	0.333	0.353	0.237

* Values for UST refer to 6 months

7.2.7 Mortality

All-cause mortality is incorporated by applying a risk of death during each model cycle. The mortality risk is not assumed to be structurally related to response or treatments received. Instead a common excess mortality risk is assumed for all PsA patients compared to general population mortality risks. The general population mortality risk is obtained from life tables for England and Wales and is specified separately for males and females, although the model averages across these as it does not generate results separately for males and females. Similar to the previous York model, a Gompertz function was fitted to life table data (see Table 78). The excess mortality risk associated with PSA is modelled assuming a hazard ratio of 1.36[14] compared to the general population. This value is based on an updated analysis of the same source used in the previous York model and hence employs a different estimate than previously assumed.

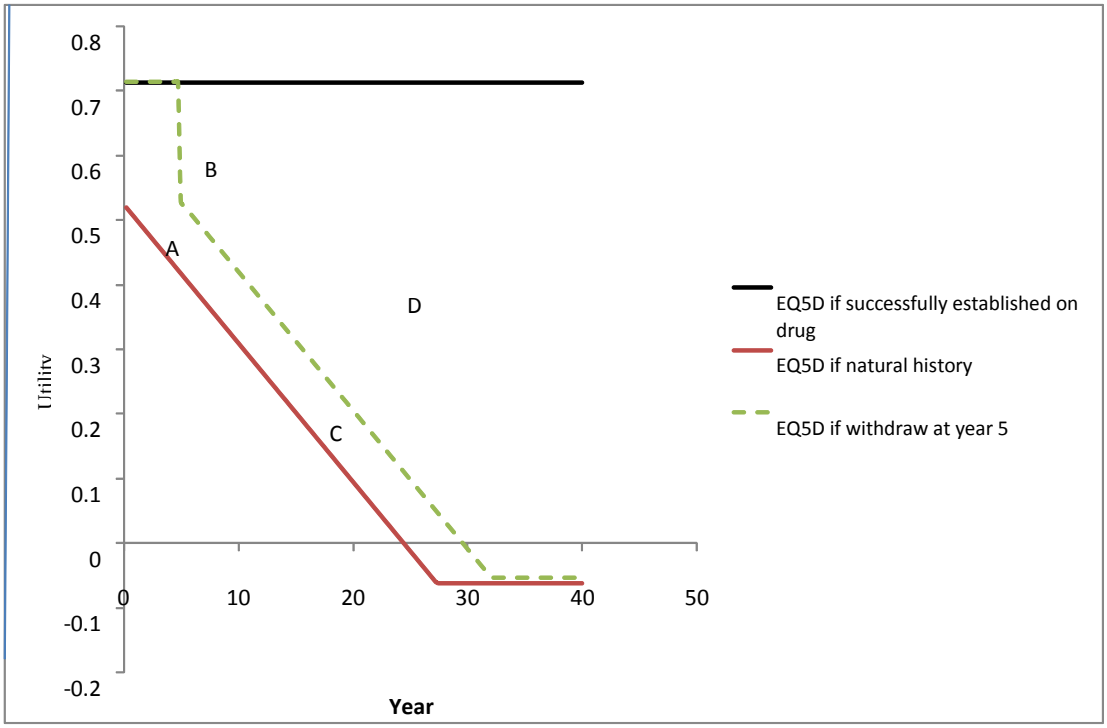
7.2.8 Sources of utility data

Health utility is measured as a function of HAQ and PASI. A separate search was undertaken to identify alternative utility algorithms (see Appendix 12.9). In the absence of finding any published sources reporting alternative algorithms to the one applied in the previous York model, the same algorithm was used. This algorithm is based on a linear function relating the expected utility to HAQ and PASI. The same utility function is applied to all subpopulations, subgroups and treatments.

Figure 19 shows the trajectories of utility according to a patients HAQ score over time, for BSC, remaining on treatment and treatment withdrawal at 5 years. The equation below shows this relationship

$$Expected\ Utility = 0.897 - 0.298 * HAQ - 0.004 * PASI$$

Figure 19 Utility corresponding to alternative HAQ trajectories



The utility function provided by one of the companies (Novartis) includes coefficients, namely baseline EQ-5D score, which cannot be utilised easily in the current model structure. UCB used a similar function to the previous York model but with smaller co-efficient for PASI (0.001 compared to 0.004). Given that this algorithm is very similar to the previous York model, separate scenarios, using alternative utility algorithms are not considered.

7.2.9 Sources of resource utilisation and costs data

Costs in the model are determined from the treatment costs (acquisition, administration and monitoring) and changes in health service utilisation driven by disease status (HAQ and PASI scores). The resource use assumptions and costs applied to each of these categories are discussed in the sections below. Further searches were conducted to identify alternative sources of health state costs. The searches and results are described in Appendix 12.10.

7.2.9.1 Treatment costs

Table 82 shows the treatment related costs applied in the updated York model. These costs are based on the list prices for SEC and CZP (biosimilar costs and PAS prices are used in separate analysis). Costs are presented for the first and subsequent cycles and in terms of annual costs.

Table 82 Intervention related costs applied in the updated York model

	ETN	INF	ADA	GOL	CZP	SEC 150mg	SEC 300mg	UST
1st cycle	£2,541	£7,887	£2,506	£2,498	£3,784	£4,475	£8,741	£4,503
Subsequent cycles	£2,336	£3,672	£2,301	£2,293	£2,149	£1,832	£3,661	£2,151
Annual cost	£9549	£18902	£9409	£9377	£10232	£9972	£19722	£10957

Each of the existing models (published and company submissions) presents different resource use assumptions and unit costs, which are used to cost drug treatment, administration and monitoring of patients. Different assumptions have been used regarding the dosing of drugs and resource use for administration and monitoring (see Sections 6.2.2.9 and 6.2.3.6). The current York model sought to specify the most appropriate resource use associated with drug acquisition, administration and monitoring patients for each of the treatment options.

The resource use items from the previous York model[94]have been updated for ETN, INF and ADA, reflecting evidence from a recent appraisal in ankylosing spondylosis.[98] The assumptions regarding resource use for GOL have been taken from the GOL STA[65] and the assumptions regarding the resource use for UST have been taken from the UST STA.[116] The resource use for SEC and CZP has been derived using the SPCs, MIMs, clinical advice and BSR guidelines. The treatments' dosing schedules were obtained from the summary product characteristics found on the Electronic Medicines Compendium website.

The dose for INF was determined by patients' weight, 5mg for each 1kg. These weights were derived using the weight distribution reported in the RAPID-PsA trials. All assumptions made regarding resource use have been validated with the clinical expert for this appraisal.

Table 83 summarises the drug acquisition, administration and monitoring costs used in the updated York model. Further details of these costs are given in the sections below.

Table 83 Summary of drug acquisition, administration and monitoring costs used in economic model

	1st cycle (13 weeks)				Subsequent cycles			
	Acquisition	**Administration**	**Monitoring**	**Total**	**Acquisition**	**Administration**	**Monitoring**	**Total**
ETN	£2,332	£43	£166	£2,541	£2,332	0	£4	£2,336
INF	£7,147	£574	£166	£7,887	£3,395	£273	£4	£3,672
ADA	£2,297	£43	£166	£2,506	£2,297	0	£4	£2,301
GOL	£2,289	£43	£166	£2,498	£2,289	0	£4	£2,293
CZP	£3,575	£43	£166	£3,784	£2,145	0	£4	£2,149
SEC 150mg	£4,266	£43	£166	£4,475	£1,828	0	£4	£1,832
SEC 300mg	£8,532	£43	£166	£8,741	£3,656	0	£4	£3,661
UST	£4,294	£43	£166	£4,503	£2,147	0	£4	£2,151

7.2.9.2 Drug acquisition

Table 84 shows the number of vials assumed for each treatment, during the first cycle (the loading phase) and subsequent cycles. In the loading phase, 400mg of CZP is given at weeks 0, 2 and 4. Subsequently 200mg is given every 2 weeks. Patients receive methotrexate (7.5mg) alongside CZP, in accordance with the license. For patients with mild-moderate psoriasis, the recommended dose of SEC is 150 mg, with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4. For patients with moderate-severe psoriasis, or those who are biologic experienced, the recommended dose is 300mg, with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

For the other treatments, the following assumptions were made:

- Six and a half vials of ADA are assumed given in every 3-month cycle. This does not represent vial sharing; instead the total yearly numbers of vials is equally divided by each 3 month (13 week) cycle.
- Twenty six vials of ETN are assumed given in the first cycle (two 25mg pre filled syringes, per week) followed by 26 vials for all subsequent cycles.
- GOL is given as a 50 mg dose once a month. In patients with a body weight of more than 100 kg, who do not achieve an adequate clinical response after 3 or 4 doses, the dose of GOL can be increased to 100 mg once a month. The company (Janssen Biotech, Inc) provide this double dose at the same price as the 50mg dose as part of an approved PAS scheme.

- UST is given as an initial dose of 45 mg, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg. Similarly the company (Janssen Biotech, Inc) offer this double dose at an equivalent price as part of an approved PAS scheme.

Table 84 Number of vials administered for each treatment

Treatments	First cycle (vials)	Subsequent cycles (vials)
ETN	26	26
INF	Weight based	Weighted based
ADA	6.5	6.5
GOL	3	3
CZP	10	6
SEC 150MG	7	3
SEC 300MG	7	3
UST	2	1

INF is given at 0, 2 and 6 weeks followed by every 8 weeks, with the number of vials determined by a patient's weight. Baseline weight is taken from the weight distribution reported in the RAPID-PsA trials. Table 85 shows the proportion of patients in each weight category in the RAPID-PsA trial and the number of INF vials required.

Table 85 Distribution of weights used to determined INF vials required

Patients weight (kg)	Vials required	Dose (mg)	Proportion of population
20	1	100	0.0003
40	2	200	0.0087
60	3	300	0.0878
80	4	400	0.3105
100	5	500	0.3898
120	6	600	0.1740
140	7	700	0.0273
160	8	800	0.0015

The drug acquisition costs used in the current York model are shown in Table 86. The acquisition costs of the drugs represent the list prices in the base case analysis. The list prices are taken from the BNF[131] and MIMS.[132] An analysis utilising non-list prices (biosimilar costs), for some of the comparators, is presented in Appendix 12.12. Biosimilar costs used are presented in Appendix 12.12. A separate analysis is also presented using the PAS prices for CZP and SEC as part of a separate and confidential Appendix.

A separate acquisition cost was not applied to BSC and therefore the cost of BSC is assumed to be entirely captured in terms of health state costs. These represent the full HAQ costs (without discounting the prescribing costs), and the uncontrolled psoriasis costs (see Section 7.2.9.5).

Table 86 Acquisition costs used in the updated York model

	£(2016)	Source
Treatments		
Infliximab (100mg vial): Inflextra/Remaima	419.62	MIMS
Etanercept (25mg syringe): Enbrel	89.50	MIMS
Adalimumab (40mg syringe): Humera	352.14	MIMS
Golimumab (50mg syringe): Simponi (100mg syringe)	762.97 1525.94	MIMS
Ustekinumab (45mg syringe) (90mg syringe)	2147 2147	MIMS
Secukinumab (150mg syringe)	609.39	MIMS
Certolizumab (200mg syringe)	357.5	MIMS
Methotrexate (7.5 mg)	0.30	BNF

7.2.9.3 Drug administration

For all treatments, other than INF, an administration cost was only applied on the first cycle, therefore assuming self-administration in the subsequent cycles. This was assigned a cost of a one hour nurse visit in a GP practice (£43) (PSSRU[133]). INF requires intravenous infusion and therefore the administration cost for INF, was assumed to represent the cost of delivering simple parental chemotherapy at first attendance (£159) (Reference costs 2015[133]). These costs are the same as those used in the UCB model. The administration costs assumed in the updated model are shown in Table 87.

Table 87 Administration costs used in the updated York model

Administration		
Method of administration	First cycle	Subsequent cycles
Subcutaneously	£43	-
Intravenously	£159	£159

7.2.9.4 Initiation and monitoring

A summary of the initiation and monitoring resource use assumptions is reported Table 88. The resource use assumptions for laboratory testing for biologic treatment initiation and monitoring have been sourced from the previous York model and updated using the Hospital & Community Health Services (HCHS) Pay & Prices index from the PSSRU.[133] These conform to guidelines from the British Society for Rheumatology (BSR) [121] for the use of biologics.

Table 88 Initiation and monitoring resource use and costs

	Initiation and monitoring costs		Frequency	
Item	**First cycle**	**Subsequent cycles**	**First cycle**	**Subsequent cycles**
Full blood count (FBC)	£6.18	£1.54	2	0.5
Erythrocyte sedimentation rate (ESR)	£6.11	£1.53	2	0.5
Liver function test (LFT)	£1.56	£0.39	2	0.5
Urea and Electrolytes (U&E)	£2.86	£0.72	2	0.5
Chest X-ray	£27.11	£0.00	1	0
Tuberculosis (TB) Heaf test	£9.03	£0.00	1	0
Antinuclear antibody (ANA)	£4.81	£0.00	1	0
Double-stranded (ds) DNA test	£4.81	£0.00	1	0
Specialist visit	£103.53	£0.00	1	0
Total	£166.01	£4.18		

PsA patients on biologic therapy are assumed to undertake a series of tests at treatment initiation and at 3 months when assessing initial treatment response (i.e. a Full Blood Count (FBC), Erythrocyte Sedimentation Rate (ESR), Liver Function Test (LFT), Urea and Electrolytes (U&E)). Additional testing is assumed to be conducted once during the initial period (i.e. chest X-Ray, Tuberculosis (TB) Heaf test, antinuclear antibody (ANA) and a double-stranded DNA test). Patients on biologics are also assumed to visit a specialist (rheumatologist) twice during the initial 3 month period (at treatment

initiation and when assessing response). The cost of a rheumatologist visit was only applied in the first cycle. The assumption that subsequent visit costs would be encapsulated within health state costs and has been applied in similar appraisals[98] and in the company models. The cost of a rheumatology visit was taken from the NHS Reference Costs 2014-2015.

7.2.9.5 Health state costs

In order to generate an estimate of the lifetime costs for each of the treatments, estimates of resource use and costs associated HAQ and PASI are required. As reported in Section 5, the previous York model used separate studies and assumptions to estimate HAQ and PASI related costs.

A search of the published literature was undertaken to identify alternative published evidence regarding the resource use and costs associated with the management of PsA in the UK (see Appendix 12.11).The only other alternative published source identified in the search which specifically reported estimates of costs according to HAQ and/or PASI was the study from Poole et al. [127] This study was used in the UCB submission and was previously described in Section 5.

The alternative approaches identified which could be used to estimate HAQ and PASI costs, represent an important area of remaining uncertainty. One potential advantage of the Poole study is that the estimates according to HAQ score are derived from a sample of PsA patients as opposed to from an RA sample. However, Poole et al noted important differences in their predictions with markedly higher costs predicted for equivalent HAQ scores for PsA patients compared to those previously reported for RA patients. While the authors of the Poole study stated that this could indicate important differences in the economic burden associated with PsA compared with RA, they also acknowledged that the differences might simply be attributed to differences in methods and/or the requirement to predict HAQ in the THIN data set using a separate regression model from the BSRBR. A number of further limitations were also noted in Poole et al, including: (i) the predicted HAQ did not cover the full range (0-3) and applying the GLM model to predict for the full range could result in substantial errors, particularly for the more severe event of the range; and (ii) PASI data were not available in either the BSBR or THIN data. These additional limitations are particular important in the context of the current model since HAQ predictions are required across the full range of HAQ scores and that separate PASI subgroups are modelled.

Having identified important differences in the predictions based on the separate sources and noting the potential limitations identified in the Poole et al study, the final HAQ costs were based on the same function used in the previous York model, with costs uprated to current prices. This assumption also ensures consistency across the separate NICE TAs. Despite some concerns with the Poole study, the fact that it provides the only source of costs specific to PsA make it potentially relevant for the

updated York model. The use of the Poole study is therefore explored as a separate scenario (see Section 7.2.10).

The costs according to HAQ scores address only the arthritis component of PsA, therefore additional costs were required to capture the psoriasis element of the disease. The current York model addresses three subgroups according to psoriasis severity (see Section 7.2.3). It was assumed patients without concomitant psoriasis would not incur additional psoriasis related costs. In the absence of identifying any other relevant UK costing studies to inform PASI estimates for the mild to moderate and moderate to severe PASI subgroups, the same sources and assumptions were made as the previous York model were assumed. Hence the costs assumed for treating mild-to-moderate psoriasis in patients who do not use biologics or who do not respond to biologics (PASI75) were based on NHS unit costs of phototherapy[134] and a UK RCT.[135] Similarly, for patients with moderate or severe psoriasis, costs were based on a Dutch RCT adjusted to UK price levels (Hartman et al[125]). Costs from the previous York model were uprated to the current price year.

The psoriasis related costs applied to PASI75 non responders and for patients not receiving biologics are shown in Table 89 for each of the psoriasis subgroups.

Table 89 Costs assigned for PASI75 non responders and patients not receiving biologics

Description	Without psoriasis	Mild to moderate	Moderate to severe
Baseline PASI	0.0	7.3	12.5
Costs of uncontrolled psoriasis (£)	0.0	223	638
Costs of controlled psoriasis (PASI75 response)	0.0	18	18

7.2.10 Scenario analyses

As described in Section 7.2.3, a further subgroup of subpopulation 3 was considered as part of a separate scenario analysis. This separate scenario is presented to reflect that the data reported for CZP in biologic experienced patients is only applicable to patients who initially responded to the previous biologic therapy (i.e. secondary failure of treatment) and hence is not directly comparable with the data for UST and SEC which includes primary and secondary treatment failures. This separate scenario includes only CZP and BSC. Other subgroups, in terms of extent of psoriasis (measured using PASI) are presented as part of the base case analysis.

In addition a number of scenarios are specified to explore the robustness of some of the assumptions made in the model, focusing on key areas where these deviate from assumptions made in the company submissions:

- Applying an alternative cost function from Poole, et al.[127]
- Alternative assumptions regarding withdrawals. Two scenarios were specified: 1) the withdrawal rate for SEC is assumed to be 50% of the base case value from year 2; and 2) all treatments are associated with a withdrawal rate equivalent to 50% of the base case values from year 5. The first withdrawal scenario is similar to the assumption made in the Novartis model where lower withdrawal rates are reported for SEC in the 2nd year of treatment. The second withdrawal scenario was undertaken to assess the robustness of the results to assumptions made regarding the constant rate of withdrawal applied in the model. Given the lack of longer term data to inform an alternative, time dependant withdrawal rate, an assumption was made that patients who remained on therapy at 5 years would no longer be at risk of subsequent withdrawals. This is similar to the assumption made in the UCB model but not as extreme in patients are still permitted to withdraw albeit at a reduced rate and from a slightly late time point (5 years as opposed to 4 years).
- Baseline HAQ according to subpopulation. Equivalent to the separate baseline HAQ scores assumed in the UCB model, three separate baseline scores were applied according to the subpopulation: [redacted] for subpopulation 1, [redacted] for subpopulation 2 and [redacted] for subpopulation 3.

7.2.11 Analytic methods

The expected costs and QALYs of the alternative treatment strategies are determined for each subpopulation and PASI subgroup and the relative cost-effectiveness of the strategies is then compared using standard decision rules, estimating ICERs as appropriate[136]. The ICER examines the additional cost that one strategy incurs over another and compares this with the additional benefits. The ICER estimate represents the additional cost required to generate one additional unit of health outcome (QALY). When more than two strategies are being compared, the ICERs are calculated using the following process:

- The strategies are ranked in terms of mean QALYs (from the last effective to the most effective).
- If a strategy is more costly and less effective than any previous strategy, then this strategy 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 strategy is higher than that of any more effective strategy, then this strategy is ruled out on the basis of extended dominance.
- Finally, the ICERs are recalculated, excluding any strategies that are ruled out by principles of dominance or extended dominance.

The resulting ICERs then provide the basis for establishing which strategy appears optimal based on cost-effectiveness considerations. That is, which strategy (or strategies) appears to provide good value for money to the NHS. Guidance from NICE suggests that an incremental cost per additional QALY of around £20,000-£30,000 is considered to represent an appropriate threshold to establish value for money to the NHS.[119]

In addition to determining which strategy appears optimal based on fully incremental comparisons of all treatments simultaneously, separate pair-wise ICERs are presented for each treatment vs BSC alone. These pair-wise ICERs are helpful in informing assessments of cross-validity i.e. providing a comparable basis to compare particular treatments with previously published results. These comparisons may also be informative if strategies are ruled out from the fully incremental calculations based on differences between treatments which are not considered clinically or economically significant. In this situation, comparing the pairwise ICERs for each individual treatment vs a common comparator may provide further information to inform subsequent decisions.

The model was run several times, once for the main base-case analysis (for each subpopulation and PASI subgroup) and then for a number of alternative scenarios to consider alternative assumptions related to key aspects of the base-case approach (see Section 7.2.10). Given the large number of subpopulation, subgroup and scenario combinations, it has not been possible to conduct probabilistic sensitivity analysis, although this functionality is included in the model.

7.3 Results

7.3.1 Results of the base case cost-effectiveness analysis

According to the three main subpopulations (biologic naive: 1 prior, 2 priors DMARDs and biologic experienced), results for three separate concomitant psoriasis subgroups (baseline PASI = 0, PASI = 7.5, PASI = 12.5) are presented and discussed in the following sections. For ease of presentation and interpretation, individual ICER tables are only presented for the independent analysis from the evidence synthesis in the main body of the report and summary tables used to compare with the results based on meta-regression approach. Individual ICER tables based on the meta-regression are also reported separately in in Appendix 12.13.

All results presented in Section 6.3 are based on the list prices for SEC and CZP and the originator products for INF and ETN. A separate confidential appendix is included which incorporates the confidential PAS prices for CZP and SEC. Scenarios including biosimilar prices are also presented separately in Appendix 12.12.

7.3.1.1 Subpopulation 1: biologic naïve (≤1 prior DMARD)

The cost effectiveness results for subpopulation 1 are shown for the three subgroups according to the level of concomitant psoriasis (moderate-severe, mild-moderate and no concomitant) in Table 90, Table 91 and Table 92, respectively.

In the moderate-severe psoriasis subgroup (Table 90), SEC 300mg is the most effective strategy (QALYs=8.52), followed by CZP (QALYS= 8.38) and BSC (QALYs=5.31). In terms of costs, SEC 300mg is also the mostly costly strategy (£179,692) followed by CZP (£159,951) and BSC (£95,965). Based on the fully incremental ICERs, the ICER of CZP compared with BSC is £20,870 per QALY and the ICER of SEC 300mg compared to CZP is £134,783 per QALY.

The individual pairwise ICERs for CZP and SEC 300mg compared to BSC are £20,870 and £26,064 per QALY, respectively.

Table 90 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
CZP	£159,951	8.377	£63,987	3.066	£20,870	£20,870
SEC 300mg	£179,692	8.524	£19,741	0.146	£134,783	£26,064

In the mild-moderate psoriasis group (Table 91), SEC 150mg is the most effective strategy (QALYs=8.69), followed by CZP (QALYs=8.68) and BSC (QALYs=5.68). In terms of costs, CZP is now the most costly strategy (£135,946), followed by SEC 150mg (£132,500) and BSC (£67,000). Based on the fully incremental ICERs, CZP is dominated by SEC 150mg. The ICER of SEC 150mg compared to BSC is £21,772 per QALY.

The individual pairwise ICERs for CZP and SEC 150mg compared to BSC are £23,052 and £21,772 per QALY, respectively.

Table 91 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
CZP	£135,946	8.667	-	-	D	£23,052
SEC 150mg	£132,500	8.685	£65,500	3.009	£21,772	£21,772

* D = dominated (see Section 7.2.11)

In the no concomitant psoriasis subgroup (Table 92), CZP is the most effective strategy (QALYs=9.074), followed by SEC 150mg (QALYs=9.067) and BSC (QALYs=6.188). In terms of

costs, CZP is also the most costly strategy (£122,832), followed by SEC 150mg (£120,303) and BSC (£51,436). Based on the fully incremental ICERs, the ICER for SEC 150mg compared to BSC is £23,928 per QALY and the ICER of CZP compared to SEC 150mg is £346,785 per QALY.

The individual pairwise ICERs for SEC 150mg and CZP compared to BSC are £23,928 and £24,774 per QALY, respectively.

Table 92 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
SEC 150mg	£120,303	9.067	£68,866	2.878	£23,928	£23,928
CZP	£122,832	9.074	£2,529	0.007	£346,785	£24,744

There are a number of important differences evident across the separate concomitant psoriasis subgroups for subpopulation 1. Mean costs are higher (and mean QALYs lower) for all treatments depending on the presence and severity of concomitant psoriasis, demonstrating the important contribution of psoriasis to costs and HRQoL and to subsequent ICER estimates. The difference in mean QALYs between SEC and CZP is greatest in the moderate to severe psoriasis subgroup, with SEC 300mg reported to be the most effective strategy. The difference appears largely attributed to the higher average PASI responses (PASI 50, 75 and 90) estimated for SEC 300mg compared to CZP from the independent evidence synthesis. The differences in PASI outcomes become less important as the severity of concomitant psoriasis is reduced and the differences are now based on comparisons between SEC 150mg and CZP. The difference in QALYs between SEC 150mg and CZP is subsequently reduced in the mild to moderate psoriasis subgroup (QALY difference still in favour of SEC 150mg) and reduced again in the subgroup with no concomitant psoriasis (QALY difference now in favour of CZP). As the influence of PASI outcomes is reduced, the more important differences in both the PsARC response rate and the HAQ change scores conditional on PsARC response between the treatments become. Although the PsARC response rate was estimated to be marginally higher for SEC 150mg compared to CZP (probability = 0.58 vs 0.57), marginally higher conditional HAQ changes were then estimated for CZP compared to SEC 150mg (-0.43 vs -0.39). In the no concomitant psoriasis subgroup, where differences in PASI response are no longer relevant, the higher conditional HAQ score assumed for CZP appears to offset the higher PsARC response rate for SEC 150mg. However, subsequent differences in QALY outcomes appear minor between SEC150mg and CZP (0.007 QALYs in favour of CZP).

In terms of the pairwise ICERs reported vs BSC, the ICERs for CZP vary between £20,870 (moderate to severe psoriasis) and £24,744 (no concomitant psoriasis) per QALY across the psoriasis subgroups.

The ICERs for SEC range from £23,052 (mild to moderate psoriasis) to £26,064 per QALY (moderate to severe psoriasis). The ICERs vs BSC for SEC do not follow the same pattern as for CZP (i.e. more favourable ICERs as severity of concomitant psoriasis increases) due to the different dosages assumed for SEC and the higher cost of SEC 300mg assumed in the moderate to severe psoriasis subgroup.

Table 93 illustrates the differences between the independent analysis and the meta-regression evidence synthesis for each of the subgroups in subpopulation 1 (full results are presented in Appendix 12.13). The pairwise ICERs for each of the treatments compared to BSC are presented along with the optimal (or most cost-effective) treatment strategy determined based on the fully incremental ICER comparisons at thresholds of £20,000 and £30,000 per QALY.

In summary, the differences in the pairwise ICERs estimated using the alternative synthesis models has only a minor effect. Furthermore, the optimal treatment remains consistent across the two evidence synthesis approaches using a threshold of £30,000 per QALY. At a threshold of £20,000 the optimal treatment changes in the moderate-severe subgroup. CZP is now the most cost-effective treatment as its ICER compared to BSC now falls below the threshold (£19, 908) based on the results of the meta-regression.

Table 93 Summary of differences between independent and meta regression approaches, sub population 1

	ICERs vs BSC			**Optimal treatment (£20, 000)**	**Optimal treatment (£30, 000)**
	CZP	**SEC 150**	**SEC 300**		
Moderate – severe psoriasis					
Independent analysis	£20,870	-	£26,064	BSC	CZP
Meta regression	£19,908	-	£27,033	CZP	CZP
Mild-moderate psoriasis					
Independent analysis	£23,052	£21,772	-	BSC	SEC 150MG
Meta regression	£22,446	£21,287	-	BSC	SEC 150MG
No concomitant psoriasis					
Independent analysis	£24,744	£23,928	-	BSC	SEC 150MG
Meta regression	£24,388	£23,408	-	BSC	SEC 150MG

7.3.1.2 Subpopulation 2: biologic naïve (≥2 prior DMARDs)

The cost effectiveness results for subpopulation 2 are reported according to the level of concomitant psoriasis (moderate-severe, mild-moderate and no concomitant) in Table 94, Table 95 and Table 96, respectively.

As discussed in Section 7.2.4, Table 94it is assumed that, after failing the first biologic treatment, patients move (switch) to UST as a second line treatment before moving to BSC. In the moderate-severe subgroup (Table 94), SEC 300mg treatment is compared in this population, as opposed to SEC 150mg, as its license states that a 300mg dose is appropriate for patients with severe psoriasis (PASI >10). The cost-effectiveness results for this subgroup show that SEC 300mg is dominated by other comparators (ADA, GOL and ETN) as it incurs higher costs and results in less QALYs. CZP is extendedly dominated (by a linear combination of ADA and BSC). Of the remaining non-dominated alternatives, the ICER of ADA vs BSC is £20,074 per QALY, the ICER of GOL vs ADA is £20,976 per QALY, the ICER of ETN vs GOL is £21,215 per QALY and the ICER of INF is £131,716 per QALY.

The individual pairwise ICERs for CZP and SEC 300mg compared to BSC are £21,564 and £29,569 per QALY, respectively.

Table 94 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
CZP	£137,240	7.226	-	-	ED	£21,564
SEC 300mg	£157,086	7.379	-	-	D	£29,569
ADA	£138,109	7.411	£42,144	2.100	£20,074	£20,074
GOL	£142,850	7.637	£4,741	0.226	£20,976	£20,161
ETN	£144,585	7.719	£1,735	0.082	£21,215	£20,197
INF	£167,126	7.890	£22,541	0.171	£131,716	£27,599

* D = dominated, ED = extendedly dominated (see Section 7.2.11)

Table 95 shows the results for the mild to moderate psoriasis subgroup. In this subgroup CZP is the least effective biologic treatment generating 7.537 QALYs, whereas INF generates the highest QALYs (8.161). Performing fully incremental analysis shows that CZP is dominated by SEC 150mg, GOL is dominated by ETN and ADA is extendedly dominated (linear combination of SEC 150mg and ETN). Of the remaining non-dominated alternatives, the ICER of SEC 150mg vs BSC is £22,032 per QALY, the ICER of ETN vs SEC 150mg is £23,256 per QALY and the ICER of INF vs ETN is £193,063 per QALY.

The individual pairwise ICERs for CZP and SEC 150mg compared to BSC are £24,103 and £22,032 per QALY, respectively.

Table 95 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
CZP	£111,856	7.537			D	£24,103
SEC 150mg	£108,508	7.560	£41,508	1.884	£22,032	£22,032
ADA	£114,039	7.708			ED	£23,149
GOL	£119,624	7.923			D	£23,419
ETN	£119,326	8.025	£10,818	0.465	£23,256	£22,274
INF	£145,569	8.161	£26,243	0.136	£193,063	£31,616

* D = dominated, ED = extendedly dominated (see Section 7.2.11)

For the no concomitant psoriasis subgroup (PASI=0) (Table 96), INF maintains its position as the most effective treatment (8.543 QALYs), whereas SEC 150mg is now the least effective option. As expected in this subgroup, the ICERs vs BSC increase compared to the mild-moderate and severe psoriasis subgroups, due to benefits being driven entire by HAQ as opposed to a combination of HAQ and PASI. The incremental cost-effectiveness analysis shows that GOL is dominated by ETN and SEC150mg, CZP and ADA are extendedly dominated. Of the non-dominated alternatives, the ICER of ETN vs BSC is £23,833 per QALY and the ICER of INF vs ETN is £324,502 per QALY.

The individual pairwise ICERs for CZP and SEC 150mg compared to BSC are £26,105 and £24,773 per QALY, respectively.

Table 96 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
SEC 150mg	£95,632	7.972	-	-	ED	£24,773
CZP	£98,060	7.974	-	-	ED	£26,105
ADA	£100,893	8.125	-	-	ED	£25,532
GOL	£106,895	8.325	-	-	D	£25,951
ETN	£105,592	8.456	£54,156	2.268	£23,883	£23,883
INF	£133,664	8.543	£28,071	0.087	£324,502	£34,930

* D = dominated, ED = extendedly dominated (see Section 7.2.11)

Table 97 summarises the differences between the independent analysis and the meta-regression evidence synthesis for each of the separate psoriasis subgroups within subpopulation 2 (full results are available in Appendix 12.13). The pairwise ICERs for each of the treatments compared to BSC are presented along with the optimal (or most cost-effective) treatment at thresholds of £20,000 and £30,000 per QALY, using the full incremental results. Although there are only minimal differences in the pairwise ICERs, in this subpopulation the optimal treatment alters across the two evidence synthesis approaches. Both approaches accord in terms of the optimal strategy at a threshold of £20,000 for the mild-moderate and no concomitant subgroups. In the moderate-severe subgroup, the ICER for CZP (compared to BSC – its next best) falls below £20,000, therefore at this threshold it represents the optimal treatment. Using the meta-regression estimates, CZP, as opposed to ETN, represents the most cost-effective option at a threshold value of £30, 0000 per QALY in the moderate-severe psoriasis group. The optimal treatment switches from ETN to SEC150mg in the mild-moderate and non-concomitant psoriasis subgroups. These differences are driven by the increased relative effectiveness of CZP and SEC 150mg in the meta-regression approach (see Section 5).

Table 97 Summary of differences between independent and meta regression approaches, subpopulation 2

	ICERs vs BSC							Optimal treatment (£20, 000)	Optimal treatment (£30, 000)
	CZP	SEC 150mg	SEC 300mg	ADA	GOL	ETN	INF		
Moderate – severe psoriasis									
Independent analysis	£21,564	-	£29,569	£20,074	£20,074	£20,197	£27,599	BSC	ETN
Meta regression	£19,923	-	£30,456	£20,092	£20,767	£20,552	£29,138	CZP	CZP
Mild-moderate psoriasis									
Independent analysis	£24,103	£22,032	-	£23,149	£23,419	£22,274	£31,616	BSC	ETN
Meta regression	£22,939	£21,177	-	£23,130	£23,408	£22,750	£32,703	BSC	SEC 150MG
No concomitant psoriasis									
Independent analysis	£26,105	£24,773	-	£25,532	£25,951	£23,883	£34,930	BSC	ETN
Meta regression	£25,275	£23,768	-	£25,485	£25,475	£24,460	£35,689	BSC	SEC 150MG

7.3.1.3 Subpopulation 3: biologic experienced

Table 98, Table 99 and Table 100 present the results for subpopulation 3 for the moderate-severe, mild-moderate and no concomitant psoriasis subgroups respectively. Only an independent analysis is available for this subpopulation, due to the more limited data available (see Section 7.2.6). In this subpopulation SEC 300mg is considered as a relevant comparator, alongside UST and BSC. The clinical trial data for UST and SEC 300mg includes a mix of biologic experienced patients: those who have not responded to biologic treatment (primary non-responders) and those who have responded but subsequently failed the treatment (secondary failures). CZP is not included in this model as only patients who had a primary response to a biologic treatment (secondary failures) were included in the RAPID-PsA trial. Primary non-responders were explicitly excluded in this trial and therefore the population represents a separate subgroup of the overall biologic experienced subpopulation (those that have previously had a response). The results for CZP are presented separately in Section 7.3.2.1.

Table 98 shows the results of the moderate-severe psoriasis subgroup. SEC 300mg is the most effective and expensive treatment, generating greater QALYs than UST (6.632 vs 6.334 QALYs) and incurring higher costs (£143,534 vs £118,127). In the fully incremental analysis, the ICER of UST vs BSC is £21,684 per QALY and the ICER of SEC 300mg is £85,013 per QALY.

The individual pairwise ICER for SEC 300mg compared to BSC is £36,013.

Table 98 Moderate-severe psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
UST	£118,127	6.334	£22,162	1.022	£21,684	£21,685
SEC 300mg	£143,534	6.632	£25,407	0.299	£85,013	£36,013

Table 99 shows the results of mild to moderate psoriasis subgroup. In this subgroup SEC 300mg is the most effective and expensive treatment generating more QALYs than UST (6.945 vs 6.666) and incurring higher costs (£118,564 vs £91,246). In the fully incremental analysis, the ICER of UST vs BSC is £24,510 per QALY and the ICER of SEC 300mg vs UST is £97,713 per QALY.

The individual pairwise ICER for SEC 300mg compared to BSC is £40,639.

Table 99 Mild-moderate psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
UST	£91,246	6.666	£24,246	0.989	£24,510	£24,510
SEC300mg	£118,564	6.945	£27,318	0.280	£97,713	£40,639

Table 100 shows the results of non-evaluable psoriasis subgroup. SEC 300mg is the most effective and expensive treatment generating greater QALYs than UST (7.384 vs 7.132 QALYs) and incurring higher costs (£104,973 vs £76,712). In the fully incremental analysis, the ICER of UST vs BSC is £26,797 per QALY and the ICER of SEC 300mg vs UST is £111,927 per QALY.

The individual pairwise ICER for SEC 300mg compared to BSC is £44,774.

Table 100 No concomitant psoriasis, sub population 3: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
UST	£76,712	7.132	£25,275	0.943	£26,797	£26,797
SEC 300mg	£104,973	7.384	£28,261	0.252	£111,927	£44,774

7.3.1.4 Subpopulation 4: contraindicated to TNF-alpha inhibitors

As described in Section 7.2.3, a separate scenario is required for patients who are contraindicated to existing TNF-alpha inhibitors (INF, ETN, ADA and GOL). These patients are likely to be a combination of biologic naïve and biologic experienced patients who have experienced a significant adverse event. SEC, UST and BSC were included as comparators. CZP was not included as it was assumed that patients would also be contraindicated to other TNF-alpha inhibitors, hence contraindicated to CZP. As described in Section 7.2.6, in the absence of effectiveness data specific to these patients, the analysis was undertaken using the naïve populations from the SEC and UST trials. Only an independent analysis is available for this subpopulation, due to the more limited data available (see Section 7.2.6).

Table 101 shows the results of the moderate-severe psoriasis subgroup. SEC 300mg is the most effective and expensive treatment, generating greater QALYs than UST (6.530 vs 6.274 QALYs) and

incurring higher costs (£137,936 vs £115,216). In the fully incremental analysis, the ICER of UST vs BSC is £19,969 per QALY and the ICER of SEC 300mg compared to UST is £89,302 per QALY.

The individual pairwise ICER for SEC 300mg compared to BSC is £34,445.

Table 101 Moderate-severe psoriasis, sub pop 4, contraindicated: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
UST	£115,216	6.276	£19,252	0.964	£19,969	£19,969
SEC 300mg	£137,936	6.530	£22,720	0.254	£89,302	£34,445

Table 102 shows the results of the mild-moderate psoriasis subgroup. SEC 150mg is the most effective treatment, generating greater QALYs than UST (6.739 vs 6.613 QALYs). It incurs lower costs tan UST (£87,559 vs £88,280). In the fully incremental analysis, UST is dominated by SEC 150mg. The ICER of SEC 150mg vs BSC is £19,349 per QALY.

Table 102 Mild-moderate psoriasis, sub pop 4, contraindicated: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
UST	£88,280	6.613	D		-	£22,708
SEC 150mg	£87,559	6.739	£20,558	1.063	£19,349	£19,349

* D = dominated (see Section 7.2.11)

Table 103 shows the results of the no concomitant psoriasis subgroup. SEC 150mg is the most effective and expensive treatment, generating greater QALYs than UST (7.190 vs 7.088 QALYs) and incurring higher costs (£73,798 vs £73,717). In the fully incremental analysis, UST is extendedly dominated by SEC 150mg. The ICER of SEC 150mg compared to BSC is £22,334 per QALY.

Table 103 No concomitant psoriasis, sub pop 4, contraindicated: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
UST	£73,717	7.088	-	-	ED	£24,781
SEC 150mg	£73,798	7.190	£22,362	1.001	£22,334	£22,334

* D = dominated, ED = extendedly dominated (see Section 7.2.11)

7.3.2 Results of the scenario analyses

As discussed in Section 7.2.10, a number of scenario analyses were conducted to explore the impact of various model assumptions. These scenarios were conducted for the three main subpopulations and were intended to accord with assumptions and data employed in the company submissions. These scenarios therefore aid comparison across the models (see Section 7.2.10).

Details of the scenarios are given in Section 7.2.10. Firstly, baseline HAQ is specified according to the subpopulation of interest. Secondly the costs assigned according to HAQ were taken from Poole as opposed to Kobelt. Thirdly, two alternative withdrawal scenarios were specified. The results of these alternative scenarios are summarised in Table 104, Table 105 and Table 106, for the three main subpopulations respectively. The pairwise ICERs for each of the treatments compared to BSC are presented along with the optimal (or most cost-effective) treatment at thresholds of £20,000 and £30,000 per QALY, using the fully incremental ICERs. List prices are used in all of these scenarios. Independent analyses from the evidence synthesis are also employed throughout. The HAQ costs and withdrawal scenarios are only specified for subpopulations 2 and 3.The full results for these scenarios are presented in Appendix 12.14.

Table 104 illustrates the differences between the base case and the alternative scenarios for each of the concomitant psoriasis subgroups in subpopulation 1. The optimal treatment is consistent across the two scenarios, base case and using a subpopulation specific baseline HAQ. In the moderate-severe subgroup, the optimal treatment is BSC at a threshold of £20,000 and CZP at a threshold of £30,000. In the mild-moderate and no concomitant subgroups, the optimal treatment is BSC at a threshold of £20,000 and SEC 150mg at a threshold of £30,000. The lower ICERs for SEC in these two subgroups are driven by the lower acquisition costs of the 150mg dose compared to the 300mg dose used in the moderate-severe subgroup.

Table 104 Summary of differences between base case models and alternative scenarios, subpopulation 1

	ICERs vs BSC			Optimal treatment (£20, 000)	Optimal treatment (£30, 000)
	CZP	**SEC 150mg**	**SEC 300mg**		
Moderate – severe psoriasis					
Base case	£20,870	-	£26,064	BSC	CZP
Baseline HAQ by subpopulation	£20,709	-	£25,873	BSC	CZP
Mild-moderate psoriasis					
Base case	£23,052	£21,772	-	BSC	SEC 150MG
Baseline HAQ by subpopulation	£22,874	£21,604	-	BSC	SEC 150MG
No concomitant psoriasis					
Base case	£24,744	£23,928	-	BSC	SEC 150MG
Baseline HAQ by subpopulation	£24,543	£23,732	-	BSC	SEC 150MG

Table 105 illustrates the differences between the base case and the alternative scenarios for each of the subgroups in subpopulation 2. Aside from the use of the HAQ costs reported by Poole et al, the optimal treatment is consistent across all scenarios, BSC at a threshold of £20,000 and ETN at a threshold of £30,000. Using the Poole costs significantly reduces the ICERs for all treatments relative to BSC, as it estimates a much higher cost for BSC. As a result, ETN, as opposed to BSC is considered to be the most cost-effective treatment at a threshold of £20,000. At a threshold of £30,000 ETN remains the optimal treatment despite the reduced ICERs for all the treatments.

Table 105 Summary of differences between base case models and alternative scenarios, subpopulation 2

	ICERs vs BSC							Optimal treatment (£20, 000)	Optimal treatment (£30, 000)
	CZP	**SEC 150mg**	**SEC 300mg**	**ADA**	**GOL**	**ETN**	**INF**		
Moderate – severe psoriasis									
Base case	£21,564	-	£29,569	£20,074	£20,074	£20,197	£27,599	BSC	ETN
Baseline HAQ by subpopulation	£21,809	-	£29,877	£20,295	£20,384	£20,409	£27,866	BSC	ETN
Poole HAQ costs	£3,115	-	£13,500	£3,069	£3,244	£2,842	£13,036	ETN	ETN
Withdrawal scenario 1	£21,560	-	£30,461	£20,074	£20,161	£20,197	£27,599	BSC	ETN
Withdrawal scenario 2	£21,791	-	£29,562	£20,406	£20,545	£20,555	£27,750	BSC	ETN
Mild-moderate psoriasis									
Base case	£24,103	£22,032	-	£23,149	£23,419	£22,274	£31,616	BSC	ETN
Baseline HAQ by subpopulation	£24,395	£22,294	-	£23,418	£23,687	£22,514	£31,938	BSC	ETN
Poole HAQ costs	£3,205	£1,698	-	£3,171	£3,358	£2,913	£13,526	ETN	ETN
Withdrawal scenario 1	£24,107	£21,291	-	£23,153	£23,418	£22,274	£31,616	BSC	ETN
Withdrawal scenario 2	£24,459	£22,267	-	£23,623	£23,946	£22,734	£31,911	BSC	ETN
No concomitant psoriasis									
Base case	£26,105	£24,773	-	£25,532	£25,951	£23,883	£34,930	BSC	ETN
Baseline HAQ by subpopulation	£26,444	£25,096	-	£25,851	£26,267	£24,150	£35,311	BSC	ETN
Poole HAQ costs	£3,341	£1,794	-	£3,328	£3,531	£3,018	£14,279	ETN	ETN
Withdrawal scenario 1	£26,117	£24,219	-	£25,542	£25,951	£23,883	£34,930	BSC	ETN
Withdrawal scenario 2	£26,570	£25,138	-	£26,129	£26,604	£24,427	£35,352	BSC	ETN

Table 106 illustrates the differences between the base case and the alternative scenarios for each of the subgroups in subpopulation 3. Like subpopulation 2, aside from the use of the Poole costs, the optimal treatment is consistent across all scenarios; BSC at a threshold of £20,000 and UST at a threshold of £30,000. Using the Poole costs significantly reduces the ICERs for all treatments relative to BSC, as it estimates a much higher cost for BSC (see Appendix 12.14.1.2). As a result, UST, as opposed to BSC is considered to be the most cost-effective treatment at a threshold of £20,000. At a

threshold of £30,000, UST remains the optimal treatment, despite the reduced ICERs across all treatments.

Table 106 Summary of differences between base case models and alternative scenarios, subpopulation 3

	ICERs vs BSC		Optimal treatment (£20, 000)	Optimal treatment (£30, 000)
	UST	SEC 300mg		
Moderate – severe psoriasis				
Base case	£21,685	£36,013	BSC	UST
Baseline HAQ by subpopulation	£22,309	£26,926	BSC	UST
Poole HAQ costs	£2,778	£20,154	UST	UST
Withdrawal scenario 1	£21,685	£35,876	BSC	UST
Withdrawal scenario 2	£21,829	£36,276	BSC	UST
Mild-moderate psoriasis				
Base case	£24,510	£40,639	BSC	UST
Baseline HAQ by subpopulation	£25,239	£41,721	BSC	UST
Poole HAQ costs	£2,870	£20,981	UST	UST
Withdrawal scenario 1	£24,510	£40,749	BSC	UST
Withdrawal scenario 2	£24,763	£41,081	BSC	UST
No concomitant psoriasis				
Base case	£26,797	£111,927	BSC	UST
Baseline HAQ by subpopulation	£27,638	£46,057	BSC	UST
Poole HAQ costs	£3,010	£22,264	UST	UST
Withdrawal scenario 1	£26,797	£45,105	BSC	UST
Withdrawal scenario 2	£27,142	£45,389	BSC	UST

7.3.2.1 Results of subgroup analysis: biologic experienced secondary failures

As discussed in Section Subpopulation 3: biologic experienced (Section 7.3.1.3) the RAPID-PsA trial only includes experienced patients who had a primary response to a biologic treatment (secondary failures), representing a specific subgroup of the overall biologic experienced subpopulation. In the absence of data for other comparators for this subgroup, the comparison is restricted to CZP and BSC. The results for this subgroup of biologic experienced patients are presented in Table 107, Table 108 and Table 109.

In the biologic experienced subgroup including only secondary failures, the ICERs of CZP vs BSC are £16,573, £19,113 and £20,973 for moderate-severe, mild-moderate and no concomitant psoriasis patients respectively.

Table 107 Moderate- severe psoriasis, sub pop 4, secondary failures: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs BSC
BSC	£95,965	5.312	-	-	-
CZP	£121,314	6.841	£25,349	1.530	£16,573

Table 108 Mild-moderate psoriasis, sub pop 4, secondary failures: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs BSC
BSC	£67,000	5.676	-	-	-
CZP	£95,470	7.166	£28,470	1.490	£19,113

Table 109 No concomitant psoriasis, sub pop 4, secondary failures: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs BSC
BSC	£51,436	6.188	-	-	-
CZP	£81,447	7.622	£30,011	1.433	£20,937

7.3.2.2 Summary of the model results

The current York model specifies three main subpopulations according to the positon in the pathway of treatment:

- Subpopulation 1: Biologic naïve, one previous cDMARD
- Subpopulation 2: Biologic naïve, ≥ two previous cDMARDs
- Subpopulation 3: Biologic experienced

For subpopulation 3, CZP was excluded on the basis that data were only available for a subset of experienced patients (see Section 7.2.37.2.4). A separate scenario was conducted for secondary failures owing to the availability of data for CZP. This scenario only includes CZP versus BSC.

Three subgroups are also specified within each of the three subpopulations. These subgroups refer to the severity of concomitant psoriasis:

- no concomitant psoriasis

- mild to moderate concomitant psoriasis
- moderate to severe concomitant psoriasis

A fourth subpopulation is also specified, which defines a population contraindicated to TNF-alpha inhibitors (subpopulation 4). A number of scenarios are specified to explore the robustness of some of the assumptions made in the model: rate of withdrawals beyond the first cycle and source of costs relating to HAQ. In addition, separate analyses were conducted using biosimilar prices for ETN and INF and PAS prices for CZP and SEC.

Base case results

Under base case assumptions and using the independent analysis from the evidence synthesis, the results for each of the three subpopulations can be summarised as:

- For subpopulation 1:
    - CZP is likely to be the optimal treatment in the moderate-severe psoriasis group (ICER = £20,870 compared to BSC). The individual pairwise ICER for SEC300mg compared to BSC is £26,064 per QALY.
    - In the mild-moderate psoriasis group CZP is dominated by SEC 150mg, which has an ICER of £21,772 compared to BSC. The individual pairwise ICER for CZP compared to BSC is £23,052 per QALY.
    - In the no concomitant psoriasis subgroup, CZP is no longer dominated by SEC 150mg, however its ICER is substantial compared to SEC150mg (£346,785). The ICER for SEC 150mg increases to £23,928, compared to BSC. The individual pairwise ICER for CZP compared to BSC is £24,774 per QALY.
- For subpopulation 2:
    - ETN is likely to be the optimal treatment in the moderate-severe subgroup, with an ICER of £21,210 compared to GOL. The individual pairwise ICERs for CZP and SEC300mg compared to BSC are £21,564 and £29,569 per QALY, respectively.
    - For the mild to moderate psoriasis subgroup, again ETN appears to be the optimal treatment, with an ICER of £23,256 compared to SEC150mg. The individual pairwise ICERs for CZP and SEC 150mg compared to BSC are £24,103 and £22,032 per QALY, respectively.
    - For the no concomitant psoriasis subgroup, the ICERs increase for all treatments. ETN is likely to be the optimal treatment in this subgroup with ICER of £23,883 compared to BSC. The individual pairwise ICERs for CZP and SEC 150mg compared to BSC are £24,103 and £22,032 per QALY, respectively.
- For subpopulation 3:

- UST is likely to be the optimal treatment for the moderate-severe psoriasis subgroup, with an ICER of £21,684 compared to BSC. The individual pairwise ICERs for SEC 300mg compared to BSC is £36,013 per QALY.
- In the mild to moderate psoriasis subgroup ICER for UST compared to BSC increases to £24,510. The individual pairwise ICER for SEC 300mg compared to BSC is £40,639 per QALY.
- In the non-evaluable psoriasis subgroup, UST is likely to be the optimal treatment, at thresholds below £30,000, with an ICER of £26,797 compared to BSC. The individual pairwise ICER for SEC 300mg compared to BSC is £44,774 per QALY.

For subpopulations 1 and 2, separate effectiveness results are also available utilising a meta-regression approach. The differences between the independent analysis and the meta-regression can be summarised as:

- In subpopulation 1 the use of the meta-regression evidence has a minimal impact on the pairwise ICERs, however at a threshold of £20,000 the optimal treatment changes in the moderate-severe subgroup. CZP is now likely to be the most cost-effective treatment, as its ICER, compared to BSC, falls below the threshold (£19, 908).
- In subpopulation 2, again there are only minimal differences in the pairwise ICERs; however the optimal treatment is not consistent across the two evidence synthesis approaches. Both approaches accord in terms of the optimal strategy at a threshold of £20,000 for the mild-moderate and no concomitant subgroups. In the moderate-severe subgroup, the ICER for CZP (compared to BSC – its next best) falls below £20,000, therefore at this threshold it represents the optimal treatment. Using the meta-regression estimates, CZP, as opposed to ETN, represents the most cost-effective optimal treatment at a threshold value of £30, 0000 per QALY in the moderate-severe psoriasis group. Also, the optimal treatment switches from ETN to SEC150mg in the mild-moderate and non-concomitant psoriasis subgroups.

In the contraindicated subgroup (subpopulation 4):

- UST appears to the most cost-effective treatment in moderate-severe psoriasis patients, with an ICER of £19,969 compared to BSC. The individual pairwise ICER for SEC 300mg compared to BSC is £34,445 per QALY.
- In mild-moderate psoriasis patients UST is dominated by SEC 150mg. SEC 150mg has an ICER of £19,349 compared to BSC.
- In the no concomitant psoriasis patients UST is extendedly dominated by SEC 150mg. SEC 150mg has an ICER of £22,334 compared to BSC.

In the biologic experienced subgroup, including only secondary failures, CZP seems to be cost effective treatment compared to BSC, with ICERs of £16,573, £19,113 and £20,973 for moderate-severe, mild-moderate and no concomitant psoriasis patients respectively.

Results using biosimilar prices

When using biosimilar prices for ETN and INF in subpopulation 2, the ICERs for ETN compared to BSC, and the ICERs for INF compared ETN, decrease. The ICER for ETN compared to its next best alternative (BSC) in the moderate-severe subgroup falls below the threshold of £20,000, therefore at this threshold, using the biosimilar prices for ETN, the optimal treatments switches from BSC to ETN. For the mild-moderate and no concomitant psoriasis subgroups the optimal treatments remains unchanged.

Scenario results

A number of scenarios were specified to explore the sensitivity of results to some of the assumptions made in the model. Alternative scenarios were specified for the three main subpopulations, although withdrawal scenarios and use of Poole costs were only conducted for subpopulations 2 and 3. List prices and originator products (ETN and INF) are used in all of these scenarios. Independent analyses from the evidence synthesis are also employed throughout. The results can be summarised as:

- In subpopulation 1, the optimal treatment is consistent across the two scenarios, base case and using a subpopulation specific baseline HAQ.
- In subpopulation 2, aside from the use of the Poole HAQ costs, the optimal treatment is consistent across all scenarios. Using the Poole costs significantly reduces the ICERs for all treatments relative to BSC, as it estimates a much higher cost for BSC. As a result, ETN, as opposed to BSC is identified to be the most cost-effective treatment at a threshold of £20,000 per QALY. At a threshold of £30,000 per QALY, ETN remains the optimal treatment despite the reduced ICERs for all the treatments.
- In subpopulation 3, aside from the use of the Poole costs, the optimal treatment is consistent across all scenarios. Using the Poole costs significantly reduces the ICERs for all treatments relative to BSC, as it estimates a much higher cost for BSC. As a result, UST, as opposed to BSC is considered to be the most cost-effective treatment at a threshold of £20,000 per QALY. At a threshold of £30,000 per QALY, UST remains the optimal treatment despite the reduced ICERs across all treatments.

7.3.3 External validation of results

7.3.3.1 Comparison of updated York model results with company model results

In the absence of a list price analysis from either of the companies, it is not possible to make direct comparisons between the updated York model results and those from the Novartis and UCB

submissions. In general the structure and approaches of both company models were similar in many key respects to the updated York model and models developed as part of previous appraisals. However, as highlighted in Section 6, further challenges arise when trying to make comparisons between the results of the updated York model as were faced when trying to make comparisons between the company submissions, given the differences identified in the approaches and data sources employed. On this basis we consider direct comparisons between the ICER results would not be sufficiently meaningful.

The main advantage of the York model is that facilitates a more consistent basis for evaluating CZP and SEC by ensuring comparability in methods and inputs (including prices). In addition, the York model attempts to include all relevant treatments within each subpopulation and more explicitly considers issues around the appropriate dosing for SEC by undertaking separate subgroup analyses based on the presence and severity of concomitant psoriasis.

7.3.3.2 Comparison of updated York model results with published models results

It is possible to compare some of the results of the updated York model with those from previously published models, namely the three models developed as part of previous appraisals in this area (TA199[94, TA220{Cummins, 2012 #299] and TA340[116]) and a published update of the previous York model by Cawson, et al[31] (see Table 3). This comparison is somewhat restricted by the more limited scope in previously published models. In TA199, TA220 and Cawson, et al, only subpopulation 2 was considered. TA340 also included an analysis for subpopulations 3 and 4 together (experienced and contraindicated (termed ineligible). All previously published models looked at the extent of concomitant psoriasis, however this was only included as limited scenario analyses and full results are only available for the average severity of psoriasis; mild-moderate. It is also noted that none of the previously published models included the comparators CZP or SEC.

In terms of the results for subpopulation 2, the ICERs for ETN vs the next best treatment are broadly consistent across the updated York model and the four published models (£16,426 in Cawson, et al to £23,256 in the updated York model, mild-moderate psoriasis subgroup). For subpopulation 3, TA340 included a separate analysis of a biologic experienced/contraindicated population for UST. In this analysis the ICER for UST compared to BSC was £25,393. This result is very similar to those from subpopulation 3 of the updated York model results, in which the ICER for UST compared to BSC, in the mild to moderate psoriasis subgroup, is £24,510. In the contraindicated subgroup (subpopulation 4 of the York model), in mild-moderate psoriasis patients, the ICER for UST compared to BSC is again broadly consistent at £22,708. In the full incremental analysis for this subpopulation, however, UST is dominated by SEC 150mg and SEC 150mg has an ICER of £19,349 compared to BSC.

7.4 Discussion of York model

The previous York model has been updated for this appraisal. This includes an update of the evidence used to populate model the model and a number of updates to the model structure and assumptions. Specifically the updated York model differs from the previous York in terms of:

- The model now incorporates subsequent biologic treatments following primary lack of response or secondary failure.
- The model now includes the three-subpopulations specified in the NICE scope for this appraisal.
- Rather than presenting a single base case reflecting an 'average' PsA patient, heterogeneity in terms of baseline PASI is now formally addressed by presenting results for three distinct subgroups within each subpopulation.

In addition, the updated York model includes the comparators CZP and SEC and considers the cost-effectiveness of these treatments in each of the subpopulations. The updated York model also considers several key uncertainties: the acquisition cost of SEC and CZP (list or PAS prices), the products for ETN and INF (originator or biosimilar), the source algorithm used to link progression in HAQ to costs, and assumptions regarding the longer term rate of withdrawal for primary responders.

The model utilises all currently available evidence to generate estimates of clinical effectiveness using NMA. Alternative models are specified for the NMA, and a more limited set of models is chosen on the basis of model fit, goodness of fit statistics and clinical plausibility. These alternative models (independent analysis and meta-regression) are each used in the economic model and the sensitivity of model results to these alternative evidence synthesis models assessed.

Using list prices, SEC and CZP are likely to only be considered cost-effective in subpopulation 1 (biologic naïve: 1 prior DMARD). In subpopulation 2, ETN is likely to be the optimal treatment across all psoriasis subgroups, and in subpopulation 3, UST is likely to be the optimal treatment across all psoriasis subgroups. The cost-effectiveness results, are however sensitive to a number of assumptions made in the model, namely the choice of NMA model used to determine clinical effectiveness and the algorithm used to link HAQ to health state costs.

The updated York model also has a number of limitations, which have largely been imposed by a lack of available data to inform aspects of the model. Firstly subpopulation 1 only includes the comparators CZP, SEC and BSC, as per the NICE scope. It is recognised however, that there may be other comparators relevant for this subpopulation. In particular, patients who have only received 1 prior DMARD may be eligible to receive a 2nd DMARD. It was not possible within the scope of this appraisal to assess the evidence for DMARDs and therefore include this as a formal comparator in

this subpopulation. The extremely low cost of DMARDs (7.5 mg of MTX is £0.30) make it likely that these would be considered cost-effective in this population. In addition, the licenses for the other biologic treatments (ETN, INF, ADA and GOL) do not preclude their use in the 1DMARD population, and therefore these could be considered to be relevant comparators in subpopulation 1. Indeed, this subpopulation appears to not have been considered in previously published models largely because the scope of these models have closely followed existing BSR guidelines and criteria for commencing biologic treatments (i.e. that the PsA has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination) as opposed to reflecting important differences in the licenses of existing biologic treatments and those for SEC and CZP.

Secondly, the clinical effectiveness evidence synthesised in the NMA, does not differentiate between subpopulations 1 and 2 due to limited data availability. This means that it was only possible to differentiate these two populations on the basis of the comparators included and the subsequent treatments received following primary failure or secondary withdrawal. Related to this, the subpopulation 1 analysis makes the assumption that ETN is the next treatment received, following failure of SEC 150mg or CZP. It is likely that other treatments could be used as second line in this population. Due to the large number of possible treatment sequences for subpopulation 1, it was not feasible as part of this appraisal to determine the optimal sequence for all potential treatments. Modelling multiple lines of biologic treatments would also require evidence on any degradation effect for subsequent lines. Such evidence is sparse in PsA and that which exists does not consider the full set of biologic treatments considered in this appraisal.

Finally, it has not been possible to update a number of the assumptions in the York model, specifically the rate of withdrawal for primary responders, the progression in HAQ for those receiving and the progression of HAQ for those remaining on treatment. These assumptions rely on non-experimental data, and unfortunately within the time constraints of this appraisal, it was not possible to gain access to registry data to update these assumptions, although attempts to do so were made.

Given these uncertainties and possible limitations and the lack of direct head to head evidence for the alternative treatments, the results from the fully incremental cost-effectiveness analyses should be carefully considered alongside the separate pairwise comparisons presented against BSC. The significant efficacy of all biologic treatments was evident in the important QALY differences reported compared to BSC alone. In contrast, differences between the alternative biologic therapies were much less significant and in some instances may not be clinically meaningful. Hence, there remains considerable uncertainty in relation to defining an optimal treatment or pathway of care.

8 Assessment of factors relevant to the NHS and other parties

The potential extra cost to the NHS of providing secukinumab and certolizumab pegol to adult patients with psoriatic arthritis is unclear, since the prevalence of UK PsA patients in subpopulation 1 is somewhat uncertain.

9 Discussion

9.1 Statement of principal findings

The systematic review of the efficacy of secukinumab, certolizumab pegol and relevant comparator therapies in patients with psoriatic arthritis identified an evidence base of generally high-quality randomised trials. The results of the pivotal randomised trials of secukinumab (FUTURE 2) and certolizumab pegol (RAPID-PsA) demonstrated their short-term efficacy for treating psoriatic arthritis. When considering the whole trial populations, both secukinumab and certolziumab pegol were associated with statistically significant improvements in all key clinical outcomes. At 3 months, patients taking secukinumab were around six times more likely to be ACR 50 responders – an important clinical outcome to patients – than patients taking placebo. Patients taking certolizumab pegol were around three times more likely to be ACR 50 responders than placebo patients. Clinically important improvements in activities of daily living (assessed using HAQ-DI) were also evident for both therapies, particularly in patients who were PsARC responders. Secukinumab and certolizumab pegol both also significantly improved measures of health-related quality of life and the resolution of enthesitis and dactylitis.

However, when the populations from these two trials were split into subgroups based on previous biologic experience, results for the biologic-experienced subgroups became difficult to interpret. This was due both to the low numbers of placebo patients (and placebo events) and to the differences in placebo response rates across subgroups; it was therefore not possible to make robust conclusions about the relative efficacy of secukinumab and certolizumab pegol across these subgroups.

Subgroup results from psoriatic arthritis patients recruited to trials of patients with quite severe psoriasis suggested secukinumab may be particularly efficacious in treating the psoriasis symptoms of PsA.

Results from open-label trial extension studies which radiographically assessed joint damage indicated that, after two years of treatment, certolizumab pegol effectively reduced disease progression with benefits being similar to those observed in the open-label studies for the other biologics. For secukinumab, fewer result details were available at two years although results also indicated effective reduction in radiographic disease progression. Meaningful treatment comparisons of longer-term data for other outcomes were difficult to undertake due to the variation in both time points assessed and in methodological approaches used for data analyses [redacted]

The trials identified to inform a comparison of secukinumab and certolizumab pegol with other biologics were performed across a 15 year period and variation in placebo response was evident for some important outcomes, with larger placebo response rates seen in the more recent trials. Furthermore, there was important heterogeneity across trials with regard to patients' previous use of a biologic therapy: subgroups of biologic-experienced patients were only recruited in more recent trials. Our network meta-analyses (NMA) were therefore performed on the biologic-naïve and -experienced subgroups separately, and included models which adjusted for and explored the different rates of placebo response across trials.

The NMA results - both adjusted and unadjusted - demonstrated that, in biologic-naïve patients, secukinumab and certolizumab pegol were more effective than placebo in terms of achieving PsARC and ACR responses. There was though some uncertainty regarding the relative effectiveness of secukinumab and certolizumab pegol when compared with each other and with all other biologics: they had fairly similar effectiveness when compared with the other anti-TNFs, though were possibly slightly more effective than ustekinumab. However, both secukinumab and certolizumab pegol appeared to be more effective than apremilast. In terms of psoriasis outcomes in biologic-naïve patients, treatment with secukinumab and infliximab resulted in the best PASI results when compared with other therapies, although the differences for most comparisons were not statistically significant.

The median HAQ-DI change, conditional on a PsARC response, was highest with infliximab and etanercept, followed by secukinumab 300 mg, but secukinumab 150mg and certolizumab pegol were worse than all treatments except for apremilast.

Only three trials recruited biologic-experienced patients: one each of secukinumab, certolizumab pegol and ustekinumab. Unfortunately data from the certolizumab pegol trial had to be excluded from the NMAs because it included a more restricted biologic-experienced population, which was not comparable with the biologic experienced populations in the other two trials. The NMA results showed that the probabilities of PsARC and ACR responses with secukinumab and ustekinumab were quite similar, as was the change in HAQ in PsARC responders. Patient numbers were particularly limited for the biologic-experienced PASI analyses, as they were based on a subgroup (prior use of a biologic) of a subgroup (psoriasis on ≥3% of body surface area), so estimates from the NMA were highly uncertain. However, the results suggested that the probabilities of achieving PASI responses were higher for secukinumab than for ustekinumab.

Results from studies of patient registries which recorded biologic use suggested that although patients benefit from a second or more anti-TNF, the expected benefit from anti-TNFs diminishes after switching, with a reduced chance of response and reduced drug survival. The paucity of observational

data on the natural history of psoriatic arthritis meant it was difficult to produce accurate estimates of yearly disease progression rates in patients not taking anti-TNF therapy.

Results from three systematic reviews of adverse events suggested that certolizumab pegol was associated with statistically significantly more serious adverse events and serious infections than placebo. Secukinumab was not included in these systematic reviews of adverse events, probably due to the limited availability of data at the time. Although secukinumab appears to have a favourable safety profile, the fairly small number of trials for which data are currently available means there is still some uncertainty regarding its safety.

9.2 Strengths and limitations of the assessment

Strengths

The systematic review was performed using transparent, reproducible and robust methods. Our comprehensive searches therefore sought to identify all relevant published and unpublished trials, which minimised the possibility of publication or language biases affecting the review results. The possibility of reviewer errors and biases affecting this assessment were minimised by performing review processes in duplicate. A thorough evaluation of the risk of bias in each randomised trial was performed. We conducted many network meta-analyses (NMA) to investigate the relative efficacy of all the comparator agents. Additionally, and in order to improve the methodological similarity of the trial data included in our analyses, we successfully obtained previously unpublished data relating to two key trials (for which manufacturer submission data were not available).

A further key strength of our review was the broadness of its scope: in addition to randomised trials we included other types of study such as non-randomised trial extension studies, registry studies of patients taking anti-TNFs, systematic reviews and other large studies of adverse effects of anti-TNFs and studies of the natural history of psoriatic arthritis. Our review was reported based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

The updated York model confers several advantages over current published cost-effectiveness studies, namely the inclusion of the three subpopulations according to the position in the pathway of treatment, the explicit consideration of the severity of concomitant psoriasis and the modelling of subsequent treatments following primary non-response or secondary failure. Like the company models, the updated York model includes the comparators CZP and SEC. In addition it considers the cost-effectiveness of these treatments in each of the subpopulations and more explicitly considers issues around the appropriate dosing for SEC by undertaking separate subgroup analyses based on the presence and severity of concomitant psoriasis.

The updated York model also considers several key uncertainties: the acquisition cost of SEC and CZP (list or PAS prices), the products for ETN and INF (branded or biosimilars), the source algorithm used to link progression in HAQ to costs and assumptions regarding the longer term rate of withdrawal for primary responders.

The model utilises all currently available evidence to generate estimates of clinical effectiveness using a NMA. Alternative models are specified for the NMA, and a more limited set of models is chosen on the basis of model fit, goodness of fit statistics and clinical plausibility. These alternative models (independent analysis and meta-regression) are each used in the economic model and the sensitivity of model results to these alternative evidence synthesis models assessed. The York model facilitates a more consistent basis for evaluating CZP and SEC by ensuring comparability in methods and inputs.

Limitations

Data from randomised, fully-blinded populations were only available for up to around three or four months for most of the trials included in our review (after which patients could cross-over to active treatments); much of the RCT evidence was therefore quite short-term in nature. Some of the earlier trials were also limited by small sample sizes (increasing the possibility of results being due to chance, rather than being due to treatment). The variation in placebo responses over time was also a limitation of the available data, though we sought to address this in our network meta-analyses (using meta-regression adjustments). Although we also evaluated long-term results from studies which were not RCTs, their data may have been affected by biases or confounding and key method details were often either absent from publications or methods were found to be sub-optimal. Much less reliability and certainty could therefore be ascribed to the results obtained from these other studies.

As discussed previously the updated York model does have a number of limitations, which have largely been imposed by a lack of available data to inform aspects of the model.

Of particular note is the fact that subpopulation 1 only includes the comparators CZP, SEC and BSC, as per the NICE scope. It is recognised however, that there may be other comparators relevant for this subpopulation. In particular patients who have only received 1 prior DMARD may be eligible to receive a 2nd DMARD. It was not possible within the scope of this appraisal to assess the evidence for DMARDs and therefore include this as a formal comparator in this subpopulation. In addition, the licenses for the other biologic treatments (ETN, INF, ADA and GOL) do not appear to preclude the use in the 1DMARD population, and therefore these could be considered to be relevant comparators in subpopulation 1. Indeed, this subpopulation appears to not have been considered in previous models largely because the scope of these models have closely followed existing BSR guidelines and criteria for commencing biologic treatments (i.e. that the PsA has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination) as opposed to

reflecting important differences in the licenses of existing biologic treatments and those for SEC and CZP.

9.3 Uncertainties

- The magnitude of secukinumab and certolizumab pegol treatment effects in biologic-experienced patients is uncertain because the trial subgroup sample sizes were small and the subgroup in the certolizumab pegol trial was not appropriately representative of the biologic-experienced population which would be seen in clinical practice.
- The limitations and variations in the design and reporting of long-term studies means there is uncertainty whether or not there are differences in efficacy and safety between the different therapies in the long term.
- The long-term impact of secukinumab and certolizumab pegol (and other anti-TNFs) on other important outcomes such as cardiovascular disease and mortality is uncertain.

The cost-effectiveness results are potentially sensitive to a number of assumptions made in the model, namely the choice of NMA model used to determine clinical effectiveness and the algorithm used to link HAQ to health state costs. Given these uncertainties and the lack of direct head-to-head evidence for the alternative treatments, the results from the fully incremental cost-effectiveness analyses should also be considered alongside the separate pairwise comparisons presented against BSC. The significant efficacy of all biologic treatments was evident in the important QALY differences reported compared to BSC alone. In contrast, differences between the alternative biologic therapies were much less significant and in some instances may not be clinically meaningful. Hence, there remains considerable uncertainty in relation to defining an optimal treatment or pathway of care.

10 Conclusions

Although the network meta-analyses were based on data from high quality randomised trials, heterogeneity across trials meant the analyses had to be performed in biologic-naïve and -experienced subpopulations separately, and also needed to include models which adjusted for the different rates of placebo response evident across trials. The network meta-analysis results for the biologic-naïve subpopulation indicated that whilst secukinumab and certolizumab pegol were effective across all outcomes after three months' therapy, their relative effectiveness compared with etanercept, adalimumab, golimumab and infliximab and with each other, was uncertain: the rankings of treatment varied with outcome and analysis. However, both agents did seem consistently more effective than apremilast. The results also indicated that secukinumab and infliximab were the most effective in terms of treating psoriasis (PASI response). Only secukinumab and ustekinumab could be included in the analyses of the biologic-experienced subpopulation. The results showed that across all outcomes analysed both secukinumab and ustekinumab were significantly more effective than placebo. Most of the results suggested secukinumab may be better than ustekinumab. However, the patient numbers in this subpopulation were quite low; the results were therefore uncertain (with wide overlapping credible intervals).

Results from open-label trial extension studies which radiographically assessed joint damage suggest that both certolizumab pegol and secukinumab effectively reduce disease progression. Published systematic reviews of adverse events suggested certolizumab pegol was associated with statistically significantly more serious adverse events and serious infections than placebo. Although secukinumab appears to have a favourable safety profile, the fairly small number of trials for which data are currently available means there is still some uncertainty regarding its safety.

Economic modelling found that these new biologics can be considered a cost-effective use of NHS resources when compared with the other therapies currently recommended by NICE for treating psoriatic arthritis. Which treatment is most cost-effective depends on which previous treatments a patient has tried and not responded to, the severity of the psoriasis symptoms, and the price of the treatment. Some of the study's results were somewhat limited due to there not being enough relevant clinical trial data available.

10.1 Implications for service provision

- The clinical evidence indicates that secukinumab and certolizumab pegol are one of a number of effective treatments for the treatment of active psoriatic arthritis.
- For patients with PsA and significant psoriasis, secukinumab may be one of the more effective biologic treatments.

- The limited long-term evidence suggests some beneficial impact of radiographic disease progression.

10.2 Suggested research priorities

- Adequately powered randomised trials are needed to inform the clinic effectiveness of biologics in biologic-experienced populations.
- Future trials should consider using newer composite disease outcome measures which have recently been developed for psoriatic arthritis, such as the Composite Psoriatic arthritis Disease Activity Index (CPDAI) and the psoriatic arthritis disease acticity score (PASDAS).
- Further research is required to better elucidate the impact of biologics on radiographic disease progression and HAQ in the long-term
- With the continuing introduction of new biologic drugs and continued collection of data through biologic registries further analysis of the data to investigate patterns of drug switching is warranted.

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12 Appendices

12.1 Appendix 1 Database search strategies

MEDLINE

via Ovid http://ovidsp.ovid.com/

1946 to November Week 3 2015

Searched on: 1st December 2015

Records retrieved: 712

The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in Ovid MEDLINE: sensitivity-maximizing version was used to limit retrieval to clinical trials (lines 25-35).[137]

The search was updated on 28th April 2016 and retrieved 749 records.

1 Arthritis, Psoriatic/ (4144)

2 (psoria$ adj2 (arthrit$ or arthropath$)).ti,ab. (6043)

3 1 or 2 (6887)

4 (Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7).af. (763)

5 3 and 4 (53)

6 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (88)

7 3 and 6 (18)

8 (golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5).af. (431)

9 (2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).ed. (4809341)

10 3 and 8 and 9 (89)

11 (apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9).af. (92)

12 (2014$ or 2015$).ed. (1668230)

13 3 and 11 and 12 (22)

14 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (536)

15 (2012$ or 2013$ or 2014$ or 2015$).ed. (3233078)

16 3 and 14 and 15 (86)

17 (inflectra or remsima or CT-P13).af. (17)

18 3 and 17 (1)

19 (etanercept or enbrel or 185243-69-0).af. (5831)

20 (infliximab or remicade or 170277-31-3).af. (9674)

21 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (4205)

22 19 or 20 or 21 (14458)

23 (2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).ed. (5535938)

24 3 and 22 and 23 (650)

25 randomized controlled trial.pt. (417039)

26 controlled clinical trial.pt. (92231)

27 randomized.ab. (308924)

28 placebo.ab. (159456)

29 drug therapy.fs. (1860741)

30 randomly.ab. (218795)

31 trial.ab. (321356)

32 groups.ab. (1376975)

33 or/25-32 (3513844)

34 exp animals/ not humans/ (4152952)

35 33 not 34 (2995700)

36 5 or 7 or 10 or 13 or 16 or 18 or 24 (765)

37 35 and 36 (712)

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

ed = entry date – date added to the database

pt = publication type

fs = floating subheading

adj = terms next to each other (order specified)

adj2 = terms within two words of each other (any order)

MEDLINE In-Process & Other Non-Indexed Citations

via Ovid http://ovidsp.ovid.com/

November 30, 2015

Searched on: 1st December 2015

Records retrieved: 157

The search was updated on 28th April 2016 and retrieved 168 records.

1 Arthritis, Psoriatic/ (0)

2 (psoria$ adj2 (arthrit$ or arthropath$)).ti,ab. (655)

3 1 or 2 (655)

4 (Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7).af. (126)

5 3 and 4 (16)

6 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (45)

7 3 and 6 (10)

8 (golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5).af. (97)

9 3 and 8 (13)

10 (apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9).af. (45)

11 3 and 10 (25)

12 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (148)

13 3 and 12 (36)

14 (inflectra or remsima or CT-P13).af. (19)

15 3 and 14 (0)

16 (etanercept or enbrel or 185243-69-0).af. (542)

17 (infliximab or remicade or 170277-31-3).af. (994)

18 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (631)

19 16 or 17 or 18 (1560)

20 3 and 19 (97)

21 5 or 7 or 9 or 11 or 13 or 15 or 20 (157)

Key:

/ = 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 11 of 12, November 2015

Searched on: 1st December 2015

Records retrieved: 225

The strategy below was used to search CENTRAL and CDSR.

The search was updated on 28th April 2016 and retrieved 249 records from CENTRAL.

#1 MeSH descriptor: [Arthritis, Psoriatic] this term only 199

#2 (psoria* near/2 (arthrit* or arthropath*)):ti,ab,kw 560

#3 #1 or #2 560

#4 (Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7):ti,ab,kw 191

#5 #3 and #4 24

#6 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6):ti,ab,kw 124

#7 #3 and #6 28

#8 (golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5):ti,ab,kw Publication Year from 2010 to 2015 210

#9 #3 and #8 40

#10 (apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9):ti,ab,kw Publication Year from 2014 to 2015 35

#11 #3 and #10 21

#12 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0):ti,ab,kw Publication Year from 2012 to 2015 102

#13 #3 and #12 39

#14 (inflectra or remsima or CT-P13):ti,ab,kw 15

#15 #3 and #14 4

#16 (etanercept or enbrel or 185243-69-0):ti,ab,kw Publication Year from 2009 to 2015 577

#17 (infliximab or remicade or 170277-31-3):ti,ab,kw Publication Year from 2009 to 2015 655

#18 (adalimumab or humira or D2E7 or (D2 next E7) or 331731-18-1):ti,ab,kw Publication Year from 2009 to 2015 722

#19 #16 or #17 or #18 1551

#20 #3 and #19 116

#21 #5 or #7 or #9 or #11 or #13 or #15 or #20 250

#22 #5 or #7 or #9 or #11 or #13 or #15 or #20 in Cochrane Reviews (Reviews and Protocols) and Trials 228

NB: 228 results at line #22 include Cochrane Reviews or Protocols as well as trials from CENTRAL

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

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Issue 12 of 12, December 2015

Searched on: 1st Decmeber 2015

Records retrieved: 3

See above under CENTRAL for search strategy used.

The search was updated on 28th April 2016 and retrieved 3 records from CDSR.

Database of Abstracts of Reviews of Effects (DARE)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 1st December 2015

Records retrieved: 13

The strategy below was used to search DARE and NHS EED.

As DARE and NHS EED were no longer receiving new records after 31st March 2015 these searches were not updated.

1	MeSH DESCRIPTOR Arthritis, Psoriatic	55
2	((psoria* NEAR2 (arthrit* or arthropath*)))	88
3	(((arthrit* or arthropath*) NEAR2 psoria*))	68
4	(Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7)	33
5	(secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6)	7
6	(golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5) WHERE LPD FROM 01/01/2010 TO 31/03/2015	31
7	(apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9) WHERE LPD FROM 01/01/2014 TO 31/03/2015	1
8	(ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0) WHERE LPD FROM 01/01/2012 TO 31/03/2015	22
9	(inflectra or remsima or CT-P13)	5
10	(etanercept or enbrel or 185243-69-0) WHERE LPD FROM 01/01/2009 TO 31/03/2015	137
11	(infliximab or remicade or 170277-31-3) WHERE LPD FROM 01/01/2009 TO 31/03/2015	204
12	(adalimumab or humira or D2E7 or D2-E7 or 331731-18-1) WHERE LPD FROM 01/01/2009 TO 31/03/2015	152
13	#1 OR #2 OR #3	92
14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	321
15	#13 AND #14	39
16	(#13 AND #14) IN DARE	13
17	(#13 AND #14) IN NHSEED	8
18	(#13 AND #14) IN HTA	18

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

NEAR2 = terms within two words of each other (order specified)

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2015 November 30

Searched on: 1st December 2015

Records retrieved: 639

A search strategy developed by Lefebvre et al. to limit retrieval of studies to RCTs was used (see lines 38-52).[138]

The search was updated on 28th April 2016 and retrieved 744 records.

1 psoriatic arthritis/ (13050)

2 (psoria$ adj2 (arthrit$ or arthropath$)).ti,ab. (11246)

3 1 or 2 (15353)

4 certolizumab pegol/ (3506)

5 (Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7).af. (4212)

6 4 or 5 (4212)

7 3 and 6 (548)

8 secukinumab/ (601)

9 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (679)

10 8 or 9 (679)

11 3 and 10 (199)

12 golimumab/ (2969)

13 (golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5).af. (3054)

14 12 or 13 (3054)

15 (2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).em. (8021136)

16 3 and 14 and 15 (708)

17 apremilast/ (456)

18 (apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9).af. (490)

19 17 or 18 (490)

20 (2014$ or 2015$).em. (3442925)

21 3 and 19 and 20 (170)

22 ustekinumab/ (2445)

23 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (2559)

24 22 or 23 (2559)

25 (2012$ or 2013$ or 2014$ or 2015$).em. (6165443)

26 3 and 24 and 25 (565)

27 (inflectra or remsima or CT-P13).af. (123)

28 3 and 27 (21)

29 etanercept/ (21668)

30 (etanercept or enbrel or 185243-69-0).af. (22500)

31 infliximab/ (33968)

32 (infliximab or remicade or 170277-31-3).af. (34643)

33 adalimumab/ (18932)

34 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (19317)

35 or/29-34 (47513)

36 (2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).em. (9378944)

37 3 and 35 and 36 (3116)

38 random$.ti,ab. (1044993)

39 factorial$.ti,ab. (26816)

40 crossover$.ti,ab. (55631)

41 cross-over$.ti,ab. (24911)

42 placebo$.ti,ab. (230032)

43 (doubl$ adj blind$).ti,ab. (163599)

44 (singl$ adj blind$).ti,ab. (16962)

45 assign$.ti,ab. (278181)

46 allocat$.ti,ab. (100141)

47 volunteer$.ti,ab. (201600)

48 Crossover Procedure/ (45294)

49 double blind procedure/ (127551)

50 Randomized Controlled Trial/ (392436)

51 single blind procedure/ (21379)

52 or/38-51 (1651603)

53 7 or 11 or 16 or 21 or 26 or 28 or 37 (3624)

54 52 and 53 (639)

55 animal/ (1708125)

56 exp animal experiment/ (1900985)

57 nonhuman/ (4661466)

58 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (5213728)

59 or/55-58 (7584705)

60 exp human/ (16613065)

61 human experiment/ (345688)

62 60 or 61 (16614514)

63 59 not (59 and 62) (5821013)

64 54 not 63 (639)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = all fields

pt = publication type

sh = subject heading field

adj2 = terms within two words of each other (any order)

em = entry week - date added to the database

Health Technology Assessment database (HTA)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 1st December 2015

Records retrieved: 18

The search was updated on 28th April 2016 and retrieved 20 records.

1	MeSH DESCRIPTOR Arthritis, Psoriatic	55
2	((psoria* NEAR2 (arthrit* or arthropath*)))	88
3	(((arthrit* or arthropath*) NEAR2 psoria*))	68
4	(Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7)	33
5	(secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6)	7
6	(golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5) WHERE LPD FROM 01/01/2010 TO 01/12/2015	31
7	(apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9) WHERE LPD FROM	4

	01/01/2014 TO 01/12/2015	
8	(ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0) WHERE LPD FROM 01/01/2012 TO 01/12/2015	28
9	(inflectra or remsima or CT-P13)	5
10	(etanercept or enbrel or 185243-69-0) WHERE LPD FROM 01/01/2009 TO 01/12/2015	176
11	(infliximab or remicade or 170277-31-3) WHERE LPD FROM 01/01/2009 TO 01/12/2015	267
12	(adalimumab or humira or D2E7 or D2-E7 or 331731-18-1) WHERE LPD FROM 01/01/2009 TO 01/12/2015	204
13	#1 OR #2 OR #3	92
14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	403
15	#13 AND #14	46
16	(#13 AND #14) IN HTA	18

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

NEAR2 = terms within two words of each other (order specified)

PubMed

http://www.ncbi.nlm.nih.gov/pubmed/

Searched on: 1st December 2015

Records retrieved: 779

The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in PubMed sensitivity-maximizing version was used to limit retrieval to clinical trials.[137]

The search was updated on 28th April 2016 and retrieved 844 records.

Search ((((((((((("Arthritis, Psoriatic"[Mesh:noexp]) OR (psoria*[Title/Abstract] AND arthrit*[Title/Abstract]) OR (psoria*[Title/Abstract] AND arthropath*[Title/Abstract]))) AND ((Certolizumab OR Cimzia OR CZP OR CDP870 OR CDP-870 OR 428863-50-7)))) OR ((((("Arthritis, Psoriatic"[Mesh:noexp]) OR (psoria*[Title/Abstract] AND arthrit*[Title/Abstract]) OR (psoria*[Title/Abstract] AND arthropath*[Title/Abstract]))) AND ((secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6)))) OR ((((("Arthritis, Psoriatic"[Mesh:noexp]) OR (psoria*[Title/Abstract] AND arthrit*[Title/Abstract]) OR (psoria*[Title/Abstract] AND arthropath*[Title/Abstract]))) AND (((golimumab OR simponi OR CNTO148 OR CNTO-148 OR 476181-74-5)) AND ("2010/01/01"[Date - Entrez] : "3000"[Date - Entrez])))) OR ((((("Arthritis, Psoriatic"[Mesh:noexp]) OR (psoria*[Title/Abstract] AND arthrit*[Title/Abstract]) OR (psoria*[Title/Abstract] AND arthropath*[Title/Abstract]))) AND (((apremilast OR otezla OR otezia OR CC10004 OR CC-10004 OR 608141-41-9)) AND ("2014/01/01"[Date - Entrez] : "3000"[Date - Entrez])))) OR ((((("Arthritis, Psoriatic"[Mesh:noexp]) OR (psoria*[Title/Abstract] AND arthrit*[Title/Abstract]) OR (psoria*[Title/Abstract] AND arthropath*[Title/Abstract]))) AND (((ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0)) AND ("2012/01/01"[Date - Entrez] : "3000"[Date - Entrez])))) OR ((((("Arthritis, Psoriatic"[Mesh:noexp]) OR (psoria*[Title/Abstract] AND arthrit*[Title/Abstract]) OR (psoria*[Title/Abstract] AND arthropath*[Title/Abstract]))) AND ((inflectra OR remsima OR CT-P13)))) OR ((((("Arthritis, Psoriatic"[Mesh:noexp]) OR (psoria*[Title/Abstract] AND arthrit*[Title/Abstract]) OR (psoria*[Title/Abstract] AND arthropath*[Title/Abstract]))) AND (((((((etanercept OR enbrel OR 185243-69-0))) AND ("2009/01/01"[Date - Entrez] : "3000"[Date - Entrez]))) OR ((((infliximab OR remicade OR 170277-31-3))) AND ("2009/01/01"[Date - Entrez] : "3000"[Date - Entrez]))) OR ((((adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1))) AND ("2009/01/01"[Date - Entrez] : "3000"[Date - Entrez])))))) AND ((((((((((randomized controlled trial[Publication Type]) OR controlled clinical trial[Publication Type]) OR randomized[Title/Abstract]) OR placebo[Title/Abstract]) OR drug therapy[sh]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract])) NOT (animals[mh] NOT humans[mh]))

Key:

[Mesh] = exploded indexing term (MeSH heading)

[mh] = exploded indexing term (MeSH heading)

[Mesh:NoExp] = indexing term (MeSH heading) not exploded

* = truncation

[Title/Abstract]) = terms in either title or abstract fields

[Publication Type] = terms in the publication type field

[Date - Entrez] = date added to the database

[sh] = subheading

Science Citation Index

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1900 – 28th November 2015

Searched on: 1st December 2015

Records retrieved: 712

Strategy below was used to search Science Citation Index and the Conference Proceedings Citation Index: Science. As both databases were searched together the records retrieved refer to results from both databases.

The search was updated on 28th April 2016 and retrieved 796 records from both databases.

# 27	712	#26 AND #25 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 26	1,284	#18 OR #13 OR #11 OR #9 OR #7 OR #5 OR #3 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 25	5,529,680	#23 NOT #24 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 24	3,812,114	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, CPCI-S Timespan=All years*
# 23	6,341,875	#22 OR #21 OR #20 OR #19 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 22	5,414,453	TS=(placebo* or random* or control* or prospectiv* or volunteer*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 21	486,891	TS=(clinic* SAME trial*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*

# 20	227,219	TS=((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 19	1,143,892	TS=((study or studies) SAME design*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 18	973	#17 AND #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 17	13,195	#16 OR #15 OR #14 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2009-2015*
# 16	4,497	TS=(adalimumab or humira or D2E7 or (D2 NEAR/1 E7) or 331731-18-1) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2009-2015*
# 15	8,564	TS=(infliximab or remicade or 170277-31-3) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2009-2015*
# 14	4,505	TS=(etanercept or enbrel or 185243-69-0) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2009-2015*
# 13	4	#12 AND #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 12	48	TS=(inflectra or remsima or CT-P13) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 11	151	#10 AND #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 10	632	TS=(ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2012-2015*
# 9	61	#8 AND #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*

# 8	126	TS=(apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2015*
# 7	137	#6 AND #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 6	594	TS=(golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2010-2015*
# 5	54	#4 AND #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 4	257	TS=(secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 3	101	#2 AND #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 2	1,386	TS=(Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 1	9,294	TS=(psoria* NEAR/2 (arthrit* or arthropath*)) *Indexes=SCI-EXPANDED, 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 within the same sentence

2. On-going, unpublished or grey literature search strategies

ClinicalTrials.gov

https://clinicaltrials.gov/

Searched on: 7th December 2015

Records retrieved: 99

The searches were updated on 28th April 2016 and retrieved 110 records.

1. 6 studies found for: ((psoriatic arthritis OR psoriatic arthropathy) AND (Certolizumab OR Cimzia OR CZP OR CDP870 OR CDP-870 OR 428863-50-7))

2. 11 studies found for: ((psoriatic arthritis OR psoriatic arthropathy) AND (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6))

3. 13 studies found for: (psoriatic arthritis OR psoriatic arthropathy) AND (golimumab OR simponi OR CNTO148 OR CNTO-148 OR 476181-74-5) | received from 01/01/2010 to 12/07/2015

4. 2 studies found for: (psoriatic arthritis OR psoriatic arthropathy) AND (apremilast OR otezla OR otezia OR CC10004 OR CC-10004 OR 608141-41-9) | received from 01/01/2014 to 12/07/2015

5. 3 studies found for: (psoriatic arthritis OR psoriatic arthropathy) AND (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0) | received from 01/01/2012 to 12/07/2015

6. 2 studies found for: (psoriatic arthritis OR psoriatic arthropathy) AND (inflectra OR remsima OR CT-P13)

7. 18 studies found for: (psoriatic arthritis OR psoriatic arthropathy) AND (etanercept OR enbrel OR 185243-69-0) | received from 01/01/2009 to 07/12/2015

8. **11 studies found for**: (psoriatic arthritis OR psoriatic arthropathy) AND (infliximab OR remicade OR 170277-31-3) | received from 01/01/2009 to 07/12/2015

9. 33 studies found for: (psoriatic arthritis OR psoriatic arthropathy) AND (adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1) | received from 01/01/2009 to 07/12/2015

Conference Proceedings Citation Index: Science

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1990 – 28th November 2015

Searched on: 1st December 2015

Records retrieved: 712

See above under Science Citation Index for search strategy used. As both databases were searched together the records retrieved refers to results from both databases.

The search was updated on 28th April 2016 and retrieved 796 records from both databases.

EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/ctr-search/search

Searched on: 7th December 2015

Records retrieved: 29

The searches were updated on 28th April 2016 and retrieved 2 new records.

1. 13 result(s) found for: (psoriatic arthritis OR psoriatic arthropathy) AND (Certolizumab OR Cimzia OR CZP OR CDP870 OR CDP-870 OR 428863-50-7 OR secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6 OR inflectra OR remsima OR CT-P13)

2. 4 result(s) found for: (psoriatic arthritis OR psoriatic arthropathy) AND (golimumab OR simponi OR CNTO148 OR CNTO-148 OR 476181-74-5) date limit 01/01/2010-07/12/2015

3. 0 result(s) found for: (psoriatic arthritis OR psoriatic arthropathy) AND (apremilast OR otezla OR otezia OR CC10004 OR CC-10004 OR 608141-41-9) date limits – 01/01/2014-07/12/2015

4. 3 result(s) found for: (psoriatic arthritis OR psoriatic arthropathy) AND (ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0) date limits 01/01/2012-07/12/2015

5. 9 result(s) found for: (psoriatic arthritis OR psoriatic arthropathy) AND (etanercept OR enbrel OR 185243-69-0 OR infliximab OR remicade OR 170277-31-3 OR adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1) date limits 01/01/2009-07/12/2015

PROSPERO

http://www.crd.york.ac.uk/PROSPERO/

Searched on: 4th December 2015

Records retrieved: 25

Search: Psoriatic arthritis in all fields.

The search was updated on 28th April 2016 and retrieved 9 new records.

WHO International Clinical Trials Registry Platform

http://www.who.int/ictrp/search/en/

Searched on: 7th December 2015

Records retrieved: 113

The searches were updated on 28th April 2016 and retrieved 5 new records.

1. Condition: (psoriatic arthritis OR psoriatic arthropathy) AND Intervention: (Certolizumab OR Cimzia OR CZP OR CDP870 OR CDP-870 OR 428863-50-7 OR secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6 OR inflectra OR remsima OR CT-P13)

29 trials found.

2. Condition: (psoriatic arthritis OR psoriatic arthropathy) AND Intervention: (golimumab OR simponi OR CNTO148 OR CNTO-148 OR 476181-74-5) limits 01/01/2010-07/12/2015

16 trials found.

3. Condition: (psoriatic arthritis OR psoriatic arthropathy) AND Intervention: (apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9) limits 01/01/2014-07/12/2015

0 records found.

4. Condition: (psoriatic arthritis OR psoriatic arthropathy) AND Intervention: (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0) limits 01/01/2012-07/12/2015

2 trials found.

5. Condition: (psoriatic arthritis OR psoriatic arthropathy) AND Intervention: (etanercept OR enbrel OR 185243-69-0 OR infliximab OR remicade OR 170277-31-3 OR adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1) limits 01/01/2009-07/12/2015

86 trials found.

3. Extra searches for systematic reviews

As DARE ceased at the end of March 2015, searches for systematic reviews were carried out on MEDLINE and EMBASE to ensure that any relevant systematic reviews were identified.

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2015 November 30

Searched on: 1st December 2015

Records retrieved: 82

The following strategy includes a search strategy designed to locate reviews for DARE in Ovid EMBASE (see lines 35-129).[139]

The search was updated on 28th April 2016 and retrieved 139 records.

1 psoriatic arthritis/ (13050)

2 (psoria$ adj2 (arthrit$ or arthropath$)).ti,ab. (11246)

3 1 or 2 (15353)

4 certolizumab pegol/ (3506)

5 (Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7).af. (4212)

6 4 or 5 (4212)

7 3 and 6 (548)

8 secukinumab/ (601)

9 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (679)

10 8 or 9 (679)

11 3 and 10 (199)

12 golimumab/ (2969)

13 (golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5).af. (3054)

14 12 or 13 (3054)

15 3 and 14 (806)

16 apremilast/ (456)

17 (apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9).af. (490)

18 16 or 17 (490)

19 3 and 18 (231)

20 ustekinumab/ (2445)

21 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (2559)

22 20 or 21 (2559)

23 3 and 22 (754)

24 (inflectra or remsima or CT-P13).af. (123)

25 3 and 24 (21)

26 etanercept/ (21668)

27 (etanercept or enbrel or 185243-69-0).af. (22500)

28 infliximab/ (33968)

29 (infliximab or remicade or 170277-31-3).af. (34643)

30 adalimumab/ (18932)

31 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (19317)

32 or/26-31 (47513)

33 3 and 32 (4302)

34 7 or 11 or 15 or 19 or 23 or 25 or 33 (4863)

35 systematic$ review$.ti,ab. (95091)

36 systematic$ literature review$.ti,ab. (6884)

37 "systematic review"/ (98895)

38 "systematic review (topic)"/ (13418)

39 meta analysis/ (102483)

40 "meta analysis (topic)"/ (23719)

41 meta-analytic$.ti,ab. (5089)

42 meta-analysis.ti,ab. (92607)

43 metanalysis.ti,ab. (351)

44 metaanalysis.ti,ab. (4420)

45 meta analysis.ti,ab. (92607)

46 meta-synthesis.ti,ab. (333)

47 metasynthesis.ti,ab. (173)

48 meta synthesis.ti,ab. (333)

49 meta-regression.ti,ab. (4113)

50 metaregression.ti,ab. (569)

51 meta regression.ti,ab. (4113)

52 (synthes$ adj3 literature).ti,ab. (2047)

53 (synthes$ adj3 evidence).ti,ab. (5649)

54 (synthes$ adj2 qualitative).ti,ab. (939)

55 integrative review.ti,ab. (1084)

56 data synthesis.ti,ab. (10020)

57 (research synthesis or narrative synthesis).ti,ab. (1100)

58 (systematic study or systematic studies).ti,ab. (9606)

59 (systematic comparison$ or systematic overview$).ti,ab. (2447)

60 (systematic adj2 search$).ti,ab. (14698)

61 systematic$ literature research$.ti,ab. (172)

62 (review adj3 scientific literature).ti,ab. (1182)

63 (literature review adj2 side effect$).ti,ab. (11)

64 (literature review adj2 adverse effect$).ti,ab. (2)

65 (literature review adj2 adverse event$).ti,ab. (9)

66 (evidence-based adj2 review).ti,ab. (2599)

67 comprehensive review.ti,ab. (9891)

68 critical review.ti,ab. (13722)

69 critical analysis.ti,ab. (6783)

70 quantitative review.ti,ab. (596)

71 structured review.ti,ab. (712)

72 realist review.ti,ab. (93)

73 realist synthesis.ti,ab. (61)

74 (pooled adj2 analysis).ti,ab. (10726)

75 (pooled data adj6 (studies or trials)).ti,ab. (1727)

76 (medline and (inclusion adj3 criteria)).ti,ab. (13602)

77 (search adj (strateg$ or term$)).ti,ab. (23159)

78 or/35-77 (313391)

79 medline.ab. (82933)

80 pubmed.ab. (59842)

81 cochrane.ab. (49544)

82 embase.ab. (49331)

83 cinahl.ab. (14619)

84 psyc?lit.ab. (963)

85 psyc?info.ab. (11667)

86 lilacs.ab. (4162)

87 (literature adj3 search$).ab. (41110)

88 (database$ adj3 search$).ab. (38127)

89 (bibliographic adj3 search$).ab. (1761)

90 (electronic adj3 search$).ab. (13296)

91 (electronic adj3 database$).ab. (18556)

92 (computeri?ed adj3 search$).ab. (3348)

93 (internet adj3 search$).ab. (2745)

94 included studies.ab. (12116)

95 (inclusion adj3 studies).ab. (10022)

96 inclusion criteria.ab. (73458)

97 selection criteria.ab. (23235)

98 predefined criteria.ab. (1684)

99 predetermined criteria.ab. (980)

100 (assess$ adj3 (quality or validity)).ab. (62963)

101 (select$ adj3 (study or studies)).ab. (56413)

102 (data adj3 extract$).ab. (46092)

103 extracted data.ab. (9890)

104 (data adj2 abstracted).ab. (5666)

105 (data adj3 abstraction).ab. (1428)

106 published intervention$.ab. (148)

107 ((study or studies) adj2 evaluat$).ab. (168567)

108 (intervention$ adj2 evaluat$).ab. (9530)

109 confidence interval$.ab. (302095)

110 heterogeneity.ab. (130769)

111 pooled.ab. (71894)

112 pooling.ab. (10965)

113 odds ratio$.ab. (209779)

114 (Jadad or coding).ab. (151963)

115 evidence-based.ti,ab. (89257)

116 or/79-115 (1249442)

117 review.pt. (2121803)

118 116 and 117 (155285)

119 review.ti. (354800)

120 116 and 119 (79064)

121 (review$ adj10 (papers or trials or trial data or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ti,ab. (349461)

122 (retriev$ adj10 (papers or trials or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ti,ab. (17449)

123 78 or 118 or 120 or 121 or 122 (648468)

124 letter.pt. (918884)

125 editorial.pt. (497918)

126 124 or 125 (1416802)

127 123 not 126 (636540)

128 (animal/ or nonhuman/) not exp human/ (4935282)

129 127 not 128 (611316)

130 34 and 129 (558)

131 2015$.em. (1962120)

132 130 and 131 (82)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

? = optional wildcard – one or no characters

ti,ab = terms in either title or abstract fields

af = all fields

pt = publication type

sh = subject heading field

adj2 = terms within two words of each other (any order)

em = entry week - date added to the database

MEDLINE

via Ovid http://ovidsp.ovid.com/

1946 to November Week 3 2015

Searched on: 1st December 2015

Records retrieved: 9

The following strategy includes a search strategy designed to locate reviews for DARE in Ovid MEDLINE (see lines 22-98).[139]

The search was updated on 28th April 2016 and retrieved 25 records.

1 Arthritis, Psoriatic/ (4144)

2 (psoria$ adj2 (arthrit$ or arthropath$)).ti,ab. (6043)

3 1 or 2 (6887)

4 (Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7).af. (763)

5 3 and 4 (53)

6 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (88)

7 3 and 6 (18)

8 (golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5).af. (431)

9 3 and 8 (104)

10 (apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9).af. (92)

11 3 and 10 (29)

12 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (536)

13 3 and 12 (114)

14 (inflectra or remsima or CT-P13).af. (17)

15 3 and 14 (1)

16 (etanercept or enbrel or 185243-69-0).af. (5831)

17 (infliximab or remicade or 170277-31-3).af. (9674)

18 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (4205)

19 16 or 17 or 18 (14458)

20 3 and 19 (1129)

21 5 or 7 or 9 or 11 or 13 or 15 or 20 (1267)

22 systematic$ review$.ti,ab. (62767)

23 meta-analysis as topic/ (15063)

24 meta-analytic$.ti,ab. (3875)

25 meta-analysis.ti,ab,pt. (80432)

26 metanalysis.ti,ab. (130)

27 metaanalysis.ti,ab. (1122)

28 meta analysis.ti,ab. (61044)

29 meta-synthesis.ti,ab. (245)

30 metasynthesis.ti,ab. (143)

31 meta synthesis.ti,ab. (245)

32 meta-regression.ti,ab. (2799)

33 metaregression.ti,ab. (315)

34 meta regression.ti,ab. (2799)

35 (synthes$ adj3 literature).ti,ab. (1446)

36 (synthes$ adj3 evidence).ti,ab. (4369)

37 integrative review.ti,ab. (943)

38 data synthesis.ti,ab. (7556)

39 (research synthesis or narrative synthesis).ti,ab. (821)

40 (systematic study or systematic studies).ti,ab. (6891)

41 (systematic comparison$ or systematic overview$).ti,ab. (1891)

42 evidence based review.ti,ab. (1253)

43 comprehensive review.ti,ab. (6999)

44 critical review.ti,ab. (10688)

45 quantitative review.ti,ab. (474)

46 structured review.ti,ab. (490)

47 realist review.ti,ab. (58)

48 realist synthesis.ti,ab. (44)

49 or/22-48 (164741)

50 review.pt. (2034742)

51 medline.ab. (60574)

52 pubmed.ab. (36054)

53 cochrane.ab. (34003)

54 embase.ab. (33609)

55 cinahl.ab. (11111)

56 psyc?lit.ab. (871)

57 psyc?info.ab. (7994)

58 (literature adj3 search$).ab. (27401)

59 (database$ adj3 search$).ab. (26195)

60 (bibliographic adj3 search$).ab. (1303)

61 (electronic adj3 search$).ab. (9505)

62 (electronic adj3 database$).ab. (11568)

63 (computeri?ed adj3 search$).ab. (2654)

64 (internet adj3 search$).ab. (1771)

65 included studies.ab. (7960)

66 (inclusion adj3 studies).ab. (7019)

67 inclusion criteria.ab. (37933)

68 selection criteria.ab. (21191)

69 predefined criteria.ab. (1159)

70 predetermined criteria.ab. (756)

71 (assess$ adj3 (quality or validity)).ab. (42982)

72 (select$ adj3 (study or studies)).ab. (39117)

73 (data adj3 extract$).ab. (31055)

74 extracted data.ab. (7660)

75 (data adj2 abstracted).ab. (3467)

76 (data adj3 abstraction).ab. (878)

77 published intervention$.ab. (108)

78 ((study or studies) adj2 evaluat$).ab. (110270)

79 (intervention$ adj2 evaluat$).ab. (6324)

80 confidence interval$.ab. (243474)

81 heterogeneity.ab. (97658)

82 pooled.ab. (48633)

83 pooling.ab. (7960)

84 odds ratio$.ab. (161734)

85 (Jadad or coding).ab. (123582)

86 or/51-85 (846853)

87 50 and 86 (138063)

88 review.ti. (262483)

89 88 and 86 (51780)

90 (review$ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)).ti,ab. (105599)

91 49 or 87 or 89 or 90 (305581)

92 letter.pt. (928972)

93 editorial.pt. (379192)

94 comment.pt. (631763)

95 92 or 93 or 94 (1437876)

96 91 not 95 (297485)

97 exp animals/ not humans/ (4152952)

98 96 not 97 (287212)

99 21 and 98 (96)

100 2015$.ed. (777364)

101 99 and 100 (9)

Key:

/ = indexing term (MeSH heading)

exp = exploded indexing term (MeSH heading)

$ = truncation

? = optional wildcard – one or no characters

ti,a. = terms in either title or abstract fields

af = terms in any field

ed = entry date – date added to the database

pt = publication type

adj = terms next to each other (order specified)

adj2 = terms within two words of each other (any order)

12.2 Appendix 2 Inclusion/exclusion criteria of the included studies

Study and drug	Inclusion criteria	Exclusion criteria
FUTURE 2 Secukinumab[43]	• active PsA with ≥3 tender and swollen joints and met the (CASPAR) criteria, despite previous treatment with NSAIDs, DMARDs, anti-TNFs • Concomitant oral corticosteroids (≤10 mg/day prednisone or equivalent) and MTX (≤25 mg/week) were allowed provided the dose was stable for at least 2 weeks and at least 4 weeks before randomisation	• previously received biologic immunomodulating agents, except for those targeting TNF • previously been treated with > 3 different TNF inhibitors • ongoing use of prohibited psoriasis treatments/medications (e.g. topical corticosteroids, ultraviolet therapy) at randomisation (the following washout periods were required to be observed: oral or topical retinoids 4 weeks; photochemotherapy 4 weeks; phototherapy 2 weeks; topical skin treatments [except in face, eyes, scalp, and genital area during screening, only corticosteroids with mild to moderate potency] 2 weeks) • active, ongoing inflammatory diseases other than psoriatic arthritis; • active tuberculosis (patients with latent tuberculosis had to commence treatment for latent tuberculosis before study entry) • a history of hepatitis B or C, human immunodeficiency virus, or any active systemic infection within the 2 weeks before baseline • history of ongoing, chronic, or recurrent infections, or evidence of active tuberculosis infection • history of malignancy within the past 5 years (except for basal cell carcinoma or actinic keratosis that has been treated with no evidence of recurrence in the past 3 months, in-situ cervical cancer or non-invasive malignant colon polyps that had been removed) • underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromised the patient and/or placed the patient at unacceptable risk for participation • pregnant or nursing (lactating) women and women of child-bearing potential unwilling to use effective contraception during the study and for

Study and drug	Inclusion criteria	Exclusion criteria
		16 weeks after stopping treatment
ERASURE Secukinumab[44] 140	• Moderate and severe plaque-type psoriasis diagnosed for at least 6 months • Severity of psoriasis disease meeting all of the following three criteria: o Psoriasis Area and Severity Index (PASI) score of 12 or greater o Investigator's Global Assessment (IGA) score of 3 or greater o Total body surface area (BSA) affected of 10% or greater • Inadequate control by prior use of topical treatment, phototherapy and/or systemic therapy	• Current forms of psoriasis other than chronic plaque-type psoriasis (for example, pustular, erythrodermic, guttate) • Current drug-induced psoriasis • Previous use of secukinumab or any drug that targets IL-17 or IL-17 receptor • Methotrexate, cyclosporine A, corticosteroids, cyclophosphamid • Significant medical problems such as uncontrolled hypertension, congestive heart failure or a condition that significantly immunocompromises the subject • Hematological abnormalities • History of an ongoing, chronic or recurrent infectious disease, or evidence of untreated tuberculosis • History of lymphoproliferative disease or history of malignancy of any organ system within the past 5 years • Pregnant or nursing (lactating) women • Subjects not willing to limit UV light exposure during the study
FIXTURE Secukinumab[44]	• Moderate and severe plaque-type psoriasis diagnosed for at least 6 months • Severity of psoriasis disease meeting all of the following three criteria: o Psoriasis Area and Severity Index (PASI) score of 12 or greater, o Investigator's Global Assessment (IGA) score of 3 or greater, o Total body surface area (BSA) affected of 10% or greater. • Inadequate control by prior use of topical treatment, phototherapy and/or systemic therapy	• Previous used of etanercept • Current forms of psoriasis other than chronic plaque-type psoriasis (for example, pustular, erythrodermic, guttate) • Current drug-induced psoriasis • Previous use of secukinumab or any drug that targets IL-17 or IL-17 receptor • Methotrexate, cyclosporine A, corticosteroids, cyclophosphamid • Significant medical problems such as uncontrolled hypertension, congestive heart failure or a condition that significantly immunocompromises the subject

Study and drug	Inclusion criteria	Exclusion criteria
[140]		• Hematological abnormalities • History of an ongoing, chronic or recurrent infectious disease, or evidence of untreated tuberculosis • History of lymphoproliferative disease or history of malignancy of any organ system within the past 5 years • Pregnant or nursing (lactating) women • Subjects not willing to limit UV light exposure during the study
CLEAR Secukinumab [57] [58]	• Moderate and severe plaque-type psoriasis diagnosed for at least 6 months. • patients eligible for systemic therapy with inadequately controlled psoriasis	• forms of psoriasis other than plaque type psoriasis • previous exposure to secukinumab, ustekinumab, or other biologic drugs targeting (IL)-17A or IL-17RA
SPIRIT-P1[a] Adalimumab [52,]	• Presents with established diagnosis of active psoriatic arthritis for at least 6 months, and currently meets Classification for Psoriatic Arthritis (CASPAR) criteria • Active psoriatic arthritis (PsA) defined as the presence of at least 3 tender and at least 3 swollen joints • Presence of active psoriatic skin lesion or a history of plaque psoriasis (Ps) • Men must agree to use a reliable method of birth control or remain abstinent during the study • Women must agree to use reliable birth control or remain abstinent	• Current or prior use of biologic agents for treatment of Ps or PsA • Inadequate response to greater than or equal to 4 conventional disease-modifying antirheumatic drugs (DMARDs) • Current use of more than one conventional DMARD • Evidence of active inflammatory arthritic syndromes or spondyloarthropathies other than PsA • Have participated in any study with interleukin 17 (IL-17) antagonists, including ixekizumab • Serious disorder or illness other than psoriatic arthritis

Study and drug	Inclusion criteria	Exclusion criteria
[62]	during the study and for at least 12 weeks after stopping treatment	• Serious infection within the last 3 months • Breastfeeding or nursing (lactating) women
RAPID-PsA Certolizumab[42]	[redacted]	[redacted]
PALACE 1,2,3 Apremilast[55, 60, 64 56]	• ≥3 tender and swollen joint • CASPAR criteria • stable dose (oral or parenteral methotrexate ≤25 mg/week; leflunomide ≤ 20 mg/day sulfasalazine ≤2 g/day; or a combination) for at least 4 weeks before the screening visit • prednisone • ≤10 mg/day or equivalent for at least 1 month and • non-steroidal anti-inflammatory drugs ≥2 weeks • at least one ≥ 2 cm plaque psoriasis lesion [b]	• >3 agents for PsA (DMARDs or biologics) or >1anti-TNF • history of or current (1) inflammatory rheumatic or autoimmune joint disease other than PsA • (2) erythrodermic guttate or generalised pustular psoriasis; • (3) were functional class IV, defined by the American College of Rheumatology (ACR) Classification of Functional Status in Rheumatoid Arthritis • (4) had used phototherapy or DMARDs • other than methotrexate, leflunomide or sulfasalazine within 4 weeks of randomisation; • (5) had used adalimumab, etanercept, • golimumab, infliximab, certolizumab pegol or tocilizumab within 12 weeks of randomisation or alefacept or ustekinumab within 24 weeks of

Study and drug	Inclusion criteria	Exclusion criteria
		randomisation • (6) had prior treatmentwith apremilast. • topical therapy for psoriasis within 2 weeks • Patients with active TB or a history of incompletely treated TB
PUSMMIT 2 Ustekinumab[54, 61]	• ≥3 months (DMARD) therapy, ≥4 weeks (NSAIDs) therapy and/or ≥ 8(etanercept, adalimumab, golimumab, certolizumabpegol) or 14 (infliximab) continuous weeks • ≥5/66 swollen and ≥5/68 tender joints • (CRP) ≥6.0 mg/L (modified to ≥3.0 mg/L after study start upper limit of normal10 mg/L) • active/documented history of plaque psoriasis • Concomitant methotrexate (MTX) was permitted if started ≥3 months prior to study start and at a stable dose (≤25 mg/week) for ≥4 weeks	• Have other inflammatory diseases, including but not limited to rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, or Lyme disease • Have used any therapeutic agent targeted at reducing IL-12 or IL-23 agent or abatacept • Have a medical history of latent or active granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis, prior to screening • Have any known malignancy or have a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years of the beginning of the study
PUSMMIT 1 Ustekinuma	• (≥5 tender and swollen joints, C-reactive protein ≥3.0 mg/L), documented history of plaque psoriasis • MTX ≤25 mg/week at least 3 months prior • if currently not using MTX, must have not received MTX for at least 4 weeks prior to the first administration of the study agent	• Have other inflammatory diseases, including but not limited to rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, or Lyme disease • Have used any therapeutic agent targeted at reducing interleukin (IL)-12 or IL-23, including but not limited to ustekinumab and briakinumab (ABT-874) • Have used any biologic agents that are targeted for reducing tumor necrosis factor-alpha, including but not limited to infliximab, etanercept, adalimumab, and golimumab

Study and drug	Inclusion criteria	Exclusion criteria
b[61]		• Have a medical history of latent or active granulomatous infection • Have any known malignancy or have a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years of the beginning of the study
Atteno[59] ETA vs ADA vs INF	• patients >18 years with active PsA who experienced an inadequate response to a previous DMARD therapy • CASPAR criteria	• previous usage of anti-TNF-α inhibitors • the usage of DMARDs other than sulfasalazine, methotrexate, azathioprine, and leflunomide within 4 weeks of enrolment • the usage of more than 10 mg prednisone daily • variation of dosage of NSAIDs or prednisone within 2 weeks of enrolment
GO-REVEAL Golim	• ≥3 swollen and 3 tender joints • negative rheumatoid factor, at least 1 subset of PsA, and • the presence of plaque psoriasis with a qualifying lesion at least 2 cm in diameter • Previous use of anti-TNF agents, rituximab, natalizumab, or cytotoxic agents was prohibited • Stable doses of (MTX), NSAIDs, and corticosteroids (prednisone 10	• No prior treatment with biologic anti-TNF agents (infliximab, etanercept, adalimumab) • No treatment with alefacept or efalizumab within 3 months prior to the first study drug injection • No DMARDs other than methotrexate, or immunosuppressive drugs within 4 weeks prior to the first study drug injection.

Study and drug	Inclusion criteria	Exclusion criteria
umab[45]	mg/day) were allowed • Patients in whom latentTuberculosis could participate if they were treated for latent tuberculosis prior to or concurrent with administration of the study agent	
Genovese 2007 Adalimumab[51]	• ≥3 swollen and tender joints • Plaque psoriasis • Had received/receiving concomitant DMARD therapy or had a history of DMARD therapy with an inadequate response • prednisone ≤10 mg/day and had been stable • stable dose of MTX ≤30 mg/week and other DMARDs except cyclosporine and tacrolimus was allowed if within 4 weeks of the baseline visit	• history of previous anti-TNF therapy • intravenous infusions or intraarticular injections of corticosteroids within 4 weeks of baseline • topical psoriasis therapies within 2 weeks of baseline • UVA phototherapy, using tanning booth within 2 weeks • Oralretinoids within 4 weeks • alefacept or siplizumab within 12 weeks • any other biologic or investigational therapy within 6 weeks • currently using or likely to need antiretroviral therapy • Patients with persistent or severe infections or a history of active tuberculosis,or who had an active nonpsoriatic skin disease • significant history of cardiac, renal, neurologic, psychiatric, endocrinologic, metabolic, or hepatic disease; neurologic symptoms suggestive of central nervous systemic demyelinating disease; and a history of malignancy other than carcinoma *in situ* of the cervix or adequately treated nonmetastatic squamous or basal cell skin carcinoma.
ADEPT Ad	• ≥3 swollen and tender joints • Patients required to have inadequate response or intolerance to NSAIDs • MTX was allowed only if it had been taken for at least 3 months with the dosage stable for at least 4 weeks prior to the baseline visit	• treatment within 4 weeks of the baseline visit with cyclosporine, tacrolimus, DMARDs other than MTX, or oral retinoids • topical treatments for psoriasis within 2 weeks of baseline, other than medicated shampoos or low-potency topical steroids

Study and drug	Inclusion criteria	Exclusion criteria
alimumab[50]		• concurrent treatment with MTX at dosages **>30 mg**/week and/or corticosteroids in a prednisone-equivalent dosage of >10 mg/day • anti-TNF therapy • history of neurologic symptoms suggestive of central nervous system demyelinating disease, a history of active tuberculosis (TB) or listeriosis, or the presence of a severe infection requiring hospitalization or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days of study entry
IMPACT Infliximab[46]	• Diagnosed psoriatic arthritis for ≥ 6 months • previous failure of treatment with ≥1 DMARDs. • active arthritis with ≥5 tender and swollen joints • (ESR) ≥28 mm/hour, (CRP) level ≥15 mg/liter, and/or morning stiffness lasting 45 minutes or longer • negative results of serum tests for rheumatoid factor and negative results for active or latent tuberculosis • Patients were allowed to • receive concomitant therapy with 1 of the following DMARDs • methotrexate (MTX; dosage of 15 mg/week or more, with folic • acid supplementation), leflunomide, sulfasalazine, hydroxyl-chloroquine, intramuscular gold, penicillamine, or azathioprine • Standard topical treatments for psoriatic lesions (e.g., topical steroids) were permitted	• Use of intramuscular or intravenous corticosteroids, cyclosporine, or tacrolimus within 4 weeks of screening and throughout the study • Therapy with psoralen ultraviolet A • received any investigational drug within 3 months of screening or any previous treatment with a monoclonal antibody or fusion protein.
IMPACT 2 Infliximab	• Diagnosed psoriatic arthritis for >= 6 months • active arthritis with >= 5 tender and swollen joints • (CRP) levels of at least 15 mg/l and/or morning stiffness lasting 45 minutes or longer • inadequate response to current or previous DMARDs or (NSAIDs) • Active plaque psoriasis with at least one qualifying target lesion at	• evidence of latent or active tuberculosis • had chronic or clinicallysignificant infection, malignancy, or congestive heart failure;or if they had used TNFa inhibitors previously • Concomitant methotrexate (MTX) treatment ≥25 mg/week and >10 mg prednisone • DMARDs (other than MTX) or intra-articular Corticosteroids within 4

Study and drug	Inclusion criteria	Exclusion criteria
mab [47]	least 2 cm in diameter • negative test for rheumatoid factor in their serum • Concurrent use of topical or systemic drugs/ treatments for psoriasis was not permitted during the study except low potency topical corticosteroids on the face or groin	weeks prior to enrollment in the study and DMARD use other than MTX was not allowed during the trial
Mease 2004 Etanercept [49] (NCT00317499)	• Active PsA with ≥3 swollen and tender joints • Inadequaten response to non-steroidal anti-inflammatory drugs • had at least 1 of the following clinical subtypes of PsA (distal interphalangeal (DIP) joint involvement, polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis), arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis–like arthritis) • plaque psoriasis with a qualifying lesion at least 2 cm in diameter • Concomitant methotrexate a stable dosage of ≤25 mg/week and prednisolone ≤10 mg/day • discontinued other DMARDs at least 4 weeks before the study	• Phototherapy was discontinued at least 2 weeks before the study start. Oral retinoids, topical vitamin A or D analog preparations, and anthralin were not allowed. Topical therapies were permitted on the scalp, axillae, and groin only • Significant concurrent medical diseases including: o Diabetes mellitus requiring insulin o Uncompensated congestive heart failure o Myocardial infarction within 12 months of screening visit o Unstable or stable angina pectoris o Uncontrolled hypertension o Severe pulmonary disease (requiring medical or oxygen therapy) o History of cancer (other than resected cutaneous basal or squamous cell carcinoma or in situ cervical cancer) within 5 years of screening visit o HIV positive, hepatitis B surface antigen, or hepatitis C positive o Rheumatoid arthritis, systemic lupus, scleroderma, or polymyositis o Any condition judged by the subject's physician that would cause this study to be detrimental to the subject • Current or history of psychiatric disease that would interfere with ability to comply with the study protocol or give informed consent. • History of alcohol or drug abuse that would interfere with ability to comply with the study protocol

Study and drug	**Inclusion criteria**	**Exclusion criteria**
Mease 2000 Etanercept[48]	• Active PsA with ≥3 swollen and tender joints • Inadequate response to non-steroidal anti-inflammatory drugs • Patients taking methotrexate (_25 mg/week) were allowed to continue methotrexate if the dose was stable for 4 weeks before study start and remained stable throughout the study • ≤10 mg/day of prednisone, stable for at least 2 weeks before the first dose of study drug, and maintained at a constant dose throughout the study	• evidence of skin conditions other than psoriasis (such as eczema) • Other DMARDs (except MTX) were discontinued at least 2 weeks before beginning the study drug and were not allowed during the study • Topical therapies and oral retinoids for psoriasis were discontinued at least 2 weeks before the baseline evaluation and phototherapy was discontinued at least 4 weeks

[a]ixekizumab is not treatment of interest, which is excluded from the remaining of the write-up; [b]PALACE 3 only

12.3 Appendix 3 Detailed evidence synthesis

12.3.1 Detailed evidence synthesis framework

The evidence synthesis was undertaken using WinBUGS (version 1.4.3). WinBUGS is a s analysis software tool that, through the use of Markov Chain Monte Carlo, calculates posterior distributions for the parameters of interest given likelihood functions derived from data and prior probabilities (uninformative priors were used throughout). There were few individual studies on each treatment, therefore fixed-effect models were used across studies in all analyses. Parameter estimates for all functional parameters were reported from the models. These differ by outcome, and further details are presented in the subsections below. Treatment effects were expressed in relation to placebo. Due to the sparse evidence imposing a high level of uncertainty over estimates of functional parameters, point estimates are medians throughout. Some models assumed exchangeability across treatments within a class. Within such models we reported the estimates for each treatment (called shrunken estimates) rather than the class medians, allowing us to represent any residual differences across treatments.

All PsARC response, and HAQ conditional on PsARC response, models were run for 20,000 iterations after a burn-in of 30,000 on 2 chains. All PASI response and ACR response models were run for 20,000 iterations after a burn-in of 50,000 on 2 chains. The level of credibility used was 95% (i.e. 95% credible intervals, CrIs). The DIC statistic, convergence and autocorrelation were all assessed and informed model selection. Thinning was considered where autocorrelation was high. Model fit statistics are reported in form of DIC and residual deviance.

12.3.2 Data used for the ustekinumab (PSUMMIT) trials

The marketing authorisation for ustekinumab differs from the other biologics in terms of how long treatment should be continued before clinicians should consider stopping treatment. While the recommendation for ustekinumab is for doctors to consider stopping treatment if there is no response after 28 weeks, for the other biologics the stopping timeframes range between 12 and 16 weeks. However, the PSUMMIT trials had an early escape cross-over design at week 16, just like several other trials included in the NMA (including the FUTURE 2 and RAPID-PsA trials). Using the post-early escape 24 week data from the PSUMMIT trials but pre-early escape data from the other trials would introduce methodological heterogeneity across treatments, which could potentially have implications on results. With this in mind we obtained 12 week data for the PSUMMIT trials via the YODA project (see section 4.1). Although biologic naïve and experienced subgroup data were extracted for several relevant outcomes from the PSUMMIT clinical study reports, these subgroup

data were not available for PsARC at 12 weeks for PSUMMIT 2, although they were available for the full population.

The data from YODA showed that results for the PsARC and HAQ outcomes were very similar at 12 and 24 weeks in both PSUMMIT trials (Table 110). Conversely, the 12 and 24 week results appear different for the PASI outcomes, particularly at the higher thresholds. A similar pattern of results (when comparing 12 and 24 weeks) can be seen in the RAPID-PsA trial, but is less evident in the secukinumab FUTURE 2 trial (Table 110). Some differences across treatments may be due to variations in analysis approaches used with respect to non-responder imputations in early escapers. It was also noted that in the ADEPT trial of adalimumab, which was placebo-controlled and blinded up to 24 weeks *without* early escape, there was around a 10% increase in PASI 75 and PASI 90 response rates going from 12 to 24 weeks.

Table 110 12 and 24 week full population results across recent trials which used an early-escape at 16 weeks design

Trial and arm	PsARC		HAQ[a]		PASI 50		PASI 75		PASI 90	
	12	24	12	24	12	24	12	24	12	24
FUTURE 2, SEC 150mg	69	[redacted]	NR	-0.48	83	NR	53	43	33	33
FUTURE 2, SEC 300mg	72	[redacted]	NR	-0.56	83	NR	59	63	39	49
Rapid PsA, CZP 200mg	73	78	-0.45	-0.52	69	74	47	62	22	47
Rapid PsA, CZP 400mg	66	77	-0.39	-0.43	63	72	47	61	20	36
PSUMMIT 1, UST 45mg	59	56	-0.28	-0.31	61	78	39	57	19	41
PSUMMIT 2, UST 45mg	52	55	-0.21	-0.21	64	68	39	51	20	30

[a] change from baseline; results are % responders for all outcomes except HAQ; for early escapers non-responder imputations were used for all treatment groups in the FUTURE 2 and PSUMMIT trials but for the placebo group only in RAPID-PsA

Based on these observations, and to allow our analyses to include subgroup data from both the PSUMMIT trials, we used the 24 week PSUMMIT data for the analyses of PsARC and HAQ, on the assumption that they fairly reflected the 12 week results. For the analyses of PASI and ACR outcomes (where the 12 and 24 week results differed) we used the 12 week data.

12.3.3 PsARC response

12.3.3.1 Detailed methods for biologic naïve subpopulation

Each trial reported the number of events (PsARC responses) in the placebo and the number of events under treatments (r_{it}), where *i* represents a trial (i=1, …, 14), and *t* represents a treatment (*t*=1, …, 10). Across all models, it was assumed that r_{it} are binomially distributed, with probability parameter p_{it}, representing the probability of an event (PsARC response) in treatment arm *t* of trial *i*. Since the parameters of interest, p_{it}, are probabilities and therefore can only take values between 0 and 1, we

modelled these on the logit scale (log odds). We implemented separate models for the pooling of treatment effects and of placebo responses.

Treatment effect models

The treatment effect model assumed the baseline and treatment effects to be additive on the logit scale $Logit(p_{it}) = \mu_i + \delta_t$. This means that log odds ratios were pooled across trials. In the treatment effect models, the baselines were considered trial-specific (unconstrained). We implemented a set of alternative models in what concerns the specification of treatment effects. We first explored a model with independent treatment effects across treatments. We then explored the possibility of placebo response determining the effectiveness of alternative treatments (with treatment effects still assumed independent). We also explored whether there was similarity between treatment effects for treatments of the same class.

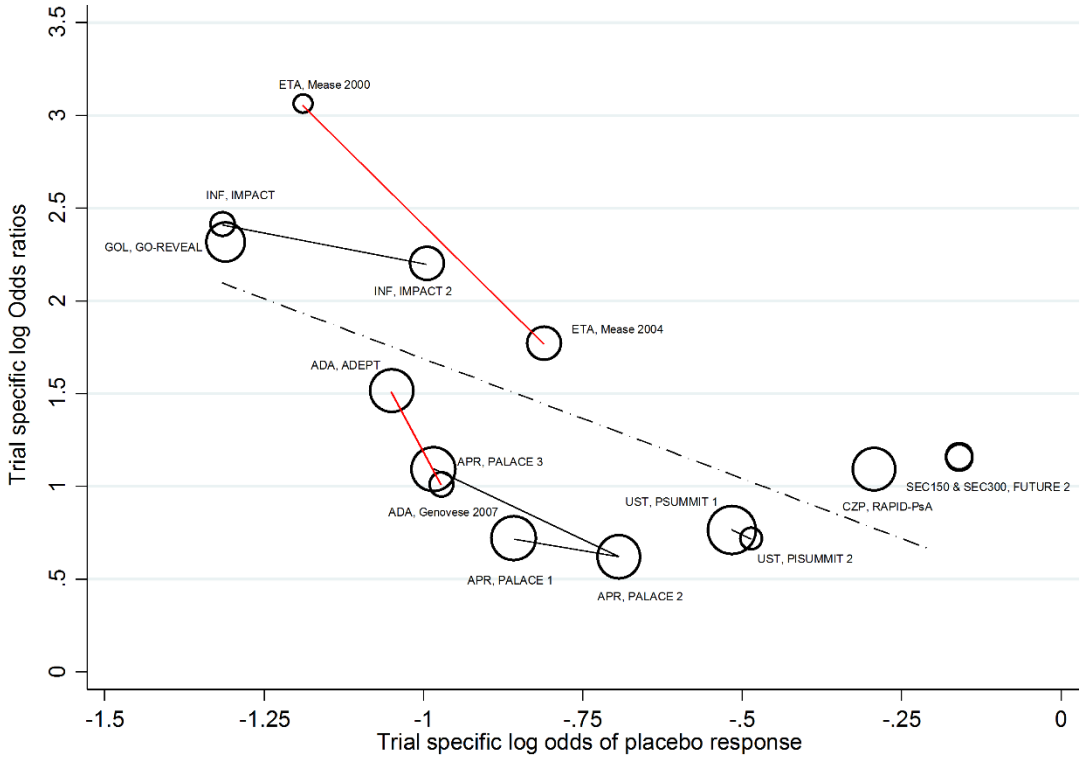
Exploring placebo response as a treatment effect modifier

The trial specific data shows that higher placebo rates are associated with lower relative effectiveness estimates. Our investigations regarding trial designs and patient characteristics did not identify a clear reason for such differences although placebo response rates appear to have increased over time. Despite, we investigated the effect of placebo response as a treatment effect modifier. It should be noted that the source of any relationship between placebo response and treatment effect is unclear the reader should interpret the results carefully and with caution.

Figure 20 shows the relationships between trial specific observed placebo responses and odds ratios on log odds scale in biologic naïve population. Considering placebo response as a treatment effect modifier in the independent treatment effects analysis, only multiple studies of the same treatment (2 or more studies) can inform the placebo effect. Hence, treatments from the single trials i.e. certolizumab, secukinumab and golimumab do not contribute to the interaction in the independent treatment effects analysis. In Figure 20, the solid lines within the plot reflect the relationship between the trials of the same treatments. Those with a steeper slope will indicate a stronger effect modification of placebo response, i.e. stronger association between placebo response and treatment effects. The highest effects are seen between trials of adalimumab and etanercept – lines in red in Figure 20. Among the trials on etanercept, the Mease 2000 trial has the smallest number of participants and the response rates in placebo and treatment arms are very different to other trials. Similarly, the smallest trial of adalimumab (Genovese 2007) reports a similar proportion of placebo responders but very different response to treatment compared with the ADEPT trial of adalimumab. Therefore, the Mease 2000 trial and the Genovese 2007 trial could contribute most (and possibly unreasonably so) to the estimation of interaction term (beta). It should be noted that the effect of placebo is consistently negative across all trials – i.e. higher placebo rates are associated with lower

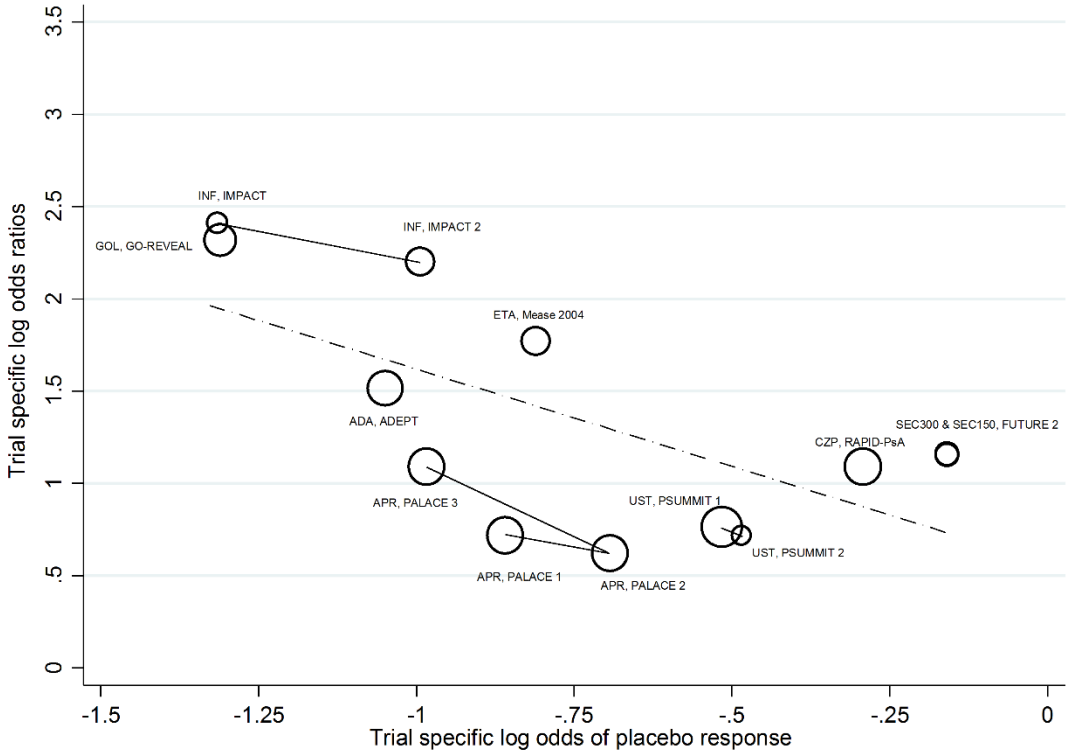
relative effectiveness estimates in the trial evidence. Exclusion of both Mease 2000 and Genovese 2007 will likely result in a much less pronounced placebo effect but it will still be negative.

Figure 20 PsARC response in biologic naïve subpopulation: Plot of trial specific observed log odds of placebo responses and odds ratios on log scale (all 13 trails)



ADA=adalimumab 40 mg; APR=apremilast 30mg; CZP=certolizumab pegol; ETA=etanercept 25mg; GOL=golimumab 50mg; INF=infliximab 5mg mg/kg; SEC150= secukinumab 150 mg; SEC300=secukinumab 300mg; UST=ustekinumab 45mg

Figure 21 PsARC response in biologic naïve subpopulation: Plot of trial specific observed log odds of placebo responses and odds ratios on log scale (excluding Mease 2000 and Genovese 2007)



ADA=adalimumab 40 mg; APR=apremilast 30mg; CZP=certolizumab pegol; ETA=etanercept 25mg; GOL=golimumab 50mg; INF=infliximab 5mg mg/kg; SEC150= secukinumab 150 mg; SEC300=secukinumab 300mg; UST=ustekinumab 45mg

Given the issue of heterogeneity in terms of unexplained differences in placebo response rates across the trials, analyses were undertaken including a meta-regression adjusting for placebo response. We used the baseline risk in each trial for the adjustment, taking into account the error in the estimation of baseline risk and its correlation to the odds ratios (OR).[107] Sensitivity analyses excluding both the Mease 2000 and Genovese 2007 trials were performed. Note that the effect of excluding these studies will be more pronounced where independent treatment effects are considered, rather than class effects. In the treatment effects as class analysis, all treatments assume to have equal or similar treatment effects, therefore all studies within the class will contribute to the interaction term (compare dashed lines in Figure 20 and Figure 21, where all biologics as a class was assumed). The meta-regression model includes an interaction term between the treatment effect (log odds ratio) and the trial-level estimate of placebo log odds of response. By including such an interaction term, analyses will assume that the relative effectiveness of each of the treatments is not constant but is associated with the response rate in the placebo arm. Treatment effects are no longer independent of the placebo response, but will be predicted for a particular value for the response rate in the placebo arm – usually the mean across the trials. The ranking of treatments is expected to differ from that estimated in the primary

analyses (without the meta-regression being imposed). This is because if, for example, the meta-regression shows that trials with higher placebo response rates are associated with lower treatment effects, then treatments such as secukinumab that have been trialled only under a high placebo response will be predicted to have had shown higher effectiveness in a different trial with a placebo response equal to the mean observed across trials.

Exploring treatment effects as class

In the context of an adjusted model for placebo response, we explored the possibility of there being class effects. Three different class groupings were considered: all treatments as a single class; all biologics as a class with apremilast separate; and to reflect the pharmacology, anti-TNFs grouped, ILs grouped and apremilast separate. Additionally we explored two within-class assumptions: assuming treatments within a class to have equal effectiveness and, alternatively, that treatments within a class have similar (exchangeable) effectiveness (described by a Normal distribution with an estimated mean and variance). Fixed effects across studies were assumed for all models. We have not considered models assuming exchangeability between classes.

Summary of all treatment effect models explored

All models implemented for evidence synthesis of PsARC response are presented in Table 41. Detailed coding of the models is presented in Table 112.

Table 111 Key assumptions of models implemented for evidence synthesis of PsARC response

Sets of analysis	Study	Treatments	Meta-regression	Class
A1	FE	independent	No baseline adjustment	No class effect
B1	FE	independent	Common interaction term with log odds of response in placebo arm	No class effect
C1	FE	Equal|class	Common interaction term with log odds of response in placebo arm	independent class effect class = {all treatments}
C2	FE	Equal|class, remaining treatments independent*		independent class effect class = APR independent; {all remaining biologics}
C3	FE	Equal|class, remaining treatments independent*		independent class effect class = {Anti-TNFs, ILs}; APR independent
D1	FE	Exchangeable|class, remaining treatments independent*	Common interaction term with log odds of response in placebo arm	independent class effect class = APR independent; {all other biologics}
D2	FE	Exchangeable|class, remaining treatments independent*		independent class effect class = {Anti-TNFs, ILs}; APR independent

*APR independent; FE=fixed effect

Table 112 Description of models and underlying assumptions for PsARC response

Model A1	**Model B1**
Likelihood $r_{it} \sim Binomial(p_{it}, n_{it})$ *Model* $Logit(p_{it}) = \mu_i + \delta_t$ Priors $\delta_t \sim dnorm(0,0.000001)$, $\mu_i \sim dnorm(0,0.000001)$	*Likelihood* $r_{it} \sim Binomial(p_{it}, n_{it})$ *Model* $Logit(p_{it}) = \mu_i + \delta_t + \beta(\mu_i - \bar{\mu})$ Priors $\delta_t \sim dnorm(0,0.000001)$, $\mu_i \sim dnorm(0,0.000001)$, $\beta \sim dnorm(0,0.000001)$
Assumptions • Baselines are unconstrained • The treatments effects are independent. • Fixed effects between studies	Assumptions • Baselines are unconstrained • The treatments effects are independent • Fixed effects between studies • Common interaction term between studies
Model C1, C2, & C3	**Model D1 & D2**
Likelihood $r_{it} \sim Binomial(p_{it}, n_{it})$ *Model* $Logit(p_{it}) = \mu_i + \delta_t + \beta(\mu_i - \bar{\mu})$ $\delta_t = \delta_c$ Priors $\delta_c \sim dnorm(0,0.000001)$ $\mu_i \sim dnorm(0,0.000001)$ $\beta \sim dnorm(0,0.000001)$	*Likelihood* $r_{it} \sim Binomial(p_{it}, n_{it})$ *Model* $Logit(p_{it}) = \mu_i + \delta_t + \beta(\mu_i - \bar{\mu})$ $\delta_t \sim dnorm(Class_c, 1/\gamma^2)$ Priors $Class_c \sim dnorm(0,0.000001)$ $\gamma \sim dunif(0,10)$ $\mu_i \sim dnorm(0,0.000001)$ $\beta \sim dnorm(0,0.000001)$
C1:class = {All biologics} C2: APR independent; class = {all other biologics}; C3: class = {Anti-TNFs, ILs}; APR independent	D1: APR independent; class = {all other biologics}; D2: class = {Anti-TNFs, ILs}; APR independent
Assumptions • Baselines are unconstrained • The treatments effects are equal within class. • Fixed effects between studies • Common interaction term between studies	Assumptions • Baselines are unconstrained • A random effect is used to describe differences between treatments (exchangeability is assumed). • Fixed effects between studies • Common interaction term between studies
Pooling of placebo effects	
Likelihood : $rplac_i \sim dbin(pplac_i, n_i)$ *Model* $Logit(pplac_i) = PD_i$ $PD_i \sim dnorm(Mean, 1/\sigma^2)$ Priors: $Mean \sim dnorm(0,0.000001)$ $\sigma \sim duni(0,10)$	
In summary, this model assumes • Common placebo effect across studies • Random effects between studies	

As stated earlier, sensitivity analysis around the adjustment for placebo response were performed: sets of analyses (model A1, B1, C1, C2, C3, D1 and D2) were conducted for PsARC response excluding the Mease 2000 and Genovese 2007 trials.

Placebo response synthesis model

To estimate baseline effect, the number of events in the placebo arm reported within each trial (r_{i1}) was assumed binomially distributed and the log-odds for placebo was pooled across trials. A random effect was assumed between studies. The trial specific effects for placebo PD_i were estimated from a common distribution $PD_i \sim dnorm(Mean, 1/\sigma^2)$. The random effect was defined using a mean and variance parameters (Mean and σ, respectively). Mean was assigned a non-informative normal prior distribution and σ was assigned a uniform prior. Results of the analysis are presented in section 12.3.3.2.

12.3.3.2 Detailed results for biologic naïve subpopulation

Summary results of PsARC response

Table 113 and Table 114 show summary results of PsARC response including and excluding Genovese 2007 and Mease 2000 studies.

Table 113 Results of PsARC response: log odds ratios (median) of treatments analysed (including Genovese 2007 and Mease 2000 studies) in biologic naïve subpopulation

Meta-reg treatments		no ind		yes ind		yes =|class		yes =|class {APR, other}		yes =|class {ILs,TNFs, APR}		yes ~|class ** {APR, other}		yes ~|class ** {ILs,TNFs, APR}	
class		no		no		{all}									
	Log Odds PLA	**A1**	r	**B1**	r	**C1**	r	**C2**	r	**C3**	r	**D1**	r	**D2**	r
SEC300	-0.16	1.178	5	2.110	1							1.844	3	1.833	3
SEC150	-0.16	1.175	6	2.104	2					1.285	2	1.839	4	1.822	4
UST	-0.51	0.758	9	1.187	7							1.197	8	1.174	8
CZP	-0.28	1.094	7	1.837	5	1.278	1	1.565	1			1.722	5	1.716	5
GOL	-1.32	2.339	1	1.619	6							1.692	6	1.712	6
ADA	-1.02	1.401	4	1.081	8					1.648	1	1.201	7	1.201	7
INF	-1.15	2.296	2	1.870	4							1.853	2	1.875	1
ETA	-0.99	2.043	3	1.917	3							1.856	1	1.872	2
APR	-0.85	0.813	8	0.765	9			0.756	2	0.779	3	0.769	9	0.771	9
Beta (mean)		-		-1.471		-0.498		-1.692		-1.061		-1.264		-1.225	
Residual deviance*		29.9		27.2		59.24		46.8		47.5		27.8		27.9	
DIC		193.1		190.5		148.0		203.8		199.1		190.0		190.3	

r – ranking of treatments according to point estimates; *compared to 27 data points; ** shrunken estimates; ind –independent; =|class – equal class effect; ~|class – exchangeable class effect

Table 114 Results of PsARC response: log odds ratios (median) of treatments analysed (excluding Genovese 2007 and Mease 2000 studies) in biologic naïve subpopulation

Meta-reg treatments		no ind		yes ind		yes =|class		yes =|class		yes =|class		yes ~|class **		yes ~|class **	
class		no		no		{all}		{APR, other}		{Il,TNF, APR}		{APR, other}		{Ils,TNFs,APR}	
	Log Odds PLA	**A1**	r	**B1**	r	**C1**	r	**C2**	r	**C3**	r	**D1**	r	**D2**	r
SEC300	-0.16	1.176	5	1.928	2							1.775	2	1.682	4
SEC150	-0.16	1.169	6	1.914	3					1.259	2	1.766	3	1.674	5
UST	-0.51	0.757	9	1.099	8							1.179	8	1.127	8
CZP	-0.28	1.092	7	1.686	6							1.665	6	1.640	6
GOL	-1.32	2.341	1	1.761	5	1.294	1	1.577	1	1.680	1	1.729	4	1.778	2
ADA	-1.05	1.526	4	1.251	7							1.344	7	1.377	7
INF	-1.15	2.301	2	1.953	1							1.864	1	1.897	1
ETA	-0.8	1.784	3	1.781	4							1.725	5	1.748	3
APR	-0.85	0.814	8	0.772	9			0.761	2	0.781	3	0.773	9	0.777	9
Beta (mean)		-		-1.149		-1.680		-1.481		-0.903		-1.131		-1.018	
Residual deviance*		23.6		22.6		52.2		38.2		36.3		22.3		22.8	
DIC		169.8		168.7		147.9		177.8		176.0		167.0		167.7	

r – ranking of treatments according to point estimates; *compared to 23 data points; ** shrunken estimates; ; ind –independent; =|class – equal class effect; ~|class – exchangeable class effect

Detailed results of PsARC response

Results of the baseline effects (placebo)

The mean baseline effect estimated to be -0.81. (Table 115)

Table 115 Result of PsARC response: baseline effect (log odds) in biologic naïve subpopulation

	Mean	**Median**	**95% CrI**	
Including Genovese 2007 and Mease 2000 studies				
Baseline effect	-0.814	-0.812	-1.023	-0.611
σ	0.290	0.277	0.102	0.550

Results of treatment effects models

More detailed results of the models, A1, B1, C1, C2, C3, D1 and D2 are presented next.

Results of analysis assuming treatments are independent including all studies:

Table 116 Results of Model A1: treatment: independent; studies: fixed effect

Treatments	Odds ratios				Treatment effects (Log odds)			
	Mean	Median	95% CrI		Mean	Median	95% CrI	
SEC300	3.499	3.246	1.559	6.886	1.181	1.178	0.444	1.930
SEC150	3.503	3.239	1.540	6.955	1.179	1.175	0.432	1.939
UST	2.172	2.134	1.489	3.070	0.759	0.758	0.398	1.122
CZP	3.082	2.985	1.880	4.813	1.096	1.094	0.631	1.571
GOL	10.890	10.370	5.865	18.980	2.343	2.339	1.769	2.943
ADA	4.159	4.059	2.703	6.212	1.403	1.401	0.994	1.827
INF	10.330	9.931	5.914	17.060	2.299	2.296	1.777	2.837
ETA	8.063	7.712	4.529	13.580	2.047	2.043	1.510	2.609
APR	2.276	2.255	1.733	2.941	0.813	0.813	0.550	1.079
Residual deviance*	29.86							
DIC	193.148							

*compared 27 data points

Meta-regression results including all studies:

Results of analysis assuming treatments are independent:

Table 117 Results of Model B1: Meta-regression, treatment: independent; studies: fixed effect

Treatments	Odds ratios				Treatment effects (Log odds)			
	Mean	Median	95% CrI		Mean	Median	95% CrI	
SEC300	10.560	8.251	3.244	26.790	2.142	2.110	1.177	3.288
SEC150	10.410	8.196	3.174	26.980	2.135	2.104	1.155	3.295
UST	3.441	3.276	2.117	5.752	1.201	1.187	0.750	1.750
CZP	7.024	6.277	3.166	14.980	1.861	1.837	1.153	2.707
GOL	5.360	5.049	2.000	10.400	1.593	1.619	0.693	2.342
ADA	2.989	2.947	1.745	4.404	1.067	1.081	0.557	1.483
INF	6.702	6.488	3.345	11.120	1.856	1.870	1.207	2.408
ETA	7.018	6.804	4.026	11.250	1.914	1.917	1.393	2.420
APR	2.160	2.150	1.684	2.691	0.763	0.765	0.521	0.990
beta					-1.471	-1.459	-2.769	-0.216
Residual deviance*	27.17							
DIC	190.495							

*compared 27 data points

Results of analyses assuming treatments as class:

Table 118 Results of Model C1: Meta-regression, treatment: equal|class; studies: fixed effect

	Odds ratios				Treatment effects (Log odds)			
	Mean	**Median**	**95% CrI**		**Mean**	**Median**	**95% CrI**	
Biologics as class	3.612	3.589	2.730	4.648	1.275	1.278	1.004	1.537
beta					-0.498	0.523	-3.711	2.483
Residual deviance*	59.24							
DIC	147.961							

*compared 27 data points

Table 119 Results of Model C2: Meta-regression, treatment: APR=independent, other biologics=equal|class; studies: fixed effect

	Odds ratios				Treatment effects (Log odds)			
	Mean	**Median**	**95% CrI**		**Mean**	**Median**	**95% CrI**	
Biologics as class (excluding APR)	4.805	4.782	4.099	5.657	1.566	1.565	1.411	1.733
APR	2.142	2.130	1.676	2.670	0.755	0.756	0.516	0.982
beta					-1.692	-1.666	-2.406	-1.122
Residual deviance*	46.83							
DIC	203.806							

*compared 27 data points

Table 120 Results of Model C3: Meta-regression, treatment: APR=independent, equal|class (ILs, Anti-TNFs); studies: fixed effect; including all studies

	Odds ratios				Treatment effects (Log odds)			
	Mean	**Median**	**95% CrI**		**Mean**	**Median**	**95% CrI**	
ILs as class	3.755	3.616	1.880	6.573	1.273	1.285	0.631	1.883
Anti-TNFs as class	5.238	5.195	4.036	6.710	1.648	1.648	1.395	1.904
APR	2.194	2.179	1.726	2.751	0.779	0.779	0.546	1.012
beta					-1.061	-1.025	-1.864	-0.462
Residual deviance*	47.54							
DIC	199.129							

*compared 27 data points

Table 121 Results of Model D1: Meta-regression, treatment: APR=independent, other biologics=exchangeable|class; studies: fixed effect; including all studies

Treatments	Odds ratios				Predicted mean distribution				Shrunken or independent Treatment effects (Log odds)			
	Mean	Median	95% CrI		Mean	Median	95% CrI		Mean	Median	95% CrI	
SEC300	5.331	5.206	3.675	7.737	1.657	1.647	0.653	2.714	1.859	1.844	1.343	2.456
SEC150									1.853	1.839	1.332	2.451
UST									1.202	1.197	0.885	1.538
CZP									1.731	1.722	1.342	2.165
GOL									1.689	1.692	1.233	2.122
ADA									1.197	1.201	0.861	1.509
INF									1.854	1.853	1.462	2.254
ETA									1.859	1.856	1.481	2.258
APR	2.166	2.157	1.765	2.609					0.768	0.769	0.568	0.959
$\gamma^{\$}$									0.437	0.398	0.187	0.924
beta									-1.264	-1.261	-1.917	-0.633
Residual deviance*	27.76											
DIC	189.961											

*compared 27 data points; $ variance parameter for the random effect across biologics (excluding APR)

Table 122 Results of Model D2: Meta-regression, treatment: APR=independent, exchangeable|class (ILs, Anti-TNFs); studies: fixed effect; including all studies

Treatments	Odds ratios				Predicted mean distribution				Shrunken or independent Treatment effects (Log odds)			
	Mean	Median	95% CrI		Mean	Median	95% CrI		Mean	Median	95% CrI	
SEC300	5.521	4.982	2.326	11.920	1.618	1.597	0.315	3.016	1.841	1.833	1.146	2.588
SEC150									1.832	1.822	1.133	2.588
UST									1.180	1.174	0.809	1.580
CZP	5.546	5.340	3.112	9.147	1.671	1.673	0.424	2.891	1.722	1.716	1.278	2.209
GOL									1.707	1.712	1.173	2.204
ADA									1.199	1.201	0.834	1.548
INF									1.874	1.875	1.430	2.306
ETA									1.874	1.872	1.476	2.287
APR	2.172	2.162	1.763	2.638					0.770	0.771	0.567	0.970
$\gamma^{\$}$									0.491	0.437	0.193	1.107
beta									-1.225	-1.227	-2.039	-0.393
Residual deviance*	27.92											
DIC	190.342											

*compared 27 data points; $ variance parameter for the random effect across biologics (excluding APR)

Results excluding Genovese 2007 and Mease 2000 studies:

Table 123 Results of Model A1: treatment: independent; studies: fixed effect; excluding Genovese 2007 and Mease 2000 studies

Treatments	Odds ratios				Treatment effects (Log odds)			
	Mean	Median	95% CrI		Mean	Median	95% CrI	
SEC300	3.492	3.240	1.554	6.920	1.178	1.176	0.441	1.934
SEC150	3.486	3.218	1.543	6.982	1.174	1.169	0.434	1.943
UST	2.168	2.131	1.486	3.062	0.757	0.757	0.396	1.119
CZP	3.076	2.980	1.861	4.820	1.094	1.092	0.621	1.573
GOL	10.910	10.390	5.869	18.920	2.345	2.341	1.770	2.940
ADA	4.746	4.602	2.856	7.491	1.527	1.526	1.049	2.014
INF	10.380	9.983	5.954	17.210	2.303	2.301	1.784	2.845
ETA	6.269	5.956	3.264	11.070	1.787	1.784	1.183	2.404
APR	2.278	2.257	1.739	2.931	0.814	0.814	0.553	1.075
Residual deviance*	23.63							
DIC	169.761							

*compared 23 data points

Meta-regressions results excluding Genovese 2007 and Mease 2000 studies:

Results of analysis assuming treatments are independent:

Table 124 Results of Model B1: Meta-regression, treatment: independent; studies: fixed effect; excluding Genovese 2007 and Mease 2000 studies

Treatments	Odds ratios				Treatment effects (Log odds)			
	Mean	Median	95% CrI		Mean	Median	95% CrI	
SEC300	9.534	6.872	2.132	23.890	1.932	1.928	0.757	3.174
SEC150	9.980	6.779	2.091	23.470	1.925	1.914	0.738	3.156
UST	3.178	3.001	1.748	5.410	1.103	1.099	0.558	1.688
CZP	6.248	5.400	2.241	13.770	1.695	1.686	0.807	2.622
GOL	8.068	5.818	2.233	14.620	1.757	1.761	0.803	2.682
ADA	3.647	3.494	1.940	5.920	1.245	1.251	0.663	1.778
INF	7.572	7.049	3.629	13.280	1.952	1.953	1.289	2.587
ETA	6.218	5.936	3.477	10.280	1.783	1.781	1.246	2.330
APR	2.181	2.165	1.707	2.729	0.772	0.772	0.535	1.004
beta					-1.149	-1.151	-2.727	0.406
Residual deviance*	22.601							
DIC	168.708							

*compared 23 data points

Results of analyses assuming treatments as class:

Table 125 Results of Model C1: Meta-regression, treatment: equal|class; studies: fixed effect: excluding Genovese 2007 and Mease 2000 studies

	Odds ratios				Treatment effects (Log odds)			
	Mean	**Median**	**95% CrI**		**Mean**	**Median**	**95% CrI**	
Biologics as class	3.679	3.649	2.749	4.794	1.293	1.294	1.011	1.567
beta					-1.680	-2.560	-4.050	2.094
Residual deviance*	52.16							
DIC	147.920							

*compared 23 data points

Table 126 Results of Model C2: Meta-regression, treatment: APR=independent, other biologics=equal|class; studies: fixed effect; excluding Genovese 2007 and Mease 2000 studies

	Odds ratios				Treatment effects (Log odds)			
	Mean	**Median**	**95% CrI**		**Mean**	**Median**	**95% CrI**	
Biologics as class (excluding APR)	4.867	4.843	4.192	5.682	1.580	1.577	1.433	1.737
APR	2.151	2.141	1.730	2.622	0.760	0.761	0.548	0.964
beta					-1.481	-1.455	-2.122	-0.996
Residual deviance*	38.16							
DIC	177.825							

*compared 23 data points

Table 127 Results of Model C3: Meta-regression, treatment: APR=independent, equal|class(ILs, anti-TNFs); studies: fixed effect; excluding Genovese 2007 and Mease 2000 studies

	Odds ratios				Treatment effects (Log odds)			
	Mean	**Median**	**95% CrI**		**Mean**	**Median**	**95% CrI**	
ILs as class	3.559	3.520	2.289	5.069	1.250	1.259	0.828	1.623
Anti-TNFs as class	5.392	5.363	4.500	6.460	1.681	1.680	1.504	1.866
APR	2.195	2.183	1.796	2.652	0.781	0.781	0.586	0.976
beta					-0.903	-0.906	-1.725	-0.087
Residual deviance*	36.30							
DIC	175.979							

*compared 23 data points

Table 128 Results of Model D1: Meta-regression, treatment: APR=independent, exchangeable|class; studies: fixed effect; excluding Genovese 2007 and Mease 2000 studies

Treatments	Odds ratios				Predicted mean distribution				Shrunken or independent Treatment effects (Log odds)			
	Mean	Median	95% CrI		Mean	Median	95% CrI		Mean	Median	95% CrI	
SEC300	5.214	5.115	3.706	7.350	1.637	1.633	0.713	2.563	1.787	1.775	1.296	2.335
SEC150									1.778	1.766	1.273	2.338
UST									1.180	1.179	0.857	1.507
CZP									1.668	1.665	1.283	2.067
GOL									1.733	1.729	1.329	2.157
ADA									1.341	1.344	0.991	1.669
INF									1.869	1.864	1.499	2.264
ETA									1.731	1.725	1.355	2.141
APR	2.177	2.167	1.791	2.621					0.773	0.773	0.583	0.964
$\gamma^{\$}$									0.385	0.350	0.148	0.824
beta									-1.131	-1.128	-1.750	-0.528
Residual deviance*	22.34											
DIC	167.044											

*compared 23 data points; $ variance parameter for the random effect across biologics (excluding APR)

Table 129 Results of Model D2: Meta-regression, treatment: APR=independent, exchangeable|class (ILs, Anti-TNFs); studies: fixed effect; excluding Genovese 2007 and Mease 2000 studies

Treatments	Odds ratios				Predicted mean distribution				Shrunken or independent Treatment effects (Log odds)			
	Mean	Median	95% CrI		Mean	Median	95% CrI		Mean	Median	95% CrI	
SEC300	4.805	4.428	2.225	9.507	1.503	1.478	0.383	2.754	1.688	1.682	1.012	2.390
SEC150									1.679	1.674	0.998	2.399
UST									1.127	1.127	0.756	1.498
CZP	5.566	5.408	3.436	8.554	1.695	1.689	0.670	2.750	1.640	1.640	1.218	2.064
GOL									1.781	1.778	1.314	2.258
ADA									1.376	1.377	0.985	1.757
INF									1.904	1.897	1.512	2.329
ETA									1.752	1.748	1.359	2.165
APR	2.187	2.176	1.796	2.642					0.778	0.777	0.586	0.972
$\gamma^{\$}$									0.407	0.362	0.123	0.968
beta									-1.018	-1.019	-1.781	-0.245
Residual deviance*	22.77											
DIC	167.708											

*compared 23 data points; $ variance parameter for the random effect across biologics (excluding APR)

12.3.3.3 Preferred models

The unadjusted model A1 fits the data as well as any of the other models and generates results that reflect the observed results. The placebo response adjusted model B1 fits well compared with the unadjusted model A1 (smaller DIC and residual deviance) but not significantly so, as the difference in DIC is less than 5 points. Considering the placebo adjusted models, it must be borne in mind that without any clear rationale for the placebo effect, the results must be interpreted with caution. The results (rankings) generated by Model B1 are very different from the observed trial results.

Regarding possible class effects, the analyses found that an assumption of equal class effect for the treatments does not produced a better-fitting model (models C1, C2, C3) than assuming independent treatment effects (models A1, B1) or similar treatment effects (models D1, D2). There was a little difference in goodness of fit statistics (DIC and residual deviance) between models D1 and D2, and we consider the exchangeable class effect model (D2) which utilised two classes (interleukins and anti-TNFs) with apremilast separate, to be most clinically plausible. The results (rankings) generated by Model D1 and D2 are same, but are very different from the observed trial results.

Comparing treatment effects in A1 B1 and D2, the treatment effects are very different to each other. Secukinumab 300mg and Infliximab appeared to be the most effective in model B1 and D2 respectively, but golimumab is the most effective in Model A1. Ustekinumab appeared to be least effective in Model A1, whereas apremilast appeared to be least effective in Model B1 and D2.

In the sensitivity analyses on Genovese 2007 and Mease 2000, excluding those two studies from the analysis affects the treatment effects resulting in changes in the ranking of the treatment effects. Despite the results of the adjusted model (B1) being sensitive to the exclusion of Mease 2000 and Genovese 2007 (with rankings changing), there are two reasons why this analyses has not been adopted as main. Firstly, exclusion of these studies may appear to be selective and secondly it is less relevant in the context of our preferred model that assumes a class effect (compare D2 with and without Mease 2000 and Genovese 2007). Therefore, these two trials were not excluded from our preferred analysis.

Hence, we consider models A1 and D2 including Genovese 2007 and Mease 2000 to be our preferred models.

12.3.3.4 Comparison of NMA of PsARC responses in company submissions (Novartis and UCB), previous MTA (Rodgers et al. 2010) and current Assessment Group (AG)

Each of the two company submissions combined evidence using Bayesian evidence synthesis methods to estimate probability of PsARC responses to inform economic model. UCB and AG included analysis of subpopulations in the main NMA and analysed both subpopulations (biologic

naïve and experienced) separately. Whereas, Novartis considered over-all population as main NMA, and the analysis included more complete set of treatments and trials. AG refers to the Novartis NMA of sub-group (i.e. biologic naïve) in this comparison. A brief comparison of the methods used and key model assumptions by the assessment group, CS and previous MTA are presented in Table 130 and Table 131.

A key differences between the NMAs presented concerns the trials included in each analysis. Only the AG NMA for biologic naïve subgroup includes all comparators and all trials. The UCB analysis for biologic naïve subgroup includes all treatments but misses only some apremilast trials. The Novartis NMA does not include certolizumab or apremilast for biologic naïve subgroup analysis and does not include all trials for the other treatments. The Rodgers et al. 2010 analysis was limited to the treatments available at that time.

The evidence synthesis is not clear in UCB's main submission for biologic experienced subgroup, and did not report results for this subgroup. Novartis didn't conduct NMA for the biologic experienced subgroup. Therefore, it was not plausible to compare AG NMA with CS for the biologic experienced subgroup.

Another key difference relates to the primary timepoint analysed: most NMA used 12 week, but the UCB analysis used 24 weeks as their primary time point, although it did include a 12 week sensitivity analysis.

All analyses considered a binomial logit model (both companies, previous MTA and AG). Both the AG and UCB consider fixed effect on studies, whereas Novartis considers random effects. Both AG and UCB consider baseline risk adjustment to reflect effects of differences in trial specific placebo response on treatment effects in biologic naïve population. Whereas, Novartis did not consider such adjustment for subgroup analysis.

Another key difference relates to the PsARC responses data included in the analysis. An inconsistency was identified by AG in the Novartis submission in PsARC response data for secukinumab and a revised PsARC response data was provided late in the assessment. Therefore, it is plausible that Novartis NMA used the incorrect data for the analysis. Additionally, AG's extracted PsARC response data from some studies does not match with Novartis, particularly for Mease 2004 trial and two adalimumab trials (ADEPT, Genovese 2007). The plausible explanation for the difference is that AG consistently used ITT denominators rather than the 'modified ITT' approach which sometimes used by CS (whereby only patients who've received at least one dose of their randomised treatment are considered).

Table 130 Comparison of evidence synthesis of PsARC responses in company submissions (Novartis and UCB), previous MTA (Rodgers et al. 2010) and Assessment Group

	Rodgers et al. 2010	Novartis	UCB	Assessment Group
Model	Binomial logit model	Binomial logit model	Binomial logit model	Binomial logit model
Results reported	Probability of PsARC response for each treatment	Relative risks of each treatment compared to secukinumab; and probability of PsARC response for each treatment[#]	Odds ratios reported for the biologic naïve subpopulation; but results were not reported for the biologic experienced subpopulation	Odds ratios and probability of PsARC response for each treatment
Timepoint	At 12 weeks (data from the 12 week or closest time point after 12 weeks - normally 14 or 16 weeks)	At 12 weeks (data from the 12 week or closest time point after 12 weeks - normally 14 or 16 weeks)	Primary analysis at 24 weeks (by treatments), sensitivity analysis was conducted at 12 weeks including data on 12 weeks or closest time point after 12 weeks.[$]	At 12 weeks (data from the 12 week or closest time point after 12 weeks - normally 14 or 16 weeks); ustekinumab at 24 week were included and assumed equivalent to outcomes at 12 weeks
Comments	-	Modelled probabilities are presented graphically	-	-
Data regarding subpopulation of biologic naïve				
Studies used in the analysis	ADEPT, Genovese 2007, IMPACT, IMPACT 2, Mease 2000, Mease 2004	ADEPT, Genovese 2007, FUTURE 2, GO-REVEAL, IMPACT 2, Mease 2004	ADEPT, Genovese 2007, GO-REVEAL, IMPACT, IMPACT 2, Mease 2000, Mease 2004, RAPID-PsA (12-16 weeks analysis)	ADEPT, FUTURE 2, Genovese 2007, GO-REVEAL, IMPACT, IMPACT 2, Mease 2000, Mease 2004, PALACE 1, PALACE 2, PALACE 3, PSUMMIT 1, PSUMMIT 2, RAPID-PsA
Drugs evaluated	Adalimumab 40mg; infliximab: 5mg mg/kg, etanercept 25mg	Adalimumab 40mg; etanercept 25mg, golimumab 50mg and 100 mg; infliximab 5mg mg/kg; secukinumab 150 and 300 mg	Adalimumab 40mg; certolizumab pegol; etanercept 25mg; golimumab 50mg; infliximab: 5mg mg/kg;	Adalimumab 40 mg; apremilast 30mg; certolizumab pegol; etanercept 25mg; golimumab 50mg; infliximab: 5mg mg/kg; secukinumab 150 mg and 300mg; ustekinumab 45mg
Data regarding subpopulation of biologic experienced				
Studies used in the analysis	-	-	Not clear	FUTURE 2, PSUMMIT 2
Drugs evaluated	-	-	Not clear	Secukinumab 300mg; ustekinumab 45mg

[#]AG considers probabilities to compare with our results; [$]AG considers results at 12 week to compare with AG NMA results

Table 131 Key assumptions in the synthesis models for PsARC responses in company submissions (Novartis and UCB), previous MTA (Rodgers et al. 2010) and Assessment Group

	Rodgers et al. 2010	Novartis	UCB	Assessment Group
Model	Binomial logit model	Binomial logit model	Binomial logit model	Binomial logit model
Fixed or random effects between studies	Random effects on studies	Random effects on studies	Fixed effects on studies (for both biologic naïve and experienced subpopulation)	Fixed effects on studies (for both biologic naïve and experienced subpopulation
Baselines	Common effect model was used to estimate baseline	Common effect model was used to estimate baseline	Common effect model was used to estimate baseline	Common effect model was used to estimate baseline
Treatment effects	Treatments were assumed to be independent to each other	Treatments were assumed to be independent to each other	For biologic naïve subpopulation: treatment effects are exchangeable within classes (anti-TNFs=ADA, IFX, ETN, GOL) For biologic experienced subpopulation: Treatments were assumed to be independent to each other	For biologic naïve subpopulation: 1. treatments were assumed to be independent to each other 2. Treatments as class which considered treatments are similar within class (exchangeable class effect) which utilised two classes (interleukins and anti-TNFs) For biologic experienced subpopulation: treatments were assumed to be independent to each other
Model adjusted for placebo response	Unadjusted	Unadjusted	Adjusted for biologic naïve subpopulation, but unadjusted biologic experienced subpopulation	Independent treatment effects models was unadjusted; but analysis assuming exchangeable class effects model was adjusted for the placebo response
Interaction term (beta)	-	-	Common interaction term in adjusted model	Common interaction term in adjusted model

The results of the AG NMA are compared with those of the other NMAs in Table 132 and Table 133. Table 132 shows the probabilities of PsARC response for biologic naïve subgroup estimated by the different models: Rodgers et al. 2010, Novartis, and assessment group (the UCB results are presented only as odds ratios) and Table 133 compares the odds ratios from the AG NMA with those from the UCB analysis. The results of the AG unadjusted NMA are mostly consistent with the previous MTA as well as Novartis results except for the secukinumab. The differences are largely because Novartis included different PsARC response dataset. The estimated probabilities in assessment group's analysis are more precise than Novartis results. Given the differences in model assumptions and included studies, the ranking of the treatment effects are similar between UCB and the AG adjusted NMA (Table 133).

Table 132 Comparison of probability of PsARC response in Novartis submission, previous MTA (Rodgers et al. 2010) and Assessment Group in biologic naïve subpopulation

Treatments	Rodgers et al. 2010		Novartis	Assessment Group (unadjusted, independent treatment)		Assessment Group (adjusted for placebo response, class effects assumed)	
	Mean	95% CrI	Mean	Median	95% CI	Median	95% CI
Placebo	0.25	(0.18, 0.32)	[redacted]	0.31	(0.26, 0.36)	0.31	(0.26, 0.36)
SEC300	NC		[redacted]	0.59	(0.40, 0.76)	0.73	(0.57, 0.86)
SEC150	NC		[redacted]	0.59	(0.40, 0.76)	0.73	(0.57, 0.86)
UST	NC		NC	0.49	(0.38 to 0.60)	0.59	(0.48, 0.70)
CZP	NC		NC	0.57	(0.44 to 0.69)	0.71	(0.60, 0.81)
GOL*	NC		[redacted]	0.82	(0.71 to 0.90)	0.71	(0.58, 0.81)
ADA	0.59	(0.44, 0.71)	[redacted]	0.64	(0.53 to 0.75)	0.60	(0.49, 0.69)
INF	0.80	(0.67, 0.89)	[redacted]	0.81	(0.71 to 0.89)	0.74	(0.63, 0.83)
ETA	0.71	(0.57, 0.83)	[redacted]	0.77	(0.65 to 0.86)	0.74	(0.64, 0.82)
APR	NC		NC	0.50	(0.41 to 0.59)	0.49	(0.41, 0.57)

NC = Not conducted; *GOL = golimumab 50mg;

Table 133 Comparison of PsARC response (odds ratios) at 12 weeks between UCB submission and Assessment Group in biologic naïve subpopulation

	UCB	Assessment Group (unadjusted, independent treatment)	Assessment Group (adjusted for placebo response, class effects assumed)
treatments	Mean (95% CrI)	Median (95% CrI)	Median (95% CrI)
SEC300	NC	3.25 (1.56, 6.89)	6.25 (3.15, 13.31)
SEC150	NC	3.24 (1.54, 6.96)	6.18 (3.10, 13.30)
UST	NC	2.13 (1.49, 3.07)	3.24 (2.25, 4.86)
CZP	[redacted]	2.99 (1.88, 4.81)	5.56 (3.59, 9.11)
GOL	[redacted]	10.37 (5.87, 18.98)	5.54 (3.23, 9.06)
ADA	[redacted]	4.06 (2.70, 6.21)	3.33 (2.30, 4.70)
INF	[redacted]	9.93 (5.91, 17.06)	6.52 (4.18, 10.04)
ETA	[redacted]	7.71 (4.53, 13.58)	6.50 (4.38, 9.85)
APR	NC	2.26 (1.73, 2.94)	2.16 (1.76, 2.64)

NC = Not conducted

12.3.3.5 WinBUG codes of preferred model

Model A1:

```
model {
for(i in 1:N) {
        r[i] ~ dbin(p[i],n[i])
        logit(p[i]) <- mu[s[i]] + (d[t[i]]-d[b[i]])*(1-equals(t[i],b[i]))
        rhat[i] <- p[i] * n[i]
        dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  + (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
                }
        totresdev <- sum(dev[])     #total resedual deviance
for (j in 1:ns) { mu[j]~dnorm(0,0.000001) }
d[1]<-0
for (k in 2:nt){ d[k] ~ dnorm(0,0.000001)
        OR[k]<- exp(d[k])           }
        }
```

Model D2:

```
model {
for(i in 1:N) {
        r[i] ~ dbin(p[i],n[i])
        logit(p[i]) <- mu[s[i]] + (d[t[i]]-d[b[i]])*(1-equals(t[i],b[i]))
         + (beta[t[i]]-beta[t[1]])*(mu[s[i]]-(Mean))*(1-equals(t[i],b[i]))
        rhat[i] <- p[i] * n[i]
        dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  + (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
                }
totresdev <- sum(dev[])
d[1]<-0
for (i in 2:3) {d[i] ~ dnorm(D.c[1], prec.d)}
d[4] ~ dnorm(D.c[2], prec.d)
d[5] ~ dnorm(D.c[1], prec.d)
for (i in 6:9) {d[i] ~ dnorm(D.c[2], prec.d)}
d[10]<- D.c[3]
for (i in 1:3) { D.c[i]~dnorm(0.0,0.000001)}
prec.d<-1/(sd.d*sd.d)
sd.d~dunif(0,10)
for (i in 1:2) {D.pred[i]~dnorm(D.c[i],prec.d)}
beta[1]<-0
for (i in 2:nt) { beta[i]<- betaplac }
betaplac ~ dnorm(0,0.000001)
for (j in 1:ns) { mu[j]~dnorm(0,0.000001)}
A ~ dnorm (meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k] }
for (k in 1:nt) { OR[k]<- exp(d[k])}
}
```

d[1]=PLA, d[2]=SEC300, d[3]=SEC150, d[4]=CZP, d[5]=UST, d[6]=GOL, d[7]=ADA, d[8]=INF, d[9]=ETA, d[10]=APR

12.3.4 HAQ changes conditional on PsARC response/non-response

12.3.4.1 Detailed methods for biologic naïve subpopulation

We consider three models to estimate the HAQ changes conditional on PsARC response. Model E1 considers treatments are independent and considers fixed effects across studies. Models E2 and E3

apply a class effects on three groups: anti-TNFs, ILS, and apremilast. This class effect reflects the best fitting class effect model for PsARC (see section 12.3.3.2). Model E2 assumes that the treatments are similar within class (exchangeable) and fixed effect across studies; and model E3 considers that the treatments are equal within class and fixed effect across studies. A detailed description of the model and underlying assumptions are presented in Table 134.

Table 134 Description of the models and underlying assumptions for HAQ changes conditional on PsARC response

Model: E1	Model: E2	Model: E3
Likelihood $HAQ_{PNRi} \sim dnorm(\mu_{PNRi}, 1/\text{var}_{PNRi})$ $HAQ_{PRi} \sim dnorm(\mu_{PRi}, 1/\text{var}_{PRi})$ $HAQ_{TNRij} \sim dnorm(\mu_{TNRij}, 1/\text{var}_{TNRij})$ $HAQ_{TRij} \sim dnorm(\mu_{TRij}, 1/\text{var}_{TRij})$ *Model* $\mu_{PNRi} = baseline_i$ $\mu_{PRi} = \mu_{PNRi} + \delta.diff_{PR}$ $\mu_{TNRij} = \mu_{PNRi} + \delta.diff_{TNRj}$ $\mu_{TRij} = \mu_{PNRi} + \delta.diff_{TRj}$ Priors $baseline_i \sim dnorm(0,0.000001)$ $\delta.diff_{PR} \sim dnorm(0,0.000001)$ $\delta.diff_{TNRj} \sim dnorm(0,0.000001)$ $\delta.diff_{TRj} \sim dnorm(0,0.000001)$	*Likelihood* $HAQ_{PNRi} \sim dnorm(\mu_{PNRi}, 1/\text{var}_{PNRi})$ $HAQ_{PRi} \sim dnorm(\mu_{PRi}, 1/\text{var}_{PRi})$ $HAQ_{TNRij} \sim dnorm(\mu_{TNRij}, 1/\text{var}_{TNRij})$ $HAQ_{TRij} \sim dnorm(\mu_{TRij}, 1/\text{var}_{TRij})$ *Model* $\mu_{PNRi} = baseline_i$ $\mu_{PRi} = \mu_{PNRi} + \delta.diff_{PR}$ $\mu_{TNRij} = \mu_{PNRi} + \delta.diff_{TNRj}$ $\mu_{TRij} = \mu_{PNRi} + \delta.diff_{TRj}$ $\delta.diff_{TNRj} \sim dnorm(\delta.diff_{TNR.C}, 1/\gamma^2_{TNR})$ $\delta.diff_{TRj} \sim dnorm(\delta.diff_{TR.C}, 1/\gamma^2_{TR})$ Priors $baseline_i \sim dnorm(0,0.000001)$ $\delta.diff_{PR} \sim dnorm(0,0.000001)$ $\delta.diff_{TNR.C} \sim dnorm(0,0.000001)$ $\delta.diff_{TR.C} \sim dnorm(0,0.000001)$ $\gamma_{TNR} \sim dunif(0,10)$ $\gamma_{TNR} \sim dunif(0,10)$	*Likelihood* $HAQ_{PNRi} \sim dnorm(\mu_{PNRi}, 1/\text{var}_{PNRi})$ $HAQ_{PRi} \sim dnorm(\mu_{PRi}, 1/\text{var}_{PRi})$ $HAQ_{TNRij} \sim dnorm(\mu_{TNRij}, 1/\text{var}_{TNRij})$ $HAQ_{TRij} \sim dnorm(\mu_{TRij}, 1/\text{var}_{TRij})$ *Model* $\mu_{PNRi} = baseline_i$ $\mu_{PRi} = \mu_{PNRi} + \delta.diff_{PR}$ $\mu_{TNRij} = \mu_{PNRi} + \delta.diff_{TNRj}$ $\delta.diff_{TNRj} = \delta.diff_{TNR.C}$ $\mu_{TRij} = \mu_{PNRi} + \delta.diff_{TRj}$ $\delta.diff_{TRj} = \delta.diff_{TR.C}$ Priors $baseline_i \sim dnorm(0,0.000001)$ $\delta.diff_{PR} \sim dnorm(0,0.000001)$ $\delta.diff_{TNR.C} \sim dnorm(0,0.000001)$ $\delta.diff_{TR.C} \sim dnorm(0,0.000001)$
Assumption: • The treatments effects are independent • PNR: unconstrained • Difference between PR and PNR: pooled using FE • Difference between TNR and PNR: treatments as independent, pooled within treatments using FE • Difference between TR and PNR: treatments as independent; pooled within treatments using FE	Assumption: • A random effect is used to describe differences between treatments (exchangeability is assumed) • PNR: unconstrained • Difference between PR and PNR: pooled using FE • Difference between TNR and PNR: treatments as independent, pooled within treatments using FE • Difference between TR and PNR: treatments as independent; pooled within treatments using FE	Assumption: • The treatments effects are equal within class • PNR: unconstrained • Difference between PR and PNR: pooled using FE • Difference between TNR and PNR: treatments as independent, pooled within treatments using FE • Difference between TR and PNR: treatments as independent; pooled within treatments using FE

The model defines TR as treatment responders, TNR as treatment non- responders, PR as placebo responders and PNR as placebo non-responders, *I* represents the trial and *j* the alternative treatments. The observed quantities (i.e. HAQ changes in placebo responders and non-responders, and in treatment responders and non-responders) have a normal distribution for the likelihood.

Changes in HAQ in all groups are assumed relative to changes in HAQ in PNR (placebo non-responders) - μ_{PNRi}. This parameter was left unconstrained (allowed to differ between trials) and non-

informative normal prior distributions were assigned ($baseline_i$).The relative effects of placebo on those that respond in placebo arm ($\delta.diff_{PR}$) was assumed additive to μ_{PNRi} and was pooled across trials. The relative effects of treatments on those that do not respond ($^{\delta.diff_{TNRj}}$) and on those that respond ($^{\delta.diff_{TRj}}$) are additive to $^{\mu_{PNRi}}$, and were assumed to be treatment specific. In pooling these parameters, we assumed fixed effects across studies. Within a fixed effects model, parameters $\delta.diff_{PR}$, $\delta.diff_{TNRj}$, and $\delta.diff_{TRj}$ were assigned non-informative normal prior distributions.

12.3.4.2 Detailed results for biologic naïve subpopulation

Summary results of HAQ changes conditional on PsARC response

The summary results from three models are presented in Table 47 as absolute changes in HAQ in relation to baseline.

Table 135 Results of HAQ changes (median) conditional on PsARC response/nonresponse in biologic naïve subpopulation

treatments	ind treat		Exchangeable|class		Equal|class							
studies	FE		FE		FE							
	E1		**E2****		**E3**							
	PsARC response	PsARC non-response	PsARC response	PsARC non-response	PsARC response	PsARC non-response	PsARC resp vs. non-rep					
							E1	r	**E2****	r	**E3**	r
Placebo	-0.26		-0.26		-0.25		-0.26	10	-0.26	10	-0.25	4
SEC150	-0.39	-0.08	-0.44	-0.09			-0.31	8	-0.35	8		
SEC300	-0.55	-0.05	-0.51	-0.08	-0.47	-0.08	-0.49	1	-0.43	3	-0.39	1
UST	-0.49	-0.10	-0.48	-0.09			-0.39	4	-0.39	4		
CZP	-0.43	-0.07	-0.47	-0.12			-0.36	6	-0.35	7		
GOL	-0.44	-0.06	-0.49	-0.11	-0.52	-0.13	-0.38	5	-0.37	5	-0.39	1
ADA	-0.49	-0.13	-0.50	-0.13			-0.36	7	-0.37	6		
INF	-0.66	-0.20	-0.60	-0.14			-0.46	2	-0.46	1		
ETA	-0.64	-0.20	-0.59	-0.14			-0.44	3	-0.45	2		
APR	-0.36	-0.09	-0.36	-0.09	-0.36	-0.09	-0.27	9	-0.27	9	-0.27	3
DIC	-126.0		-133.0		-131.4							

r – ranking of treatments according to point estimates; **shrunken estimates; ind treat=independent treatment; FE=fixed effect

Detailed results of HAQ changes conditional on PsARC response

The results of HAQ score changes conditional on PsARC response or non-response are presented here.

Table 136 Results of Model E1: Treatment: independent; difference between PR/TNR/TR and PNR pooled using fixed effects

	HAQ changes in PsARC response in relation to PNR				**HAQ changes in PsARC non response in relation to PNR**			
	mean	**median**	**95% CrI**		**mean**	**median**	**95% CrI**	
Placebo/baseline effect	-0.263	-0.263	-0.301	-0.224				
SEC150	-0.394	-0.395	-0.553	-0.236	-0.083	-0.083	-0.389	0.220
SEC300	-0.547	-0.547	-0.722	-0.369	-0.053	-0.053	-0.288	0.182
UST	-0.488	-0.488	-0.597	-0.379	-0.098	-0.097	-0.208	0.012
CZP	-0.429	-0.429	-0.530	-0.326	-0.069	-0.069	-0.194	0.057
GOL	-0.439	-0.439	-0.585	-0.293	-0.063	-0.064	-0.182	0.055
ADA	-0.489	-0.489	-0.583	-0.395	-0.135	-0.134	-0.237	-0.032
INF	-0.660	-0.660	-0.771	-0.548	-0.196	-0.196	-0.311	-0.083
ETA	-0.640	-0.640	-0.767	-0.515	-0.200	-0.200	-0.348	-0.054
APR	-0.362	-0.362	-0.432	-0.291	-0.089	-0.089	-0.157	-0.022
DIC	-125.96							

Table 137 Results of Model E2: Treatment: exchangeable|class(Ils,Anti-TNF), APR=independent; difference between PR/TNR/TR and PNR pooled using fixed effects

	HAQ changes in PsARC response in relation to PNR								HAQ changes in PsARC non response in relation to PNR							
	predicted mean				Shrunken /independent estimates				predicted mean				Shrunken/independent estimates			
	mean	median	95% CrI		mean	median	95% CrI		mean	median	95% CrI		mean	median	95% CrI	
Placebo					-0.258	-0.258	-0.296	-0.220								
SEC150					-0.432	-0.435	-0.557	-0.294					-0.085	-0.085	-0.228	0.057
SEC300	-0.475	-0.474	-0.751	-0.203	-0.512	-0.509	-0.658	-0.378	-0.083	-0.083	-0.253	0.086	-0.077	-0.078	-0.205	0.062
UST					-0.481	-0.480	-0.580	-0.383					-0.088	-0.087	-0.186	0.009
CZP					-0.468	-0.470	-0.558	-0.370					-0.116	-0.118	-0.196	-0.021
GOL					-0.482	-0.486	-0.594	-0.354					-0.110	-0.114	-0.188	-0.013
ADA	-0.530	-0.529	-0.784	-0.279	-0.499	-0.500	-0.581	-0.414	-0.130	-0.130	-0.274	0.012	-0.133	-0.132	-0.209	-0.058
INF					-0.605	-0.603	-0.716	-0.502					-0.147	-0.144	-0.240	-0.071
ETA					-0.593	-0.591	-0.717	-0.486					-0.147	-0.143	-0.255	-0.063
APR					-0.361	-0.361	-0.430	-0.289					-0.088	-0.088	-0.155	-0.020
DIC	-133.03															

Table 138 Results of Model E3: Treatment: equal|class (Ils,Anti-TNF), APR=independent; difference between PR/TNR/TR and PNR pooled using fixed effects

	HAQ changes in PsARC response in relation to PNR				HAQ changes in PsARC non response in relation to PNR			
	mean	median	95% CrI		mean	median	95% CrI	
Placebo/baseline effect	-0.254	-0.254	-0.291	-0.217				
ILs as class	-0.473	-0.473	-0.554	-0.393	-0.083	-0.083	-0.176	0.013
Anti-TNFs as class	-0.524	-0.524	-0.575	-0.474	-0.131	-0.131	-0.185	-0.077
APR	-0.359	-0.359	-0.430	-0.290	-0.087	-0.087	-0.155	-0.018
DIC	-131.37							

12.3.4.3 Preferred models

The model fit statistics (DIC) indicate that neither class effect model (E2 or E3) is a better fit for the data than the unadjusted, independent treatments model (E1). The fit of both of the class effect models were similar, but the one that allowed exchangeability within classes (E2) was considered to be the most clinically plausible. For the purposes of the economic model in Section 6, Models E1 and E2 were the preferred models.

12.3.4.4 Comparison of NMA of HAQ conditional on PsARC response/non-response in company submissions (Novartis and UCB), previous MTA (Rodgers et al. 2010) and current Assessment Group

The previous MTA by Rodgers et al. 2010 and the current AG assessment conducted a NMA for HAQ score changes conditional on PsARC response/non-response outcome using Bayesian methods. Novartis didn't conduct a meta-analysis for this outcome. UCB conducted meta-analysis for HAQ-DI change in PsARC responders and non-responders with data extracted from Rodgers et al. 2010 HTA report, and assumed an additive effect for the effect of treatment in treatment responders versus that for placebo responders. (UCB submission, pg.133). Although, results of the analysis were presented in the economic section of UCB submission, detailed information about evidence synthesis was not provided. Hence, it is difficult to compare it with the AG evidence synthesis. The key assumptions for the NMA are presented in Table 139.

Table 139 Comparison of evidence synthesis of HAQ score changes conditional on PsARC responses/nonresponse in UCB submission, previous MTA (Rodgers et al. 2010) and Assessment Group

	Rodgers et al. 2010	**UCB**	**Assessment Group***
Key assumptions for model	• Random effect on studies • For each of the different trials the true effect may be study specific and vary across studies although remain common across biologics • Changes in HAQ given placebo non-responders as common baseline • Effects of treatment response and non-response on HAQ change are treatment specific and additive to the placebo probability of non-response • Difference between treatment response and placebo non-response pooled within treatments using random effect • Difference between treatment non-response and placebo non-response pooled within treatments using random effect • Difference between placebo response and placebo non-response pooled using random effect	Not clear from the submission	• Fixed effect on studies • Treatments effects are independent • Changes in HAQ given placebo non-responders as common baseline and considered trial-specific • Effects of treatment response and non-response on HAQ change are treatment specific and additive to placebo non-response • Difference between treatment response and placebo non-response pooled within treatments using fixed effect • Difference between treatment non-response and placebo non-response pooled within treatments using fixed effect • Difference between placebo response and placebo non-response pooled using fixed effect
Time points	HAQ at 12 weeks conditional on PsARC response at 12 weeks	At 24 weeks	HAQ at 12 weeks conditional on PsARC response at 12 weeks
Results reported	changes in HAQ given PsARC response/nonresponse to treatment	Changes in HAQ given PsARC response/nonresponse to treatment^	Changes in HAQ given PsARC response/nonresponse to treatment
Data regarding subpopulation of biologic naïve			
Studies used in the analysis	ADEPT, Genovese 2007, IMPACT, IMPACT 2, Mease 2000, Mease 2004	ADEPT, FUTURE 2, GO-REVEAL, IMPACT 2, Ixekizumab Phase III trial, Mease 2004, RAPID-PsA (24 weeks)	ADEPT, FUTURE 2, Genovese 2007, GO-REVEAL, IMPACT, IMPACT2, Mease 2004, PALACE 1, PALACE 2, PALACE 3, PSUMMIT1, PSUMMIT2, RAPID-PsA
Drugs evaluated	Adalimumab 40mg; ; infliximab: 5mg mg/kg, etanercept 25mg	Adalimumab 40 mg; certolizumab pegol; etanercept 25mg; golimumab 50mg; infliximab: 5mg mg/kg; secukinumab	Adalimumab 40 mg; apremilast 30mg; certolizumab pegol; etanercept 25mg; golimumab 50mg; infliximab: 5mg mg/kg; secukinumab 150 mg and 300mg; ustekinumab 45mg
Data regarding subpopulation of biologic experienced			
Studies used in the analysis	-	FUTURE 2, PSUMMIT 2, RAPID-PsA (24 weeks)	FUTURE 2, PSUMMIT 2
Drugs evaluated	-	certolizumab pegol; secukinumab; ustekinumab 45mg	Secukinumab 300mg; ustekinumab 45mg

*To compare with CS and previous MTA, AG only presented independent treatment effect model assumptions; ^results reported in economic section of the submission

As mentioned before the NMA of UCB is difficult to compare with AG NMA, therefore only NMA of Rodgers et al. was compared with AG NMA.

A key differences between the NMA presented is the trials included in each analysis. AG NMA includes nine active treatments and 13 trials, whereas the Rodgers et al. 2010 analysis was limited to the treatments available at that time. Another key differences between Rodgers et al. 2010 and AG analysis was the assumption of the effects on studies. Rodgers et al. assumed random effect on studies, whereas the AG considered fixed effect on studies. Despite difference in model assumption the results of current assessment are fairly similar with Rodgers et al. 2010 (Table 140).

Table 140 HAQ changes conditional on PsARC response model results in biologic naïve subpopulation

	Rodgers et. al. 2010		**Assessment Group (independent treatments)**	
	Mean	**95% CrI**	**Median**	**95% CrI**
HAQ changes conditional on PsARC response				
Placebo	-0.244	(-0.337, -0.151)	-0.263	(-0.301, -0.224)
SEC150	NC		-0.395	(-0.553, -0.236)
SEC300	NC		-0.547	(-0.722, -0.369)
CZP	NC		-0.429	(-0.530, -0.326)
UST	NC		-0.488	(-0.597, -0.379)
GOL	NC		-0.439	(-0.585, -0.293)
ADA	-0.477	(-0.596, -0.351)	-0.489	(-0.583, -0.395)
INF	-0.657	(-0.793, -0.523)	-0.660	(-0.771, -0.548)
ETA	-0.630	(-0.805, -0.455)	-0.640	(-0.767, -0.515)
APR	NC		-0.362	(-0.432, -0.291)
HAQ changes conditional on PsARC non-response				
SEC150	NC		-0.083	(-0.389, 0.220)
SEC300	NC		-0.053	(-0.288, 0.182)
CZP	NC		-0.069	(-0.194, 0.057)
UST	NC		-0.097	(-0.208, 0.012)
GOL	NC		-0.064	(-0.182, 0.055)
ADA	-0.130	(-0.188, 0.065)	-0.134	(-0.237, -0.032)
INF	-0.194	(-0.333, -0.057)	-0.196	(-0.311, -0.083)
ETA	-0.190	(–0.381, 0.000)	-0.200	(-0.348, -0.054)
APR	NC		-0.089	(-0.157, -0.022)

NC=not conducted; *shrunken estimates

12.3.4.5 WinBUG codes of preferred model

Model E1:

```
model {
        for (i in 1:13) {
                prec.HAQ.TR[i] <- 1/(se.HAQ.TR[i] *se.HAQ.TR[i])
                prec.HAQ.PR[i] <- 1/(se.HAQ.PR[i]*se.HAQ.PR[i])
                prec.HAQ.TNR[i] <-  1/(se.HAQ.TNR[i] * se.HAQ.TNR[i])
                prec.HAQ.PNR[i] <-  1/(se.HAQ.PNR[i] * se.HAQ.PNR[i])

                HAQ.TR[i] ~ dnorm(TR[i], prec.HAQ.TR[i])
                HAQ.PR[i] ~ dnorm(PR[i], prec.HAQ.PR[i])
                HAQ.TNR[i] ~ dnorm(TNR[i], prec.HAQ.TNR[i])
                HAQ.PNR[i] ~ dnorm(PNR[i], prec.HAQ.PNR[i])

                PNR[i]<-baselineHAQ[i]
                PR[i] <- baselineHAQ[i]+ PR.diff

                TNR[i] <-baselineHAQ[i]+ TNR.diff[trial.tnf[i]]
                TR[i] <-baselineHAQ[i]+ TR.diff[trial.tnf[i]]
                        }
baselineHAQ[i ]~ dnorm(0,0.000001)
for (j in 1:9) {
        TR.diff[j]~ dnorm(0,0.000001)
        TNR.diff[j]~ dnorm(0,0.000001)
                }
PR.diff~ dnorm(0,0.000001)
for (i in 1:13) { HAQ.PNR[i] ~dnorm(0,0.000001)}
        }
```

Model E2:

```
model {
        for (i in 1:13) {
                prec.HAQ.TR[i] <- 1/(se.HAQ.TR[i] *se.HAQ.TR[i])
                prec.HAQ.PR[i] <- 1/(se.HAQ.PR[i]*se.HAQ.PR[i])
                prec.HAQ.TNR[i] <-  1/(se.HAQ.TNR[i] * se.HAQ.TNR[i])
                prec.HAQ.PNR[i] <-  1/(se.HAQ.PNR[i] * se.HAQ.PNR[i])

                HAQ.TR[i] ~ dnorm(TR[i], prec.HAQ.TR[i])
                HAQ.PR[i] ~ dnorm(PR[i], prec.HAQ.PR[i])
                HAQ.TNR[i] ~ dnorm(TNR[i], prec.HAQ.TNR[i])
                HAQ.PNR[i] ~ dnorm(PNR[i], prec.HAQ.PNR[i])

baselineHAQ[i ]~ dnorm(0,0.000001)

PNR[i]<-baselineHAQ[i]
PR[i] <- baselineHAQ[i]+ PR.diff

TNR[i] <-baselineHAQ[i]+ TNR.diff[trial.tnf[i]]
TR[i] <-baselineHAQ[i]+ TR.diff[trial.tnf[i]]
                        }

for (i in 1:2) {TR.diff[i] ~ dnorm(D.TR.c[1], prec.TR)}
TR.diff[3] ~ dnorm(D.TR.c[2], prec.TR)
TR.diff[4] ~ dnorm(D.TR.c[1], prec.TR)
for (i in 5:8) {TR.diff[i] ~ dnorm(D.TR.c[2], prec.TR)}
TR.diff[9] <- D.TR.c[3]
```

```
for (i in 1:2) {TNR.diff[i] ~ dnorm(D.TNR.c[1], prec.TNR)}
TNR.diff[3] ~ dnorm(D.TNR.c[2], prec.TNR)
TNR.diff[4] ~ dnorm(D.TNR.c[1], prec.TNR)
for (i in 5:8) {TNR.diff[i] ~ dnorm(D.TNR.c[2], prec.TNR)}
TNR.diff[9] <- D.TNR.c[3]

for (j in 1:3) {
        D.TR.c[j]~ dnorm(0,0.000001)
        D.TNR.c[j]~ dnorm(0,0.000001)
                }
for (j in 1:2) {
        D.pred.TR[j]~dnorm(D.TR.c[j],prec.TR)
        D.pred.TNR[j]~dnorm(D.TNR.c[j],prec.TNR)
                }
prec.TR<-1/(sd.TR*sd.TR)
sd.TR~dunif(0,10)
prec.TNR<-1/(sd.TNR*sd.TNR)
sd.TNR~dunif(0,10)

PR.diff~ dnorm(0,0.000001)
for (i in 1:13) { HAQ.PNR[i] ~dnorm(0,0.000001)}
}
d[1]=SEC150, d[2]=SEC300, d[3]=CZP, d[4]=UST, d[5]=GOL, d[6]=ADA, d[7]=INF, d[8]=ETA, d[9]=APR
```

12.3.5 PASI response

12.3.5.1 Detailed methods for biologic naïve subpopulation

Treatment effect models

The 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 single model included all categories of PASI and generated a single effect estimate for each treatment and also probabilities of achieving PASI 50, 75 and 90. Specifically, the model considered a multinomial likelihood and a probit link for ordered categorical data.[109]

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,….., see table X) belongs to category *j* (*j* =1,2,3). We use the probit link function, the inverse of the normal cumulative distribution function Φ, to define the p_{ikj} as a function of a set of threshold values, zj. The threshold values (estimated within the model) are such that the probability that the standard normal (probit score) will take a value less than or equal to z1 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 z2 will reflect the probability of obtaining a PASI response lower than 75%, that is, 1-PASI75, and analogously, evaluating Φ at z3 will approximate 1- PASI95. 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*.

We assumed that the baselines, μ_i, were trial-specific (unconstrained) and has 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 $z_{j.}$

Analogously to the analyses on PsARC, alternative assumptions were tested in two analyses. The first assumed independent treatment effects and did not include any meta-regression for placebo effects (Model F1). As the number of trials to inform each treatment effect was small, a fixed effect model was used. In a second analysis, we explored the impact on treatment effects of adjusting for placebo responses i.e. baseline effects (meta-regression model). As can be seen from section 5.4.1.1, there are large differences between trials for PASI responses in placebo arms, ranging between zero and 27% (0% in IMPACT and 27% RAPID-PsA). The IMPACT trial had very small sample size and reported zero response in placebo arm and 100% response in treatment arm which leads to very extreme values for placebo adjustment. Therefore, the IMPACT trial could not be included in the meta-regression analysis. Unlike the analysis for PsARC, for PASI, we did not assume a class effect as the evidence from individual trials does not support such an assumption. Table 51 presents the key assumptions for the models implemented for PASI response and detailed coding of the models are presented in Table 142.

Table 141 Summary of models implemented for evidence synthesis of PASI response

Sets of analyses	Study	Treatment	Meta-regression	Thresholds, i.e. Cut-offs	Baseline effect for meta-regression
F1	FE	Independent	No baseline adjustment	FE	-
G1	FE	Independent	No baseline adjustment	FE	-
G2	FE	Independent	Common interaction term with baseline effect	FE	Adjusted with trial specific baseline effects

FE=fixed effect

Table 142 Description of models and underlying assumptions for PASI response and ACR response

Model F1 & G1	Model G2
$Likelihood$ $r_{ikj} \sim Binomial(p_{ikj}, n_{ikj})$ $Model$ $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ Priors $\delta_t \sim dnorm(0,0.000001)$ $\mu_i \sim dnorm(0,0.000001)$ $z_j \sim dunif(0,5)$	$Likelihood$ $r_{ikj} \sim Binomial(p_{ikj} n_{ikj})$ $Model$ $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j + \beta(\mu_i - \bar{\mu})$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ Priors $\delta_t \sim dnorm(0,0.01)$ $\mu_i \sim dnorm(0,0.01)$ $\beta \sim dnorm(0,0.01)$ $z_j \sim dunif(0,5)$
Assumptions • Baselines are unconstrained • Treatments effects are independent. • Fixed effects between studies • Fixed effect for each of the *j-1* categories over all trials.	Assumptions • Baselines are unconstrained • Treatments effects are independent. • Fixed effects between studies • Fixed effect for each of the *j-1* categories over all trials. • Common interaction term between studies

Model F1 considers that treatments are independent to each other and fixed effect on cut-offs/ thresholds. Model G1 considers same assumption as model F1, but the IMPACT trial was excluded from the analysis. Model G2 assumes treatments are independent to each other, but treatment effects are adjusted with the trial specific baseline effects assuming a common interaction term (beta).

The preferred model was used to evaluate estimated probability of achieving PASI50,75,90 responses on treatment *t* , using $T_{jt} = 1 - \Phi(A + \delta_t + z_j)$, where A is the pooled baseline effect described below.

We adopted the WinBUG code presented in the DSU2[redacted] 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.

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 (in this case NS=13).

12.3.5.2 Detailed results for biologic naïve subpopulation

Summary results of PASI response

Table 52 presents the results of the treatment effects for PASI responses estimated from the three models with measures of goodness of fit. There were no issues with convergence.

Table 143 Results of PASI response: treatment effects (median) on probit scale in biologic naïve subpopulation

Meta-regression treatments	no ind		no ind		yes ind	
Cut-offs	FE		FE		FE	
	F1	**r**	**G1**	**r**	**G2**	**r**
PLA	1.024	-	0.983	-	1.015	-
SEC300	-1.936	2	-1.932	2	-1.864	1
SEC150	-1.870	3	-1.865	3	-1.798	2
CZP	-0.875	7	-0.873	7	-1.424	4
UST	-1.134	6	-1.131	6	-1.342	6
GOL	-1.645	4	-1.635	4	-1.141	7
ADA	-1.477	5	-1.476	5	-1.422	5
INF	-2.412	1	-2.276	1	-1.798	2
ETA	-0.798	8	-0.797	8	-0.849	8
APR	-0.749	9	-0.748	9	-0.815	9
Beta	--		--		-1.310	
Residual deviance	76.6*		62.5$		58.4$	
DIC	318.9		297.2		293.7	
	*Compared 65 data points		$Compared 61 data points			

r– ranking of treatments according to point estimates; ind=independent; FE=fixed effect

Detailed results of PASI response

More detailed results of the models, F1, G1, and G2 are presented next.

Table 144 Results of model F1: Treatment effects (on probit scale) and the different cut-off points (PASI50, PASI75 & PASI90)

	Treatment effects			
	Mean	**Median**	**97% CrI**	
Baseline effect	1.025	1.024	0.903	1.149
SEC300	-1.941	-1.936	-2.628	-1.280
SEC150	-1.877	-1.870	-2.540	-1.238
CZP	-0.877	-0.875	-1.239	-0.523
UST	-1.135	-1.134	-1.407	-0.868
GOL	-1.647	-1.645	-2.100	-1.212
ADA	-1.480	-1.477	-1.831	-1.142
INF	-2.414	-2.412	-2.841	-2.006
ETA	-0.801	-0.798	-1.639	0.025
APR	-0.750	-0.749	-0.987	-0.513
z1, PASI50	-			
z2,PASI75	0.586	0.585	0.523	0.651
z3, PASI90	1.153	1.153	1.059	1.251
Residual deviance*	76.6			
DIC	318.948			

*Compared 65 data points

Table 145 Results of Model G1: Treatment effects (on probit scale) and the different cut-off points (PASI50, PASI75 & PASI90)

	Treatment effects			
	Mean	**Median**	**97% CrI**	
Baseline effect	0.984	0.983	0.867	1.103
SEC300	-1.935	-1.932	-2.612	-1.287
SEC150	-1.869	-1.865	-2.528	-1.236
CZP	-0.874	-0.873	-1.237	-0.519
UST	-1.131	-1.131	-1.402	-0.863
GOL	-1.641	-1.635	-2.097	-1.212
ADA	-1.478	-1.476	-1.834	-1.136
INF	-2.280	-2.276	-2.730	-1.847
ETA	-0.800	-0.797	-1.645	0.021
APR	-0.748	-0.748	-0.983	-0.510
z1, PASI50	-			
z2,PASI75	0.578	0.577	0.516	0.642
z3, PASI90	1.136	1.136	1.043	1.235
Residual deviance*	62.54			
DIC	297.153			

*Compared 61 data points

Table 146 Results of Model G2: Treatment effects (on probit scale) and the different cut-off points (PASI50, PASI75 & PASI90)

	Treatment effects			
	Mean	**Median**	**97% CrI**	
Baseline effect	1.016	1.015	0.888	1.153
SEC300	-1.860	-1.864	-2.330	-1.363
SEC150	-1.793	-1.798	-2.231	-1.316
CZP	-1.433	-1.424	-1.888	-1.040
UST	-1.346	-1.342	-1.596	-1.121
GOL	-1.127	-1.141	-1.499	-0.667
ADA	-1.421	-1.422	-1.668	-1.167
INF	-1.788	-1.798	-2.173	-1.313
ETA	-0.846	-0.849	-1.478	-0.198
APR	-0.816	-0.815	-0.999	-0.640
Beta	-1.310	-1.297	-2.164	-0.495
z1, PASI50	-			
z2,PASI75	0.582	0.582	0.520	0.647
z3, PASI90	1.141	1.141	1.044	1.238
Residual deviance*	58.44			
DIC	293.702			

*Compared 61 data points

12.3.5.3 Preferred models

The results of models G1 and F1 are similar except for a small effect on the estimate of effect for infliximab; therefore model F1 is the preferred unadjusted model as it does not exclude a trial. In Model G2, DIC and residual deviance are lower than model G1, indicating that model fits well with the existing data and the data supports the assumption of adjustment with baseline effects. Therefore, we considered model F1 and G2 to be our preferred model.

12.3.5.4 Comparison of evidence synthesis of PASI responses in company submissions (Novartis and UCB), previous MTA (Rodgers et al. 2010) and current Assessment Group

Both the Novartis and the UCB submissions combined PASI response evidence using Bayesian evidence synthesis methods. Each of the two CS estimated probability of achieving PASI responses in three categories (50/75/90) to inform economic model. A brief comparison of the methods used with key model assumptions, by the AG, CS and previous MTA are presented in Table 147 and Table 148.

As mentioned before, UCB and AG included subpopulations in the main NMA and analysed both subpopulations (biologic naïve and experienced) separately. Whereas, Novartis considered over-all population as main NMA, and the analysis included more complete set of treatments and trials. This comparison refers to the Novartis NMA of subgroup (i.e. biologic naïve).

A key differences between the NMAs presented concerns the trials included in each analysis. Only the AG NMA for biologic naïve subgroup includes all comparators and all trials. The Rodgers et al. 2010 analysis was limited to the treatments available at that time. The UCB analysis for biologic naïve subgroup includes all treatments, but misses only some apremilast trials. The Novartis NMA for biologic naïve subgroup does not include certolizumab or apremilast and does not include all trials for the other treatments. AG considered to exclude RAPID-PsA trial in the NMA for biologic experienced subgroup, whereas UCB included in the analysis. Novartis didn't conducted NMA for this outcome for biologic experienced subgroup.

Another key difference between the models was assumption of effects on studies. AG and Rodgers et al. consider fixed effects on studies, whereas UCB and Novartis consider random effect on studies for biologic naïve subgroup and fixed effect on studies for biologic experienced subgroup analysis. Another difference was the primary timepoint used. The AG, previous MTA and Novartis used 12 weeks, whereas, UCB conducted primary analysis at 24 weeks and sensitivity analysis considering 12 week time point.

Table 147 Comparison of evidence synthesis of PASI responses in company submissions (Novartis and UCB), previous MTA (Rodgers et al. 2010) and Assessment Group

	Rodgers et al. 2010	Novartis	UCB	Assessment Group
Model	conditional multinomial probit model	Conditional multinomial probit model	Conditional multinomial probit model	Conditional multinomial probit model
Results reported	Probability of PASI response in three categories 50/75/90	Probability of PASI response in three categories 50/75/90	Probability of PASI response in three categories 50/75/90	Probability of PASI response in three categories 50/75/90
Time points	At 12 weeks (data from the 12 week or closest time point after 12 weeks–- normally 14 or 16 weeks)	At 12 weeks (data from the 12 week or closest time point after 12 weeks–- normally 14 or 16 weeks)	Primary analysis at 24 weeks (by treatments), sensitivity analysis was conducted at 12 weeks including data on 12 weeks or closest time point after 12 weeks.[$]	At 12 weeks (data from the 12 week or closest time point after 12 weeks–- normally 14 or 16 weeks)
Comments		Modelled probabilities are presented graphically.		
Data regarding subpopulation of biologic naïve				
Studies used in the analysis	ADEPT , IMPACT, IMPACT 2, Mease 2000, Mease 2004	ADEPT, FUTURE 2, GO-REVEAL, IMPACT 2	ADEPT, GO-REVEAL, IMPACT, IMPACT 2, Ixekizumab Phase III trial, Mease 2000, RAPID-PsA (12-16 weeks analysis)	ADEPT, FUTURE 2, GO-REVEAL, IMPACT, IMPACT 2, Mease 2000, PALACE 1, PALACE 2, PALACE 3, PSUMMIT 1, PSUMMIT 2, RAPID-PsA, SPIRIT-P1
Drugs evaluated	Adalimumab 40mg; ; infliximab: 5mg mg/kg, etanercept 25mg	Adalimumab 40mg; golimumab 50mg and 100 mg; infliximab 5mg mg/kg; secukinumab 150 and 300 mg	Adalimumab 40mg; certolizumab pegol; etanercept 25mg; golimumab 50mg; infliximab: 5mg mg/kg	Adalimumab 40 mg; apremilast 30mg; certolizumab pegol; etanercept 25mg; golimumab 50mg; infliximab: 5mg mg/kg; secukinumab 150 mg and 300mg; ustekinumab 45mg
Data regarding subpopulation of biologic experienced				
Studies used in the analysis	-	-	FUTURE 2, PSUMMIT-2, RAPID-PsA (24 weeks analysis)	FUTURE 2, PSUMMIT 2
Drugs evaluated	-	-	Certolizumab pegol, secukinumab 300mg; ustekinumab 45mg	Secukinumab 300mg; ustekinumab 45mg

[$]AG considers results at 12 week to compare with our results

Table 148 Key assumptions in the synthesis models for PASI responses in company submissions (Novartis and UCB), previous MTA (Rodgers et al. 2010) and Assessment Group

	Rodgers et al. 2010	**Novartis**	**UCB**	**Assessment Group**
Model	Conditional multinomial probit model	Conditional multinomial probit model	Conditional multinomial probit model	Conditional multinomial probit model
Fixed or random effects between studies	Fixed effects on studies	Random effects on studies for biologic naïve subpopulation analysis	Random effect on studies for biologic naïve subpopulation analysis and fixed effect for biologic experienced subpopulation analysis	Fixed effects on studies (for both biologic naïve and experienced subpopulation)
Baselines	Common effect model was used to estimate baseline	Common effect model was used to estimate baseline	Common effect model was used to estimate baseline	Common effect model was used to estimate baseline
Treatment effects	Treatments were assumed to be independent to each other	Treatments were assumed to be independent to each other	Treatments were assumed to be independent to each other	Treatments were assumed to be independent to each other
Model adjusted for the placebo response	Unadjusted	Unadjusted	Unadjusted	Considered both unadjusted and adjusted model for biologic naïve subpopulation; Considered unadjusted model for biologic experienced subpopulation
Interaction term (beta)	-	-	-	Common interaction term for adjusted model
Probit/logit score thresholds	Thresholds were assumed to be fixed across trials	Thresholds were assumed to be fixed across trials	Thresholds were assumed to be fixed across trials	Thresholds were assumed to be fixed across trials

Table 149 shows the NMA results for (probabilities of) PASI response for biologic naïve subpopulation estimated by the four NMAs. Across all the analyses, infliximab has the highest effectiveness following secukinumab among the treatment evaluated. The estimated probabilities in assessment group's analysis are more precise than either of the company submissions.

Given the differences in model assumptions and included studies, the results are slightly different in golimumab, adalimumab and etanercept. Between previous and current assessment, difference in adalimumab estimates are the result of additional data on adalimumab from the SPRIRIT-P1. In Novartis submission, the estimated probabilities are much lower for golimumab 50mg. The difference are plausible as AG and Novartis used different sets of data and model assumption. In UCB submission, the estimated probabilities are much lower for etanercept compared to the result of previous and current assessment. The difference is largely because UCB used different PASI50 response data in the analysis.

Table 149 Comparison of PASI response in company submissions (Novartis and UCB), previous MTA (Rodgers et al. 2010) and Assessment Group in biologic naïve subpopulation

Treatments	Probability of PASI responses in biologic naïve subpopulation at 12 weeks (12-16 weeks)								
		Rodgers et al. 2010		Novartis	UCB		Assessment Group (Unadjusted)		Assessment Group (Adjusted)	
		Mean	95% CrI	Mean	Mean	95% CI	Median	95% CI	Median	95% CI
Placebo	PASI50	0.131	(0.09, 0.18)	[redacted]	[redacted]	[redacted]	0.15	(0.13, 0.18)	0.16	(0.12, 0.19)
	PASI75	0.045	(0.03, 0.07)	[redacted]	[redacted]	[redacted]	0.05	(0.04, 0.07)	0.06	(0.04, 0.07)
	PASI90	0.017	(0.01, 0.03)	[redacted]	[redacted]	[redacted]	0.02	(0.01, 0.02)	0.02	(0.01, 0.02)
SEC300	PASI50	NC		[redacted]	NC		0.82	(0.61, 0.94)	0.80	(0.62, 0.91)
	PASI75			[redacted]			0.63	(0.38, 0.84)	0.60	(0.40, 0.78)
	PASI90			[redacted]			0.41	(0.19, 0.67)	0.38	(0.21, 0.58)
SEC150	PASI50	NC		[redacted]	NC		0.80	(0.59, 0.93)	0.78	(0.60, 0.90)
	PASI75			[redacted]			0.60	(0.36, 0.82)	0.58	(0.38, 0.75)
	PASI90			[redacted]			0.38	(0.18, 0.63)	0.36	(0.19, 0.54)
CZP	PASI50	NC		NC	[redacted]		0.44	(0.31, 0.59)	0.66	(0.50, 0.82)
	PASI75				[redacted]		0.23	(0.14, 0.36)	0.43	(0.29, 0.63)
	PASI90				[redacted]		0.10	(0.05, 0.18)	0.23	(0.13, 0.41)
UST	PASI50	NC		NC	NC		0.54	(0.44, 0.65)	0.63	(0.52, 0.74)
	PASI75						0.32	(0.23, 0.42)	0.40	(0.30, 0.52)
	PASI90						0.15	(0.09, 0.22)	0.21	(0.14, 0.31)
GOL*	PASI50	NC		[redacted]	[redacted]		0.73	(0.58, 0.86)	0.55	(0.36, 0.70)
	PASI75			[redacted]	[redacted]		0.51	(0.35, 0.68)	0.32	(0.17, 0.48)
	PASI90			[redacted]	[redacted]		0.30	(0.17, 0.47)	0.15	(0.07, 0.27)
ADA	PASI50	0.738	(0.55, 0.88)	[redacted]	[redacted]		0.68	(0.55, 0.78)	0.66	(0.54, 0.76)
	PASI75	0.477	(0.28, 0.69)	[redacted]	[redacted]		0.45	(0.32, 0.58)	0.43	(0.32, 0.55)
	PASI90	0.257	(0.12, 0.45)	[redacted]	[redacted]		0.24	(0.15, 0.36)	0.23	(0.15, 0.33)
INF	PASI50	0.913	(0.82, 0.97)	[redacted]	[redacted]		0.92	(0.84, 0.96)	0.78	(0.61, 0.88)
	PASI75	0.769	(0.59, 0.90)	[redacted]	[redacted]		0.79	(0.67, 0.88)	0.58	(0.39, 0.73)
	PASI90	0.557	(0.35, 0.77)	[redacted]	[redacted]		0.59	(0.44, 0.73)	0.36	(0.20, 0.52)
ETA	PASI50	0.403	(0.24, 0.59)	NC	[redacted]		0.41	(0.15, 0.72)	0.43	(0.20, 0.69)
	PASI75	0.177	(0.09, 0.31)		[redacted]		0.21	(0.05, 0.50)	0.23	(0.08, 0.47)

	PASI90	0.074	(0.03, 0.15)		[redacted]	0.08	(0.01, 0.29)	0.10	(0.02, 0.26)
APR	PASI50	NC		NC	NC	0.39	(0.31, 0.49)	0.42	(0.33, 0.52)
	PASI75					0.20	(0.14, 0.27)	0.22	(0.16, 0.30)
	PASI90					0.08	(0.05, 0.12)	0.09	(0.06, 0.14)

NC = Not conducted; *GOL = golimumab 50mg;

Rodgers et al. 2010 and Novartis did not include an analysis for the treatment experienced subgroup. Table 150 presents the PASI results from the AG and UCB NMAs for the biologic experienced subpopulation. However, the results are not comparable between the AG and UCB analyses as probabilities were estimated at two different time points (12 weeks and 24 weeks) and it is evident that the PASI response differes between these two timepoint.

Table 150 Comparison of PASI response in UCB submission, and Assessment Group in biologic experienced subpopulation

Treatments	**Probability of PASI responses in biologic experienced subpopulation**				
		UCB, at 24 weeks		**Assessment Group, at 12 weeks (12-16 weeks)**	
		Mean	**95% CI**	**Mean**	**95% CI**
Placebo	PASI50	[redacted]		0.088	(0.01 to 0.28)
	PASI75	[redacted]		0.012	(0.00 to 0.06)
	PASI90	[redacted]		0.002	(0.00 to 0.02)
SEC300	PASI50	[redacted]		0.875	(0.46 to 1.00)
	PASI75	[redacted]		0.598	(0.23 to 0.89)
	PASI90	[redacted]		0.365	(0.08 to 0.75)
UST	PASI50	[redacted]		0.628	(0.29 to 0.89)
	PASI75	[redacted]		0.279	(0.07 to 0.61)
	PASI90	[redacted]		0.120	(0.01 to 0.42)
CZP	PASI50	[redacted]		NC	
	PASI75	[redacted]			
	PASI90	[redacted]			

NC = Not conducted

12.3.5.5 WinBUG codes of preferred model

Model F1:

```
model{
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]] + (d[t[i]] - d[t[1]])*(1-equals(t[i],b[i])) + z[z.index[i,j]]
                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])
        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])
                        }
        }
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]
                }
d[1] <- 0
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
for(i in 1:ns){ mu[i] ~ dnorm(0,.000001)}
for (i in 1:ns) {mu1[i]<-mu[i]*equals(t[1],1)}
A<-sum(mu1[])/ns
# calculate prob of achieving PASI50,75,90 on treat k
for (k in 1:nt) {
for (j in 1: Cmax-1) { T[j,k] <- 1 - phi(A + d[k] + z[j]) }
}
}
```

Model G2:

```
model{
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]] + d[t[i]] + z[z.index[i,j]]
                        + betaplac * (mu[s[i]] - Mean) * (1-equals(t[i],1))
                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])
        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])
                 }
```

```
        }
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]
                }
d[1] <- 0
for (k in 2:nt){ d[k] ~ dnorm(0,0.01) }
for(i in 1:ns){ mu[i] ~ dnorm(0,0.01)}
betaplac ~ dnorm(0,0.01)
for (i in 1:ns) {mu1[i]<-mu[i]*equals(t[1],1)}
A<-sum(mu1[])/ns
# calculate prob of achieving PASI50,75,90 on treat k
for (k in 1:nt) {
for (j in 1: Cmax-1) { T[j,k] <- 1 - phi(A + d[k] + z[j]) }
}
}
```

d[1]=PLA, d[2]=SEC300, d[3]=SEC150, d[4]=CZP, d[5]=UST, d[6]=GOL, d[7]=ADA, d[8]=INF, d[9]=ETA, d[10]=APR

12.3.6 ACR response

12.3.6.1 Detailed methods for biologic naïve subpopulation

The NMA for ACR utilised a similar framework of analysis that used to estimate probability of PASI responses. In brief, the model considered a multinomial likelihood and a probit link for ordered categorical data[redacted]

Analogously to the analyses on PsARC, sets of alternative assumptions were tested. We explored the effect of differences in trial specific placebo responses on treatment effect undertaking a meta-regression. In the context of an adjusted model for placebo response, we explored the possibility of there being class effects. Three different class groupings were considered: all treatments as a single class; all biologics as a class with apremilast separate; and to reflect the pharmacology, anti-TNFs grouped, ILs grouped and apremilast separate. Additionally we explored two within-class assumptions: assuming treatments within a class to have equal effectiveness and, alternatively, those treatments within a class have similar (exchangeable) effectiveness. Fixed effects across studies were assumed for all models. We have not considered models assuming exchangeability between classes.

Summary of all treatment effect models explored

All models implemented for evidence synthesis of ACR response are presented in Table 41. Detailed coding of the models is presented in

Table 152.

Table 151 Key assumptions of models implemented for evidence synthesis of ACR response

Sets of analysis	Study	Treatments	Meta-regression	Class
H1	FE	independent	No baseline adjustment	No class effect
I1	FE	independent	Common interaction term with baseline effect	No class effect
J1	FE	Equal|class	Common interaction term with baseline effect	independent class effect class = {all treatments}
J2	FE	Equal|class, remaining treatments independent*		independent class effect class = APR independent; {all remaining biologics}
J3	FE	Equal|class, remaining treatments independent*		independent class effect class = {Anti-TNFs, ILs}; APR independent
K1	FE	Exchangeable|class, remaining treatments independent*	Common interaction term with baseline effect	independent class effect class = APR independent; {all other biologics}
K2	FE	Exchangeable|class, remaining treatments independent*		independent class effect class = {Anti-TNFs, ILs}; APR independent

*APR independent; FE=fixed effect

Table 152 Description of models and underlying assumptions for ACR response

Model H1	**Model I1**
Likelihood $r_{ikj} \sim Binomial(p_{ikj}, n_{ikj})$ *Model* $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ $\Pr iors(anti-TNF-naive-analysis)$ $\delta_t \sim dnorm(0,0.000001)$ $\mu_i \sim dnorm(0,0.000001)$ $z_j \sim dunif(0,5)$ $\Pr iors(anti-TNF-\exp eriensed-analysis)$ $\delta_t \sim dnorm(0,0.01)$ $\mu_i \sim dnorm(0,0.01)$ $z_j \sim dunif(0,5)$	*Likelihood* $r_{ikj} \sim Binomial(p_{ikj} n_{ikj})$ *Model* $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j + \beta(\mu_i - \bar{\mu})$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ $\Pr iors$ $\delta_t \sim dnorm(0,0.01)$ $\mu_i \sim dnorm(0,0.01)$ $\beta \sim dnorm(0,0.01)$ $z_j \sim dunif(0,5)$
Assumptions • Baselines are unconstrained • Treatments effects are independent. • Fixed effects between studies • Fixed effect for each of the *j-1* categories over all trials.	Assumptions • Baselines are unconstrained • Treatments effects are independent. • Fixed effects between studies • Fixed effect for each of the *j-1* categories over all trials. • Common interaction term between studies
Model J1, J2, J3	**Model K1, K2**

Likelihood $r_{ikj} \sim Binomial(p_{ikj} n_{ikj})$ *Model* $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j + \beta(\mu_i - \bar{\mu})$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ $\delta_t \sim \delta_c$ Priors $\delta_c \sim dnorm(0,0.01)$ $\mu_i \sim dnorm(0,0.01)$ $\beta \sim dnorm(0,0.01)$ $z_j \sim dunif(0,5)$	*Likelihood* $r_{ikj} \sim Binomial(p_{ikj} n_{ikj})$ *Model* $q_{ikj} = 1-(p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j + \beta(\mu_i - \bar{\mu})$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ $\delta_t \sim dnorm(Class_c, 1/\gamma^2)$ Priors $Class_c \sim dnorm(0,0.01)$ $\mu_i \sim dnorm(0,0.01)$ $\beta \sim dnorm(0,0.01)$ $z_j \sim dunif(0,5)$ $\gamma \sim dunif(0,10)$
J1:class = {All biologics} J2: APR independent; class = {all other biologics} J3: class = {Anti-TNFs, iLs}; APR independent	K1: APR independent; class = {all other biologics} K2: class = {Anti-TNFs, iLs}; APR independent
Assumptions • Baselines are unconstrained • The treatments effects are equal within class. • Fixed effects between studies • Fixed effect for each of the *j-1* categories over all trials. • Common interaction term between studies	Assumptions • Baselines are unconstrained • A random effect is used to describe differences between treatments (exchangeability is assumed). • Fixed effects between studies • Fixed effect for each of the *j-1* categories over all trials. • Common interaction term between studies

Model H1 considers the treatments' effectiveness are independent of each other. Model I1 considers the relative effectiveness of the alternative treatments as independent from each other, but that all depend on the response in the placebo arm. Model J1 considers the treatments as equal in terms of their effectiveness, but dependent on the effect of the placebo arm. Model J2 and J3 consider the treatments as equal in terms of their effectiveness within class, but dependent on the effect of the placebo arm. Model K1 and K2 assume the treatments to have a similar, but not equal effectiveness and dependent on the effect of the placebo arm; this model introduces more flexibility than assuming treatment effects to be equal (models J2 and J3), but does not fully assume treatments to differ as in model H1. It does imply that there are differences between the effectiveness of treatments that we may not be able to explain but that we should consider. These may be a result of differences between the treatments themselves or because of differences in the design of the trials used to evaluate each treatment.

12.3.6.2 Detailed results for biologic naïve subpopulation

Summary results of ACR response

Table 58 presents the results of the treatment effects for ACR responses estimated from the seven models with measures of goodness of fit. There were no issues with convergence.

Table 153 Results of ACR response: treatment effects (median) on probit scale in biologic naïve subpopulation

Meta-reg	no	yes	yes	yes	yes	yes	yes
treatments	ind	ind	=|class	=|class	=|class	~|class **	~|class **

					{all}		{APR,other }		{ILs,TNFs, APR}		(APR, other)		(ILs, TNFs, APR)	
Cut-offs	FE		FE		FE		FE		FE		FE		FE	
	H1	**r**	**I1**	**r**	**J1**	**r**	**J2**	**r**	**J3**	**r**	**K1**	**r**	**K2**	**r**
PLA	0.952		0.961		0.882		0.966		0.966		0.963		0.961	
SEC300	-0.914	6	-1.397	2							-1.274	2	-1.236	3
SEC150	-0.932	5	-1.415	1			-1.094	1	-1.095	1	-1.283	1	-1.246	2
UST	-0.570	8	-0.722	8							-0.750	8	-0.732	8
CZP	-0.811	7	-1.265	3	-0.830	1					-1.193	5	-1.176	5
GOL	-1.429	2	-0.918	7							-1.010	7	-1.040	7
ADA	-1.072	4	-1.126	6					-0.609	2	-1.121	6	-1.124	6
INF	-1.617	1	-1.212	5							-1.246	3	-1.269	1
ETA	-1.362	3	-1.214	4							-1.215	4	-1.228	4
APR	-0.509	9	-0.592	9			-0.610	2	-0.014	3	-0.581	9	-0.576	9
Beta (mean)			-1.276		1.327		-1.627		-1.621		-1.099		-1.018	
Residual deviance*	120.0		119.1		156.1		148.3		148.3		120.0		120.4	
DIC	482.22		480.94		511.66		503.43		503.37		480.90		481.1	

r – ranking of active treatments according to point estimates; *compared to 92 data points; ** shrunken estimates; ind-independent; =|class – equal class effect; ~|class – exchangeable class effect

Detailed results of ACR response

More detailed results of the models, H1, I1, J1, J2, J3, K1 and K2 are presented here.

Table 154 Results of Model H1: Treatment effects (on probit scale) and the different cut-off points (ACR20, ACR50 & ACR70)

	Treatment effects			
	Mean	**Median**	**97% CrI**	
Baseline effect	0.952	0.952	0.874	1.031
SEC300	-0.915	-0.914	-1.319	-0.512
SEC150	-0.932	-0.932	-1.347	-0.525
UST	-0.570	-0.570	-0.797	-0.349
CZP	-0.811	-0.811	-1.090	-0.530
GOL	-1.431	-1.429	-1.810	-1.068
ADA	-1.072	-1.072	-1.274	-0.870
INF	-1.619	-1.617	-1.943	-1.306
ETA	-1.364	-1.362	-1.688	-1.050
APR	-0.509	-0.509	-0.672	-0.346

z1, ACR20	-			
z2, ACR50	0.661	0.661	0.615	0.709
z3, ACR70	1.284	1.283	1.213	1.356
Residual deviance*	120.00			
DIC	482.22			

*Compared 92 data points

Table 155 Results of Model I1: Treatment effects (on probit scale) and the different cut-off points (ACR20, ACR50 & ACR70)

	Treatment effects			
	Mean	**Median**	**97% CrI**	
Baseline effect	0.962	0.961	0.880	1.046
SEC300	-1.402	-1.397	-1.890	-0.939
SEC150	-1.421	-1.415	-1.920	-0.953
UST	-0.725	-0.722	-0.939	-0.526
CZP	-1.268	-1.265	-1.666	-0.874
GOL	-0.910	-0.918	-1.362	-0.433
ADA	-1.127	-1.126	-1.290	-0.973
INF	-1.207	-1.212	-1.578	-0.812
ETA	-1.209	-1.214	-1.455	-0.931
APR	-0.594	-0.592	-0.738	-0.459
Beta	-1.276	-1.297	-2.164	-0.274
z1, ACR20	-	-	-	-
z2, ACR50	0.661	0.661	0.615	0.709
z3, ACR70	1.283	1.282	1.212	1.356
Residual deviance*	119.10			
DIC	480.94			

*Compared 92 data points

Table 156 Results of Model J1: Treatment effects (on probit scale) and the different cut-off points (ACR20, ACR50 & ACR70)

	Treatment effects			
	Mean	**Median**	**97% CrI**	
Baseline effect	0.882	0.882	0.812	0.953
All Biologics as a class	-0.825	-0.830	-0.992	-0.624
Beta	1.327	1.236	0.399	2.792

z1, ACR20	-			
z2, ACR50	0.656	0.655	0.610	0.702
z3, ACR70	1.272	1.272	1.201	1.345
Residual deviance*	156.1			
DIC	511.66			

*Compared 92 data points

Table 157 Results of Model J2: Treatment effects (on probit scale) and the different cut-off points (ACR20, ACR50 & ACR70)

	Treatment effects			
	Mean	**Median**	**97% CrI**	
Baseline effect	0.967	0.966	0.886	1.051
All Biologics (except APR)	-1.095	-1.094	-1.190	-1.005
APR	-0.614	-0.610	-0.773	-0.474
Beta	-1.627	-1.627	-2.365	-0.926
z1, ACR20	-			
z2, ACR50	0.657	0.656	0.611	0.704
z3, ACR70	1.272	1.271	1.201	1.345
Residual deviance*	148.30			
DIC	503.43			

*Compared 92 data points

Table 158 Results of Model J3: Treatment effects (on probit scale) and the different cut-off points (ACR20, ACR50 & ACR70)

	Treatment effects			
	Mean	**Median**	**97% CrI**	
Baseline effect	0.967	0.966	0.886	1.049
ILs as class	-1.095	-1.095	-1.189	-1.005
Anti-TNFs as class	-0.612	-0.609	-0.767	-0.474
APR	0.021	-0.014	-19.450	19.720
Beta	-1.621	-1.619	-2.349	-0.918

z1, ACR20				
z2, ACR50	0.657	0.656	0.611	0.704
z3, ACR70	1.272	1.271	1.201	1.344
Residual deviance*	148.30			
DIC				

*Compared 92 data points

Table 159 Results of Model K1: Treatment effects (on probit scale) and the different cut-off points (ACR20, ACR50 & ACR70)

	Predicted mean distribution				**Shrunken or independent estimates**			
	Mean	**Median**	**97% CrI**		**Mean**	**Median**	**97% CrI**	
Baseline effect	-	-	-	-	0.963	0.963	0.880	1.049
SEC300	-1.137	-1.135	-1.750	-0.534	-1.278	-1.274	-1.582	-0.994
SEC150					-1.287	-1.283	-1.597	-0.998
UST					-0.750	-0.750	-0.919	-0.582
CZP					-1.195	-1.193	-1.437	-0.961
GOL					-1.007	-1.010	-1.264	-0.733
ADA					-1.122	-1.121	-1.257	-0.990
INF					-1.244	-1.246	-1.479	-1.005
ETA					-1.214	-1.215	-1.410	-1.013
APR	-	-	-	-	-0.581	-0.581	-0.700	-0.465
Beta	-	-	-	-	-1.099	-1.103	-1.646	-0.534
$\gamma^{\$}$	-	-	-	-	0.264	0.240	0.123	0.547
z1, ACR20	-	-	-	-	-	-	-	-
z2, ACR50	-	-	-	-	0.660	0.660	0.614	0.709
z3, ACR70	-	-	-	-	1.280	1.280	1.209	1.354
Residual deviance*	120.00							
DIC	480.90							

*Compared 92 data points

Table 160 Results of Model K2: Treatment effects (on probit scale) and the different cut-off points (ACR20, ACR50 & ACR70)

	Predicted mean distribution				**Shrunken or independent estimates**			
	Mean	**Median**	**97% CrI**		**Mean**	**Median**	**97% CrI**	
Baseline effect	-	-	-	-	0.961	0.961	0.878	1.046
SEC300	-1.069	-1.054	-1.869	-0.345	-1.234	-1.236	-1.609	-0.845
SEC150					-1.243	-1.246	-1.628	-0.854
UST					-0.733	-0.732	-0.913	-0.552
CZP	-1.167	-1.170	-1.862	-0.464	-1.178	-1.176	-1.443	-0.924
GOL					-1.038	-1.040	-1.350	-0.718
ADA					-1.123	-1.124	-1.259	-0.988
INF					-1.268	-1.269	-1.530	-1.003

ETA				-1.228	-1.228	-1.432	-1.021
APR	-	-	- -	-0.576	-0.576	-0.700	-0.453
Beta				-1.018	-1.028	-1.671	-0.334
$\gamma^{\$}$				0.280	0.248	0.107	0.643
z1, ACR20	-	-	- -	-	-	-	-
z2, ACR50				0.661	0.660	0.615	0.708
z3, ACR70				1.281	1.281	1.210	1.354
Residual deviance*	120.40						
DIC							

*Compared 92 data points

12.3.6.3 Preferred models

The unadjusted model H1 fits the data as well as any of the other models and generates results that reflect the observed results. Considering the placebo adjusted models, Model I1 generated results (rankings) which do not reflect well the observed trial results; and it must be borne in mind that without any clear rationale for the placebo effect, the results must be interpreted with caution. Using an assumption of equal class effect for the treatments does not produced a better-fitting model (model J1, J2, J3) than assuming independent treatment effects (model H1, I1) or similar (exchangeable) treatment effects (model K1, K2). In addition, there was a little difference in goodness of fit statistics (DIC and residual deviance) between models K1 and K2, and we consider the exchangeable class effect model which utilised two classes (interleukins and anti-TNFs), with apremilast separate to be most clinically plausible. Hence, our preferred models are models H1 and K2.

12.3.6.4 Comparison of evidence synthesis of ACR responses in company submissions, previous MTA and assessment group

Both the Novartis and the UCB submissions combined ACR outcome evidence using Bayesian evidence synthesis methods. Both submissions estimated probability of achieving ACR responses in three categories (20/50/70) and conducted binary analysis of the ACR categories separately to inform clinical effectiveness. However, AG and previous MTA estimated probability of achieving ACR responses in three categories (20/50/70) to inform clinical effectiveness. Therefore, the comparison between CS and AG are limited to the estimation of probability of achieving ACR responses in three categories (20/50/70). A brief comparison of the methods used with key model assumptions, by the AG, CS and previous MTA are presented in Table 147 and Table 148.

Like other outcomes, a key differences between the ACR NMAs presented concerns the trials included in each analysis. AG NMA for biologic naïve subgroup includes all comparators and all trials. The Rodgers et al. 2010 analysis was limited to the treatments available at that time. The UCB analysis for biologic naïve subgroup includes all treatments but misses one apremilast trials. Novartis NMA for biologic naïve subgroup included more complete set of treatments and trials for this outcome. Both submissions included RAPID-PsA trial in the biologic experienced subgroup analysis, whereas, AG excluded from the analysis. It should be noted that this comparison refers to the Novartis NMAs of subgroups. As mentioned before, the Novartis submission presented a NMA for all patients (treatment naïve and experienced combined).

A key difference between models was assumption of effects on studies. AG and Rodgers et al. 2010 consider fixed effects on studies, whereas UCB and Novartis consider random effect on studies for biologic naïve subgroup and fixed effect on studies for biologic experienced subgroup analysis. Like other outcome, another key difference relates to the primary timepoint used. The AG, previous MTA and Novartis used 12 weeks, whereas, UCB conducted primary analysis at 24 weeks and sensitivity analysis considering 12 week time point.

Table 161 Comparison of evidence synthesis of ACR responses in company submissions (Novartis and UCB), previous MTA (Rodgers et al. 2010) and Assessment Group

	Rodgers et al. 2010	Novartis	UCB	Assessment Group
Model	Conditional multinomial probit model	Conditional multinomial probit model	Conditional multinomial probit model	Conditional multinomial probit model
Results reported	Probability of ACR response in three categories 20/50/70	Probability of ACR response in three categories 20/50/70	Probability of ACR response in three categories 20/50/70 for experienced subpopulation, but did not present probabilities for biologic naïve subpopulation	Probability of ACR response in three categories 20/50/70
Time points	At 12 weeks (data from the 12 week or closest time point after 12 weeks–- normally 14 or 16 weeks)	At 12 weeks (data from the 12 week or closest time point after 12 weeks–- normally 14 or 16 weeks)	Primary analysis at 24 weeks (by treatments), sensitivity analysis was conducted at 12 weeks including data on 12 weeks or closest time point after 12 weeks.[$]	At 12 weeks (data from the 12 week or closest time point after 12 weeks–- normally 14 or 16 weeks)
Comments		Modelled probabilities are presented graphically		
Data regarding subpopulation of biologic naïve				
Studies used in the analysis	ADEPT , Genovese 2007, IMPACT, IMPACT 2, Mease 2000, Mease 2004	ADEPT, FUTURE 2, Genovese 2007, GO-REVEAL, IMPACT 2, Mease 2004, PALACE 1, PSUMMIT 1, PSUMMIT 2, RAPID-PsA	ADEPT, Genovese 2007, GO-REVEAL, IMPACT, IMPACT 2, Ixekizumab Phase III trial, PALACE 1, PALACE 3, PSUMMIT 1, Mease 2004, Mease 2000, RAPID-PsA (12-16 weeks analysis)	ADEPT, FUTURE 2, Genovese 2007, GO-REVEAL, IMPACT, IMPACT 2, Mease 2000, Mease 2004, PALACE 1, PALACE 2, PALACE 3, PSUMMIT 1, PSUMMIT 2, RAPID-PsA, SPIRIT-P1
Drugs evaluated	Adalimumab 40mg; infliximab: 5mg mg/kg, etanercept 25mg	Adalimumab 40mg; apremilast 20mg and 30mg; certolizumab pegol 200mg and 400mg; etanercept 25mg; golimumab 50mg and 100mg; infliximab 5mg mg/kg; secukinumab 150mg and 300mg; ustekinumab 45mg and 90mg	Adalimumab 40mg; apremilast 20mg and 30mg; certolizumab pegol; etanercept 25mg; golimumab 50mg; infliximab: 5mg mg/kg	Adalimumab 40mg; apremilast 30mg; certolizumab pegol; etanercept 25mg; golimumab 50mg; infliximab: 5mg mg/kg; secukinumab 150mg and 300mg; ustekinumab 45mg
Data regarding subpopulation of biologic experienced				
Studies used in the analysis	NC	FUTURE 2, PALACE 1, PSUMMIT 2, RAPID-PsA	FUTURE 1^, FUTURE 2, PSUMMIT-2, RAPID-PsA (24 weeks analysis)	FUTURE 2, PSUMMIT 2
Drugs evaluated	NC	Apremilast 20mg and 30mg; certolizumab pegol 200mg and 400mg; secukinumab 150mg and 300mg; ustekinumab 45mg and 90mg	Certolizumab pegol, secukinumab 300mg; ustekinumab 45mg	Secukinumab 300mg; ustekinumab 45mg

[$] AG considers results at 12 week to compare with our results; ^included patients from the Latin America sites

Table 162 Key assumptions in the synthesis models for ACR responses in company submissions (Novartis and UCB), previous MTA (Rodgers et al. 2010) and Assessment Group

	Rodgers et al. 2010	**Novartis**	**UCB**	**Assessment Group**
Model	Conditional multinomial probit model	Conditional multinomial probit model	Conditional multinomial probit model	Conditional multinomial probit model
Fixed or random effects between studies	Fixed effects on studies	Random effect on studies for biologic naïve subgroup analysis; and fixed effects on studies for biologic experienced subgroup analysis	Random effect on studies for biologic naïve subpopulation analysis and fixed effect for biologic experienced subpopulation analysis	Fixed effects on studies (for both subpopulation analysis)
Baselines	Common effect model was used to estimate baseline	Common effect model was used to estimate baseline	Common effect model was used to estimate baseline	Common effect model was used to estimate baseline
Treatment effects	Treatments were assumed to be independent to each other	Treatments were assumed to be independent to each other	Treatments were assumed to be independent to each other	For biologic naïve subpopulation: 1. treatments were assumed to be independent to each other 2. class effects which considered treatments are similar within class (exchangeable class effect) which utilised two classes: interleukins and anti-TNFs For biologic experienced subpopulation: treatments were assumed to be independent to each other
Model adjusted for the placebo response	Unadjusted	Unadjusted	Unadjusted	Independent treatment effects model was unadjusted; but analysis assuming exchangeable class effects model was adjusted for the placebo response
Interaction term (beta)	-	-	-	Common interaction term for adjusted model
Probit/logit score thresholds	Thresholds were assumed to be fixed across trials	Thresholds were assumed to be fixed across trials	Thresholds were assumed to be fixed across trials	Thresholds were assumed to be fixed across trials

Table 149 shows the three NMA results for (probabilities of) ACR response for biologic naïve subpopulation. In comparison with Novartis analysis and AG unadjusted analysis, the estimated probabilities in three categories are lower for infliximab but higher for adalimumab. The differences are largely because Novartis included different dataset. In UCB chose binary analysis of ACR 20 and 50 over probability of achieving ACR responses in three categories (20/50/70) to be the preferred

analysis, and did not present the results of probability of ACR responses for biologic naïve subgroup. Therefore, it was not plausible to compare AG's results for biologic naïve population with UCB.

Table 163 Comparison of ACR response in company submissions (Novartis and UCB), previous MTA (Rodgers et al. 2010) and Assessment Group in biologic naïve subpopulation

Treatments	Probability of ACR responses in biologic naïve subpopulation at 12 weeks (12-16 weeks)							
		Rodgers et al. 2010		Novartis	Assessment Group (Unadjusted)		Assessment Group (Adjusted)	
		Mean	95% CrI	Mean	Median	95% CI	Median	95% CI
Placebo	ACR20	0.14	(0.11, 0.17)	[redacted]	0.17	(0.15, 0.19)	0.17	(0.15, 0.19)
	ACR50	0.05	(0.04, 0.07)	[redacted]	0.05	(0.04, 0.06)	0.05	(0.04, 0.06)
	ACR70	0.01	(0.01, 0.03)	[redacted]	0.01	(0.01, 0.02)	0.01	(0.01, 0.02)
SEC300	ACR20		NC	[redacted]	0.49	(0.33, 0.64)	0.61	(0.46, 0.75)
	ACR50			[redacted]	0.24	(0.14, 0.38)	0.35	(0.22, 0.50)
	ACR70			[redacted]	0.09	(0.04, 0.18)	0.16	(0.08, 0.27)
SEC150	ACR20		NC	[redacted]	0.49	(0.34, 0.65)	0.61	(0.46, 0.75)
	ACR50			[redacted]	0.25	(0.14, 0.39)	0.35	(0.22, 0.51)
	ACR70			[redacted]	0.10	(0.04, 0.19)	0.16	(0.08, 0.27)
UST[^]	ACR20		NC	[redacted]	0.35	(0.27, 0.44)	0.41	(0.34, 0.49)
	ACR50			[redacted]	0.15	(0.10, 0.21)	0.19	(0.14, 0.25)
	ACR70			[redacted]	0.05	(0.03, 0.08)	0.07	(0.04, 0.10)
CZP	ACR20		NC	[redacted]	0.44	(0.34, 0.55)	0.58	(0.49, 0.69)
	ACR50			[redacted]	0.21	(0.14, 0.30)	0.33	(0.24, 0.43)
	ACR70			[redacted]	0.08	(0.04, 0.13)	0.14	(0.09, 0.22)
GOL*	ACR20		NC	[redacted]	0.68	(0.55, 0.80)	0.53	(0.40, 0.66)
	ACR50			[redacted]	0.43	(0.30, 0.57)	0.28	(0.18, 0.40)
	ACR70			[redacted]	0.21	(0.12, 0.33)	0.11	(0.06, 0.19)
ADA	ACR20	0.56	(0.43, 0.69)	[redacted]	0.55	(0.47, 0.62)	0.56	(0.50, 0.63)
	ACR50	0.31	(0.21, 0.44)	[redacted]	0.29	(0.23, 0.36)	0.31	(0.26, 0.37)
	ACR70	0.13	(0.08, 0.21)	[redacted]	0.12	(0.09, 0.17)	0.13	(0.10, 0.17)
INF	ACR20	0.68	(0.53, 0.81)	[redacted]	0.75	(0.65, 0.83)	0.62	(0.51, 0.72)
	ACR50	0.43	(0.29, 0.59)	[redacted]	0.50	(0.39, 0.62)	0.36	(0.26, 0.47)
	ACR70	0.20	(0.11, 0.33)	[redacted]	0.27	(0.18, 0.38)	0.17	(0.10, 0.24)
ETA	ACR20	0.61	(0.46, 0.75)	[redacted]	0.66	(0.55, 0.76)	0.61	(0.51, 0.69)
	ACR50	0.36	(0.23, 0.52)	[redacted]	0.40	(0.29, 0.52)	0.35	(0.27, 0.43)
	ACR70	0.16	(0.09, 0.26)	[redacted]	0.19	(0.12, 0.29)	0.16	(0.11, 0.21)
APR[$]	ACR20		NC	[redacted]	0.33	(0.27, 0.39)	0.35	(0.30, 0.41)
	ACR50			[redacted]	0.13	(0.10, 0.17)	0.15	(0.12, 0.19)
	ACR70			[redacted]	0.04	(0.03, 0.06)	0.05	(0.03, 0.07)

NC = Not conducted; [^] UST=ustekinumab 45mg; *GOL = golimumab 50mg; [$]APR= apremilast 30mg

In comparison of the biologic experienced subgroup analyses, the results are not comparable between AG and UCB analyses as probabilities were estimated at two different time points (12 weeks and 24 weeks). There are differences in Novartis and AG estimates, which, largely because Novartis included different dataset. (Table 164)

Table 164 Comparison of ACR response in UCB submission, and Assessment Group in biologic experienced subpopulation

Treatments	**Probability of ACR responses in biologic experienced subpopulation**					
		Novartis	**UCB, at 24 weeks**		**Assessment Group, at 12 weeks (12-16 weeks)**	
		Mean	**Mean**	**95% CrI**	**Median**	**95% CrI**
Placebo	ACR20	[redacted]	[redacted]	[redacted]	0.14	(0.08, 0.22)
	ACR50	[redacted]	[redacted]	[redacted]	0.03	(0.01, 0.06)
	ACR70	[redacted]	[redacted]		0.01	(0.00, 0.02)
SEC300	ACR20	[redacted]	[redacted]	[redacted]	0.36	(0.19, 0.57)
	ACR50	[redacted]	[redacted]	[redacted]	0.11	(0.04, 0.25)
	ACR70	[redacted]	[redacted]		0.03	(0.01, 0.11)
UST[$]	ACR20	[redacted]	[redacted]	[redacted]	0.42	(0.26, 0.59)
	ACR50	[redacted]	[redacted]	[redacted]	0.14	(0.06, 0.27)
	ACR70	[redacted]	[redacted]		0.05	(0.01, 0.12)
CZP	ACR20	[redacted]	[redacted]	[redacted]	NC	
	ACR50	[redacted]	[redacted]	[redacted]		
	ACR70	[redacted]	[redacted]			

NC = Not conducted; [$] UST=ustekinumab 45mg

12.3.6.5 WinBUG codes of preferred model

Model H1:

```
model{
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]] + (d[t[i]] - d[t[1]])*(1-equals(t[i],b[i])) + z[z.index[i,j]]
                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])
        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])
                    }
        }
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]
                }
d[1] <- 0
for (k in 2:nt){ d[k] ~ dnorm(0,0.000001) }
for(i in 1:ns){ mu[i] ~ dnorm(0,0.000001)}

for (i in 1:ns) {
mu1[i]<-mu[i]*equals(t[1],1)}
A<-sum(mu1[])/ns

# calculate prob of achieving ACR20/50/70 on treat k
for (k in 1:nt) {
for (j in 1: Cmax-1) { T[j,k] <- 1 - phi(A + d[k] + z[j]) }
}
}
```

Model K2:

```
model{
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]] + d[t[i]] + z[z.index[i,j]]
                        + betaplac * (mu[s[i]] - Mean) * (1-equals(t[i],1))
                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])
        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])
        }
}
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]
                        }
d[1] <- 0
for (k in 2:4){ d[k] ~dnorm( D.c[1], prec.d) }
for (k in 5:9){ d[k] ~dnorm( D.c[2], prec.d) }
d[10] <-D.c[3]
for (i in 1:3) {D.c[i] ~ dnorm(0,0.01) }
prec.d<- 1/(sd.d*sd.d)
```

```
sd.d~dunif(0,10)
for (i in 1:2) {D.pred[i]~dnorm(D.c[i],prec.d)}
for(i in 1:ns){ mu[i] ~ dnorm(0,0.01)}
betaplac ~ dnorm(0,0.01)

for (i in 1:ns) {
mu1[i]<-mu[i]*equals(t[1],1)}
A<-sum(mu1[])/ns

# calculate prob of achieving ACR20/50/70 on treat k
for (k in 1:nt) {
for (j in 1: Cmax-1) { T[j,k] <- 1 - phi(A + d[k] + z[j]) }
}
}
d[1]=PLA, d[2]=SEC300, d[3]=SEC150, d[4]=UST, d[5]=CZP, d[6]=GOL, d[7]=ADA, d[8]=INF, d[9]=ETA,
d[10]=APR
```

12.4 Appendix 4 Search strategy for cost-effectiveness studies

MEDLINE & MEDLINE In-Process & Other Non-Indexed Citations

The search strategy was developed in MEDLINE (Ovid) by an information specialist with input from the project team. The strategy included terms for psoriatic arthritis combined, using the Boolean operator AND, with terms for the 8 drugs. No language, or geographical limits were applied. A search strategy to limit retrieval to economic evaluations was used where available. The search strategy was adapted for use in the other resources searched.

The following databases were searched: MEDLINE & MEDLINE In-Process, Cochrane Central Register of Controlled Trials (CENTRAL), Conference Proceedings Citation Index – Science, EconLIT, EMBASE, NHS Economic Evaluations Database (NHS EED), PubMed, and the Science Citation Index.

The results from the searches were imported into an EndNote x7 library and de-duplicated. After de-duplication in EndNote a total of 722 records were available for screening.

via Ovid http://ovidsp.ovid.com/

1946 to Present

Searched on: 15th February 2016

Records retrieved: 73

1 Arthritis, Psoriatic/ (4255)

2 (psoria$ adj2 (arthrit$ or arthropath$)).ti,ab. (6719)

3 1 or 2 (7560)

4 Certolizumab Pegol/ (329)

5 (Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7).af. (873)

6 4 or 5 (873)

7 3 and 6 (69)

8 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (144)

9 3 and 8 (33)

10 (golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5).af. (530)

11 (2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$ or 2016$).ed. (5936425)

12 3 and 10 and 11 (93)

13 (apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9).af. (142)

14 (2014$ or 2015$ or 2016$).ed. (2019613)

15 3 and 13 and 14 (29)

16 Ustekinumab/ (386)

17 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (684)

18 16 or 17 (684)

19 (2012$ or 2013$ or 2014$ or 2015$ or 2016$).ed. (3931892)

20 3 and 18 and 19 (97)

21 (inflectra or remsima or CT-P13).af. (45)

22 3 and 21 (2)

23 Etanercept/ (4522)

24 (etanercept or enbrel or 185243-69-0).af. (6317)

25 Infliximab/ (7584)

26 (infliximab or remicade or 170277-31-3).af. (10459)

27 Adalimumab/ (3151)

28 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (4791)

29 or/23-28 (15794)

30 (2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$ or 2016$).ed. (6691099)

31 3 and 29 and 30 (686)

32 7 or 9 or 12 or 15 or 20 or 22 or 31 (846)

33 economics/ (26633)

34 exp "costs and cost analysis"/ (193882)

35 economics, dental/ (1876)

36 exp "economics, hospital"/ (21057)

37 economics, medical/ (8845)

38 economics, nursing/ (3933)

39 economics, pharmaceutical/ (2601)

40 (economic$ or cost$ or price or prices or pricing or pharmacoeconomic$).ti,ab. (563319)

41 (expenditure$ not energy).ti,ab. (20845)

42 value for money.ti,ab. (1132)

43 budget$.ti,ab. (21354)

44 or/33-43 (695859)

45 ((energy or oxygen) adj cost).ti,ab. (3171)

46 (metabolic adj cost).ti,ab. (962)

47 ((energy or oxygen) adj expenditure).ti,ab. (18791)

48 or/45-47 (22130)

49 44 not 48 (690811)

50 letter.pt. (901537)

51 editorial.pt. (393586)

52 historical article.pt. (326263)

53 or/50-52 (1605365)

54 49 not 53 (659853)

55 exp animals/ not humans/ (4184674)

56 54 not 55 (613314)

57 32 and 56 (73)

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

ed = entry date – date added to database

pt = publication type

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 1 of 12, January 2016

Searched on: 16th February 2016

Records retrieved: 240

#1 MeSH descriptor: [Arthritis, Psoriatic] this term only 224

#2 (psoria* near/2 (arthrit* or arthropath*)):ti,ab,kw 582

#3 #1 or #2 582

#4 MeSH descriptor: [Certolizumab Pegol] this term only 57

#5 (Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7):ti,ab,kw 211

#6 #4 or #5 211

#7 #3 and #6 29

#8 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6):ti,ab,kw 140

#9 #3 and #8 30

#10 (golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5):ti,ab,kw Publication Year from 2010 to 2016 227

#11 #3 and #10 Publication Year from 2010 to 2016 43

#12 (apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9):ti,ab,kw Publication Year from 2014 to 2016 48

#13 #3 and #12 Publication Year from 2014 to 2016 24

#14 MeSH descriptor: [Ustekinumab] this term only 48

#15 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0):ti,ab,kw Publication Year from 2012 to 2016 111

#16 #14 or #15 Publication Year from 2012 to 2016 111

#17 #3 and #16 Publication Year from 2012 to 2016 41

#18 (inflectra or remsima or CT-P13):ti,ab,kw 16

#19 #3 and #18 4

#20 MeSH descriptor: [Etanercept] this term only 381

#21 (etanercept or enbrel or 185243-69-0):ti,ab,kw Publication Year from 2009 to 2016 638

#22 MeSH descriptor: [Infliximab] this term only 431

#23 (infliximab or remicade or 170277-31-3):ti,ab,kw Publication Year from 2009 to 2016 718

#24 MeSH descriptor: [Adalimumab] this term only 236

#25 (adalimumab or humira or D2E7 or (D2 next E7) or 331731-18-1):ti,ab,kw Publication Year from 2009 to 2016 775

#26 #20 or #21 or #22 or #23 or #24 or #25 Publication Year from 2009 to 2016 1685

#27 #3 and #26 Publication Year from 2009 to 2016 123

#28 #7 or #9 or #11 or #13 or #17 or #19 or #27 265

#29 #7 or #9 or #11 or #13 or #17 or #19 or #27 in Trials 240

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

Conference Proceedings Citation Index – Science

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1990 – 12th February 2016

Searched on: 15th February 2016

Records retrieved: 4

# 22	4	#21 OR #19 *Indexes=CPCI-S Timespan=All years*
# 21	3	#20 not #16 *Indexes=CPCI-S Timespan=2009-2016*
# 20	3	#15 AND #14 AND #3 *Indexes=CPCI-S Timespan=2009-2016*
# 19	1	#18 not #16 *Indexes=CPCI-S Timespan=All years*
# 18	1	#17 AND #15 AND #3 *Indexes=CPCI-S Timespan=All years*
# 17	868	#9 OR #8 OR #7 OR #6 OR #5 OR #4 *Indexes=CPCI-S Timespan=All years*
# 16	305,948	TS=(rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep or guinea*) *Indexes=CPCI-S Timespan=All years*
# 15	389,653	TS=(economic* or cost* or price or prices or pricing or pharmacoeconomic*) *Indexes=CPCI-S Timespan=All years*
# 14	1,811	#13 *Indexes=CPCI-S Timespan=2009-2016*
# 13	4,801	#12 OR #11 OR #10 *Indexes=CPCI-S Timespan=All years*
# 12	1,317	TS=(adalimumab or humira or D2E7 or D2-E7 or 331731-18-1) *Indexes=CPCI-S Timespan=All years*
# 11	2,706	TS=(infliximab or remicade or 170277-31-3) *Indexes=CPCI-S Timespan=All years*
# 10	1,338	TS=(etanercept or enbrel or 185243-69-0) *Indexes=CPCI-S Timespan=All years*

# 9	7	TS=(inflectra or remsima or CT-P13) *Indexes=CPCI-S Timespan=All years*
# 8	177	TS=(ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0) *Indexes=CPCI-S Timespan=All years*
# 7	69	TS=(apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9) *Indexes=CPCI-S Timespan=All years*
# 6	176	TS=(golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5) *Indexes=CPCI-S Timespan=All years*
# 5	76	TS=(secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6) *Indexes=CPCI-S Timespan=All years*
# 4	367	TS=(Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7) *Indexes=CPCI-S Timespan=All years*
# 3	1,638	#2 OR #1 *Indexes=CPCI-S Timespan=All years*
# 2	30	TS=(psoria* same arthropath*) *Indexes=CPCI-S Timespan=All years*
# 1	1,625	TS=(psoria* same arthrit*) *Indexes=CPCI-S Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

“ “ = phrase search

EconLIT

via Ovid http://ovidsp.ovid.com/

1886 to January 2016

Searched on: 15th February 2016

Records retrieved: 1

1 (psoria$ adj2 (arthrit$ or arthropath$)).ti,ab. (4)

2 (Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7).af. (0)

3 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (0)

4 (golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5).af. (1)

5 (apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9).af. (0)

6 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (0)

7 (inflectra or remsima or CT-P13).af. (1)

8 (etanercept or enbrel or 185243-69-0).af. (9)

9 (infliximab or remicade or 170277-31-3).af. (11)

10 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (4)

11 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (16)

12 1 and 11 (1)

Key:

$ = truncation

ti,ab = terms in either title or abstract fields

af = all fields

adj2 = terms within two words of each other (any order)

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2016 February 12

Searched on: 15th February 2016

Records retrieved: 429

1 psoriatic arthritis/ (13665)

2 (psoria$ adj2 (arthrit$ or arthropath$)).ti,ab. (11842)

3 1 or 2 (16004)

4 certolizumab pegol/ (3636)

5 (Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7).af. (4412)

6 4 or 5 (4412)

7 3 and 6 (593)

8 secukinumab/ (674)

9 (secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6).af. (752)

10 8 or 9 (752)

11 3 and 10 (236)

12 golimumab/ (3205)

13 (golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5).af. (3296)

14 12 or 13 (3296)

15 (2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$ or 2016$).em. (7964340)

16 3 and 14 and 15 (734)

17 apremilast/ (493)

18 (apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9).af. (529)

19 17 or 18 (529)

20 (2014$ or 2015$ or 2016$).em. (3487544)

21 3 and 19 and 20 (180)

22 ustekinumab/ (2546)

23 (ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0).af. (2662)

24 22 or 23 (2662)

25 (2012$ or 2013$ or 2014$ or 2015$ or 2016$).em. (6135553)

26 3 and 24 and 25 (579)

27 (inflectra or remsima or CT-P13).af. (137)

28 3 and 27 (20)

29 etanercept/ (22267)

30 (etanercept or enbrel or 185243-69-0).af. (23098)

31 infliximab/ (34699)

32 (infliximab or remicade or 170277-31-3).af. (35399)

33 adalimumab/ (19622)

34 (adalimumab or humira or D2E7 or (D2 adj E7) or 331731-18-1).af. (20032)

35 or/29-34 (48727)

36 (2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$ or 2016$).em. (9322795)

37 3 and 35 and 36 (3158)

38 7 or 11 or 16 or 21 or 26 or 28 or 37 (3754)

39 Health Economics/ (35095)

40 exp Economic Evaluation/ (238057)

41 exp Health Care Cost/ (228961)

42 pharmacoeconomics/ (6245)

43 39 or 40 or 41 or 42 (427297)

44 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (717152)

45 (expenditure$ not energy).ti,ab. (27886)

46 (value adj2 money).ti,ab. (1653)

47 budget$.ti,ab. (27874)

48 44 or 45 or 46 or 47 (744311)

49 43 or 48 (940487)

50 letter.pt. (924109)

51 editorial.pt. (499866)

52 note.pt. (628173)

53 50 or 51 or 52 (2052148)

54 49 not 53 (858063)

55 (metabolic adj cost).ti,ab. (1050)

56 ((energy or oxygen) adj cost).ti,ab. (3462)

57 ((energy or oxygen) adj expenditure).ti,ab. (23424)

58 55 or 56 or 57 (27048)

59 54 not 58 (852398)

60 animal/ (1703995)

61 exp animal experiment/ (1909383)

62 nonhuman/ (4685261)

63 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (5233856)

64 60 or 61 or 62 or 63 (7617710)

65 exp human/ (16737281)

66 human experiment/ (347954)

67 65 or 66 (16738727)

68 64 not (64 and 67) (5838485)

69 59 not 68 (781570)

70 38 and 69 (429)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

ti,ab = terms in either title or abstract fields

af = all fields

pt = publication type

sh = subject heading field

adj2 = terms within two words of each other (any order)

em = entry week - date added to the database

NHS Economic Evaluations Database (NHS EED)

http://www.crd.york.ac.uk/CRDWeb/

Inception to 31st March 2015

Searched on: 16th February 2016

Records retrieved: 14

1	(MeSH DESCRIPTOR Arthritis, Psoriatic) IN NHSEED	11
2	(((psoria* NEAR2 (arthrit* or arthropath*)))) IN NHSEED	17
3	(((arthrit* or arthropath*) NEAR2 psoria*)) IN NHSEED	12
4	MeSH DESCRIPTOR Certolizumab Pegol IN NHSEED	2
5	((Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7)) IN NHSEED	3
6	((secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6)) IN NHSEED	0
7	((golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5)) IN NHSEED WHERE LPD FROM 01/01/2010 TO 31/03/2015	2
8	((apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9)) IN NHSEED WHERE LPD FROM 01/01/2014 TO 31/03/2015	0
9	MeSH DESCRIPTOR Ustekinumab IN NHSEED	7
10	((ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0)) IN NHSEED WHERE LPD FROM 01/01/2012 TO 31/03/2015	9
11	((inflectra or remsima or CT-P13)) IN NHSEED	0
12	MeSH DESCRIPTOR Etanercept IN NHSEED	52
13	MeSH DESCRIPTOR Infliximab IN NHSEED	75
14	MeSH DESCRIPTOR Adalimumab IN NHSEED	47
15	((etanercept or enbrel or 185243-69-0)) IN NHSEED WHERE LPD FROM 01/01/2009 TO 31/03/2015	61
16	((infliximab or remicade or 170277-31-3)) IN NHSEED WHERE LPD FROM 01/01/2009 TO 31/03/2015	85
17	((adalimumab or humira or D2E7 or D2-E7 or 331731-18-1)) IN NHSEED WHERE LPD FROM 01/01/2009 TO 31/03/2015	64
18	#1 OR #2 OR #3	17
19	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	135
20	#18 AND #19	14

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

NEAR2 = terms within two words of each other (order specified)

PubMed

http://www.ncbi.nlm.nih.gov/pubmed/

Searched on: 16th February 2016

Records retrieved: 58

((economic evaluation*[TIAB] OR economic analy*[TIAB] OR cost analy*[TIAB] OR cost effectiveness[TIAB] OR cost benefit*[TIAB] OR cost utilit*[TIAB]) OR ("Costs and Cost Analysis"[Mesh])) AND ((((("Arthritis, Psoriatic"[Mesh:noexp]) OR (psoria*[Title/Abstract] AND arthrit*[Title/Abstract]) OR (psoria*[Title/Abstract] AND arthropath*[Title/Abstract]))) AND (("Certolizumab Pegol"[Mesh:noexp]) OR (Certolizumab OR Cimzia OR CZP OR CDP870 OR CDP-870 OR 428863-50-7) OR (secukinumab OR Cosentyx OR AIN457 OR AIN-457 OR 1229022-83-6) OR ((golimumab OR simponi OR CNTO148 OR CNTO-148 OR 476181-74-5) AND "2010/01/01"[Date - Entrez] : "3000"[Date - Entrez]) OR ((apremilast OR otezla OR otezia OR CC10004 OR CC-10004 OR 608141-41-9) AND ("2014/01/01"[Date - Entrez] : "3000"[Date - Entrez])) OR ("Ustekinumab"[Mesh:noexp]) OR ((ustekinumab OR stelara OR CNTO1275 OR CNTO-1275 OR 815610-63-0) AND ("2012/01/01"[Date - Entrez] : "3000"[Date - Entrez])) OR (inflectra OR remsima OR CT-P13) OR ("Etanercept"[Mesh:noexp]) OR ((etanercept OR enbrel OR 185243-69-0) AND ("2009/01/01"[Date - Entrez] : "3000"[Date - Entrez])) OR ("Infliximab"[Mesh:noexp]) OR ((infliximab OR remicade OR 170277-31-3) AND ("2009/01/01"[Date - Entrez] : "3000"[Date - Entrez])) OR ("Adalimumab"[Mesh:noexp]) OR ((adalimumab OR humira OR D2E7 OR D2-E7 OR 331731-18-1) AND ("2009/01/01"[Date - Entrez] : "3000"[Date - Entrez]))))

Key:

[Mesh] = exploded indexing term (MeSH heading)

[Mesh:noexp] = indexing term (MeSH heading) not exploded

* = truncation

[Title/Abstract]) = terms in either title or abstract fields

[Date - Entrez] = date added to the database

Science Citation Index

via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1900 - 12th February 2016

Searched on: 15th February 2016

Records retrieved: 111

# 23	111	#22 OR #19 *Indexes=SCI-EXPANDED Timespan=All years*
# 22	95	#21 *Indexes=SCI-EXPANDED Timespan=2009-2016*
# 21	143	#20 not #16 *Indexes=SCI-EXPANDED Timespan=All years*
# 20	149	#15 AND #14 AND #3 *Indexes=SCI-EXPANDED Timespan=All years*
# 19	38	#18 not #16 *Indexes=SCI-EXPANDED Timespan=All years*
# 18	39	#17 AND #15 AND #3 *Indexes=SCI-EXPANDED Timespan=All years*
# 17	3,371	#9 OR #8 OR #7 OR #6 OR #5 OR #4 *Indexes=SCI-EXPANDED Timespan=All years*
# 16	3,889,643	TS=(rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep or guinea*) *Indexes=SCI-EXPANDED Timespan=All years*
# 15	1,036,604	TS=(economic* or cost* or price or prices or pricing or pharmacoeconomic*) *Indexes=SCI-EXPANDED Timespan=All years*
# 14	23,253	#13 *Indexes=SCI-EXPANDED Timespan=All years*
# 13	23,253	#12 OR #11 OR #10 *Indexes=SCI-EXPANDED Timespan=All years*
# 12	6,187	TS=(adalimumab or humira or D2E7 or D2-E7 or 331731-18-1) *Indexes=SCI-EXPANDED Timespan=All years*
# 11	15,582	TS=(infliximab or remicade or 170277-31-3) *Indexes=SCI-EXPANDED Timespan=All years*
# 10	8,277	TS=(etanercept or enbrel or 185243-69-0) *Indexes=SCI-EXPANDED Timespan=All years*
# 9	56	TS=(inflectra or remsima or CT-P13) *Indexes=SCI-EXPANDED Timespan=All years*
# 8	962	TS=(ustekinumab or stelara or CNTO1275 or CNTO-1275 or 815610-63-0) *Indexes=SCI-EXPANDED Timespan=All years*

# 7	240	TS=(apremilast or otezla or otezia or CC10004 or CC-10004 or 608141-41-9) *Indexes=SCI-EXPANDED Timespan=All years*
# 6	709	TS=(golimumab or simponi or CNTO148 or CNTO-148 or 476181-74-5) *Indexes=SCI-EXPANDED Timespan=All years*
# 5	275	TS=(secukinumab or Cosentyx or AIN457 or AIN-457 or 1229022-83-6) *Indexes=SCI-EXPANDED Timespan=All years*
# 4	1,407	TS=(Certolizumab or Cimzia or CZP or CDP870 or CDP-870 or 428863-50-7) *Indexes=SCI-EXPANDED Timespan=All years*
# 3	11,992	#2 OR #1 *Indexes=SCI-EXPANDED Timespan=All years*
# 2	659	TS=(psoria* same arthropath*) *Indexes=SCI-EXPANDED Timespan=All years*
# 1	11,744	TS=(psoria* same arthrit*) *Indexes=SCI-EXPANDED Timespan=All years*

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields

* = truncation

SAME = terms within the same sentence

12.5 Appendix 5 Quality assessment checklists for published cost-effectiveness models

Checklist for Rodgers model

Study question	**Grade**	**Comments**
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	x	ustekinumab, golimumab, secukinumab and certolizumab not included
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		

9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✓	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	WinBUGS code presented
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	✓	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately.	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	N/A	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	N/A	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	N/A	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✓	

33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

Checklist for Golimumab model

Study question	**Grade**	**Comments**
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✕	Biologics compared to palliative care, which is defined as DMARDs Comparators ustekinumab, secukinumab and certolizumab not included
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✕	Does not describe what the series of DMARDs are.
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✓	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	WinBUGS code presented
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	**N/A**	

18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately.	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	N/A	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	N/A	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	N/A	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✓	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✗	Calculated incorrectly
38. Major outcomes are presented in a disaggregated as well as aggregated form	✗	
39. Applicable to the NHS setting	✓	

Checklist for ustekinumab model

Study question	Grade	Comments
1. Costs and effects examined	✓	

2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✗	Conventional management was not specifically defined, but reflects treatment with non-biologics secukinumab and certolizumab not included.
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✗	Does not describe what the series of DMARDs are.
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✓	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	WinBUGS code presented
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	**N/A**	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately.	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	N/A	

28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	N/A	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	N/A	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✓	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

Checklist for Cawson, et al model

Study question	Grade	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✗	Conventional management was not specifically defined, but reflects treatment with non-biologics secukinumab and certolizumab not included.
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✗	Does not describe what the series of DMARDs are.
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	

11. Potential biases identified (especially if data not from RCTs)	✓	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	WinBUGS code presented
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	**N/A**	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately.	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	N/A	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	N/A	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	N/A	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✓	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	

35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

12.6 Appendix 6 Quality assessment checklists for company submitted models

Checklist for Novartis model

✓ ✕		
Study question	**Grade**	**Comments**
1. Costs and effects examined	✓	
2. Alternatives compared	**X**	In the one prior DMARD population and the anti-TNF experienced population
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	**X**	In the one prior DMARD population, other anti-TNFs can be applicable
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	

8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✓	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	WinBUGS code presented
Costs		
13. All the important and relevant resource use included	**X**	Severe psoriasis costs are not accounted
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	✓	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately.	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	N/A	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	N/A	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	N/A	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✓	

33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

Checklist for UCB model

✓ ✕		
Study question	**Grade**	**Comments**
1. Costs and effects examined	✓	
2. Alternatives compared	**X**	In the one prior DMARD population
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✓	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	**X**	It was not clear how the secukinumab was modelled as the cost refers to a mix of the two strengths of secukinumab, 150mg and 300mg
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✓	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	WinBUGS code presented
Costs		
13. All the important and relevant resource use included	**X**	Severe psoriasis costs are not accounted
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	✓	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately.	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	

Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	N/A	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	N/A	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	N/A	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✓	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	**X**	Reporting the incremental results was not performed properly.
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

12.7 Appendix 7 Clinical effectiveness inputs applied in the company models

12.7.1 Subpopulation 1: Biologic naïve - 1 prior DMARD

Table 165 Response parameters applied in model for subpopulation 1 (UCB)

Therapy	PsARC	PASI 50	PASI 75	PASI 90	Source
CZP	[redacted]	[redacted]	[redacted]	[redacted]	RAPID-PSA subgroup (1 prior DMARD)
cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	RAPID-PSA subgroup (1 prior DMARD)

Table 166 Response parameters applied in model for subpopulation 1 (Novartis)

Therapy	PsARC	PASI 50	PASI 75	PASI 90	Source
SEC 150mg	[redacted]	[redacted]	[redacted]	[redacted]	FUTURE 2 subgroup (1 prior DMARD)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	FUTURE 2 subgroup (1 prior DMARD)

Table 167 HAQ change according to PsARC response for subpopulation 1 (UCB)

Therapy	PsARC responders	PsARC non-responders	Source
CZP	[redacted]	[redacted]	RAPID-PSA subgroup (1 prior DMARD)
cDMARD	[redacted]	[redacted]	RAPID-PSA subgroup (1 prior DMARD)

Table 168 HAQ change according to PsARC response for subpopulation 1 (Novartis)

Therapy	PsARC responders	PsARC non-responders	Source
SEC 150mg	[redacted]	[redacted]	FUTURE 2 subgroup (1 prior DMARD)
SoC	[redacted]	[redacted]	FUTURE 2 subgroup (1 prior DMARD)

12.7.2 Subpopulation 2: Biologic naïve – (1 or more prior DMARDs – UCB; 2 or more prior DMARDs – Novartis)

Table 169 Response parameters applied in model for subpopulation 1 (UCB)

Therapy	PsARC	PASI 50	PASI 75	PASI 90	Source
CZP	[redacted]	[redacted]	[redacted]	[redacted]	NMA naïve population
SEC 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	NMA naïve population

INF	[redacted]	[redacted]	[redacted]	[redacted]	NMA naïve population
ADA	[redacted]	[redacted]	[redacted]	[redacted]	NMA naïve population
GOL	[redacted]	[redacted]	[redacted]	[redacted]	NMA naïve population

Table 170 Response parameters applied in model for subpopulation 2 (Novartis)

Therapy	PsARC	PASI 50	PASI 75	PASI 90	Source
SEC 150mg	[redacted]	[redacted]	[redacted]	[redacted]	NMA overall population
CZP	[redacted]	[redacted]	[redacted]	[redacted]	NMA overall population
ETN	[redacted]	[redacted]	[redacted]	[redacted]	NMA overall population
INF	[redacted]	[redacted]	[redacted]	[redacted]	NMA overall population
ADA	[redacted]	[redacted]	[redacted]	[redacted]	NMA overall population
GOL	[redacted]	[redacted]	[redacted]	[redacted]	NMA overall population
SoC	[redacted]	[redacted]	[redacted]	[redacted]	NMA overall population

Table 171 HAQ change according to PsARC response for subpopulation 2 (UCB)

Therapy	PsARC responders	PsARC non-responders	Source
CZP	[redacted]	[redacted]	NMA naïve population
SEC 150mg	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	NMA naïve population

GOL	[redacted]	[redacted]	[redacted]

Table 172 HAQ change according to PsARC response for subpopulation 2 (Novartis)

Therapy	PsARC responders	PsARC non-responders	Source
SEC 150mg	[redacted]	[redacted]	FUTURE 2
CZP	-0.558	-0.15	Assumption: average TNF effect
ETN	-0.64	-0.2	Cawson et al (2014)
INF	-0.66	-0.2	Cawson et al (2014)
ADA	-0.49	-0.14	Cawson et al (2014)
GOL	-0.44	-0.06	Cawson et al (2014)
SoC	[redacted]	[redacted]	FUTURE 2

12.7.3 Subpopulation 3: Biologic experienced

Table 173 Response parameters applied in model for subpopulation 3 (UCB)

Therapy	PsARC	PASI 50	PASI 75	PASI 90	Source
CZP	[redacted]	[redacted]	[redacted]	[redacted]	RAPID-PSA experienced subgroup
SEC 300mg	[redacted]	[redacted]	[redacted]	[redacted]	Assumption
UST	[redacted]	[redacted]	[redacted]	[redacted]	Assumption
Mix/SoC	[redacted]	[redacted]	[redacted]	[redacted]	RAPID-PSA experienced subgroup

Table 174 Response parameters applied in model for subpopulation 3 (Novartis)

Therapy	PsARC	PASI 50	PASI 75	PASI 90	Source

SEC 300mg	[redacted]	[redacted]	[redacted]	[redacted]	Common efficacy reduction from FUTURE 2
CZP	[redacted]	[redacted]	[redacted]	[redacted]	Common efficacy reduction from FUTURE 2
UST	[redacted]	[redacted]	[redacted]	[redacted]	Common efficacy reduction from FUTURE 2
SoC	[redacted]	[redacted]	[redacted]	[redacted]	Common efficacy reduction from FUTURE 2

Table 175 HAQ change according to PsARC response for subpopulation 3 (UCB)

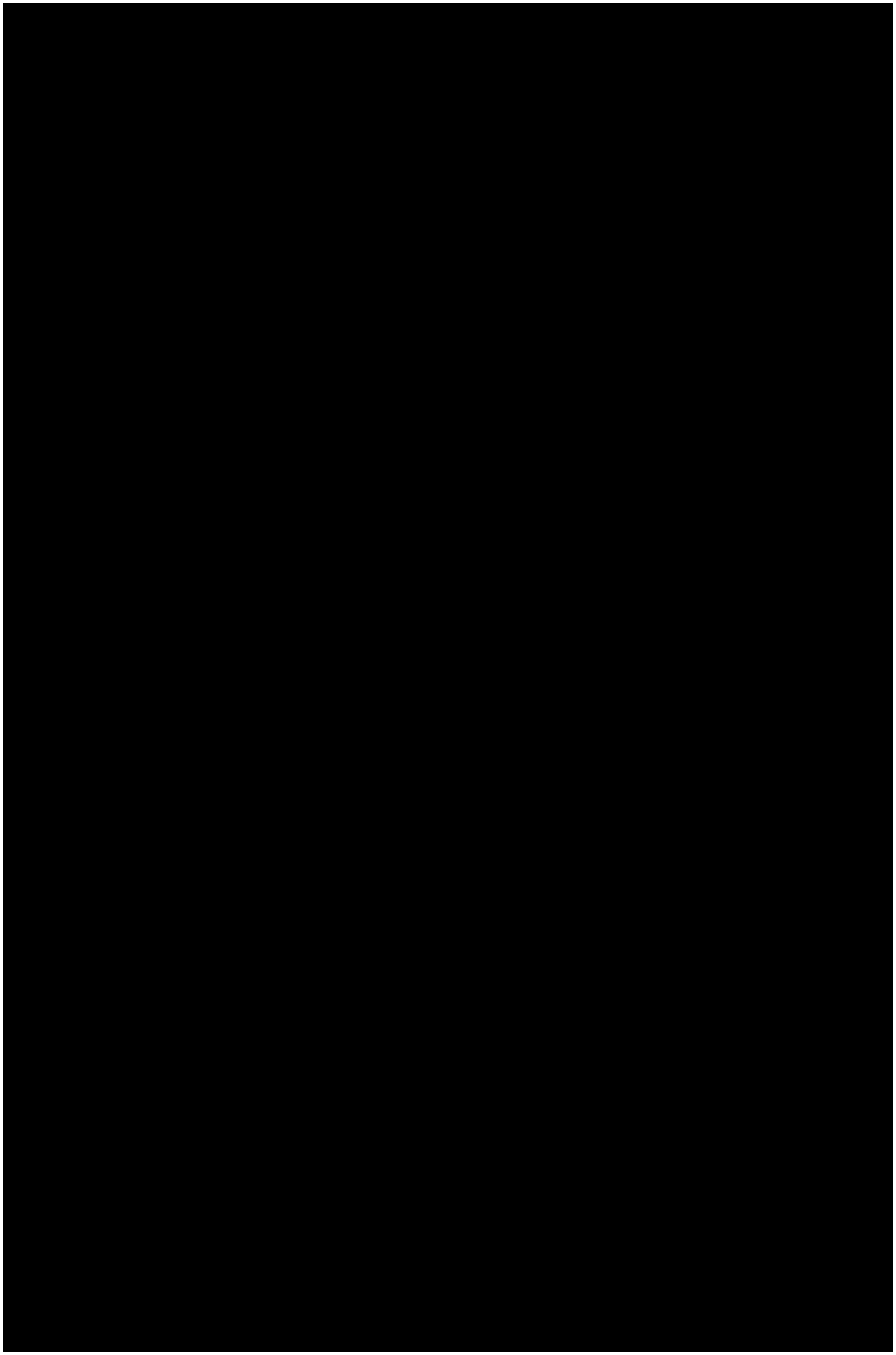
Therapy	PsARC responders	PsARC non-responders	Source
CZP	[redacted]	[redacted]	RAPID-PSA
SEC 300mg	[redacted]	[redacted]	Assumption
UST	[redacted]	[redacted]	Assumption
Mix/SoC	[redacted]	[redacted]	RAPID-PSA

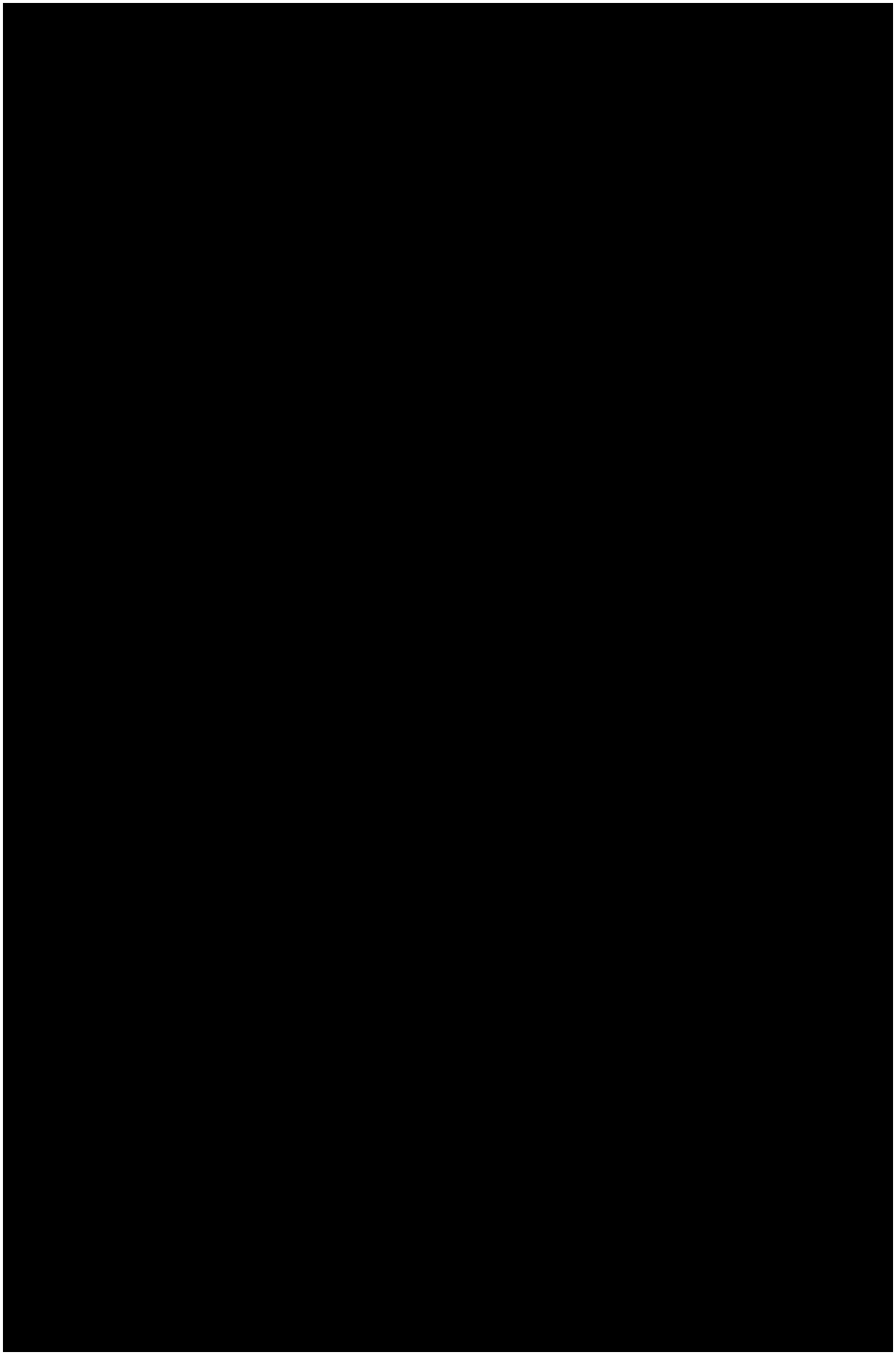
Table 176 HAQ change according to PsARC response for subpopulation 3 (Novartis)

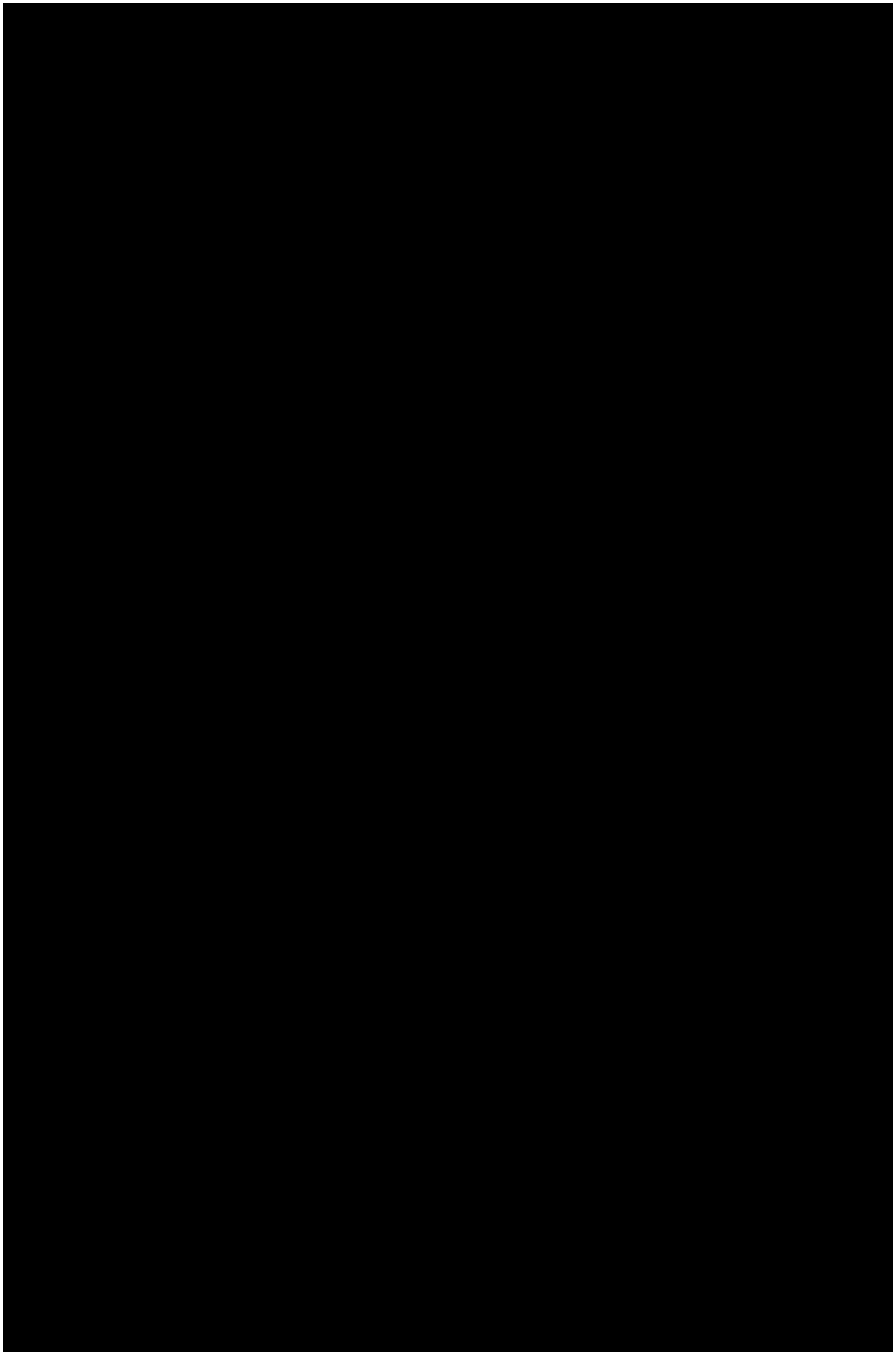
Therapy	PsARC responders	PsARC non-responders	Source
SEC 300mg	[redacted]	[redacted]	Assumption
CZP	[redacted]	[redacted]	Assumption
UST	[redacted]	[redacted]	Assumption
SoC	[redacted]	[redacted]	Assumption

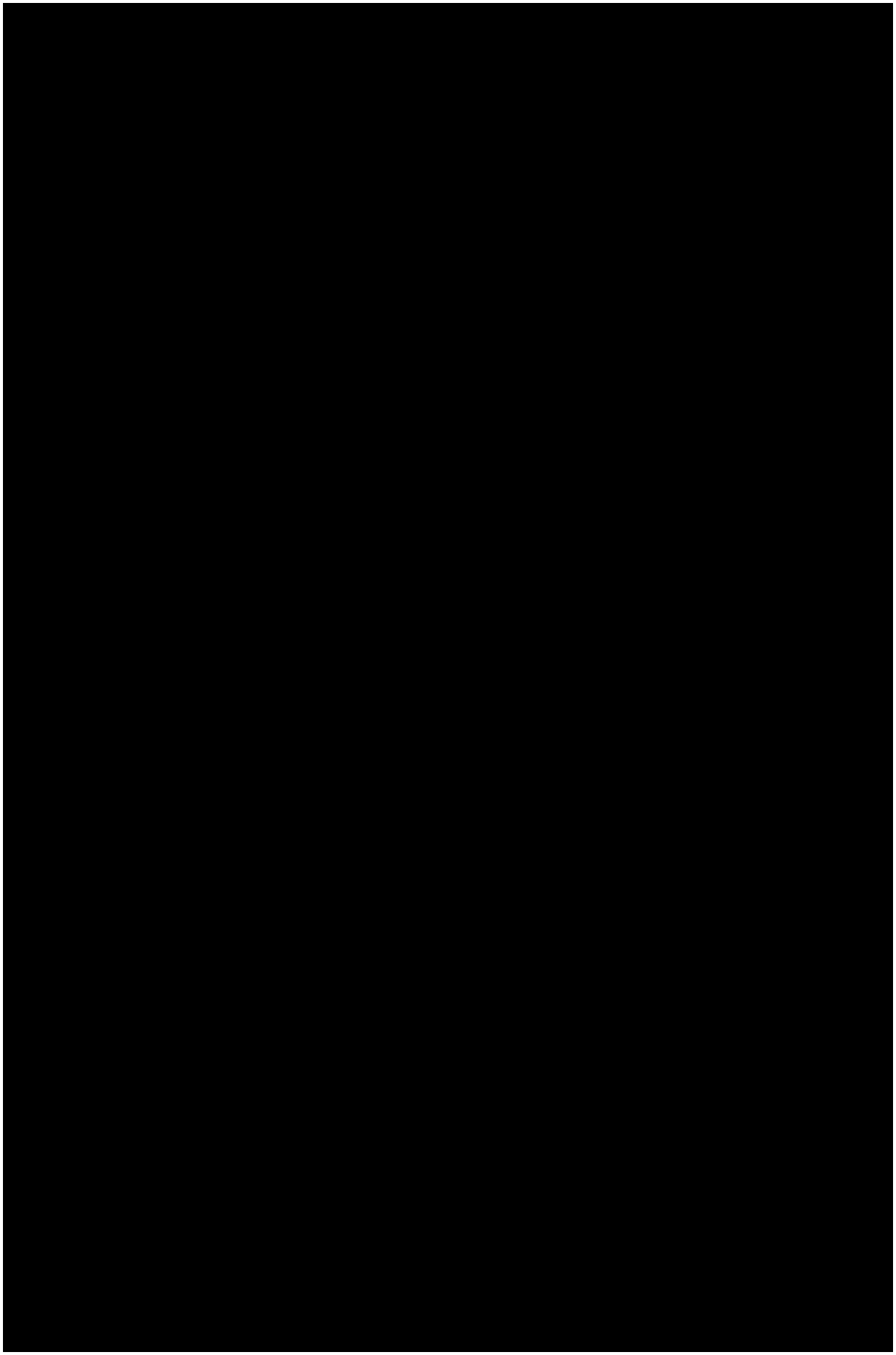
12.8 Appendix 8 R code for updated York model

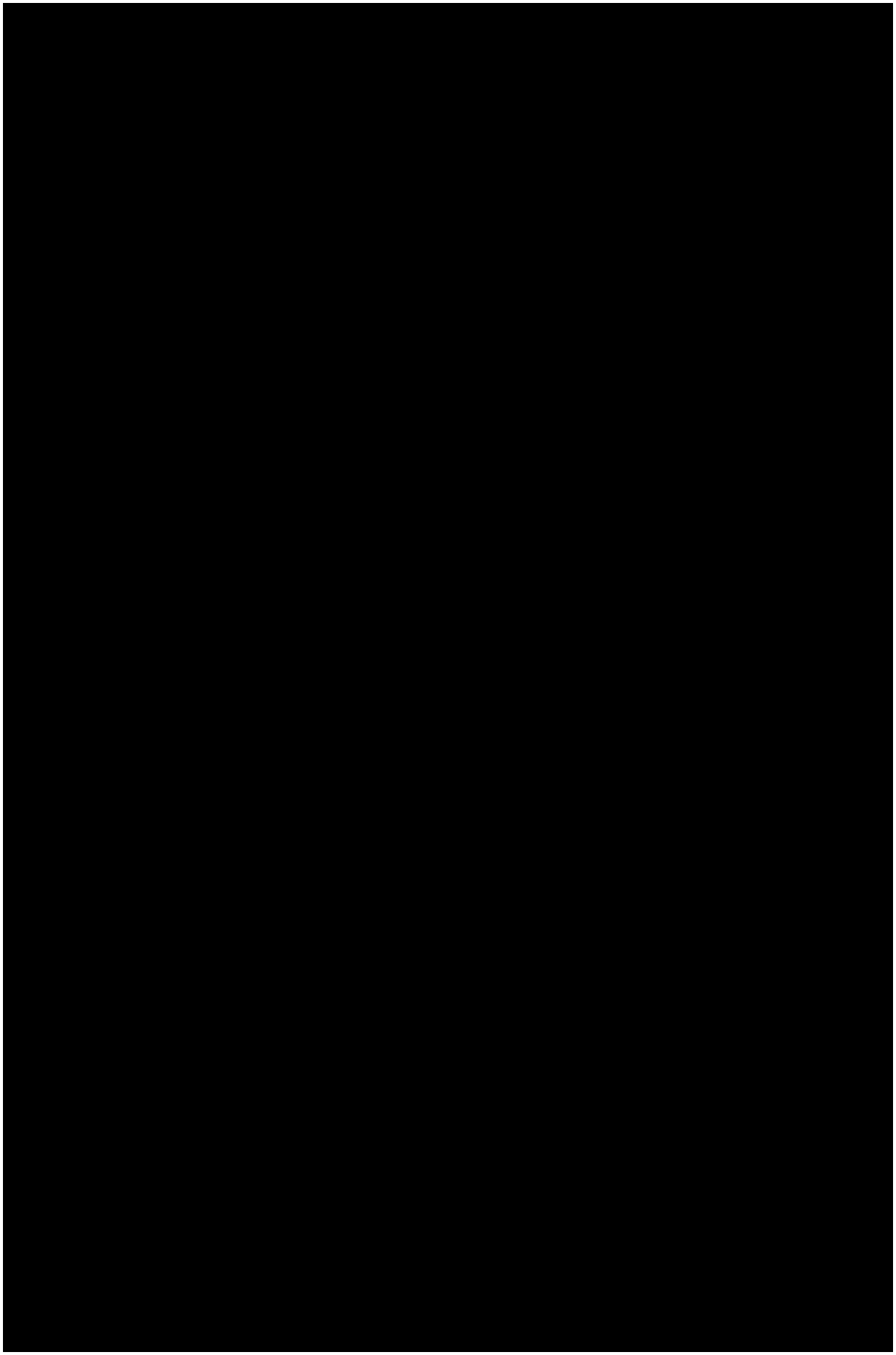
[redacted]

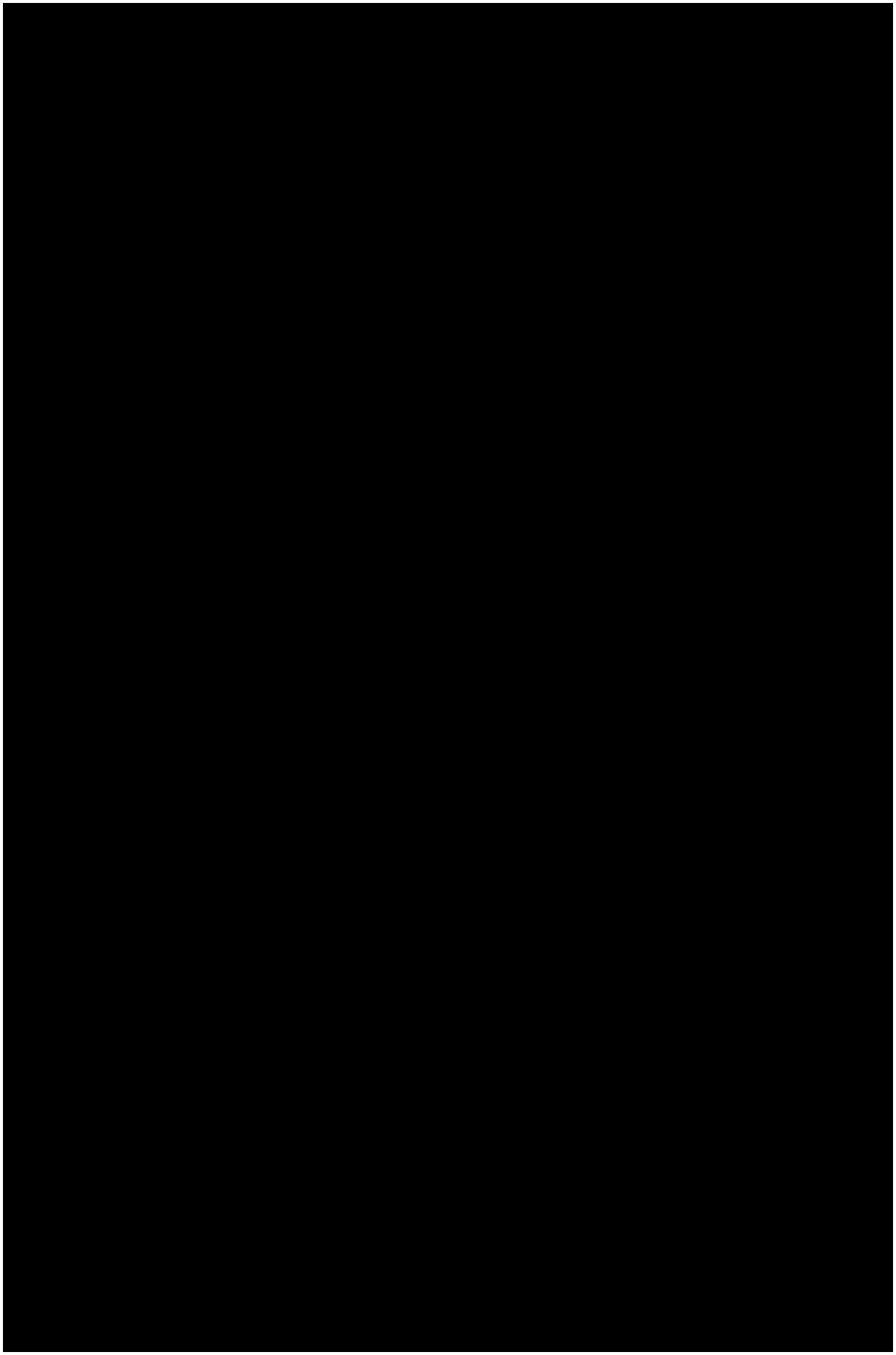












[redacted]

12.9 [redacted]Appendix 9 Estimating health related quality of life for the updated York model

In order to generate an estimate of the lifetime QALYs for each of the treatments, the disease specific measures, HAQ and PASI, at each cycle of the model, must be mapped onto the utilities scores associated with particular HAQ and PASI combinations. This assumes that HAQ and PASI capture all of the relevant information regarding a PsA patient's quality of life. In the previous York model[94] this relationship was estimated from analyses provided by the company (Wyeth), who carried out OLS regressions of EQ5D utility versus HAQ, PASI and an interaction term HAQ*PASI, in participants in key RCTs. The utility function is given below:

Expected utility = 0.897 – 0.298 x HAQ -0.004 x PASI

(SE) (0.006) (0.006) (0.0003)

The interaction between HAQ and PASI did not reach statistical significance at the 5% level and was therefore excluded from the regression model.

Table 177 Full results of Wyeth linear regressions of utility versus HAQ, PASI and HAQ x PASI

	Coefficients					**Variance-covariance matrices**				
Wyeth										
	Mean	SE	z	P>z			Intercept	HAQ	PASI	HAQ x PASI
Intercept	0.895	0.007	128.652	0.000		Intercept	0.000048430			
HAQ	-0.295	0.008	-37.157	0.000		HAQ	-0.000030080	0.000062880		
PASI	-0.004	0.000	-9.039	0.000		PASI	-0.000001640	0.000000947	0.000000207	
HAQ x PASI	0.000	0.000	-0.669	0.504		HAQ x PASI	0.000001311	-0.000002207	-0.000000136	0.000000183

The PRESTA (Psoriasis Randomized Etanercept STudy in Subjects with Psoriatic Arthritis) trial was used to determine this algorithm. PRESTA is a 24-week clinical study comparing two forms of etanercept and includes 752 patients with PsA. The study was originally designed to detect any differences in treatment efficacy for skin manifestations of psoriasis, but these patients also had diagnosed (by a Rheumatologist) PsA.

Comparison of the Wyeth algorithm with that from other companies, in the previous York model, showed that the results were similar in all datasets. This indicates that the relationship between HAQ, PASI and utility is stable across independent clinical trials, and gives some assurance about the generalizability to the wider PsA population.

We performed a systematic search to identify any subsequent papers which include mapping functions from HAQ and PASI to utilities (post December 2009). This was not restricted to utilities measured using the EQ-5D. The search strategy can be seen in Appendix 12.10. This identified 2573 potentially relevant records after deduplication. After initial screening 40 of these records actually related to psoriatic arthritis and contained information on (preference rated) quality of life. Of these only 11 suggested the use of a mapping function to link a preference based measure of quality of life, such as the EQ-5D or the SF-36, to disease specific measures, including the HAQ and PASI. Five of these were only available as conference abstracts. The remaining five papers were screened for inclusion (see Table 178for a summary of these studies). In conclusion none of the papers offer a mapping function that will allow the disease specific measures, HAQ and PASI to be mapped onto a utility score. The existing York utility algorithm is therefore used in the current version of the economic model.

Table 178 Utilities papers screened for inclusion

Study	Population	Measures included	Mapping function made explicit in paper?	Relevant for economic model?
Adams, et al (2010)	Patients with RA and PsA (n=504)	HAQ, SF-6D, EQ-5D, EULAR, DAS	Yes presented separately for EQ-5D and SF-6D	Does not include PASI
Adams, et al (2011)	Patients with RA and PsA (n=504)	HAQ, SF-36, EQ-5D (revised), EQ-5D (original)	Yes presented separately for EQ-5D and SF-6D	Does not include PASI
Brodszky, et al (2010)	Patients with PsA (n=183)	Hungarian versions of HAQ, EQ-5D, PsAQoL, DAS28, VAS, PASI and	No. Looked at correlations between measures individually, but no	No

		BASAI	mapping	
Grataos, et al (2014)	Patients with PsA (n=287)	PASI, HAQ, number of swollen and tender joints, SF-36, EQ-5D	Yes multivariate analysis conducted	Does not include HAQ in the EQ-5D model; instead includes swollen and tender joints and PASI. EQ-5D not included in the HAQ model.
Leung, et al (2013)	Patients with PsA (n=86)	EQ-5D, SF-6D	Not undertaken. Does not include HAQ or PASI	No
Picchianti-Diamanti, et al (2010)	Patients with RA and PsA (n=80)	HAQ, SF-36, DAS	Not undertaken. Reports scores separately.	No

12.10 Appendix 10 Search strategy for utility studies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 (sf36 or sf 36).ti,ab. (15462)

2 (eq5d or eq 5d or euroqol or euro qol).ti,ab. (5427)

3 (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab. (7310)

4 (hrql or hrqol or h qol or hql or hqol).ti,ab. (12181)

5 (hye or hyes or health$ year$ equivalent$ or health utilit$).ti,ab. (1375)

6 health related quality of life.ti,ab. (26941)

7 rosser.ti,ab. (74)

8 (standard gamble$ or time trade off or time tradeoff or "tto" or willingness to pay).ti,ab. (4653)

9 (utilities or utility or daly or dalys or disability adjusted life).ti,ab. (140271)

10 "Quality of Life"/ (132981)

11 (quality of life or life quality).ti,ab. (178851)

12 health status indicators/ (20944)

13 quality adjusted life year/ (8035)

14 (qaly$ or quality adjusted).ti,ab. (9209)

15 (qwb$ or hui or hui1 or hui2 or hui3 or qwi).ti,ab. (1249)

16 (quality of wellbeing or quality of well being).ti,ab. (360)

17 preference based.ti,ab. (841)

18 (dermatology life quality index or health status).ti,ab. (42673)

19 (state$ adj2 (value or values or valuing or valued)).ti,ab. (2630)

20 (dlqi or hspv).ti,ab. (688)

21 general health questionnaire.ti,ab. (3748)

22 nottingham health profile.ti,ab. (1019)

23 patient generated index.ti,ab. (44)

24 sickness impact profile.ti,ab. (1019)

25 (ghq or nhp or pgi or sip or uksip or wtp).ti,ab. (10048)

26 or/1-25 (425323)

27 (PSAQoL or psoriatic arthritis quality of life or PsA quality of life).ti,ab. (14)

28 (PASI or psoriasis area severity index).ti,ab. (1737)

29 (PsARC or Psoriatic Arthritis Response Criteria).ti,ab. (44)

30 (HAQ or Health Assessment Questionnaire).ti,ab. (3581)

31 or/27-30 (5285)

32 Arthritis, Psoriatic/ (4270)

33 (psoria$ adj2 (arthrit$ or arthropath$)).ti,ab. (6737)

34 32 or 33 (7581)

35 26 and 34 (655)

36 31 and 34 (424)

37 35 or 36 (918)

38 (letter or editorial or comment).pt. (1456654)

39 37 not 38 (902)

40 exp animals/ not humans/ (4189142)

41 39 not 40 (899)

42 limit 41 to yr="2009 -Current" (595)

12.11 Appendix 11 Identifying additional PsA health state costs

12.11.1 Methods

This is a very broad literature, and an exhaustive review was beyond the time constraints of this appraisal. Instead, a rapid review was undertaken of the following sources, since the previous MTA (December 2009):

- evidence presented to previous NICE appraisals of psoriatic arthritis treatments,
- the company submissions to the current appraisal,
- citation searches using Rodgers, et al

Relevant cost data for the economic model must satisfy the following criteria:

- The data should be specific to patients with psoriatic arthritis.
- The data must show a causal relationship from HAQ and PASI to subsequent health service utilisation and costs.
- The data should report mean costs conditional on HAQ and PASI and measures of sampling uncertainty.
- The data should measure costs not charges or prices.

- Preferably data would be taken from the UK. Where this is not possible, it is important to assess whether studies from other countries are likely to be generalisable to the UK, particularly countries with mixed public/private financing such as the US.

- The data should measure all direct healthcare costs in the hospital, outpatient and community. Productivity losses should be reported separately. The base-case model excludes productivity losses in accordance with the NICE reference case

- The data should estimate the costs of medications separately from those of other health services. The economic model includes these costs separately from the effect of HAQ/PASI on costs.

- The data should state the price year, the currency and other data to allow adjustment to the UK in 2016.

12.11.2 Results

An additional relevant reference was found from the recent STA for apremilast in psoriatic arthritis. In this the company identified a paper by Poole et al.[127] The citation searches for Rodgers, et al did not identify any further published studies. One conference abstract was identified[141], however the costs relating to PsA patients have not been published and contact with the author did not receive a response. The Golimumab and Ustekinumab STAs both used the Rodgers, et al algorithms for costs. The advantages and disadvantages of the previous York HAQ costs and the Poole, et al costs are discussed in Section 7.2.9.5.

12.12 Appendix 12 Cost-effectiveness results using INF and ETN biosimilar prices, subpopulation 2

In a separate scenario analysis, biosimilar prices[132], as opposed to list prices for ETN and INF, were used in subpopulation 2 (see Section 7.2.4). This reduces the acquisition cost for ETN from £2,332 to £2139 in the first cycle and subsequent cycles. For INF the acquisition costs falls from £7147 to £6432 in the first cycle and from £3395 to £3056 in subsequent cycles. The results for the three subgroups according to concomitant psoriasis are shown below (Table 179, Table 180 and Table 181).

Table 179 shows the results for the mild to moderate psoriasis subgroup. In this subgroup CZP is the least effective biologic treatment, generating 7.226 QALYs, whereas INF generates the highest QALYs (7.890). Performing fully incremental analysis shows that SEC 300mg is dominated by ADA, GOL and ETN, GOL is dominated by ETN and CZP and ADA are extendedly dominated. Of the

remaining non-dominated alternatives, the ICER of ETN vs BSC is £18,906 per QALY, the ICER of INF vs ETN is £114,044 per QALY.

The individual pairwise ICERs for CZP and SEC 300mg compared to BSC are £21,560 and £29,564 per QALY, respectively

Table 179 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, biosimilar prices

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
CZP	£137,240	7.226	ED		-	£21,560
SEC 300mg	£157,086	7.379	D		-	£29,564
ADA	£138,109	7.411	ED		-	£20,074
GOL	£142,850	7.637	D		-	£20,161
ETN_Sim	£141,477	7.719	£45,512	2.407	£18,906	£18,906
INF_Sim	£160,993	7.890	£19,517	0.171	£114,044	£25,220

Table 180 shows the results for the mild to moderate psoriasis subgroup. In this subgroup CZP is the least effective biologic treatment, generating 7.537 QALYs, whereas INF generates the highest QALYs (8.161). Performing fully incremental analysis shows that CZP is dominated by SEC 150mg, GOL is dominated by ETN, and SEC 150mg and ADA are extendedly dominated. Of the remaining non-dominated alternatives, the ICER of ETN vs BSC is £20,951 per QALY, the ICER of INF vs ETN is £170,815 per QALY.

The individual pairwise ICERs for CZP and SEC 150mg compared to BSC are £24,107 and £22,032 per QALY, respectively

Table 180 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, biosimilar prices

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
CZP	£111,856	7.537	D		-	£24,107
SEC 150mg	£108,508	7.560	ED			£22,032
ADA	£114,039	7.708	ED		-	£23,153
GOL	£119,624	7.923	D		-	£23,418
ETN_Sim	£116,218	8.025	£49,217	2.349	£20,951	£20,951
INF_Sim	£139,436	8.161	£23,218	0.136	£170,815	£29,148

For the no concomitant psoriasis subgroup (PASI=0) (Table 181), INF maintains its position as the most effective treatment (8.543 QALYs), whereas SEC 150mg is now the least effective treatment (7.972). As expected in this subgroup, the ICERs vs BSC increase compared to the mild-moderate and severe psoriasis subgroups, due to benefits being driven entire by HAQ benefits as opposed to HAQ and PASI. The incremental cost-effectiveness analysis shows that GOL is dominated by ETN. SEC150mg, CZP and ADA are extendedly dominated. Of the non-dominated alternatives, the ICER of ETN vs BSC is £22,512 per QALY and the ICER of INF vs ETN is £289,542 per QALY.

The individual pairwise ICERs for CZP and SEC 150mg compared to BSC are £26,117 and £24,782 per QALY, respectively

Table 181 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, biosimilar prices

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
SEC 150mg	£95,632	7.972	ED		-	£24,782
CZP	£98,060	7.974	ED		-	£26,117
ADA	£100,893	8.125	ED		-	£25,542
GOL	£106,895	8.325	D		-	£25,951
ETN_Sim	£102,484	8.456	£51,047	2.268	£22,512	£22,512
INF_Sim	£127,531	8.543	£25,047	0.087	£289,542	£32,325

12.13 Appendix 13 Meta regression results

Results utilising the meta-regression estimates for effectiveness parameters are presented in the tables below for each of the subpopulations and subgroups.

12.13.1 Subpopulation 1

Table 182 Treatment effects from meta regression for moderate-severe psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
CZP	£161,347	8.596	£65,382	3.284	£19,908	£19,908
SEC 300mg	£186,956	8.677	£25,609	0.082	£313,571	£27,033

Table 183 Treatment effects from meta regression for mild-moderate psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
SEC 150mg	£134,957	8.869	£67,956	3.192	£21,287	£21,287
CZP	£138,698	8.870	£3,741	0.002	£2,010,048	£22,446

Table 184 Treatment effects from meta regression for no concomitant psoriasis, subpopulation 1: Fully-incremental cost-effectiveness analysis

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
SEC 150mg	£122,938	9.243	£71,502	3.055	£23,408	£23,408
CZP	£126,253	9.256	£3,315	0.013	£252,218	£24,388

12.13.2 Subpopulation 2

Table 185 Treatment effects from meta-regression for moderate-severe psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
ADA	£136,766	7.342	-	-	ED	£20,092
GOL	£141,113	7.486	-	-	D	[redacted]
CZP	£139,489	7.496	£43,524	2.185	£19,923	£19,923
SEC 300mg	£165,222	7.586	-	-	D	[redacted]
ETN	£143,538	7.626	£4,049	0.130	£31,090	£20,552
INF	£165,132	7.685	£21,594	0.059	£366,216	£29,138

Table 186 Treatment effects from meta-regression analysis for mild-moderate psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
ADA	£112,468	7.642			D	£23,130
GOL	£116,438	7.788			D	[redacted]
CZP	£115,516	7.791			D	[redacted]

SEC 150mg	£111,894	7.796	£44,894	2.120	£21,177	£21,177
ETN	£118,339	7.933	£6,445	0.137	£47,137	£22,750
INF	£142,056	7.971	£23,717	0.038	£616,950	£32,703

Table 187 Treatment effects from meta-regression for no concomitant psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
ADA	£99,209	8.063		-	ED	£25,485
SEC 150mg	£99,225	8.199	£47,789	2.011	£23,768	£23,768
CZP	£102,418	8.205			ED	[redacted]
GOL	£102,993	8.212			ED	[redacted]
ETN	£104,635	8.363	£5,410	0.164	£32,926	£24,460
INF	£129,401	8.373	£24,766	0.010	£2,571,503	£35,689

12.14 Appendix 14 Results from alternative scenarios

12.14.1.1 Baseline HAQ according to subpopulation

Table 188 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis, subpopulation specific baseline HAQ

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£95,460	5.540	-	-	-	-
CZP	£159,431	8.629	£63,971	3.089	£20,709	£20,709
SEC 300mg	£179,172	8.775	£19,741	0.146	£134,880	£25,873

Table 189 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis, subpopulation specific baseline HAQ

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£66,495	5.904	-	-	-	-
CZP	£135,426	8.917	D		-	£22,874
SEC 150mg	£131,980	8.935	£65,485	3.031	£21,604	£21,604

Table 190 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis, subpopulation specific baseline HAQ

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£50,931	6.414	-	-	-	-
SEC 150mg	£119,783	9.315	£68,852	2.901	£23,732	£23,732
CZP	£122,312	9.322	£2,529	0.007	£351,603	£24,543

Table 191 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, subpopulation specific baseline HAQ

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£96,544	5.049	-	-	-	-
CZP	£137,839	6.942	ED		-	£21,809
SEC 300mg	£157,685	7.095	D		-	£29,877
ADA	£138,709	7.127	£42,165	2.078	£20,295	£20,295
GOL	£143,451	7.350	ED		-	£20,384
ETN	£145,186	7.432	£6,477	0.306	£21,183	£20,409
INF	£167,727	7.603	£22,541	0.171	£131,805	£27,866

Table 192 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, subpopulation specific baseline HAQ

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£67,580	5.416	-	-	-	-
CZP	£112,455	7.255	D		-	£24,395
SEC 150mg	£109,107	7.278	£41,527	1.863	£22,294	£22,294
ADA	£114,639	7.425	ED		-	£23,418
GOL	£120,225	7.638	ED		-	£23,687
ETN	£119,927	7.741	£10,820	0.462	£23,400	£22,514
INF	£146,170	7.876	£26,243	0.136	£193,511	£31,938

Table 193 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, subpopulation specific baseline HAQ

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£52,016	5.930	-	-	-	-
SEC 150mg	£96,231	7.692	ED		-	£25,096

CZP	£98,659	7.694	ED		-	£26,444
ADA	£101,493	7.844	ED		-	£25,851
GOL	£107,496	8.042	D		-	£26,267
ETN	£106,193	8.173	£54,178	2.243	£24,150	£24,150
INF	£134,265	8.259	£28,072	0.086	£326,736	£35,311

Table 194 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, subpopulation specific baseline HAQ

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£97,192	4.756	-	-	-	-
UST	£119,384	5.750	£22,192	0.995	£22,309	£22,309
SEC 300mg	£144,796	6.045	£25,412	0.294	£86,320	£36,926

Table 195 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, subpopulation specific baseline HAQ

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£68,228	5.124	-	-	-	-
UST	£92,503	6.086	£24,276	0.962	£25,239	£25,239
SEC 300mg	£119,826	6.361	£27,323	0.275	£99,385	£41,721

Table 196 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, subpopulation specific baseline HAQ

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£52,664	5.641	-	-	-	-
UST	£77,968	6.556	£25,305	0.916	£27,638	£27,638
SEC 300mg	£106,235	6.804	£28,267	0.248	£114,170	£46,057

12.14.1.2 Alternative HAQ cost from Poole, et al

Table 197 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, HAQ costs from Poole

Treatment	**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**ICER vs NBO**	**ICER vs BSC**
BSC	£137,167	5.312	-	-	-	-

CZP	£143,130	7.226	ED		-	£3,115
SEC 300mg	£165,077	7.379	D		-	£13,500
ADA	£143,610	7.411	ED		-	£3,069
GOL	£144,712	7.637	D		-	£3,244
ETN	£144,009	7.719	£6,843	2.407	£2,842	£2,842
INF	£170,780	7.890	£26,771	0.171	£156,435	£13,036

Table 198 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, HAQ costs from Poole

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£137,167	5.676	-	-	-	-
CZP	£143,130	7.537	D		-	£3,205
SEC 150mg	£140,366	7.560	£3,199	1.884	£1,698	£1,698
ADA	£143,610	7.708	ED		-	£3,171
GOL	£144,712	7.923	D		-	£3,358
ETN	£144,009	8.025	£3,643	0.465	£7,832	£2,913
INF	£170,780	8.161	£26,771	0.136	£196,949	£13,526

Table 199 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, HAQ costs from Poole

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£137,167	6.188	-	-	-	-
SEC 150mg	£140,366	7.972	£3,199	1.783	£1,794	£1,794
CZP	£143,130	7.974	ED		-	£3,341
ADA	£143,610	8.125	ED		-	£3,328
GOL	£144,712	8.325	D		-	£3,531
ETN	£144,009	8.456	£6,843	2.268	£3,018	£3,018
INF	£170,780	8.543	£26,771	0.087	£309,469	£14,279

Table 200 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, HAQ costs from Poole

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£137,167	5.312	-	-	-	-
UST	£140,006	6.334	£2,840	1.022	£2,778	£2,778
SEC 300mg	£163,788	6.632	£23,781	0.299	£79,576	£20,154

Table 201 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, HAQ costs from Poole

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£137,167	5.676	-	-	-	-
UST	£140,006	6.666	£2,840	0.989	£2,870	£2,870
SEC 300mg	£163,788	6.945	£23,781	0.280	£85,064	£20,981

Table 202 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, HAQ costs from Poole

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£137,167	6.188	-	-	-	-
UST	£140,006	7.132	£2,840	0.943	£3,010	£3,010
SEC 300mg	£163,788	7.384	£23,781	0.252	£94,184	£22,264

12.14.1.3 Withdrawal scenario 1

Table 203 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, withdrawal scenario 1

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
CZP	£137,240	7.226	ED		-	£21,560
ADA	£138,109	7.411	£42,144	2.100	£20,074	£20,074
GOL	£142,850	7.637	£4,741	0.226	£20,976	£20,161
ETN	£144,585	7.719	£1,735	0.082	£21,215	£20,197
SEC 300mg	£172,821	7.835	D		-	£30,461
INF	£167,126	7.890	£22,541	0.171	£131,716	£27,599

Table 204 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, withdrawal scenario 1

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
CZP	£111,856	7.537	ED		-	£24,107
ADA	£114,039	7.708	ED		-	£23,153
GOL	£119,624	7.923	D		-	£23,418

SEC 150mg	£115,157	7.938	£48,157	2.262	£21,291	£21,291
ETN	£119,326	8.02548	£4,169	0.087	£47,734	£22,274
INF	£145,569	8.161	£26,243	0.136	£193,063	£31,616

Table 205 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, withdrawal scenario 1

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
CZP	£98,060	7.974	ED		-	£26,117
ADA	£100,893	8.125	ED		-	£25,542
SEC 150mg	£103,136	8.323	ED		-	£24,219
GOL	£106,895	8.325	D		-	£25,951
ETN	£105,592	8.456	£54,156	2.268	£23,883	£23,883
INF	£133,664	8.543	£28,071	0.087	£324,502	£34,930

Table 206 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, withdrawal scenario 1

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
UST	£118,127	6.334	£22,162	1.022	£21,685	£21,685
SEC 300mg	£164,019	7.208	£45,892	0.875	£52,454	£35,876

Table 207 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, withdrawal scenario 1

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
UST	£91,246	6.666	£24,246	0.989	£24,510	£24,510
SEC 300mg	£141,128	7.495	£49,881	0.830	£60,105	£40,749

Table 208 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, withdrawal scenario 1

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC

BSC	£51,436	6.188	-	-	-	-
UST	£76,712	7.132	£25,275	0.943	£26,797	£26,797
SEC 300mg	£128,564	7.898	£51,852	0.767	£67,626	£45,105

12.14.1.4 Withdrawal scenario 2

Table 209 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, withdrawal scenario 2

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
CZP	£145,291	7.575	ED		-	£21,791
SEC 300mg	£168,369	7.761	D		-	£29,562
ADA	£146,695	7.798	ED		-	£20,406
GOL	£152,626	8.069	£56,661	2.758	£20,545	£20,545
ETN	£154,686	8.168	£2,060	0.099	£20,827	£20,555
INF	£180,980	8.375	£26,294	0.207	£127,152	£27,750

Table 210 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, withdrawal scenario 2

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
CZP	£120,762	7.874	D			£24,459
SEC 150mg	£116,558	7.902	£49,558	2.226	£22,267	£22,267
ADA	£123,771	8.080	ED		-	£23,623
GOL	£130,746	8.338	D		-	£23,946
ETN	£130,329	8.462	£13,771	0.560	£24,593	£22,734
INF	£161,129	8.626	£30,800	0.164	£187,663	£31,911

Table 211 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis, withdrawal scenario 2

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
SEC 150mg	£104,305	8.292	ED		-	£25,138

CZP	£107,389	8.294	ED		-	£26,570
ADA	£111,192	8.475	ED		-	£26,129
GOL	£118,682	8.716	D		-	£26,604
ETN	£117,041	8.874	£65,605	2.686	£24,427	£24,427
INF	£150,067	8.978	£33,026	0.104	£316,876	£35,352

Table 212 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, withdrawal scenario 2

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
UST	£122,062	6.507	£26,098	1.196	£21,829	£21,829
SEC 300mg	£152,067	6.858	£30,004	0.351	£85,485	£36,276

Table 213 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, withdrawal scenario 2

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
UST	£95,632	6.833	£28,631	1.156	£24,763	£24,763
SEC 300mg	£127,960	7.160	£32,328	0.328	£98,657	£41,081

Table 214 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis, withdrawal scenario 2

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs NBO	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
UST	£81,319	7.289	£29,883	1.101	£27,142	£27,142
SEC 300mg	£114,795	7.584	£33,476	0.295	£113,494	£45,389

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Addendum to Assessment Group's Report

Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs

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

Date: 12/09/2016

Addendum to Section 7 (Economic model) of the Assessment Report

1 Probabilistic sensitivity analysis

1.1 Methods

Probabilistic sensitivity analysis (PSA) is used to assess the implications of parameter uncertainty (the imprecision with which input parameters are estimated) in terms of the estimates of cost-effectiveness. The uncertainty in each parameter was represented using a probability distribution and the probabilistic sensitivity analysis was carried out using Monte Carlo simulation. The rate of change of HAQ while not on treatment was assigned a gamma distribution to ensure that values are strictly positive. All other uncertain parameters were assigned normal distributions using the mean and SE. The treatment effect parameters used in the model, PsARC response, conditional change in HAQ and PASI responses, utilise the CODA output from the evidence synthesis models (see Section 7 of the main report).

This analysis reflects the decision uncertainty associated with the optimal treatment. PSA generates distributions (20,000 iterations) of total costs and QALYs and shows the probability that a treatment is cost-effective at thresholds of £20,000 and £30,000. This was performed for the three sub-populations, defined by the patient's position in the treatment's pathway and also on the three sub-groups of concomitant psoriasis severity. This analysis utilised the two evidence synthesis outputs, the independent and the meta regression analyses.

Given the mathematically intensive operations, represented by 20,000 iterations for each of the 15 versions of the model, the computation time is a major challenge. This may potentially reach two months on a desktop machine. Therefore, there was a need to run the probabilistic model on The University of York supercomputer. This necessitated some flexibility in the code allowing the model to be run in parallel on hundreds of processors within the supercomputer.

1.2 Results

According to the three main subpopulations (biologic naive: 1 prior, 2 priors DMARDs and biologic experienced), results for three separate concomitant psoriasis subgroups (baseline PASI = 0, PASI = 7.5, PASI = 12.5) are presented and discussed in the following sections. For ease of presentation and interpretation, tables are only presented for the independent analysis from the evidence synthesis in the main body of the report and summary tables are used to compare with the results based on meta regression approach.

All results presented in Section 1.2 are based on the list prices for SEC and CZP and the originator products for INF and ETN. A separate confidential appendix is included which incorporates the PAS prices for CZP and SEC.

In each of the 15 versions of the model, the expected model outputs are not equal to the output evaluated at the expected values of the parameters of the model (deterministic analysis (DA)), showing that the model is non-linear.

1.2.1 Subpopulation 1: biologic naïve (≤1 prior DMARD)

The probabilistic cost effectiveness results for subpopulation 1 are shown for the three subgroups according to the level of concomitant psoriasis (moderate-severe, mild-moderate and no concomitant) in **Error! Reference source not found.**, **Error! Reference source not found.** and **Error! Reference source not found.**, respectively.

The means from the PSA imply the same optimal treatment (CZP) as the DA. The probability that CZP is cost effective at threshold of £20,000 is 0.39. At a threshold of £30,000 this increases to 0.53. Using the meta regression results increases the likelihood of CZP being cost effective; 0.46 at a £20,000 threshold and 0.63 at a £30,000 threshold.

Table 1 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC	Prob. CE@20k	Prob. CE@30k
BSC	£95,849	5.363	-	-	-	-	0.51	0.20
CZP	£160,096	8.363	£64,247	3.000	£21,417	£21,417	0.39	0.53
SEC300	£179,594	8.661	£19,498	0.298	£65,416	£25,394	0.10	0.26

In the mild-moderate psoriasis group (Table 2), again the cost-effectiveness results from the means of the PSA are similar to the results obtained from the DA; SEC150mg represents the optimal treatment at a threshold between £20,000 and £30,000. This is highly uncertain; the probability that CZP is cost effective at threshold of £20,000 is 0.17. At a threshold of £30,000 this increases to 0.30. Using the meta regression results again produces similar results.

Table 2 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC	Prob. CE@20k	Prob. CE@30k
BSC	£66,885	5.727	-	-	-	-	0.46	0.20
CZP	£135,999	8.653	£69,114	2.926	D	£23,621	0.17	0.30
SEC150	£132,284	8.822	-£3,714	0.168	£21,136	£21,136	0.37	0.50

* D = dominated, ED = extendedly dominated

In the no concomitant psoriasis subgroup (Table 3), the probabilistic results again imply the same optimal treatment (SEC150mg). The probability that SEC150mg is cost effective at threshold of £20,000 is 0.28. This increases to 0.45 at a threshold of £30,000. Using meta regression analysis gives very similar results.

Table 3 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC	Prob. CE@20k	Prob. CE@30k
BSC	£51,321	6.239	-	-	-	-	0.59	0.26
CZP	£122,839	9.061	£71,518	2.822	D	£25,342	0.13	0.29
SEC150	£120,028	9.204	-£2,810	0.142	£23,177	£23,177	0.28	0.45

* D = dominated, ED = extendedly dominated

Table 4 illustrates the differences between the independent analysis and the meta regression evidence synthesis for each of the subgroups in subpopulation 1 using the means from the PSA. The pairwise ICERs for each of the treatments compared to BSC are presented along with the optimal (or most cost-effective) treatment strategy determined based on the fully incremental ICER comparisons at thresholds of £20,000 and £30,000 per QALY.

In summary, the differences in the pairwise ICERs estimated using the alternative synthesis models has only a minor effect. Furthermore, the optimal treatment remains consistent across the two evidence synthesis approaches using a threshold of £30,000 per QALY. At a threshold of £20,000 the optimal treatment is BSC, unlike the DA results. The ICER for CZP compared to BSC now is beyond the threshold (£20,621) based on the results of the meta regression.

Table 4 Summary of differences between independent and meta regression approaches, sub population 1

	ICERs vs BSC			Optimal treatment (£20, 000)	Optimal treatment (£30, 000)
	CZP	SEC 150	SEC 300		
Moderate – severe psoriasis					
Independent analysis	£21,417	-	£25,394	BSC	CZP
Meta regression	£20,621	-	£26,766	BSC	CZP
Mild-moderate psoriasis					
Independent analysis	£23,621	£21,136	-	BSC	SEC 150MG
Meta regression	£23,280	£20,993	-	BSC	SEC 150MG
No concomitant psoriasis					
Independent analysis	£25,342	£23,177	-	BSC	SEC 150MG
Meta regression	£25,334	£23,090	-	BSC	SEC 150MG

1.2.2 Subpopulation 2: biologic naïve (≥2 prior DMARDs)

The means from the PSA for subpopulation 2 are reported according to the level of concomitant psoriasis (moderate-severe, mild-moderate and no concomitant) in **Error! Reference source not found.**, **Error! Reference source not found.** and **Error! Reference source not found.**, respectively.

In the moderate-severe subgroup (Table 5), the PSA results imply a different optimal treatment than the DA results; it switches from ETN to GOL. This is driven by the skewed nature of the PASI75 data. Figure 1.1 shows that the PASI 75 data for ETN have the widest variation with the mean having greater value than the median indicating that the data are rightly skewed. PASI 75 response plays a more important role in this sub-group compared to the mild-moderate and no concomitant psoriasis patients.

Table 5 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC	Prob. CE@20k	Prob. CE@30k
BSC	£95,849	5.363	-	-	-	-	0.26	0.10
CZP	£137,306	7.255	£41,457	1.893	ED	£21,906	0.13	0.11
ADA	£138,117	7.494	£811	0.239	ED	£19,831	0.16	0.16
SEC300	£156,926	7.531	£18,809	0.036	D	£28,176	0.03	0.07
GOL	£142,645	7.753	-£14,281	0.223	£19,577	£19,577	0.20	0.23
ETA	£144,518	7.800	£1,873	0.047	£39,854	£19,968	0.21	0.26
INF	£166,776	8.075	£22,257	0.275	£81,064	£26,153	0.01	0.08

* D = dominated, ED = extendedly dominated

There is a high degree of uncertainty around the choice of optimal treatment (GOL); the probability that GOL is cost effective is 0.20 at threshold of £20,000 and 0.23 at a threshold of £30,000. Using the meta regression estimates reduces the difference between the QALYs for GOL and ETN, making ETN within the threshold of £30,000 at £25,886 per QALY compared to GOL. Again this decision is highly uncertain; probability of being cost-effective is 0.20 and 0.25 at threshold of£20,000 and £30,000 respectively.

Figure 1.1 Range of values and distributions for PASI 75 response for the treatments

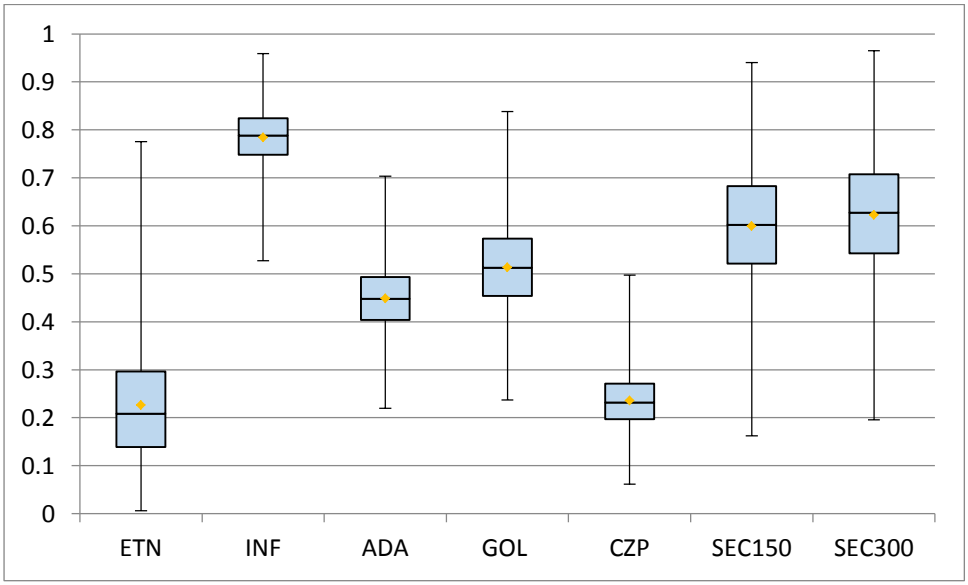

Table 6 shows the results for the mild to moderate psoriasis subgroup. In this subgroup, the optimal treatment (ETN) is consistent for the PSA and DA results. The probability that ETN is cost-effective is 0.13 at threshold of £20,000 and 0.22 at a threshold of £30,000. Using the meta regression estimates increases the decision uncertainty, associated with ETN and makes SEC150mg the optimal treatment within a threshold of £30,000, with a probability of being cost-effective of 0.21.

Table 6 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC	Prob. CE@20k	Prob. CE@30k
BSC	£66,885	5.727	-	-	-	-	0.28	0.13
CZP	£111,852	7.567	£44,967	1.839	D	£24,446	0.14	0.12
SEC150	£108,252	7.712	-£3,600	0.145	£20,844	£20,844	0.20	0.18
ADA	£113,980	7.791	£5,728	0.079	ED	£22,819	0.11	0.13
GOL	£119,349	8.040	£5,369	0.248	D	£22,691	0.13	0.18
ETA	£119,168	8.107	-£181	0.068	£27,619	£21,969	0.13	0.22
INF	£145,152	8.346	£25,985	0.238	£108,986	£29,893	0.00	0.05

* D = dominated, ED = extendedly dominated

For the no concomitant psoriasis subgroup (PASI=0) (Table 7), the choice of optimal treatment (ETN) is consistent across the PSA and DA results. The probability that ETN is cost effective is highly uncertain at 0.12 for a threshold of £20,000 and 0.22 for a threshold of £30,000. Using met-regression switches the optimal treatment (see Table 8). The uncertainty associated with the optimal treatment (SEC150mg) is somewhat less uncertain at 0.19.

Table 7 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 2: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC	Prob. CE@20k	Prob. CE@30k
BSC	£51,321	6.239	-	-	-	-	0.33	0.16
CZP	£98,022	8.004	£46,701	1.765	D	£26,461	0.14	0.13
SEC150	£95,329	8.123	-£2,693	0.119	£23,356	£23,356	0.19	0.17
ADA	£100,800	8.208	£5,471	0.085	ED	£25,129	0.10	0.13
GOL	£106,585	8.441	£5,785	0.233	D	£25,095	0.11	0.16
ETA	£105,389	8.538	-£1,196	0.097	£24,248	£23,517	0.12	0.22
INF	£133,214	8.726	£27,826	0.188	£148,259	£32,932	0.00	0.03

* D = dominated, ED = extendedly dominated

Table 8 summarises the differences between the independent analysis and the meta regression evidence synthesis for each of the separate psoriasis subgroups within subpopulation 2. Although there are only minimal differences in the pairwise ICERs in this subpopulation, the optimal treatment alters across the two evidence synthesis approaches. In the moderate-severe sub-group, it switches from ETN to GOL due to the skewness of the PASI 75 data for ETN. In the mild-moderate and no concomitant subgroups, the optimal treatment switches from ETN to SEC150mg in the mild-moderate and non-concomitant psoriasis subgroups. These differences are driven by the increased relative effectiveness of SEC 150mg in the meta regression approach.

Table 8 Summary of differences between independent and meta regression approaches, subpopulation 2

	ICERs vs BSC							Optimal treatment (£20, 000)	Optimal treatment (£30, 000)
	CZP	SEC 150mg	SEC 300mg	ADA	GOL	ETN	INF		
Moderate – severe psoriasis									
Independent analysis	£21,906	-	£28,176	£19,831	£19,577	£19,968	£26,153	BSC	GOL
Meta regression	£20,256	-	£29,289	£19,812	£20,038	£20,285	£27,411	BSC	ETN
Mild-moderate psoriasis									
Independent analysis	£24,446	£20,844	-	£22,819	£22,691	£21,969	£29,893	BSC	ETN
Meta regression	£23,279	£20,262	-	£22,752	£22,543	£22,406	£30,690	BSC	SEC 150MG
No concomitant psoriasis									
Independent analysis	£26,461	£23,356	-	£25,129	£25,095	£23,517	£32,932	BSC	ETN
Meta	£25,630	£22,675	-	£25,023	£24,484	£24,052	£33,391	BSC	SEC

regression									150MG

1.2.3 Subpopulation 3: biologic experienced

Table 9, Table 10 and Table 11 presents the results for subpopulation 3 for the moderate-severe, mild-moderate and no concomitant psoriasis subgroups respectively. Similar to the DA results, UST is the optimal treatment at thresholds of £20,000 and £30,000. The probability of UST being cost effective at threshold of £20,000 is 0.48. This increases to 0.50 using a threshold of £30,000.

Table 9 Moderate-severe psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC	Prob. CE@20k	Prob. CE@30k
BSC	£95,849	5.363	-	-	-	-	0.44	0.34
UST	£117,666	6.605	£21,817	1.242	£17,571	£17,571	0.48	0.50
SEC300	£143,629	6.636	£25,964	0.032	£818,886	£37,524	0.09	0.16

Table 10 shows the results for the mild to moderate psoriasis subgroup. The optimal treatment remains UST, with the probability that it is cost effective at threshold of £20,000 at 0.45. This increases to 0.49 at a threshold of £30,000.

Table 10 Mild-moderate psoriasis, subpopulation 3: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC	Prob. CE@20k	Prob. CE@30k
BSC	£66,885	5.727	-	-	-	-	0.47	0.36
UST	£90,719	6.935	£23,835	1.208	£19,731	£19,731	0.45	0.49
SEC300	£118,576	6.950	£27,857	0.014	£1,961,907	£42,295	0.07	0.14

Table 11**Error! Reference source not found.** shows the results of non-evaluable psoriasis subgroup. In this sub-group again the choice of optimal treatment (UST) is consistent across the PSA and DA. The probability that UST is cost effective at threshold of £20,000 is 0.43 and 0.49 at a threshold of £30,000.

Table 11 No concomitant psoriasis, sub population 3: Fully incremental cost-effectiveness analysis

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC	Prob. CE@20k	Prob. CE@30k
BSC	£51,321	6.239	-	-	-	-	0.50	0.38
SEC300	£104,944	7.389	£53,624	1.150	D	£46,617	0.07	0.13
UST	£76,152	7.400	-£28,792	0.010	£21,394	£21,394	0.43	0.49

* D = dominated, ED = extendedly dominated

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15th September 2016

Re: Novartis response to the Assessment Group report for ID579

Dear Sir/Madam,

Thank you for the opportunity to comment on the Assessment Group (AG) report for this appraisal. Novartis welcomes the conclusion that secukinumab is clinically effective for the treatment of active psoriatic arthritis (PsA) and that it is one of the more effective biologic treatments for patients with PsA and significant psoriasis. We further welcome the results of the economic analysis demonstrating the cost-effectiveness of secukinumab, and note that cost-effectiveness will be further improved across all the populations assessed when incorporating the Patient Access Scheme (PAS) price for secukinumab.

Having reviewed the AG report, we consider the AG's methods to be generally robust and appropriate. However, we have identified a number of issues that we request the AG and committee to consider, as follows.

1. *Class effect in the network meta-analysis (NMA)*

Novartis agrees with the AG's approach to exploring different NMA models in order to estimate the relative efficacy of all comparators. However, we strongly disagree with the AG's choice to impose a class effect on secukinumab and ustekinumab in their preferred meta-regression model on the basis that they are both 'anti-interleukins'. The mechanism of action of secukinumab and ustekinumab are distinct, with secukinumab specifically targeting interleukin (IL)-17A, whereas ustekinumab targets the p40 subunit common between IL-12 and IL-23.[1, 2] These drugs act at entirely different parts of the immune process involved in PsA and have different levels of efficacy. It may be noted, for example, that secukinumab has demonstrated significantly superior efficacy to ustekinumab in the treatment of psoriasis in the head-to-head CLEAR study: secukinumab (79.0%) was superior to ustekinumab (57.6%) as assessed by Psoriasis Area Severity Index (PASI) 90 response (primary endpoint) at Week 16 ($p<0.0001$).[1] In the subgroup of patients with moderate to severe psoriasis and concomitant PsA, a higher proportion of patients in the secukinumab group achieved a PASI 90 response at Week 16 compared with ustekinumab; 79.1% versus 65.4%, respectively ($p=0.063$).[3] The difference in PASI 90 score between secukinumab and ustekinumab for psoriasis patients with concomitant PsA was also observed at Week 52.[4] Week 24 results for the biologic experienced populations in the PSUMMIT2 and FUTURE 2 trials of ustekinumab and secukinumab, respectively, are also supportive of a difference in efficacy between these therapies, based on the ACR20 response: secukinumab (45%) versus ustekinumab (36.7%) and PASI 75 response: secukinumab 64% versus ustekinumab (45.55%).[5, 6]

The diversity of mechanistic pathways between secukinumab and ustekinumab stands in contrast to the homogeneous mode of action of the comparators placed by the AG in the anti-tumour necrosis factor (TNF) class, which all act on a single signalling point by targeting the TNF signalling molecule.

Whist from a methodological perspective the imposition of the 'anti-IL' class effect may be an attractive approach to simplify the issues in hand, this generalisation is not plausible from a biological or clinical perspective. As such, Novartis considers it to be inappropriate to pool secukinumab and ustekinumab as a class effect and request that the AG conduct an NMA (for the HAQ outcome) that removes the 'anti-IL' class effect and models secukinumab and ustekinumab to be independent (as apremilast is modelled to be independent), with the class effect only retained for the anti-TNF comparators where it is better justified. Furthermore, we request that the AG's preferred meta-regression NMA models should be B1 for the PsARC outcome and I1 for the ACR outcome.

2. *Placebo adjusted NMA models*

Novartis agrees with the AG that placebo adjustment of the NMA is an important factor in correctly assessing the relative efficacy of the comparators. This adjustment is required due to the observed high placebo response rates over time, termed "*placebo creep*" – an effect which the AG report states has also been noted in other clinical areas (AG report: page 137).

As such, Novartis does not believe that it is appropriate to present the unadjusted PsARC and PASI NMAs as the base case for the appraisal. This approach is subject to the significant artificial ceiling effects on comparators investigated in more recent trials (including secukinumab in FUTURE 2, amongst others), as identified and discussed in the AG report in Sections 4.6 and 5. To present the unadjusted NMAs as a base case risks creating a false impression that the older comparators have demonstrated higher efficacy. Novartis therefore requests that the placebo adjusted PsARC and PASI NMAs be used in the base case cost-effectiveness analysis.

3. *Withdrawal rate of secukinumab*

The Novartis company evidence submission reported the year 2 discontinuation rates incorrectly for secukinumab 150 mg ([redacted]%) and 300 mg ([redacted]%). Novartis would like to apologise for this error and also take the opportunity to clarify that the correct withdrawal rates for secukinumab 150 mg and 300 mg are [redacted]% and [redacted]% in Year 2 respectively, based on FUTURE 2. The impact of this error was assessed in the Novartis model and the differences in results are negligible.

This clarification also affects the AG's withdrawal scenario 1 analyses (withdrawal rate for secukinumab assumed to be 50% of the base case value from year 2), therefore we kindly recommend that these analyses should be reassessed.

4. *One prior disease-modifying anti-rheumatic drugs (DMARDs) subpopulation*

Novartis welcomes the inclusion of the one prior DMARD subpopulation in the appraisal, as this is an area of unmet medical need. A study that examined outcomes in PsA patients attending an early inflammatory arthritis clinic in Ireland found that, despite clinical improvement with DMARD treatment, PsA results in radiological damage in up to 47% of patients at 2 years.[7]

Secukinumab has been shown to have a significant inhibitory effect on radiographic progression.[8] Biologic treatment after one prior DMARD failure could delay disease progression and secukinumab has been demonstrated to be a cost-effective option in this

population. We note that consideration of the use of anti-TNF therapies for patients with active PsA who have received one prior DMARD has previously been recommended by the British Society for Rheumatology (2012).[9] More recent guidelines from the European League Against Rheumatism (2015), recommend using biological therapies for the treatment of PsA patients with peripheral arthritis and an inadequate response to at least one DMARD.[10] Novartis believes that the availability of secukinumab provides an important new treatment option for this population of patients with PsA.

5. *Interpretation of cost-effectiveness results*

Novartis notes that the AG report highlights the sensitivity of the cost-effectiveness results to the assumptions used in the model, including the choice of NMA model (AG report: page 255). We agree that the ranking of interventions in the economic results in terms of the quality-adjusted life years (QALYs) generated varies according to the NMA model used. As such, Novartis welcomes the suggestion in the AG report that the pairwise comparisons versus best supportive care (BSC) should also be considered in the assessment of cost-effectiveness, and agree that this is the appropriate response to the uncertainty in the choice of NMA models.

6. *Reimbursement of the 300 mg dose of secukinumab*

It is important to reiterate that secukinumab is already available to patients with severe psoriasis whose disease has failed to respond to standard systemic therapies or for which these therapies are contraindicated/not tolerated, following guidance published by NICE in TA350.[11] As such, the results for patients with no concomitant psoriasis or mild to moderate psoriasis at baseline are considered to be the most pertinent estimates of cost-effectiveness for secukinumab in this appraisal, given existing treatment practices in the UK.

7. *Further subgrouping of scope subpopulations by psoriasis severity*

As noted by the AG, the dose of secukinumab in PsA depends upon whether the patient has concomitant moderate to severe psoriasis.[8] Novartis therefore welcomes the AG analysis in which the cost-effectiveness of secukinumab is examined in subgroups based on psoriasis severity, and note the favourable cost-effectiveness of secukinumab in all subgroups when the PAS price for secukinumab is applied in the AG's economic model.

However, we note that although there are guidelines for defining the severity of psoriasis using PASI and other measures,[12, 13,19] there is little consensus on severity definitions, PASI is not routinely measured in UK NHS rheumatology clinics and systematic data on psoriasis severity in UK PsA patients are limited. In addition, and as discussed by the AG on page 43 of the report, PASI scoring has poor sensitivity to change when skin psoriasis is less than 10% body surface area involvement;[14] it is time-consuming to conduct and not practically feasible in daily clinical practice (AG report: page 43). For these reasons, we propose that the committee considers the subgroup analyses according to psoriasis sensitivity as valuable supporting information rather than a prompt to incorporate PASI scoring into future guidance for treatments for PsA.

8. *External validity of pairwise incremental cost-effectiveness results for comparator therapies versus BSC*

It was noted in the AG report that "*results from the Novartis model did not appear consistent with the cost-effectiveness reported for the comparator treatments assessed in previous NICE technology appraisals (TA199, 220 and 340).*"

The different approaches used in previous appraisals mean comparisons of results are not straightforward. A review of the Novartis model and original York (TA199) model suggests that differences in results are due to the fewer incremental QALYs for the comparators versus BSC predicted by the Novartis model. This is driven by differences in baseline PASI/HAQ scores, clinical effectiveness results (including whether adjustments were made for placebo effects) and utility algorithms.

9. *Comparators for the biologic experienced (subpopulation 3) and anti-TNF contraindicated (subpopulation 4) analyses*

Novartis agrees with the AG's decision to exclude certolizumab pegol from the biologic experienced analysis (subpopulation 3), as it would be inappropriate to compare the RAPID-PsA trial (which excluded primary failures of a prior anti-TNF from being recruited) with the secukinumab and ustekinumab trials.

Novartis considers the exclusion of certolizumab pegol (an anti-TNF inhibitor), to be appropriate for the modelling of patients who are contraindicated to anti-TNF therapies (subpopulation 4), in agreement with the approach taken by the AG (AG report: page 210).

Clarifications and corrections

Novartis 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. Novartis 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

	Description	Reference to the AG report	Clarification/correction
1	Description of mechanism of action of secukinumab as "being a monoclonal antibody which targets the interleukin 17A (IL-17A) receptor"	Page 44	This is factually incorrect as secukinumab binds directly to the IL-17A cytokine molecule itself and not to the IL-17A receptor.
2	Confidentiality marking of baseline tender joints count (TJC), swollen joints count (SJC) and HAQ in FUTURE 2	Table 4 on page 65	Confidentiality marking is not required as these are published data shown in McInnes *et al.* (2015)[6]
3	According to the AG, the risk of bias in ERASURE and FIXTURE trials with respect to incomplete outcome data were unclear	Table 6 on page 75	The statistical handling of missing data was as follows: • Last observation carried forward for HAQ outcomes in psoriasis patients with concomitant PsA • Non-responder imputation to Week 12 for PASI outcomes with multiple imputation thereafter These details are reported in the legends of

	Description	Reference to the AG report	Clarification/correction
			Figures 2 and 3 in Gottlieb *et al.* (2015)[16]
4	**Reporting inaccuracy:** PASI 75 response rate in FUTURE 2 for secukinumab 150 mg (Week 24)	Table 9 on page 82	**AG report**: 25/58 (43%) **To be corrected to**: 28/58 (48%), as reported in McInnes *et al.* (2015)[6] This may also impact on the relative response stated in Table 12 on page 84
5	**Reporting inaccuracy:** ACR20 response rate in FUTURE 2 for secukinumab 150 mg (Week 52)	Table 30 on page 104	**AG report**: 39/100 **To be corrected to**: 64/100, as reported in McInnes *et al.* (2015)[6]
6	**Reporting inaccuracy**: ACR50 response rate in FUTURE 2 for secukinumab 150 mg (Week 52)	Table 30 on page 104	**AG report**: 41/100 **To be corrected to**: 39/100, as reported in McInnes *et al.* (2015)[6]
7	**Reporting inaccuracy:** PASI 90 response rate in FUTURE 1 for secukinumab 150 mg (Week 52)	Table 31 on page 107	**AG report**: 60% **To be corrected to**: 59% due to rounding – 59.3% reported in Mease *et al.* (2015) supplementary information[17]
8	**Reporting inaccuracy:** description of the enthesitis and dactylitis outcomes in FUTURE 1	Table 31 on page 107	**AG report**: stated as the % resolution of enthesitis (and dactylitis) **To be corrected to**: the % of patients with enthesitis (and dactylitis), as reported in Mease *et al.* (2015) supplementary information[17] *The numbers presented in the AG report are correct in relation to the % of patients with enthesitis (and dactylitis).* *To present data as the % resolution of symptoms:* • *The % of patients with enthesitis at baseline in FUTURE 1 in whom it has resolved at week 52 is 100-34.1=65.9%* • *The % of patients with dactylitis at baseline in FUTURE 1 in whom it has resolved at week 52 is 100-30.8=69.2%.*
9	Sample size number for radiographic progression in FUTURE 1 at Week 104 (observed data)	Page 107	The AG noted that: *"At 104 weeks 85% of patients treated with secukinumab 150mg had no radiographic progression - defined as a change in Sharp/van der Heijde score of ≤0.5 - between baseline and week 104. This result was based on the observed population; no further details were presented and the sample size was not stated'* The reference used for this is an abstract from American College of Rheumatology (ACR) congress 2015 and the AG is correct to point out that the number of X-ray completers is not stated in the abstract.[18] We would like to clarify that the abstract was also presented as a poster at that congress; the

	Description	Reference to the AG report	Clarification/correction
			number of patients in the 150mg group with X-ray data at 104 weeks is **n=166** according to the poster.[18]
10	**Reporting inaccuracy:** the incidence of adverse events in FUTURE 2 for secukinumab 150 mg (up to Week 52)	Page 130	**AG report**: reports incidences (cases per 100 patient years) for secukinumab 300 mg rather than 150 mg • *Infection and infestation*: 79 (rounded from 78.7) • *Upper respiratory tract infection:* 18 (rounded from 17.9) • *Nasopharyngitis:* 14 (rounded from 13.5) • *Discontinuation due to adverse events:* 2% The text should be corrected to reflect that the data is for secukinumab 300mg. The data for secukinumab 150mg should be included as follows: • *Infection and infestation:* 87 (rounded from 86.7) • *Upper respiratory tract infection:* 18 (rounded from 17.6) • *Nasopharyngitis:* 12 (rounded from 12.3) • *Discontinuation due to adverse events:* 1% As reported in McInnes *et al.* (2015)[6]

Concluding remarks

Novartis notes that the conclusions of the Assessment Report are in line with those of our company submission – that secukinumab is a clinically effective and cost-effective treatment for patients with PsA, according to the populations defined in the scope of this appraisal. Novartis welcomes the opportunity to provide ongoing input into the appraisal and appreciates consideration of the points raised in this response.

Yours sincerely,

[redacted]

[redacted]

References:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Certolizumab pegol (Cimzia®) for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]

September 2016

UCB Response to Assessment Group Report

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Introduction

UCB welcomes the opportunity to respond to the Assessment Group's report on the use of certolizumab pegol and secukinumab for treating active psoriatic arthritis (PsA) following inadequate response to disease modifying antirheumatic drugs (DMARDs). UCB would also like to acknowledge the extensive work undertaken by the Assessment Group in synthetizing the existing evidence and the new approaches considered in their comparative effectiveness and cost-effectiveness analysis.

Following a review of the Assessment Group report, UCB would like to provide a number of comments and observations for consideration by the NICE committee, which UCB believes have significance for the discussion at the Appraisal Consultation meeting. A summary of the key points raised is outlined below and detailed in the next sections.

Outline of Responses

UCB has structured its comments into three discrete sections:

Section 1: General comments

This section highlights some of the key issues UCB has concerns over with regards to the Assessment Group's report, particularly in relation to the exclusion of clinical evidence for certolizumab pegol in subpopulation 3 (biologic experienced) of the final scope and the interpretation of the efficacy and safety evidence.

- Clarification of the RAPID-PsA study inclusion/exclusion criteria with respect to prior tumour necrosis factor (TNF) exposure and the clinical efficacy of certolizumab pegol in this subpopulation
- Clarification of reporting of adverse events for TNF inhibitors and the safety profile of certolizumab pegol.

Section 2: Assessment Group independent cost-effectiveness and network meta-analysis

This section highlights UCB concerns with regards to the Assessment Group's independent cost-effectiveness and network meta-analysis (NMA), particularly in relation to the deviation from the final multiple technology appraisal (MTA) scope in terms of populations.

- Populations under consideration in the final scope of the MTA
- Comparators and model inputs, including error in the certolizumab pegol cost calculation
- Presentation and interpretation of the base case results
- Relative efficacy of certolizumab pegol compared with other biologics in biologic-naïve subpopulation and accurate conclusions of the NMA results

Section 3: Clarification of the evidence of certolizumab pegol and UCB's original submission

Section 3 clarifies a number of inaccuracies in the Assessment Group's report with regards to the evidence of certolizumab pegol and the RAPID-PsA study, and how the Assessment Group have interpreted the modelling approach employed by UCB in the original submission. This subsection reiterates the justifications and approaches used in the UCB original model.

1 General comments

1.1 Clinical efficacy of certolizumab pegol in patients with prior TNF inhibitor exposure (Subpopulation 3)

1.1.1 RAPID-PsA study inclusion/exclusion criteria

During its clinical effectiveness and cost-effectiveness analysis of subpopulation 3 (biologic-experienced or contraindicated), the Assessment Group opted to exclude the clinical evidence for certolizumab pegol and justified its choice given the inclusion and exclusion criteria of the RAPID-PsA trial. For example, on page 70 of its report, the Assessment Group states that "*Of the trials which allowed recruitment of biologic-experienced patients, the RAPID-PsA trial was more selective than the FUTURE 2, PSUMMIT 2 and PALACE trials: RAPID-PsA was the only trial in which patients with primary failure of a previous anti-TNF were excluded (primary failure was defined as no response within the first 12 weeks of treatment with the anti-TNF);*." Furthermore, on page 236 it was stated that '*CZP is not included in this model as only patients who had a primary response to a biologic treatment (secondary failures) were included in the RAPID-PsA trial. Primary non-responders were explicitly excluded in this trial and therefore the population represents a separate subgroup of the overall biologic experienced subpopulation (those that have previously had a response)*'.

UCB strongly disagrees with the Assessment Group non-consideration of the evidence of certolizumab pegol in subpopulation 3, as explained thereafter.

In the management of patients with PsA in clinical practice, discontinuations due to secondary loss of efficacy far out-weigh discontinuations due to primary loss of efficacy. The latest clinical guidelines issued by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the European League Against Rheumatism (EULAR), recommend TNF inhibitors for the management of PsA as first-line biologic treatments as well as option in patients with inadequate response to first TNF inhibitors. For instance, the 2015 update of the EULAR recommendation for the management of PsA, states that for patients who fail to respond adequately to a biological DMARD switching to another biological DMARD should be considered, including switching between TNF inhibitors.[1] The EULAR systematic literature review supporting the 2015 update, noted that, based on the evidence from the RAPID-PsA study, patients still respond to a second TNF inhibitor. Furthermore, the level of response with certolizumab pegol was similar in both patient populations naïve or previously exposed to another TNF inhibitor.[2]

The Assessment Group decision to exclude the evidence for certolizumab pegol in Subpopulation 3 biologic experienced), is based on the difference in inclusion and exclusion criteria between RAPID-PsA compared to FUTURE 2 and PSUMMIT 2. A summary of the key criteria with regards to prior TNF inhibitor exposure in these three trials is provided in Table 1 below. As per the RAPID-PsA study protocol subjects were excluded if they had previous exposure to >2 biologics or >1 TNF inhibitor for the treatment of PsA or psoriasis, or primary failure of a prior TNF inhibitor (defined as no response within the first 12 weeks of treatment with the TNF inhibitor) according to investigator assessment. In other terms, patients with an early non- response (i.e. within the first 12 weeks) were excluded, but primary non-responders who were assessed after week 12 were included. This seems similar to the inclusion criteria in FUTURE 2, for instance, where patients were included if they had experienced an inadequate response after receiving an approved dose of a TNF inhibitor for at least 3 months.

As indicated in recently published data from the RAPID PsA trial, although excluding primary non-responders to a TNF inhibitor in the first 12 weeks, the study included primary non-responders who were assessed after week 12 (6.25%) as well as partial responders (7.5%) within this subpopulation,[3] indicating that the spectrum of patients included in the RAPID-PsA study reflects the broad expected

patient population to be seen in clinical practice that have been exposed to a prior TNF inhibitor, and is thus a relevant evidence for subpopulation 3.

Table 1: Inclusion and exclusion criteria relevant to prior TNF inhibitor exposure among patients in the RAPID-PsA, FUTURE2 and PSUMMIT2 studies

Trial Name (active intervention)	Study inclusion criteria related to prior TNF inhibitor exposure	Study exclusion criteria related to prior TNF inhibitor exposure
RAPID-PsA (certolizumab pegol)		Subjects may not have been exposed to more than 1 TNF inhibitor prior to the Baseline Visit and may not have been a primary failure to any TNF inhibitor therapy (defined as no response within the first 12 weeks of treatment with the TNF inhibitor).
FUTURE2 (secukinumab)	Patients who had previously received a TNF inhibitor were eligible provided they had experienced an inadequate response after receiving an approved dose for **at least** 3 months or had stopped treatment for safety or tolerability reasons.	
PSUMMIT2 (ustekinumab)	Adult patients with active PsA for ≥6 months, despite ≥3 months of DMARD therapy, ≥4 weeks of NSAIDs therapy and/or **≥8** (etanercept, adalimumab, golimumab, certolizumab pegol) **or 14** (infliximab) continuous weeks of TNF-inhibitor therapy (or less if patient was intolerant of TNF inhibitors) were eligible.	

Therefore, given the similarity of the inclusion criteria for patients with prior TNF inhibitor exposure between RAPID-PsA compared to FUTURE2 and PSUMMIT2, UCB considers that the data from RAPID-PsA in patients with prior TNF inhibitors is comparable and clinically relevant to address the decision problem for Subpopulation 3. Consequently, UCB requests that the Assessment Group includes certolizumab pegol and its supporting evidence from RAPID-PsA in both the main NMA and the main cost-effectiveness analysis, alongside the relevant comparators for Subpopulation 3.

1.1.2 Clinical efficacy of certolizumab pegol in patients with prior TNF inhibitor exposure

In its report, the Assessment Group has suggested that the study design for the RAPID-PsA study may have inflated results in patients who were previously exposed to a TNF inhibitor. For example, on page 70 the report states: '*Of the trials which allowed recruitment of biologic-experienced patients, the RAPID-PsA trial was more selective than the FUTURE 2, PSUMMIT 2 and PALACE trials: RAPID-PsA was the only trial in which patients with primary failure of a previous anti-TNF were excluded (primary failure was defined as no response within the first 12 weeks of treatment with the anti-TNF);* […] *The results for the RAPID-PsA biologic-experienced subgroup may therefore be somewhat inflated when compared with the other trials reporting results for this subgroup*.'

Furthermore, the Assessment Group suggests on page 255 that '*The magnitude of secukinumab and certolizumab pegol treatment effects in biologic-experienced patients is uncertain because the trial subgroup sample sizes were small and the subgroup in the certolizumab pegol trial was not appropriately representative of the biologic-experienced population which would be seen in clinical practice'*.

UCB strongly disagrees with the conclusions made by the Assessment Group. The efficacy of certolizumab pegol was similar across TNF inhibitor naïve and previously exposed patients in RAPID-PsA. This effect has already been seen in several RA and axSpA studies of certolizumab pegol, some of which included both primary and secondary non-responders to prior TNF inhibitors,[4-8] which showed that the efficacy of certolizumab pegol was similar regardless of prior TNF inhibitor response status, and thus is not a feature only seen in PsA. Furthermore, it is important to note that in general it is expected to observe a higher placebo response in patients that are naïve to any TNF inhibitor or a biologic vs those previously exposed to biologics. Consequently, while the absolute response to certolizumab pegol was similar in both subpopulations, the placebo response varied thereby leading to different relative effect of certolizumab pegol in these 2 subpopulations.

As noted in the previous section 1.1.1, RAPID-PsA is comparable with both FUTURE2 and PSUMMIT2 in terms of the population with prior TNF inhibitor exposure included. Furthermore, the RAPID-PsA data indicated that the study reflects the broad expected patient population to be seen in clinical practice that have been exposed to a prior TNF inhibitor, and is thus a relevant evidence for subpopulation 3.

UCB thus strongly disagrees with the statement made by the Assessment Group that the results for certolizumab pegol in Subpopulation 3 are inflated and uncertain, and requests that the Assessment Group revises its related statements. Furthermore, UCB disagrees with the statement that the subgroup of biologic-experienced population from RAPID-PsA is not representative of what would be seen in clinical practice and requests that the Assessment Group removes this statement.

1.2 Assessment Group's reporting of the adverse events

In section 4.10 of its report, the Assessment Group summarises the evidence on the safety outcomes, based on clinical trials and several literature reviews. While UCB acknowledges the work undertaken by the Assessment Group in identifying and synthetizing the evidence, UCB notes that the presentation of the results and conclusions is not unbalanced, thereby creating unwarranted concerns about the safety of certolizumab pegol and leading to an inconsistent view to that provided by regulatory authorities.

1.2.1 Limitations of reporting adverse events and serious infection rates

It is common for analyses of adverse events from trials of TNF inhibitors to include safety data across different indications. This is the case for the different reviews and meta-analyses evaluated in the Assessment Group's report, which were not based on PsA-specific populations. Although studies are combined in a meta-analysis to increase power, a number of caveats exist in doing so.

For example, the authors of the Cochrane meta-analysis, which is reviewed by the Assessment Group, acknowledged several limitations of their meta-analysis that are not reported in the Assessment Group's report.[9] Specific limitations affecting the interpretation of their results, as they relate to the serious infection rate for certolizumab pegol include, (1) inadequate adjustment for treatment exposure, (2) methodological challenges associated with dealing with zero incidence of serious infections in the placebo groups, and (3) the substantial heterogeneity associated with pooling data from all placebo controlled studies across all agents and all disease indications.

Furthermore, on page 131 of the Assessment Group's report, the authors summarise "*when compared with control treatments only infliximab and certolizumab pegol were statistically significantly associated with adverse events*." These conclusions are made with little context provided, are stated as matter-of-fact, and do not reflect that these are the conclusions of the Cochrane review.

UCB would request that additional context is added in the Assessment Group report when the results of independent meta-analyses such as the Cochrane review are summarised. Furthermore UCB requests that the limitations of the different reviews of safety data identified by the Assessment Group are also acknowledged in the report (pages 131-133, 253 and 256).

1.2.2 Certolizumab pegol safety profile

On page 133 of its report, the Assessment Group summarizes the evidence on the safety outcomes from randomized clinical trials and literature reviews stating that "*Safety assessments of new treatments can sometimes be limited in systematic reviews of RCTs due to the small number of trials and relatively short follow up durations for which data are available. Where available, safety data from trials relating to the same treatment for other indications are therefore sometimes evaluated. For this review, more data from trials of other patient populations were available for certolizumab pegol than for secukinumab. The results from three systematic reviews (which looked specifically at adverse events) suggested that certolizumab pegol was associated with statistically significantly more serious adverse events and serious infections when compared with placebo. Secukinumab was not included in these systematic reviews of adverse events, probably due to the limited availability of data at the time. Although secukinumab appears to have a favourable safety profile, the fairly small number of trials for which data are currently available means there is still some uncertainty regarding its safety*." Similar statements are made in other sections of the report, for example in the Discussions and Conclusions.

UCB would like to note that the summary above presents the evidence in an unbalanced and biased way, and consequently leads to misleading conclusions with respect to the safety profile of certolizumab pegol.

As indicated in the UCB original submission, data from RAPID-PsA showed that rates of adverse events (AEs), serious AEs, and infections were similar between treatment groups through Week 24 of the study. Moreover, no new safety signals were observed in up to Week 96, compared with the use of CZP in other indications and compared with other TNF inhibitor therapies both within PsA and in other indications. Recently published long-term data from the open-label extension of RAPID-PsA up to 4 years (Week 216), showed that the safety profile was in line with previous reports from RAPID-PsA, with no new safety signals identified from Week 96 to Week 216.[24]

Furthermore, as mentioned in the EPAR, the safety profile of certolizumab pegol was generally similar between the RAPID-PsA study and the rheumatoid arthritis (RA) studies and is consistent with other TNF inhibitor therapies. No new safety signals were identified (European Medicines Agency [2013] European public assessment report for Cimzia).[10]

A recently published update of the long-term safety analysis of all certolizumab pegol-treated patients in the RA clinical trials, included 10 completed randomised controlled trials (RCTs) and several open-label extensions, with certolizumab pegol exposure of up to 7 years in some patients.[11] The evaluation and review process of the safety data was led by an external, independent safety steering committee, which identified and defined key adverse event types, and with expert input performed a manual review of these events. Overall, 4,049 RA patients who received certolizumab pegol were included in this safety pooling, with a total exposure of 9,277 patient-years. No new or unexpected safety signals associated with certolizumab pegol emerged in this updated long-term safety analysis.

While serious infectious event rates were higher for certolizumab pegol than for placebo in RCTs, the rate decreased with continued exposure to certolizumab pegol. These rates are consistent with data previously reported for certolizumab pegol and TNF inhibitors. This evidence has been submitted to NICE as part of the previous NICE MTAs in RA and axSpA.[12,13]

UCB thus requests that the Assessment Group revises the summary on page 133 and similar statements in their Discussions and Conclusions to ensure an accurate presentation of the safety profile of certolizumab pegol, as well as a balanced, unbiased and objective presentation of the safety evidence for the two interventions.

More specifically UCB requests the Assessment Group to include in their summary the safety conclusions from the RAPID-PsA study (cf above), in a similar manner to which the secukinumab trials have been presented. UCB also notes that the use of "favourable" to describe the evidence for secukinumab in the Assessment Group summary incorrectly implies that the two interventions have been compared to each other or that the evidence cited is comparable, which is not the case due to the fact that the sources and methodologies are completely different. UCB thus requests the deletion of "favourable" from the above cited paragraph and other sections of the report. Lastly, as indicated above UCB requests that the limitations of the different reviews of safety data are acknowledged on page 133 and similar statements included in the Discussions and Conclusions.

2 Assessment Group independent cost-effectiveness analysis and network meta-analysis

2.1 Consideration of subgroups by psoriasis severity as the base case of the decision problem

In describing its approach, the Assessment Group states on page 203 that '*Rather than presenting a single base case reflecting an 'average' PsA patient, heterogeneity in terms of baseline PASI is now formally addressed by presenting results for three distinct subgroups within each subpopulation* ' and that '*Differences in baseline PASI were previously considered in the previous York model as part of a sensitivity analysis. However, since the decision problem differs across the specific subgroups due to the different licensed dosages of SEC, it was considered more appropriate to model these subgroups separately*.'

While UCB acknowledges that PsA is a heterogeneous disease, in terms of both presentation and severity, UCB strongly disagrees with the Assessment Group approach in considering the subgroups by psoriasis severity as the base case populations in the decision problem, and considers it as a deviation from the final scope of the Multiple Technology Appraisal. As per the MTA final scope, certolizumab pegol is to be appraised within its marketing authorisation, that is for treating active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate, and to be evaluated at 3 different points in the treatment pathway, specifically:

- for people who have only received 1 prior non-biological disease modifying anti-rheumatic drug (DMARD);
- for people whose disease has not responded adequately to at least 2 DMARDs;
- for people whose disease has not responded adequately to DMARDs and not adequately responded to biological therapies or biological therapies are contraindicated.

While UCB acknowledges that secukinumab has different licensed dosages for treating PsA, depending on the exposure to prior biologics and the psoriasis severity, consideration of the

subgroups by psoriasis severity as the base case populations in the decision problem treats unequally the two interventions, as certolizumab pegol is therefore not appraised in line with its license. This approach is also inconsistent with the one taken during previous Technology Appraisals for other TNF inhibitors, as well as the latest EULAR and GRAPPA recommendations for the management of PsA and could lead to inconsistent guidance between biological treatments and challenges in interpreting them.[14-16]

Furthermore, the Assessment Group's report notes on page 209 that in the absence of effectiveness data reported for the three psoriasis severity subgroups, an assumption was made that treatments are similarly effective (in relative terms) for each subgroup within the separate subpopulations and that the differences in cost-effectiveness for these subgroups are driven entirely by the different baseline PASI scores and their subsequent impact on costs and outcomes of these differences. As such UCB considers that the base case results of the Assessment Group are not accurately reflecting the health outcomes of the subgroups considered and cannot thus inform the decision problem of the final scope.

UCB thus requests that the Assessment Group considers as the base case of its cost-effectiveness analysis the three subpopulations defined in the final scope issued by NICE, to ensure accurate appraisal of certolizumab pegol within its license, and that results for subgroups by psoriasis severity within these three subpopulations are considered as additional subgroup analyses in the decision problem.

2.2 Comparators in the Assessment Group independent cost-effectiveness analysis

2.2.1 Choice of 'etanercept only' as second line in population 1

In describing its approach, the Assessment Group states on pages 210 and 211 of the report, that *'In subpopulation 1, patients may be eligible to receive further biologics. ETN is assumed to be the next biologic treatment as part of the overall sequence, on the basis that is it the lowest cost currently approved biologic and because it was consistently reported to be more cost effective than other TNFs in previously published studies. Following failure of ETN, patients are assumed to receive UST before moving onto BSC.'*

UCB disagrees with the choice of etanercept as the only second-line therapy option in subpopulation 1, as this is not reflective of current clinical practice, where different TNF inhibitors are considered as treatment choices. This is supported by the latest GRAPPA and EULAR guidelines, which do not specify any particular TNF inhibitor as second-line therapy, but allow several options.[1,2] Furthermore, specification of any single TNF inhibitor as second-line therapy implicitly identifies an optimal treatment sequence for these patients in the decision problem of the present MTA. However, the objective of this MTA is to appraise the clinical and cost-effectiveness of certolizumab pegol and secukinumab within their marketing authorisations, and not to establish the optimal treatment sequencing in PsA.

Therefore, UCB requests that the Assessment Group considers a mix or basket of TNF inhibitors in their main approach, in accordance with the clinical guidelines, and provides the related results.

2.2.2 Inappropriateness of best supportive care as a comparator in subpopulations 1 and 2

While UCB acknowledges the challenges with the modelling and the interpretation of the cost-effectiveness analysis when sequential treatment lines are considered, UCB disagrees with the Assessment Group's use of the best supportive care (BSC) only sequence (ie not followed by subsequent lines of biologics), as a comparator in subpopulations 1 and 2 (Assessment Group report

Section 7.2, page 202) as this is not aligned with the comparators described in the final scope issued by NICE (Table 22). A sequence starting with DMARDs in population 1 and followed by biologics would be an appropriate comparator, and would reflect the current recommendations for treating PsA.

Table 2: Comparators in the final scope of the MTA issued by NICE

Comparators	The interventions (i.e. certolizumab pegol and secukinumab) listed above will be compared with each other. For people who have only received 1 prior non-biological DMARD: • Disease modifying anti-rheumatic drugs For people whose disease has not responded adequately to at least 2 DMARDs: • Biological therapies (with or without methotrexate including etanercept, adalimumab, infliximab, golimumab, apremilast [subject to ongoing NICE appraisal] For people whose disease has not responded adequately to DMARDs and not adequately responded to biological therapies (including etanercept, adalimumab, infliximab and golimumab) or biological therapies are contraindicated: • Ustekinumab • Apremilast [subject to ongoing NICE appraisal] • Best supportive care

Moreover, use of a BSC-only sequence as a comparator in these two subpopulations is not in line with neither real world clinical practice nor published clinical guidelines. For example, the recently published GRAPPA guidelines for do not include BSC as neither a strongly recommended nor conditionally recommended treatment option for patients with inadequate response to DMARDs.[17] In addition the most recent guidelines published by EULAR do not recommend the use of BSC and instead state that in patients with an inadequate response to at least one DMARD, therapy with a biologic, usually a TNF inhibitor, should be commenced.[1]

Furthermore, BSC as a comparator for subpopulations 1 and 2 misleads the results of the cost-effectiveness model as it becomes the reference treatment (the cheapest one) in the incremental analysis, and could lead to alternative, relevant, options to be extensively dominated.

UCB therefore requests that the Assessment Group considers the inclusion of treatment sequencing starting with conventional DMARDs in subpopulations 1 and 2 and followed by biologics, rather than just BSC-only sequence.

2.3 Model inputs in the Assessment Group independent cost-effectiveness analysis

2.3.1 Costing of certolizumab pegol

Biologic treatment costs and the number of vials assumed in the Assessment Group model are listed in Tables 82 (page 221), Tables 83 (page 222) and Table 84 (page 223) respectively. The Assessment Group indicates that the annual cost applied to certolizumab pegol is £10,232, which includes drug acquisition, administration and monitoring costs (cf the Assessment Group report, Table 82 and Table 83).

UCB would like to note, that the total acquisition costs for certolizumab pegol in the first year is £6792.5 with the Patient Access Scheme (and £10367.5 without the Patient Access Scheme) and is £9295 in subsequent years.

UCB would thus like to seek clarification from the Assessment Group on the costing calculation for certolizumab pegol and the annual costs assumptions in the first and subsequent years, as Table 83

implies that a constant cost estimate is applied in all years, which would overestimate the certolizumab pegol related costs.

Furthermore, the Assessment Group model assumes that the number of vials of certolizumab pegol per cycle after the initial cycle is 6 (see Table 84 in the Assessment Group report), and calculates the first 3-month drug acquisition cost of certolizumab pegol as £3,575 and subsequent 3-month costs as £2,145.

UCB would like to note that the number of administrations for certolizumab pegol in the first year is of 29 vials and of 26 in subsequent years (see Tables 63 and 64 in the UCB submission) and these should also be reflected in the Assessment Group model calculations.

UCB requests that the Assessment Group clarifies the cost calculation for certolizumab pegol in all cycles and on annual basis, and corrects their analysis, if needed.

2.3.2 Disease management cost data

The Assessment Group states on page 226 of its report that "*having identified important differences in the predictions based on the separate sources and noting the potential limitations identified in the Poole et al study, the final HAQ costs were based on the same function used in the previous York model, with costs uprated to current prices.*"

The de-novo York model considered RA and psoriasis related health state costs separately, using HAQ-DI and PASI 75 scores, respectively. The approach implemented by the Assessment Group in the base case utilises an equation derived from patients with RA, which may not be representative of costs incurred by patients with PsA. To address the psoriasis element of the disease, psoriasis related costs (by PASI subgroup) were obtained from multiple studies which are either outdated or based on European data, and the Assessment Group does not justify why these studies provide a better source of costs data than the approach submitted by UCB.

The UCB submitted model utilised cost data from the Poole et al. study[18] in the base case, which was obtained from a sample of PsA patients from the British Society of Rheumatology Biologics Register (BSRBR). The Poole study should be preferred to the current approach used by the Assessment Group in its base case, rather than being explored as a separate scenario, as it is based on directly relevant real-world data obtained from a PsA population in the UK. This study includes costs associated with "prescriptions, secondary care, investigations, GP (surgery, home or telephone consultations) and nurse (community or practice nurse)" for PsA patients. As these data included all medical resource use for PsA patients, PASI-related costs were not added to the model base case to avoid double counting of costs. However, PASI-related costs were considered in the UCB sensitivity analysis, based on the method published in the York model (see Section 5.9 of the UCB submission).

UCB request that the disease management costs for PsA patients be entirely derived from comparable patients with PsA, as is the case with data obtained from the Poole et al. study, rather than deriving costs based on an RA population and employing separate assumptions for PASI costs. These cost data should therefore also form the base case scenario on the grounds of relevance to the UK PsA population.

2.3.3 Baseline HAQ scores for the three subpopulations

The Assessment Group states on page 209 that "*baseline HAQ scores are assumed the same across the separate subpopulations and PASI subgroups. Differences in baseline HAQ scores were considered in a separate sensitivity analysis based on estimates reported in the UCB submission*."

UCB would like to note that the Assessment Group's analysis in the base case should reflect subpopulation specific baseline HAQ scores, and not a unique score across all populations. HAQ score is an important model driver, as it is the primary driver of health and cost outcomes in the de novo model. It is more appropriate to model the baseline value of HAQ for different subgroups accurately, rather than assuming an average.

UCB requests that differences in baseline HAQ scores be considered in the base case analysis of the Assessment Group, rather than in a sensitivity analysis. The Assessment Group has tested in sensitivity analyses the impact of using the Poole study for disease management costs, and varying HAQ scores at baseline, independently. Both analyses show different impact on the results. However, given that baseline HAQ score was identified as a model driver, and that HAQ score has greater impact on disease management costs than PASI score in the Poole study, the combined impact of these two changes might be greater and should thus be explored.

2.4 Presentation of results of the Assessment Group independent cost-effectiveness analysis

2.4.1 Model selected for base case analysis and presentation of base case results

The Assessment Group states on page 229: "*For ease of presentation and interpretation, individual ICER tables are only presented for the independent analysis from the evidence synthesis in the main body of the report and summary tables used to compare with the results based on meta-regression approach*."

UCB acknowledges the extensive work undertaken by the Assessment Group in exploring the heterogeneity across clinical trials and the placebo creep through adjusted NMA approaches, that are further implemented in their cost-effectiveness analysis. The Assessment Group utilises and prefers both independent analysis and meta-regression models for the analysis of PsARC response, HAQ conditional on PsARC response and PASI 50, 75 and 90 in the NMA section, and subsequently uses these two approaches in the base case of the cost-effectiveness analysis. While both approaches are considered in the Assessment Group base case, the results for the independent analysis are extensively presented and interpreted in the main body of the report, including conclusions and discussions, compared to the results based on the meta-regression model. Given the relevance of both approaches in the decision problem and that the meta-regression model fits slightly better than the unadjusted model, UCB considers that the results based on both approaches should be presented in a balanced way to avoid any bias in the reporting of the CE results in favour of one set of results, to ensure these are accurately accounted for in the decision making.

UCB requests that the Assessment Group presents and interprets the de-novo cost-effectiveness model results derived from both the adjusted and unadjusted NMA in the base case analysis with at least equal weight throughout the report, including the abstract, conclusions and discussions, to ensure conclusions drawn from the cost-effectiveness results will include the implications of using the adjusted NMA in addressing the decision problem, and are thus more balanced.

2.4.2 Presentation and interpretation of cost-effectiveness results relating to the MTA scope

Throughout their report, the Assessment Group infer that their analysis aims to identify an 'optimal' treatment. For example on page 208 they state: '*it is also important to consider the impact of differences in baseline characteristics, in terms of HAQ and particularly PASI scores, and the impact that these differences have on cost-effectiveness and the choice of optimal treatment'*. As a result the

Assessment Group subsequently suggest that certain comparators can be considered 'optimal' when presenting their results in section 7.3 and other chapters of their report.

UCB would like to note that the results of the cost-effectiveness analysis conducted by the Assessment Group show very similar costs and outcomes for all biologics except infliximab and secukinumab and all ICERs are within the acceptable cost-effectiveness range (£20,000-£30,000). Furthermore, in the absence of a probabilistic sensitivity analysis (PSA) and taking the very small difference between ICERs of certolizumab pegol and its comparators (i.e. the ICERs reported by the Assessment Group were within the same range of £19,000-£21,000), the Assessment Group cannot claim one treatment is optimal compared to others. Additionally, as stated in previous section 2.2.2, the BSC-only sequence is not a relevant comparator in populations 1 and 2 and its consideration misleads the results of the cost-effectiveness model. It is therefore incorrect to conclude that BSC-only strategy would be the "optimal" treatment in some cases (see Assessment Group report tables 93 and 97 for example), conclusion which is not consistent with previous NICE recommendations for TNF inhibitors.

A PSA will reveal a range of cost-effectiveness results that can better account for the uncertainty around model parameters, and potentially establish that the results of the interventions under scope are close to the different biologic comparators. For example, the PSA results included in Section 5.9 of the UCB submission, suggests that in subpopulation 2, there is little difference in QALYs when comparing certolizumab pegol with other treatments, with the exception of infliximab and secukinumab for which the cloud of points lies below 0, suggesting that it is highly likely that both comparators are more costly than certolizumab pegol. These conclusions are supported by the cost-effectiveness acceptability curve, which indicates that subcutaneous TNF inhibitors, including CZP have a similarly high likelihood of being cost-effective at any willingness to pay threshold, whereas infliximab and secukinumab 150mg have the lowest likelihood.

Given that the objective of the current MTA is to appraise certolizumab pegol and secukinumab, there is no clear rationale or justification to select one biologic or other comparator over the other by inference of an 'optimal' treatment.

UCB thus requests that the presentation and interpretation of the Assessment Group cost-effectiveness results accurately reflects the objective of the decision problem, as outlined in the final scope, and does not drive conclusions for interventions outside of the scope. Furthermore, UCB would request the Assessment Group to provide the results of the PSA alongside either credible intervals, cost-effectiveness plane scatter plots or cost-acceptability curves, to support their appraisal of the cost-effectiveness of certolizumab pegol and secukinumab in the three subpopulations of interest.

2.5 Conclusions on the relative effectiveness of certolizumab pegol in subpopulation 2 (biologic naïve)

The Assessment Group's NMA results for the biologic-naïve subpopulation 2 indicates that the relative effectiveness of certolizumab pegol and secukinumab compared with other biologics and with each other was uncertain. For example, the Assessment Group report states on page 5 that '*the NMA results for the biologic-naïve subpopulation indicated that their relative effectiveness compared with other biologics and with each other was uncertain*'.

When trying to resolve this uncertainty, the Assessment Group seems to lean against the baseline risk models because, as suggested in the report, there is no explicit rationale for 'placebo creep', although it has been observed in several other disease areas previously. Also note that for PsARC,

PASI, and ACR, models controlling for baseline risk have slightly better fit than those not doing so, even if the difference does not reach the somewhat arbitrary threshold of a 5-point DIC difference.

UCB appreciates the Assessment Group's recognition of 'placebo creep' and its potential impact on indirect comparison. The possible reasons for increasing placebo effect are described in more detail below. It is suggested that the reason for rejection of the results is primarily that the rankings from the adjusted results do not match those seen in the trials; however, this is really only true for relative effects, as opposed to absolute effects.

In the opinion of UCB, at least equal weight should be given by the Assessment Group to the placebo-rate controlled results throughout the entire report – i.e. meta-regression results should be given the same emphasis as the standard NMA. Heterogeneity of patient populations recruited to PsA studies has been acknowledged by the authors of the EULAR guidelines[1,2] – thus UCB suggests that this reinforces the appropriateness of meta-regression. As mentioned previously, cost-effectiveness results derived from both NMA models should be equally presented in the Assessment Group's report abstract, if the placebo-rate controlled results are not the preferred ones, especially given the slightly better fit those models have in many of the analyses.

2.5.1 Potential explanations for increasing placebo effect in PsA studies

In the third systematic review technical support document (TSD) produced by the NICE Decision Support Unit (DSU), it found, in its 'baseline risk' example, a strong interaction effect between baseline risk and treatment effects. The problem seems to be common to outcomes in this area where placebo response rates are extremely low.

Two primary drivers of the increasing placebo effect that has been observed in recent PsA, RA and axSpA studies are i) a general evolution in the standard of care over time, driven by evolution in the disease management and clinical guidelines, that will increase placebo results (e.g. patients may be treated more aggressively with cDMARDs) and ii) expectancy theory whereby patients' expectancy of efficacy of treatment can result in increased placebo results. This may particularly manifest itself especially in those patients that have are naïve to biologic treatment. It is also more evident when looking at easy to reach clinical targets, rather than very stringent clinical ones (eg remission), which are more difficult to reach, but where the benefit of the biologic treatment is seen.

In addition, there are several other possible reasons behind this form of variation in placebo response:[19,20]

- Eligibility creep (i.e. patients at the point of peak disease severity actively seek care and trial enrolment when other options are unavailable)
- Outcome measures used as eligibility criteria tend to increase the placebo rate
- More active arms in a trial may lead to an increased expectancy of efficacy in placebo groups
- The Hawthorne effect may influence placebo response whereby more patient visits or more medical 'care' in turn lead to more perceived effectiveness.

Note that while any disease area can experience variation in placebo response across trials, when the baseline placebo response is very low, even a tiny methodological difference between trials can lead to a doubling or halving of relative effect.

UCB notes that the claims throughout the Assessment Group report (e.g. on page 322) that '*the results (rankings) generated by <various placebo-controlled models> are very different from the observed trial results*' are only true if one looks at relative effects of biologics – the absolute effects

(i.e. response on treatment) are just as well represented, if not more so, by the placebo-controlled analyses. The evidence across PsA, RA and axSpA seems to suggest that for outcomes with extremely low placebo response, comparing absolute effects across trials may be more realistic than comparing relative effects.

UCB requests that the Assessment Group recognise there is good clinical rationale for 'placebo creep', as seen in many other disease areas. Together with the slightly improved model fit, the placebo-adjusted NMA results should be more appropriate for drawing conclusions on relative effectiveness of certolizumab pegol in subpopulation 2, as well as the consequential cost-effectiveness analysis in this subpopulation.

2.6 NMA results for certolizumab pegol in subpopulation 3 (biologic experienced)

On page 154 the report states: '*For the biologic experienced population, trial specific PASI response data were available for three active treatments (secukinumab, certolizumab pegol, ustekinumab) from three trials, but as for the other outcomes, the data from the certolizumab pegol trial were not included in the analysis as the biologic experienced population in the RAPID-PsA trial is not comparable with the other two trials (see 5.2.2). The data included in the NMA for the treatment experienced patients are presented in Table 54.*' Similarly on page 361 it was reported that: '*In comparison of the biologic experienced subgroup analyses, the results are not comparable between Assessment Group and UCB analyses as probabilities were estimated at two different time points (12 weeks and 24 weeks).*'

According to these statements, the NMA was not carried out by the Assessment Group with certolizumab pegol in subpopulation 3, and no data related to it was presented in the section 5. However, in the economic assessment section (i.e. Table 79, page 217) the Assessment Group presented PASI data for certolizumab pegol which do not match neither the crude response rates in RAPID-PsA trial, nor the trend or results of the UCB submitted meta-regression in this subpopulation (Table 3).

Table 3: PASI outcomes for biologic experienced patients during the RAPID-PsA study and derived from the UCB submitted NMA and the AG NMA

		Assessment Group NMA results	**RAPID-PsA study results**	**RAPID-PsA study results**	**UCB NMA results**
		12 weeks	12 weeks	24 weeks	24 weeks
Certolizumab pegol combined	PASI50	0.56	0.833	0.917	[redacted]
	PASI75	0.41	0.611	0.806	[redacted]
	PASI90	0.19	0.278	0.583	[redacted]

UCB requests full clarification on what data sources were used by the Assessment Group and how the results in Table 79 of the Assessment Group report were derived, as well as clarifying the process of imputation of PASI response for certolizumab pegol. Subsequently, this information should be clearly presented in both the evidence synthesis Section 5 and economic assessment Section 7 of the Assessment Group's report.

2.7 NMA data input for subpopulation 2 (biologic-naïve)

In the Assessment Group report, NMA data inputs during the Assessment Group's analysis for subpopulation 2 (i.e. biologic-naïve) are inconsistent between the statements and tables for some trials, and lack transparency for the others.

For example on page 138, it was stated that PSUMMIT2 full population data for '*ustekinumab 24 weeks were included in the analysis and assumed equivalent to outcomes at 12 weeks'*. However, the data presented in Table 40 of the Assessment Group's report were clearly the biologic-naïve data at week 24.

Further, data from the PALACE trials of apremilast also included patients for both subpopulation 2 and 3, which were not noted in the section. On the other hand, PALACE 1 and 3 did report ACR20 data on subpopulation 2 separately, which would be more adequate for the ACR multinomial NMA. Similarly for secukinumab, subpopulation 2 data are publicly available for ACR from both the FUTURE1 and FUTURE 2 trials at week 24.

UCB suggests that it would be more accurate to use the week 12 data available in the corresponding NMA, rather than proxy from week 24, at least for FUTURE 2, and that the source data is clearly presented in the Assessment Group report.

2.8 Assumptions on ustekinumab evidence at week 12 in subpopulation 2

On page 308, the Assessment Group provide their rationale for using ustekinumab 45mg week 24 data as proxy for week 12 data in subpopulation 2, stating that '*we used the 24 week PSUMMIT data for the analyses of PsARC and HAQ, on the assumption that they fairly reflected the 12 week results*'. To justify this assumption, the Assessment Group referred to ustekinumab data provided through the YODA project (Table 110 of the Assessment Group report). The Assessment Group notes that all other analyses use week 12 data.

UCB would like to note that in both PSUMMIT trials of ustekinumab, when examining data on all enrolled patients in the trial (i.e. both biologic-naïve and experienced), the similarity of PsARC responses between week 12 and 24 is only valid for the active arm response, but not for the placebo response hence is also not true for the relative efficacy (see Table 4 below). Specifically, the placebo creep is much more prominent in biologic-naïve patients. Note that the placebo arm response from the YODA project was not presented in the Assessment Group report. This challenges the validity of using week 24 data mix with subpopulation 2 and 3 data as proxy for week 12 data of subpopulation 2.

Table 4: PSUMMIT2 study: PsARC response at 24 weeks (%)

	Subpopulation 2 (biologic naïve)	**Subpopulation 3 (biologic experienced)**
Placebo	38.1	25.8
Ustekinumab 45mg	55.8	55.0

UCB requests that placebo response data accessed through the YODA project should be jointly presented with the active arm response in the Assessment Group report, in order to justify their assumption for using Week 24 ustekinumab 45mg data as proxy for Week 12 response. At present the Assessment Group assumption is unverifiable.

2.9 Inaccurate statements regarding similarity of week 12 and week 24 data for certolizumab pegol

On page 308 the Assessment Group states: *'The data from YODA showed that results for the PsARC and HAQ outcomes were very similar at 12 and 24 weeks in both PSUMMIT trials … A similar pattern of results (when comparing 12 and 24 weeks) can be seen in the RAPID-PsA trial, but is less evident in the secukinumab FUTURE 2 trial.'*

Table 110 of the Assessment Group's report presented week 12 and 24 full population data for trials of secukinumab, certolizumab pegol and ustekinumab, based on a mix of subpopulation 2 and 3 data. The text above this table displayed a similarity of data when comparing week 12 and week 24. UCB notes that the conclusion is not accurate for certolizumab pegol and does not reflect the response rates cited in Table 110. Moreover, it is not clear from the Assessment Group report how this assumption was used in their cost-effectiveness model.

UCB would like to note that data from RAPID-PsA (UCB submission, section 4.7) does not suggest that week 12 and 24 data are similar for certolizumab pegol, and that a further improvement is seen between weeks 12 and 24.

UCB requests that the Assessment Group removes the statement regarding similarity between Week 12 and 24 data in RAPID-PsA trial, as it does not accurately reflect the clinical evidence for certolizumab pegol.

2.10 Incorrect conclusions for NMA conducted and presented in the report

- There are several instances where the conclusions drawn by the Assessment Group do not match the presented results. For example, on page 153 of the report it is reported that '*The probabilities for certolizumab pegol changed between the models, but in both it appears to be less efficacious than all other treatments excepting apremilast and etanercept in achieving PASI responses*'. This incorrect conclusion was also repeated on Page 161 of their report in the summary of findings of relative efficacy from the NMA.

The placebo-response controlled results show that certolizumab pegol is similar to adalimumab and also more efficacious than golimumab and ustekinumab, as measured by the median point estimates in Table 53, of the Assessment Group report.

UCB thus request that the conclusions made by the Assessment Group are revised throughout the report, to accurately reflect the results reported.

- The conclusion of the Assessment Group NMA results should also take into consideration the minimally important clinical difference (MCID). The language to describe differences in HAQ efficacy, for instance, in section 5.6 (page 161), is "…*The median HAQ change was highest with infliximab and etanercept, followed by secukinumab 300 mg, but secukinumab 150 mg and certolizumab pegol were worse than all treatments except for apremilast*." The difference of HAQ changes (median) between PsARC responders and non-responders was -0.35 for certolizumab pegol, -0.37 for golimumab, -0.37 for adalimumab, and -0.39 for ustekinumab. While it is technically true that -0.35 is numerically lower than -0.39, UCB feels that when a reported difference is less than 20% of the decided MCID (0.35 for HAQ), and credible intervals are not just overlapping, but widely overlapping, use of the word 'worse' implies a conclusion that is not supported by the data.

UCB therefore request that references to a particular treatment being 'worse' than another be removed unless the difference exceeds the MCID, or at least a meaningful fraction of the MCID throughout the document when applicable.

2.11 Irrelevance of inclusion of apremilast and ustekinumab in the interpretation of results for subpopulation 2

On page 33 of their report, the Assessment Group list apremilast among the overall group of treatments of interest. Additionally the Assessment Group also include comparisons with ustekinumab when interpreting results for subpopulation 2. For example on page 252, it is stated that *'…[in biologic naïve patients]….There was though some uncertainty regarding the relative effectiveness of secukinumab and certolizumab pegol when compared with each other and with all other biologics: they had fairly similar effectiveness when compared with the other anti-TNFs, though were possibly slightly more effective than ustekinumab*'.

Apremilast, as noted by the Assessment Group on page 46, is currently not recommended by NICE for the treatment of psoriatic arthritis. Moreover, ustekinumab is only recommended in patients who have had at least one TNF inhibitor, or in patients for whom TNF inhibitors would be contraindicated. NICE guidance states: '*Ustekinumab is recommended as an option, alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only when:*[21]

- *treatment with TNF-alpha inhibitors is contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis)*
- *the person has had treatment with 1 or more TNF-alpha inhibitors*.

Furthermore, in line with the NICE final scope of the present MTA, ustekinumab is only considered a comparator in subpopulation 3. Apremilast and ustekinumab trials were included in the NMA submitted by UCB to help the estimate of difference in placebo rates. The network has one common comparator (i.e. star shape via placebo) with or without apremilast and ustekinumab in the NMA would have minimum impact on the unadjusted NMA. However, it would be relevant and important data for the evaluation of placebo creep. As they are not recommended as relevant comparator by NICE, UCB has excluded them from NMA results interpretation.

UCB thus requests that the same approach is undertaken by the Assessment Group when interpreting the NMA results, which should focus only on the comparison against recommended comparators as per the final scope of the MTA.

3 Clarification of the evidence of certolizumab pegol and UCB's original submission

3.1 Additional benefits following treatment with certolizumab pegol

Overall, UCB note that the Assessment Group's report does not take into account the full spectrum of clinical evidence that is available for certolizumab pegol across all symptoms in PsA. As outlined in Section 4.5 of its report, the Assessment Group describes the short-term efficacy of certolizumab pegol in the three subpopulations in terms of PsARC, ACR 20/50/70 and PASI responses in addition to the HAQ-DI change from baseline.

UCB wishes to reiterate that the RAPID-PsA study results demonstrated that certolizumab pegol is an effective treatment for the full breadth of disease manifestations, signs and symptoms of active PsA,

regardless of prior treatments, evidence which was presented extensively in the UCB submission. In the overall population, both certolizumab pegol maintenance regimens (i.e. 200mg every two weeks and 400mg every 4 weeks) provided significantly higher and rapid improvement in the signs and symptoms of disease, across the spectrum of joint, physical functioning, skin and extra-articular disease manifestations, compared with placebo. Patients treated with both regimens also reported significant and rapid improvement in a broad spectrum of patient-relevant outcomes (including pain, fatigue and health-related quality of life) and also greater improvements in work and household productivity versus placebo.

UCB therefore requests that the Assessment Group supplements its report with these data. Moreover, it should be acknowledged that the data provided in UCB's submission provide a thorough analysis of the efficacy of certolizumab pegol across the full manifestation of disease in line with a recent working group report from GRAPPA that outlined the core set of outcomes to be assessed in PsA studies.[22]

3.2 Definition of subpopulation 2

As described on page 46 of the Assessment Group's report, subpopulation 2 of its analysis refers to patients whose disease has inadequately responded to ≥2 DMARDs. UCB wishes to clarify that in the UCB submission (Section 4.2.3) the corresponding subpopulation 2 comprised all patients who were TNF inhibitor naïve (i.e. received ≥1 DMARD) and was labelled as such to accurately reflect the evidence supporting it. This approach was taken to ensure consistency with the published evidence for the comparators, used in the indirect comparisons submitted by UCB, as a systematic review of the literature indicated that few studies reported the number of prior DMARDs consistently. (detailed rationale is provided in the UCB submission, Section 4.2.3). For completeness, and in line with NICE scope, results for selected outcomes for the subpopulation of patients with inadequate response to ≥2 DMARDs from RAPID-PsA were provided and the conclusions of the CZP efficacy were similar to the UCB defined subpopulation 2. Furthermore, UCB would like to note that the although these are labelled differently, subpopulation 2 in both the Assessment Group's report and the UCB submission are comparable in that they relate to patients who were TNF inhibitor naïve.

3.3 Clarification of the UCB modelling approach

3.3.1 UCB model includes patients with all types of PASI severity

On page 188 of the Assessment Group's report, it is stated that *'the differences in the mean PASI scores appear an important source of variation between the two submissions. By assuming a mean PASI of >10, the UCB base case results relate to an 'average' PsA patient with concomitant moderate to severe psoriasis (i.e. ≥3% of BSA and PASI >10)*.'

UCB would like to note that the model submitted was designed to represent patients with the whole range of PASI severity and that the mean PASI score >10 at baseline quoted by the Assessment group is not a minimum. Thus, the UCB modelling approach reflects the average PsA patient group overall and not just an 'average' moderate-to-severe psoriasis patient group, as incorrectly implies the Assessment Group.

As indicated in the UCB submission, PASI at baseline was further varied deterministically in the range provided in Table 72, section 5.7.3 of the UCB submission.

It is thus inappropriate and inaccurate for the Assessment Group to conclude that the UCB submitted base case results relate to a PsA population with concomitant moderate to severe psoriasis and compare its moderate-severe subgroup with the wider patient group that is presented in the UCB submission. UCB requests that the Assessment Group amend their report to accurately reflect the

fact that the UCB cost effectiveness model accounts for the full range of psoriasis severity as per the UCB submission.

3.3.2 Validity and robustness of the UCB cost-effectiveness analysis

The Assessment Group, in its report, has commented on the robustness of the UCB cost-effectiveness analysis. In one instance this was linked to the absence of a comparison with BSC; however, as described above UCB would question this approach on the grounds of best clinical practice (Response 2.2.1). Moreover, on page 201 of its report, the Assessment Group raises the issue of uncertainty of the cost-effectiveness of certolizumab pegol: '*Given the different approaches and assumptions employed by the companies, there remains considerable uncertainty regarding both the cost-effectiveness of SEC and CZP in each of the subpopulations and potential implications for the NHS. These differences make it challenging to draw robust conclusions from the current submissions*'.

UCB would like highlight that any uncertainty around model parameters was tested thoroughly extensive deterministic and probabilistic sensitivity analyses (DSA and PSA, respectively). The DSA showed that the UCB model results were robust when varying parameters' estimates with outcomes being sensitive to shorter time horizons, discount rates for health and cost outcomes, and to the inclusion of indirect costs, which lowered ICERs. Similarly, the PSA showed that in subpopulation 1, certolizumab pegol has 100% probability of being cost-effective at willingness-to-pay thresholds above £24,000 per QALY gained. In subpopulation 2, the PSA indicated that certolizumab pegol has the highest probability of being the most cost-effective alternative at any willingness-pay threshold. For subpopulation 3, the PSA indicated that certolizumab pegol has the highest probability of being the most cost-effective alternative among available treatments at willingness-to-pay thresholds above £10,000 per QALY gained.

In response to a comment made by the Assessment Group in its quality assessment checklist (page 390) which stated that '*reporting the incremental results was not performed properly*', UCB presents the corrected tables for subpopulation 2 and 3 below, based on the Tables 74, 75 and 76 from the UCB submission, where only the last column has been corrected. The base case results indicate that certolizumab pegol is a highly cost-effective treatment option versus the comparators considered, across all three subpopulations.

Table 5: Base case full incremental cost-effectiveness results in subpopulation 2 (patients who are TNF inhibitor naïve)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER versus next best option (QALYs)
CZP	[redacted]	[redacted]	[redacted]	[redacted]	-
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
SEC 150mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
IFX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 6: Base case full incremental cost-effectiveness results in subpopulation 3 (Patients who have prior TNF inhibitor exposure)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER versus next best option (QALYs)
Mix	[redacted]	[redacted]	[redacted]	-	-
CZP	[redacted]	[redacted]	[redacted]	3.98	£8,894
UST	[redacted]	[redacted]	[redacted]	-2.18	Dominated
SEC 300mg	[redacted]	[redacted]	[redacted]	0.34	Dominated

3.3.3 Clarification of assumptions made in the UCB cost-effectiveness model

3.3.3.1 Treatment discontinuation

On page 228 of its report, the Assessment Group implies that the assumption made in the UCB model that patients are not permitted to withdraw from treatment after 4 years is '*extreme'*. UCB would like to clarify that this assumption was necessary due to the model structure using trajectories that allowed incorporation of treatment sequences while maintaining integrity as a cohort model in Excel. As stated in Section 5.2.2 of the UCB submission, treatment switches are assumed to occur over the first four years of follow up only because of the paucity of data beyond that point.[23] This duration was chosen based on the data sources used in the evidence synthesis. The longest data used in the evidence synthesis was 48 months while only two studies had data for 5 years. Thus in the UCB model, after 4 years, patients are assumed to remain on treatment for the rest of the model time horizon.

UCB would like the Assessment Group to amend its wording around this assumption from 'extreme' to 'strong' assumption.

3.3.3.2 Secukinumab cost and efficacy weightings in subpopulation 2

As the Assessment Group has noted on page 186 of its report, for secukinumab in subpopulation 2, only the 150mg and 300mg dose costs were weighted in the UCB model and not the efficacy for secukinumab 150mg. This was primarily due to a lack of efficacy data that was available in the public domain for this subpopulation.

As outlined in further detail in the UCB submission (Section 5.5.1.1) secukinumab is recommended at a dose of 300mg for TNF inhibitor naïve/experienced patients with moderate-severe plaque psoriasis. To account for the prevalence of moderate-severe plaque psoriasis in subpopulation 2 (i.e. TNF inhibitor naïve), a weighted average of the acquisition cost for the 150mg and 300mg doses were used to cost secukinumab. In the F2306 study of secukinumab, 53.7% of patients on a 150mg dose had PASI >10 at baseline and were assumed to incur the cost. In the base case analysis for subpopulation 2, the acquisition cost for secukinumab was calculated as 0.463 x unit cost of 150mg + 0.537% x unit cost of 300mg. The efficacy of secukinumab was not weighted due to the lack of publicly available data as mentioned above. However, for the results to change from certolizumab pegol dominating secukinumab to secukinumab being cost-effective against certolizumab pegol, a weighted average of the secukinumab efficacy of the two doses would need to lead to an additional 1.08 QALYs as opposed to secukinumab 150mg, which is not a realistic possibility. Please note, a scenario analysis using no secukinumab price weight was presented in the executable model, albeit not in the full submission.

3.4 Factual inaccuracies

AG report page	Content from Assessment Group (AG) report	UCB comment
93	Table 24 : Incorrect rounding of PASI50 score in biologic naïve, certolizumab pegol combined group	As per the UCB submission (Table 24) the value should be 69% (submission shows 68.5%)
131	1st para states: 'In the open label extension study, 393 patients….'	The text in the AG report implies that there is a separate open label extension study. RAPID-PsA is one single study, placebo controlled and double blind until Week 24, then dose –blind until Week 48 and open label until Week 216. UCB request revision of the text in the AG report to accurately reflect the current clinical study and its design and thus suggest that the text should read (revision in bold): 'In the open label extension **phase of the RAPID-PsA study**…'
153	"*the probabilities for certolizumab changed between the models, but in both it appears to be less efficacious than all other treatments excepting apremilast and etanercept in achieving PASI responses*."	The conclusion is not correct for the results of model G2, in which, the probability for certolizumab pegol achieving PASI50, PASI75 and PASI90 is very similar to adalimumab, and better than golimumab, ustekinumab, apremilast and etanercept.
176	Table 65 - Comparators	In the biologic naïve population, the UCB model does not include the SoC as a comparator. The mention of "and SoC" should be removed.
176	Table 65 – Model Structure	The UCB submitted cohort Markov model has two periods, not three. The two periods are 1) Short-term, in which the initial response to treatment is determined (12 or 24 weeks depending on the treatment 2) Long term period (50 years). What AG refers to as the three periods is the stages of HAQ progression, not the model structure. The text in table 65 should be revised accordingly.
176	Table 65 – Model Structure	PsARC is used to determine response in the model base case, but PASI response is also considered to account for the PASI improvement.
176	Table 65 – Model Structure	The sentence "*For patients on treatment, HAQ and PASI scores remain constan*t" relates to biologics and should read "*For patients on **biologic** treatment, HAQ and PASI scores remain constant*." HAQ scores of patients on SoC/mix increase at a rate of 0.018 per 3 months.
180	The AG report states that in the UCB base case model, response is defined in terms of PsARC alone.	PsARC is used to determine response in the model base case, but PASI response is also considered to account for the PASI improvement.
180	'*This stratification is not assumed in the base case to alter the decision to continue treatment but allows alternative cost and utility assumptions to be applied according to PsARC response status'*	In the UCB sensitivity analysis, a scenario where the response to treatment was assessed with PsARC or PASI75 was tested.
180	The AG report states that in the UCB model, HAQ change for certolizumab pegol is based on the week 4 data	As per the UCB submission, in the model base case, it is the **maximum** HAQ change that is achieved at week 4. The text in the AG report should be revised accordingly.
181	The AG report states that it is also assumed that there is continued	As per the UCB submission, HAQ improvement up to week 36 is also modelled for the scenario analysis of

AG report page	Content from Assessment Group (AG) report	UCB comment
	improvement in HAQ up to week 36 post initial response.	the 12 week response time.
186	*"The proportion used as the basis for weighting is referenced to an academic in confidence study and no further details are reported"*	This was taken from study F2306. The 53.7% weighting value can be found at the bottom of Table 6 on page 30 in the following document: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003729/WC500199573.pdf
190	"*The UCB model assumes an annual discontinuation rate of 16.5% for all biologic treatments. This figure is consistent with the assumption and data used to inform the York model. A further assumption was also included in the UCB model such that if a patient continued on a therapy for at least 48 months there would be no risk of longer term withdrawal beyond this time point. This assumption was justified due to the lack of data reporting long term withdrawal rates."*	The 16.5% is the base case value. The values for the upper and lower confidence interval around the discontinuation rate (10.3% - 22.7%) were tested in the sensitivity analysis.
323 342	"*A key differences between the NMAs presented concerns the trials included in each analysis. Only the AG NMA for biologic naïve subgroup includes all comparators and all trials. The UCB analysis for biologic naïve subgroup includes all treatments but misses only some apremilast trials."* "*The UCB analysis for biologic naïve subgroup includes all treatments, but misses only some apremilast trials."*	The AG conclusion on UCB analysis is incorrect. Apremilast trials are included in the UCB NMA to help estimate the difference in placebo rates. The network has one common comparator (i.e., star shape via placebo), with or without apremilast and ustekinumab, in the NMA and this would have minimum impact on the unadjusted NMA. However, it would be relevant and important data for the evaluation of placebo creep. As they are not recommended as relevant comparator by NICE, UCB has excluded them from the NMA results presentation and interpretation. Table 36 (page 136) in UCB submission notes the studies included in the NMA, which include PALACE1 and PALACE2 (apremilast trials).
323	"*The evidence synthesis is not clear in UCB's main submission for biologic experienced subgroup, and did not report results for this subgroup. …. Therefore, it was not plausible to compare AG NMA with CS for the biologic experienced subgroup."*	This statement is incorrect. In the UCB submission, in table 36 on page 136, it clearly notes the NMA data input for subpopulation 3 (i.e., biologic experienced subgroup) included the data from FUTURE1, PSUMMIT2 and Rapid-PsA. The results are summarized on page 140, and presented in table 42 to table 44. Since both AG NMA and UCB NMA employ regular Bayesian approach without adjustments, and the network has one common comparator (i.e. stat shape via placebo), there are sufficient information to facilitate the comparison of evidence synthesis provided by UCB and produced by AG NMA.
323	*"Another key difference relates to the primary timepoint analysed: most NMA used 12 week, but the UCB analysis used 24 weeks as their primary time point, although it did include a 12 week sensitivity analysis."*	This is an incorrect statement. The UCB submission document has included NMA results for data at both 12 weeks and 24 weeks. The summary and presentation include the NMA results in parallel for both timepoints. Table 35 on page 135 clearly states both timepoints were considered as base-case analyses. Sensitivity analyses is for those studies that evaluate outcomes at times other than 12 weeks (i.e., 14 or 16 weeks).
324	Table 130 *("Odds ratios reported for the biologic naïve subpopulation; but results were not reported for the biologic*	This is inaccurate summary. ACR responses at 24 weeks, including ACR20, ACR50 and ACR70 results via univariate Bayesian NMA, are presented as odds

AG report page	Content from Assessment Group (AG) report	UCB comment
	experienced ")	ratios in table 39 on the page 96 of the appendices of the UCB submission.
324	Table 130 *"Primary analysis at 24 weeks (by treatments), sensitivity analysis was conducted at 12 weeks including data on 12 weeks or closest time point after 12 weeks."*	This is an incorrect statement. The UCB submission has included NMA results for data at both 12 weeks and 24 weeks. The summary and presentation include the NMA results in parallel for both timepoints. Table 35 on page 135 clearly states both timepoints were considered as base-case analyses. Sensitivity analyses for those studies evaluate outcomes at times other than 12 weeks (i.e., 14 or 16 weeks).
324	Table 130 Data regarding subpopulation 2 included in the NMA *"ADEPT, Genovese 2007, GO-REVEAL, IMPACT, IMPACT 2, Mease 2000, Mease 2004, RAPID-PsA (12-16 weeks analysis)"*	This is not an accurate summary. The UCB NMA includes ADEPT Genovese 2007, GO-REVEAL, IMPACT, IMPACT 2, Mease 2000, Mease 2004, PALACE 1, PALACE 3, PSUMMIT 1, SPIRIT-P1, RAPID-PsA
324	Table 130 Data regarding subpopulation 3 included in the NMA: study used in the analyses and drugs evaluated *"not clear"*	Table 36 (page 136) and figure 41 (page 129) in the UCB submission clearly note the studies contributed data from patients with prior TNF exposure to the NMA.
325 342	Table 131, *"Fixed effects on studies (for both biologic naïve and experienced subpopulation)"* The Assessment Group reports that AG and Rodgers et al. consider fixed effects on studies, whereas "*UCB and Novartis consider random effect on studies for biologic naïve subgroup and fixed effect on studies for biologic experienced subgroup analysis*."	This is an incorrect statement. Table 35 (page 135) in the UCB submission clearly notes both random- and fixed-effect model NMAs were conducted for subpopulation 2, for both probit and univariate Bayesian NMAs.
325	Table 131 *"For biologic naïve subpopulation: treatment effects are exchangeable within classes (anti-TNFs=ADA, IFX, ETN, GOL)"*	This is an inaccurate statement. The treatments included in the NMA include agents within anti-TNFs as well as agents from other classes (i.e., ustekinumab and apremilast). For subpopulation 2, the statement on page 132 of the UCB submission clarifies the approach . In the unadjusted NMA, treatments were assumed to be independent of each other for subpopulation 2.
325	Table 131 UCB NMA model "*Adjusted for biologic naïve subpopulation, but unadjusted biologic experienced subpopulation*" Assessment Group NMA model "*Independent treatment effects models was unadjusted; but analysis assuming exchangeable class effects model was adjusted for the placebo response*"	Both the UCB and AG NMA included adjusted and unadjusted models for subpopulation 2, and are not able to have adjusted models due to sparse data. The statement in table 131 could mislead readers on the real difference.
333	Table 139 For median conditional on response HAQ change, timepoint considered in UCB NMA "*at 24 week"*	This is an incorrect statement. In Table 35 (page 135) of UCB submission, the analyses for HAQ-DI change by PsARC response include both 12 and 24 weeks.
343	For PASI response, Table 147 NMA Model of UCB "*conditional multinomial probit model"* Results report *"probability of PASI response in three categories 50/75/90"* *Studies used in the analyses for subpopulation 2 "… (12-16 weeks*	It is an incorrect statement. UCB submission document, Table 35 (page 135), and statements on page 132 clearly note that three different NMA models are employed for the analyses for PASI response for both 12 and 24 weeks. Results of those analyses include both probability and odds ratios, and presented in table 39, 40 (page 143 and 144) in the submission document and in table 41 (page 98)

AG report page	Content from Assessment Group (AG) report	UCB comment
	analysis)"	in the appendices for subpopulation 2, in table 43 (page 147) of the UCB submission for subpopulation 3.
344	For PASI response, Table 148 NMA Model of UCB "*conditional multinomial probit model"* Fixed or random effects between studies *"Random effect on studies for biologic naïve subpopulation analysis and fixed effect for biologic experienced subpopulation analysis"* Model adjusted for the placebo response *"unadjusted"*	This is an incorrect statement. Three difference NMA models are employed for the PASI response at both 12 and 24 weeks for subpopulation 2, including adjusted and unadjusted for placebo effect. Again, the table 35 (page 135) in the UCB submission clearly notes both random and fixed-effect model NMA conducted for subpopulation 2, for both probit and univariate Bayesian NMA
344	The Assessment group report states: '*In UCB submission, the estimated probabilities are much lower for etanercept compared to the result of previous and current assessment. The difference is largely because UCB used different PASI50 response data in the analysis.*'	The NMA data input for one of etanercept study are collected from graph presented in the Mease 2000 (Lancet, trial noted as University of Washington in UCB submission document). The difference in data is driven by the lack of direct reporting of proportion patients who achieved PASI response. Specifically, the figure 3 in the publication indicates an approximate little less than 40% patients treated with etanercept had PASI50 at week 12 in 19 patients who had concomitant psoriasis. The round up or down process along with small sample size lead to the difference of estimate on probability of etanercept in the NMA.
346	The Assessment Group states that the PASI results are not comparable between the Assessment Group and UCB analyses as probabilities were estimated at two different time points (12 weeks and 24 weeks)	Week 12 data was also submitted by UCB
358	Table 161 states UCB used a conditional multinomial probit model	The binary/binomial model was also submitted for ACR
358	For ACR response, Table 161 NMA Model of UCB "*conditional multinomial probit model"* Results report *"Probability of ACR response in three categories 20/50/70 for experienced subpopulation, but did not present probabilities for biologic naïve subpopulation"* Drug evaluated in subpopulation 2 "*Adalimumab 40mg; apremilast 20mg and 30mg; certolizumab pegol; etanercept 25mg; golimumab 50mg; infliximab: 5mg mg/kg*"	It is an incorrect statement. Table 35 (page 135), and statements on page 132 of the UCB submission clearly note that three different NMA models are employed for the analyses for ACR response for both 12 and 24 weeks. Results of those analyses include both probability and odds ratios, and presented in table 37 (page 141) in the submission document and in table 38 (page 95) in the appendices for subpopulation 2, in table 42 (page 146) of the submission document, and in table 39 (page 96) in the appendices for subpopulation 3. Treatment evaluated in the subpopulation also include secukinumab for analyses of 24 week data, which is not included for 12 week data as such data are not available in public domain.
358	For ACR response, Table 162 NMA Model of UCB "*conditional multinomial probit model"* Fixed or random effects between studies *"Random effect on studies for biologic naïve subpopulation analysis and fixed effect for biologic experienced subpopulation analysis"* Baselines "*common effect model was used to estimate baseline"*	This is an incorrect statement. Three difference NMA models are employed for the ACR response at both 12 and 24 weeks for subpopulation 2, including adjusted and unadjusted for placebo effect. Again, the table 35 (page 135) in the UCB submission clearly notes both random and fixed-effect model NMA conducted for subpopulation 2, for both probit and univariate Bayesian NMA

AG report page	Content from Assessment Group (AG) report	UCB comment
	Model adjusted for the placebo response *"unadjusted"*	
359	Table 162 states UCB used a conditional multinomial probit model	The binary/binomial model was also submitted for ACR
359	Table 162 states UCB used an unadjusted model for placebo response	An adjusted model was also submitted by UCB
389	Checklist for UCB model – Item 2. Alternatives compared In the one prior DMARD population	We have included certolizumab pegol and standard of care in subpopulation 1 only, in the absence of published evidence for secukinumab in the first subpopulation
332 333	For median conditional on response HAQ change, the Assessment Group states "*detailed information about evidence synthesis was not provided."* Table 139 Key assumption for Model "*not clear from the submission"*	This is an incorrect statement. On page 133 of 289 of UCB submission document, the source of the data is stated, with Rodger 2010 HTA report cited as reference #136. The analyses method is noted on page 132 of 289 in the submission document. Results were presented in cost effectiveness section 5. "*Specifically to support the economic model development, meta-analyses for HAQ-DI change in PsARC responders and non-responders were conducted with data extracted from a formal HTA report, and assumed an additive effect for the effect of treatment in treatment responders versus that for placebo responders, as has been done in the HTA report. Specific results are presented in Section 5.*"

3.5 Non-confidential information incorrectly redacted by the Assessment Group

Page	Data incorrectly redacted
66	Baseline population characteristics of RAPID-PsA
150	Summary of trial specific data in biologic naïve subpopulation for PASI response outcome
195	Base case results for subpopulation 1 (Biologic naïve - 1 prior DMARD) – UCB submission (Incremental costs and Incremental QALYs only)

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Comments provided to Healthcare Improvement Scotland by:

[redacted]

Topic: Certolizumab pegol and secukinumab for active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs.

Assessment Report:

I am not aware of any relevant data that has been omitted from the assessment. It is noted that the evidence base consists largely of short term studies (albeit of generally high quality), with placebo as comparator, so comparative efficacy will inevitably be uncertain. The increase in placebo responses seen in more recent trials is an interesting observation that adds to the uncertainty re comparative efficacy.

The updated "York" model appears to allow greater investigation of positioning of therapies and includes subsequent biologics use and this is helpful. The assessment of the sub populations is informative, albeit limited by relatively small numbers of study patients. Population 1 (biologic naive after one DMARD) would represent a new positioning with respect to existing HTA advice and UK specialist society positioning (if it is suggested that Certolizumab and Secukinumab are cost effective v BSC in this group, it would anticipate a change in practice). Population 4 (unsuitable for anti TNFs) will represent very small numbers, though Secukinumab and Ustekinumab would seem reasonable comparators if one assumes that such a population exists.

It appears that the acquisition costs for existing biologics assume use of biosimilar Infliximab but originator product for Etanercept (Enbrel). I assume that this reflects the timing of this appraisal, although the lower cost of biosimilar Etanercept would now be relevant in clinical practice (particularly in biologic naive population)"

15 September 2016

Celgene Comments on Assessment Group report for CZP and SEC for PsA: NICE MTA [ID579]

Celgene welcomes the opportunity to comment on the Assessment Group (AG) report for certolizumab pegol (CZP) and secukinumab (SEC) for active PsA [ID579].

The York AG model considers three different subpopulations: subpopulation 1 is biologic-naïve patients who have received one prior DMARD; subpopulation 2 is biologic-naïve patients who have received two or more prior DMARDs, and subpopulation 3 is biologic-experienced patients or those contraindicated for DMARDs. The AG conclude that CZP and SEC are likely to be considered cost-effective in subpopulation 1 when comparing each agent versus Best Supportive Care (BSC).

According to NICE guidance (TA199,[1] TA220[2]), the NICE commissioning algorithm for biologic drugs for the treatment of psoriatic arthritis,[3] and the British Society for Rheumatology 2012 guidelines,[4] the biologic agents adalimumab, etanercept, infliximab and golimumab are recommended in patients who have not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination. Accordingly, if the cost-effectiveness of CZP and SEC is to be considered in subpopulation 1, Celgene considers that the appropriate comparator, i.e. a second non-biologic DMARD, should be used to reflect current NHS practice. Celgene notes that the marketing authorisation for CZP and SEC is aligned to that of other biologics licensed for psoriatic arthritis and considers that a similar approach to evaluating their use on the NHS should be taken to ensure consistency with previous NICE appraisals (TA199, TA220 and TA340).
Celgene notes that the York AG makes similar reference when discussing limitations of their analyses (Assessment Report p.248-9):

"…subpopulation 1 only includes the comparators CZP, SEC and BSC, as per the NICE scope. It is recognised however, that there may be other comparators relevant for this subpopulation. In particular, patients who have only received 1 prior DMARD may be eligible to receive a 2nd DMARD. It was not possible within the scope of this appraisal to assess the evidence for DMARDs and therefore include this as a formal comparator in this subpopulation. The extremely low cost of DMARDs (7.5 mg of MTX is £0.30) make it likely that these would be considered cost-effective in this population. In addition, the licenses for the other biologic treatments (ETN, INF, ADA and GOL) do not preclude their use in the 1DMARD population, and therefore these could be considered to be relevant comparators in subpopulation 1. Indeed, this subpopulation appears to not have been considered in previously published models largely because the scope of these models have closely followed existing BSR guidelines and criteria for commencing biologic treatments (i.e. that the PsA has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination) as opposed to reflecting important differences in the licenses of existing biologic treatments and those for SEC and CZP."

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Merck, Sharp & Dohme Limited Comments on the Multiple Technology Appraisal (MTA) of Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying antirheumatic drugs [ID579]

Merck, Sharp & Dohme Limited welcomes the opportunity to comment on the MTA of Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs. We have identified eight issues in the technical report and would like to draw NICE's attention to these points. Please see the table below for a summary of the issues identified.

Section	Page	Comment
4.3 Characteristics of the RCTs included in the systematic review of short-term efficacy	57	It is incorrectly stated in Table 2 that the SPC for Infliximab does not report the anticipated time to response. Section 5.1 of the SmPc states that "In IMPACT and IMPACT 2, clinical responses were observed as early as week 2".
6.2.3.3 Withdrawal from treatment and the natural history of PsA	190	In table 68 (Discontinuation rates applied in sensitivity analysis [Novartis]) golimumab has a very high discontinuation rates in years one and two at 29.5%. This is inconsistent with the literature and unlikely to provide realistic result (Kavanaugh A, et al. (2012)). Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. Arthritis Rheum. 64(8):2504-17).
7.2.9.1 Treatment costs	221	The costs for Infliximab presented in table 82 are incorrect. The total cost of £18,902 suggests that 9.5 administrations were assumed. The first year cost should assume 8.5 administrations (week 0, week 2, week 6 and every 8 weeks) and 6.5 in subsequent years (every 8 weeks) (SmPc) giving respective costs of £16,832 (first year) and £12,872 (subsequent years).
7.2.9.1 Treatment costs	221	The costs for Golimumab presented in table 82 are incorrect. The annual cost of Golimumab is £9,156 (12 syringes @ £762.97 – MIMs list price) and not £9,733 as reported in table 82.
7.2.9.2 Drug acquisition	224	There is a typographical error in table 86. It should be "Inflectra & Remsima" and not "Inflextra/Remaima".
7.2.9.2 Drug acquisition	224	It should be noted in table 82 that a patient access scheme is in place to provide the 100mg syringe of Golimumab for the same price as the 50 mg (£762.97 – list price).
7.2.9.2 Drug acquisition	224	Can NICE confirm that the incorrect unit cost of £1,525.94 for a 100mg syringe of Golimumab was not used in the analysis?
Throughout	365 - 378	A capital 'R' should be used when referring to Remicade as it is a brand name.

AG responses to commentator feedback

Response to specific Novartis comments

1. Class effect in NMA

In our analyses we explored two within-class assumptions: assuming treatments within a class to have equal effectiveness and, alternatively, that treatments within a class have similar (exchangeable) effectiveness. Our analyses therefore reflected any differences in treatment effect within a class.

3. Withdrawal rate of secukinumab

The Novartis company evidence submission reported the year 2 discontinuation rates incorrectly for secukinumab 150 mg ([redacted]) and 300 mg ([redacted]). Novartis requests that the AG reassess the withdrawal scenario 1 analyses (withdrawal rate for secukinumab assumed to be 50% of the base case value from year 2), on the basis of these updated rates.

The AG utilise the withdrawal rate from Rodgers et al, 16.5%. In an exploratory analysis, the AG applied 50% reduction from the second year and onward, which is 8.25%. This analysis was to address Novartis findings about the reduction in the withdrawal rate in the second year. The AG did not apply the 50% discount to reflect SEC trials data specifically, rather this was to utilise the withdrawal rate assumed from Rodgers et al.

Clarifications and corrections

Minor clarifications and corrections

	Description	**Reference to the AG report**	**Clarification/correction**	**AG Response**
1	Description of mechanism of action of secukinumab as "being a monoclonal antibody which targets the interleukin 17A (IL-17A) receptor"	Page 44	This is factually incorrect as secukinumab binds directly to the IL-17A cytokine molecule itself and not to the IL-17A receptor.	Text changed to: "being a monoclonal antibody which targets the interleukin 17A (IL-17A) cytokine molecule"
2	Confidentiality marking of baseline tender joints count (TJC), swollen joints count (SJC) and HAQ in FUTURE 2	Table 4 on page 65	Confidentiality marking is not required as these are published data shown in McInnes *et al.* (2015)[6]	Not a factual inaccuracy – the McInnes data only relate to whole population, which have not been marked as confidential in the report.
3	According to the AG, the risk of bias in ERASURE and	Table 6 on page 75	The statistical handling of missing data was as follows:	Not a factual inaccuracy – this is unclear as there is no

	Description	Reference to the AG report	Clarification/correction	AG Response
	FIXTURE trials with respect to incomplete outcome data were unclear		• Last observation carried forward for HAQ outcomes in psoriasis patients with concomitant PsA • Non-responder imputation to Week 12 for PASI outcomes with multiple imputation thereafter These details are reported in the legends of Figures 2 and 3 in Gottlieb *et al.* (2015)[16]	CONSORT flow chart to evaluate the numbers of drop-outs and reasons for withdrawal for the PsA patients.
4	**Reporting inaccuracy:** PASI 75 response rate in FUTURE 2 for secukinumab 150 mg (Week 24)	Table 9 on page 82	**AG report**: 25/58 (43%) **To be corrected to**: 28/58 (48%), as reported in McInnes *et al.* (2015)[6] This may also impact on the relative response stated in Table 12 on page 84	Factual inaccuracy. This should read 28/58 (48%) Relative risk in Table 12 recalculated and changed to 2.97 (1.43 to 6.14)
5	**Reporting inaccuracy:** ACR20 response rate in FUTURE 2 for secukinumab 150 mg (Week 52)	Table 30 on page 104	**AG report**: 39/100 **To be corrected to**: 64/100, as reported in McInnes *et al.* (2015)[6]	Factual inaccuracy – Should read 64/100
6	**Reporting inaccuracy**: ACR50 response rate in FUTURE 2 for secukinumab 150 mg (Week 52)	Table 30 on page 104	**AG report**: 41/100 **To be corrected to**: 39/100, as reported in McInnes *et al.* (2015)[6]	Factual inaccuracy – Should read 39/100
7	**Reporting inaccuracy:** PASI 90 response rate in FUTURE 1 for secukinumab 150 mg (Week 52)	Table 31 on page 107	**AG report**: 60% **To be corrected to**: 59% due to rounding – 59.3% reported in Mease *et al.* (2015) supplementary information[17]	Factual inaccuracy – Should read 59%
8	**Reporting inaccuracy:** description of the enthesitis and	Table 31 on page 107	**AG report**: stated as the % resolution of enthesitis (and dactylitis)	Factual inaccuracy Should read 66% enthesitis

	Description	Reference to the AG report	Clarification/correction	AG Response
	dactylitis outcomes in FUTURE 1		**To be corrected to**: the % of patients with enthesitis (and dactylitis), as reported in Mease *et al.* (2015) supplementary information[17] *The numbers presented in the AG report are correct in relation to the % of patients with enthesitis (and dactylitis).* *To present data as the % resolution of symptoms:* • *The % of patients with enthesitis at baseline in FUTURE 1 in whom it has resolved at week 52 is 100-34.1=65.9%* • *The % of patients with dactylitis at baseline in FUTURE 1 in whom it has resolved at week 52 is 100-30.8=69.2%.*	69% dactylitis
9	Sample size number for radiographic progression in FUTURE 1 at Week 104 (observed data)	Page 107	The AG noted that: *"At 104 weeks 85% of patients treated with secukinumab 150mg had no radiographic progression - defined as a change in Sharp/van der Heijde score of ≤0.5 - between baseline and week 104. This result was based on the observed population; no further details were presented and the sample size was not stated'* The reference used for this is an abstract from American College of Rheumatology (ACR) congress 2015 and the AG is correct to point out that the number of X-ray completers is not stated in the abstract.[18] We would like to clarify that the abstract was also presented as a poster at that congress; the number of patients in the 150mg group with X-ray data at 104 weeks is **n=166** according to the poster.[18]	Not a factual inaccuracy, but the n=166 has been added to the report.
10	**Reporting inaccuracy:** the	Page 130	**AG report**: reports incidences (cases per 100 patient years) for	Factual inaccuracy Dose should read

	Description	Reference to the AG report	Clarification/correction	AG Response
	incidence of adverse events in FUTURE 2 for secukinumab 150 mg (up to Week 52)		secukinumab 300 mg rather than 150 mg • *Infection and infestation*: 79 (rounded from 78.7) • *Upper respiratory tract infection:* 18 (rounded from 17.9) • *Nasopharyngitis:* 14 (rounded from 13.5) • *Discontinuation due to adverse events:* 2% The text should be corrected to reflect that the data is for secukinumab 300mg. The data for secukinumab 150mg should be included as follows: • *Infection and infestation:* 87 (rounded from 86.7) • *Upper respiratory tract infection:* 18 (rounded from 17.6) • *Nasopharyngitis:* 12 (rounded from 12.3) • *Discontinuation due to adverse events:* 1% As reported in McInnes *et al.* (2015)[6]	300mg.

Response to MSD comment

Section 7.2.9.1 Treatment costs

The assessment group utilise a weight-base dose for INF, as shown in Table 1. The weight distribution is obtained from RAPID-PsA trials. While there is a slight difference in the number of administrations per a year between the AG and those from MSD, 8.75 vs 8.5 and 6.86 vs 6.5 for the first and subsequent years respectively, this does not affect the conclusions of the analysis.

Table 1 INF doses based on the weight distribution obtained from RAPID-PsA trials along with administration, initiation and monitoring costs

Patient weight (kg)	Vials	Dose (mg)	Weight distribution	Cost per dose (£)	First cycle	Subsequent cycle
20	1	100	0.0003	£0.1	Loading administrations	Loading administrations
40	2	200	0.0087	£7.3	3	-

60	3	300	0.0878	£110.5	After loading administrations	After loading administrations
80	4	400	0.3105	£521.2	0.61	1.71
100	5	500	0.3898	£817.8	Administration cost (£159 per session)	Administration cost (£159 per session)
120	6	600	0.1740	£438.1	£574	£273
140	7	700	0.0274	£80.5	Initiation cost	Monitoring cost
160	8	800	0.0015	£5.0	£166	£4.18
Total			1.0000	£1,980.5	£7,887	£3,672
Total annual cost for the first year					£18,902 assuming 8.75 administrations	
Total annual cost for the following years					£14,688 assuming 6.86 administrations	

The assessment group use £9,377 as annual costs for golimumab. This includes both the acquisition cost but also the administration for the first time, the initiation and the monitoring costs.

The Assessment group confirm that the PAS price was used in the analysis for Golimumab 100mg

AG responses to commentator feedback

Responses to UCB's general comments (Section 1 of UCB report response document)

1.1.1 Clinical efficacy of certolizumab pegol in patients with prior TNF inhibitor exposure (Subpopulation 3)

UCB stated that, referring to RAPID-PsA:"although excluding primary non-responders to a TNF inhibitor in the first 12 weeks, the study included primary non-responders who were assessed after week 12 (6.25%) as well as partial responders (7.5%) within this subpopulation indicating that the spectrum of patients included in the RAPID-PsA study reflects the broad expected patient population to be seen in clinical practice that have been exposed to a prior TNF inhibitor, and is thus a relevant evidence for subpopulation 3.."

We do not think it's likely that the prior anti-TNF population recruited into RAPID-PsA adequately reflects the spectrum of patients seen in clinical practice. NICE guidance says anti-TNFs should be stopped where there has not been an adequate (PsARC) response at 12 weeks (the time point when patients are assessed in clinical practice). An essential difference between the CZP (RAPID-PsA) and SEC (FUTURE 2) and UST (PSUMMIT 2) trials is that patients who were primary failures at 3 months/12 weeks (i.e. non-responders) on their previous anti-TNF were *excluded* from RAPID-PsA and *included* in FUTURE 2 and PSUMMIT 2.

These different eligibility criteria may well reflect:

- The differing proportions of recruited anti-TNF experienced patients: 35% in FUTURE 2 and 20% in RAPID-PsA. PSUMMIT 2 recruited 180 (58%) anti-TNF experienced patients - the protocol specified a minimum of 150 such patients.
- The different modes of action – patients failing on an anti-TNF are unlikely to respond to another anti-TNF (such as CZP) but may have a fair chance of responding to an anti-IL (such as SEC or UST).

Although detailed data on the *type* of lack of efficacy are scarce, when considering the differing eligibility criteria, it is difficult to justify that the similarity assumption – necessary for a study's inclusion in a network meta-analysis – has been met to allow comparison of RAPID-PsA with PSUMMIT 2 in the same analysis. A key issue is that the *type* of reason for switching appears to be an important effect modifier (see response to next query).

1.1.2 Clinical efficacy of certolizumab pegol in patients with prior TNF inhibitor exposure

"UCB thus strongly disagrees with the statement made by the Assessment Group that the results for certolizumab pegol in Subpopulation 3 are inflated and uncertain, and requests that the Assessment Group revises its related statements. Furthermore, UCB disagrees with the statement that the subgroup of biologic-experienced population from RAPID-PsA is not representative of what would be seen in clinical practice and requests that the Assessment Group removes this statement."

The Assessment Group did not state the results were inflated, but rather that they *may*, or were likely to be inflated. This is in the context of the selected population included in this trial (see previous response). The proportion of primary failures (in the anti-TNF experienced subgroup) is likely to be a very important effect modifier, which is likely to differ across the trials which recruited anti-TNF experienced patients. The BSR/BHPR guideline notes that registry studies have shown that patients who switch drug due to adverse events have a higher likelihood of persistence with a second anti-TNF than those who switch due to loss of efficacy (either primary or secondary non-response).

1.2.2 Certolizumab pegol safety profile

The AG does not agree that the safety summary "*presents the evidence in an unbalanced and biased way, and consequently leads to misleading conclusions with respect to the safety profile of certolizumab pegol*."

However, to avoid a direct comparison being inferred about the two biologics, the following text has been changed:
"Although secukinumab appears to have a favourable safety profile,……."
has been amended to:
"Although the safety data for secukinumab appear promising,……."

Response to UCB's comments on cost-effectiveness and network meta-analysis (Section 2 of UCB report response document)

2.1 Consideration of subgroups by psoriasis severity as the base case of the decision problem

The three subpopulations were further defined according to level of psoriasis involvement, moderate-severe, mild-moderate and no concomitant psoriasis, primarily to reflect the higher dose of secukinumab licensed in the moderate-severe group. This implies a different set of comparators for the moderate-severe psoriasis group. In addition, PASI costs were applied according to the severity of psoriasis, with a zero cost applied for the no concomitant psoriasis group.

As verified by our clinical advisor, the distinction between severities of psoriasis reflects clinical practice, where certain treatments may be preferred for patients with significant psoriasis involvement.

2.2.1 Choice of 'etanercept only' as second line in sub-population 1

As the AG report states, the choice of etanercept as a second line treatment in sub-population 1 was made on the basis that it is the lowest cost biologic currently approved by NICE. This is consistent with guidance from TA199 which state that treatment should normally be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose). Previous published studies also showed that etanercept was consistently the most cost effective treatment. The AG consider that a 'weighted basket of biologics' would require assumptions regarding treatments market share, the details of which are not available to the AG, and that the higher costs for some treatments , make it unreasonable to assume that they would be considered for all patents as a 2nd line treatment.

2.2.2 Inappropriateness of best supportive care as a comparator in subpopulations 1 and 2

As specified in the AG report, best supportive care is defined as a combination of DMARDs and palliative care, therefore BSC does not represent a do nothing strategy but instead standard of care. The costs assigned to BSC are reflected in the health states costs. In the data used to inform the Rodgers algorithm for HAQ and PASI costs, many patients received a combination of non-biologic treatments, including methotrexate. Sone patients did receive palliative care, i.e. no systemic therapies. This is also reflected in the clinical trials, where the placebo groups also receive a combination of DMARDs and palliative care.

BSC was included as a comparator in all three of the sub-populations. In sub-population 1, BSC, interpreted as a 2nd DMARD, could be followed by a biologic treatment. This was not included in the AG model for two reasons. Firstly the set of comparators in subpopulation 1 is recognised as being a smaller sub-set of those that would be appropriate (according to their license) in this population. Secondly, including a 2nd line biologic in the BSC sequence, would likely increase the ICERs for SEC and CZP, compared to BSC (as it is now followed by a cost-effective treatment), but would not significantly alter the comparison between SEC and CZP.

2.3.1 Costing of certolizumab pegol

According to the SPCs, CZP posology is two vials at 0, 2 and 4 weeks, followed by one vial every two weeks. This implies that 10 vials are needed for the first cycle then 6 vials in the second cycle and 6.5 vials in each subsequent cycle, which is equates to 29 vials during the first year and 26 vials for each subsequent year. The AG acknowledge that the number of vials were slightly underestimated for CZP in subsequent cycles (6 vials were assumed rather than 6.5).

Table 1 summarises the differences between the number of vials used in the AG analysis and those reported by UCB. UCB considered that the AG had overestimated the cost of CZP. However, the costs referred to by UCB did not include administration, initiation and monitoring costs which were included in the AG estimates. After further checks of the estimates, the AG concludes that the costs for CZP have actually been slightly underestimated rather than overestimated.

Table 1 Differences in costing CZP between the AG and UCB comments

	AG report						UCB comments	
	Number of vials	Vial price	Admin. cost	Initial cost	Monit. cost	Drug total cost	Number of vials	
First cycle	10	£357.5	£43	£166	-	£3,784	9.5	
Subsequent cycle	6	£357.5	-	-	£4	£2,149	6.5	
First year	Number of vials			Annual cost			Number of vials	Annual cost
	28			£10,232			29	£10,367
Following year	24			£8,597			26	£9,295

Table 2 and Table 3 show the cost-effectiveness results in sub-population 1, the moderate to severe psoriasis group, using the number of vials for CZP as it is in the AG report and the number suggested by UCB respectively. The pairwise ICER of CZP compared to BSC is £21,465 using the number of vials suggested by UCB vs £20,870 as it is in the AG report. The conclusions are unchanged; however the ICER for CZP is increased slightly.

Table 2 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis – AG report

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC
BSC	£95,965	5.312	-	-	-	-
CZP	£159,951	8.377	£63,987	3.066	£20,870	£20,870
SEC 300mg	£179,692	8.524	£19,741	0.146	£134,783	£26,064

Table 3 Treatment effects from independent analysis for moderate-severe psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis – UCB number of vials

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	Pairwise ICER vs BSC

BSC	£95,965	5.312	-	-	-	-
CZP	£161,775	8.377	£65,810	3.066	£21,465	£21,465
SEC 300mg	£179,692	8.524	£19,741	0.146	£134,783	£26,064

Table 4 and Table 5 show the cost-effectiveness results in sub-population 1, mild to moderate psoriasis group, using the number of vials for CZP as it is in the AG report and the number suggested by UCB respectively. The pairwise ICER of CZP compared to BSC is £23,661 using the number of vials suggested by UCB vs £23,052 as it is in the AG report. The conclusions are unchanged and CZP s still dominated by SEC.

Table 4 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis – AG report

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
CZP	£135,946	8.667	-	-	D	£23,052
SEC 150mg	£132,500	8.685	£65,500	3.009	£21,772	£21,772

* D = dominated (see Section **Error! Reference source not found.**)

Table 5 Treatment effects from independent analysis for mild-moderate psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis – UCB number of vials

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£67,000	5.676	-	-	-	-
CZP	£137,770	8.667	-	-	D	£23,661
SEC 150mg	£132,500	8.685	£65,500	3.009	£21,772	£21,772

* D = dominated (see Section **Error! Reference source not found.**)

Table 6 and Table 7 show the cost-effectiveness results in sub-population 1, no concomitant psoriasis group, using the number of vials for CZP as it is in the AG report and the number suggested by UCB respectively. The pairwise ICER of CZP compared to BSC is £25,371 using the number of vials suggested by UCB vs £24,744 as it is in the AG report. The conclusions from the fully incremental analysis are also unchanged.

Table 6 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis – AG report

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
SEC 150mg	£120,303	9.067	£68,866	2.878	£23,928	£23,928
CZP	£122,832	9.074	£2,529	0.007	£346,785	£24,744

Table 7 Treatment effects from independent analysis for no concomitant psoriasis, subpopulation 1: Fully incremental cost-effectiveness analysis – UCB number of vials

Treatment	Cost	QALY	Incremental Cost	Incremental QALY	ICER vs next-best option	ICER vs BSC
BSC	£51,436	6.188	-	-	-	-
SEC 150mg	£120,303	9.067	£68,866	2.878	£23,928	£23,928
CZP	£124,656	9.074	£4,353	0.007	£621,886	£25,371

2.3.2 Disease management cost data

The AG has used the Rodgers algorithm for HAQ and PASI costs. This is to ensure consistency with previous NICE appraisals. As discussed in the report, the AG recognise that the Rodgers algorithm utilises data from a RA population as opposed to a PsA population, and therefore requires additional costs assigned according to PASI. The Poole, et al costs are derived from a PsA population, however as discussed in the AG report, there are a number of concerns with the Poole study, including the lack of data on concomitant psoriasis severity and the two-step regression approach used to estimate health care costs. In addition the estimated HAQ costs appear to be significantly higher than previous studies, resulting in much lower ICERs for all comparators. The AG did perform a sensitivity analysis using the Poole costs, and despite the much lower ICERs, the optimal treatment remains the same at a threshold between £20,000-£30,000.

2.3.3 Baseline HAQ scores for the three sub-populations

The AG included different baseline HAQ score for the three sub-populations as an exploratory analysis. These differential HAQ baselines are not specified in the base case analysis.

2.8 Assumptions on ustekinumab evidence at week 12 in subpopulation 2

"Specifically, the placebo creep is much more prominent in biologic-naïve patients. Note that the placebo arm response from the YODA project was not presented in the Assessment Group report. This challenges the validity of using week 24 data mix with subpopulation 2 and 3 data as proxy for week 12 data of subpopulation 2."

Just to clarify, the AG did not use a mix of subpopulation 2 and 3 data as a proxy for week 12 data of subpopulation 2. All relevant subgroup data were available at 24 weeks and most, but not all, were found for the 12 week time point via the YODA trial reports. The comparison of the mixed data (i.e. the full trial population data) across the 12 and 24 week time points was used only in the context of justifying using 24 week subgroup results as a proxy for 12 week subgroup results.

"UCB requests that placebo response data accessed through the YODA project should be jointly presented with the active arm response in the Assessment Group report, in order to justify their assumption for using Week 24 ustekinumab 45mg data as proxy for Week 12 response. At present the Assessment Group assumption is unverifiable."

The placebo group response data have been added to the assessment group report and to the list of erratum.

Responses to factual inaccuracies described by UCB

Page	Content from Assessment Group (AG)	UCB comments	AG responses
93	Table 24 : Incorrect rounding of PASI50 score in biologic naïve, certolizumab	As per the UCB submission (Table 24) the value should be	Not a factual inaccuracy: AG calculated the result to be 68.46%

	pegolcombined group	69% (submission shows 68.5%)	which was rounded down to 68%
131	First para states: 'In the open label extension study, 393 patients….'	The text in the AG report implies that there is a separate open label extension study. RAPID-PsA is one single study, placebo controlled and double blind until Week 24, then dose –blind until Week 48 and open label until Week 216. UCB request revision of the text in the AG report to accurately reflect the current clinical study and its design and thus suggest that the text should read (revision in bold): 'In the open label extension **phase of the RAPID-PsA study**…'	Not a factual inaccuracy
153	"the probabilities for certolizumab changed between the models, but in both it appears to be less efficacious than all other treatments excepting apremilast and etanercept in achieving PASI responses."	The conclusion is not correct for the results of model G2, in which, the probability for certolizumab pegol achieving PASI50, PASI75 and PASI90 is very similar to adalimumab, and better than golimumab, ustekinumab, apremilast and etanercept.	AG acknowledges that the conclusion was not correct. The text should read as "The probabilities for certolizumab changed between the models. It appears to be less efficacious than all other treatments excepting apremilast and etanercept in achieving PASI responses in unadjusted model, but in adjusted model, it appears to be more efficacious than golimumab, ustekinumab, apremilast, etanercept, and similar to adalimumab.". The text in the AG report is amended accordingly.
176	Table 65	Comparators. In the biologic naïve population, the UCB model does not include the SoC as a comparator. The mention of "and SoC" should be removed.	The AG acknowledge that the report incorrectly reports SoC as a comparator in sub-population 2.
176	Table 65 Model Structure	The UCB Markov model has two periods, not three. The two periods are 1) Short-term, in which the initial response to treatment is determined (12 or 24 weeks depending on the treatment 2) Long-term period (50 years). What AG refers to as the three periods is the stages of HAQ progression, not the model structure. The text in table 65 should be revised accordingly.	The AG agrees that this is what is stated in the UCB submission document; however in the economic model it is somewhat unclear what the distinct time periods are. In the "Markov sheet", the model time per years does not follow a constant sequence. For example, in sub-population 1, the first ten cycles are ordered from 0 to 2.5 years with 0.25 year step, and then the following cycle is 3. In sub-population 2, the first five cycles are ordered from 0 to 1.25 with 0.25 year step, and then moved directly to 2. In sub-population 3, only the first two cycles are 0 and 0.25 and then moved to one year cycle. The AG did not find any explanation in the UCB report for this.

General response to UCB's 21 comments on the AG report pages 323 to 359 which refer to the "Comparison of NMA/evidence synthesis" [AG report in the appendix sections 12.3.3.4, 12.3.4.4, 12.3.5.4, and 12.3.6.4]

- It should be noted that "Comparison of NMA/evidence synthesis" sections were not a full critique of the NMA sections of the company submissions. The "Comparison of NMA/evidence synthesis" sections were focused on comparing the AG's preferred model with the manufacturer primary or preferred or main NMA analysis; and the comparisons were focused only on major key differences in evidence and methods which explain the differences in the NMA results between the AG NMA and manufacturer NMA. Therefore, all methodological approaches

which were conducted in the submission were not explicitly mentioned in the AG's report.

- AG compared NMA results of the four outcomes separately in AG report appendix sections 12.3.3.4, 12.3.4.4, 12.3.5.4, and 12.3.6.4. The AG NMA results were compared where those were plausible to compare with the CS (company submission) and previous MTA results. A clear justification was given where it was not plausible to compare.
- AG also explicitly mentioned that both submissions (Novartis and UCB) conducted binary analysis of the categories of ACR and PASI separately to inform clinical effectiveness. However, AG and previous MTA estimated probability of achieving ACR/PASI responses in three categories to inform clinical effectiveness. Therefore, the comparison between CS and AG are limited to the estimation of probability of achieving ACR/PASI responses in all three categories, and AG didn't compare the results of the binary analyses for these two outcomes.
- Response on the primary time point: In the UCB submission at results of the NMA section, it is clearly mentioned that the main MTC analysis was conducted at week 24 (UCB submission, page 137-140), it is also reported in the Table 37 to 39 and 41, UCB submission. [e.g. *"As mentioned in the previous section, the main MTC analysis was conducted at Week 24, with additional sensitivity analyses conducted for Week 12."* and "*Following these recommendations, the main MTC analysis was conducted at Week 24, with additional sensitivity analyses conducted for Week 12.",* pg. 137, UCB submission]

Page	Content from Assessment Group (AG)	UCB comments	AG responses
323 342	"*A key differences between the NMAs presented concerns the trials included in each analysis. Only the AG NMA for biologic naïve subgroup includes all comparators and all trials. The UCB analysis for biologic naïve subgroup includes all treatments but misses only some apremilast trials."* "*The UCB analysis for biologic naïve subgroup includes all treatments, but misses only some apremilast trials."*	The AG conclusion on UCB analysis is incorrect. Apremilast trials are included in the UCB NMA to help estimate the difference in placebo rates. The network has one common comparator (i.e., star shape via placebo), with or without apremilast and ustekinumab, in the NMA and this would have minimum impact on the unadjusted NMA. However, it would be relevant and important data for the evaluation of placebo creep. As they are not recommended as relevant comparator by NICE, UCB has excluded them from the NMA results presentation and interpretation. Table 36 (page 136) in UCB submission notes the studies included in the NMA, which include PALACE1 and PALACE2 (apremilast trials).	Not a factual inaccuracy. The AG's conclusion was based on the information presented in the UCB submission, Table 36, pg.136, where it was noted that PALACE 1 and PALACE 2 (apremilast trials) were not included for PsARC/PASI outcomes analyses for biologic naïve subgroup.
323	"*The evidence synthesis is not clear in UCB's main submission for biologic experienced subgroup, and did not report results for this subgroup. …. Therefore, it was not plausible to compare AG NMA with CS for the*	This statement is incorrect. In the UCB submission, in table 36 on page 136, it clearly notes the NMA data input for subpopulation 3 (i.e., biologic experienced subgroup) included the data from FUTURE1, PSUMMIT2 and Rapid-PsA. The results are summarized on	Not a factual inaccuracy. In the AG report, the statement was in context of results of PsARC response for biologic experienced subgroup, and the result for this subgroup was not reported in the submission.

	biologic experienced subgroup."	page 140, and presented in table 42 to table 44. Since both AG NMA and UCB NMA employ regular Bayesian approach without adjustments, and the network has one common comparator (i.e. stat shape via placebo), there are sufficient information to facilitate the comparison of evidence synthesis provided by UCB and produced by AG NMA.	The results of ACR, PASI responses and HAQ-DI Mean change in TNF inhibitor exposed were summarised in the mentioned page 140 and Table 42 to Table 44 of UCB submission.
323	*"Another key difference relates to the primary timepoint analysed: most NMA used 12 week, but the UCB analysis used 24 weeks as their primary time point, although it did include a 12 week sensitivity analysis."*	This is an incorrect statement. The UCB submission document has included NMA results for data at both 12 weeks and 24 weeks. The summary and presentation include the NMA results in parallel for both timepoints. Table 35 on page 135 clearly states both timepoints were considered as base-case analyses. Sensitivity analyses is for those studies that evaluate outcomes at times other than 12 weeks (i.e., 14 or 16 weeks).	Not a factual inaccuracy. See general response (above) to UCB's comments on "Comparison of NMA/evidence synthesis"
324	Table 130 ("*Odds ratios reported for the biologic naïve subpopulation; but results were not reported for the biologic experienced*")	This is inaccurate summary. ACR responses at 24 weeks, including ACR20, ACR50 and ACR70 results via univariate Bayesian NMA, are presented as odds ratios in table 39 on the page 96 of the appendices of the UCB submission.	Not a factual inaccuracy. Table 130 in AG report presents the comparison of evidence synthesis of PsARC response, not the ACR response.
324	Table 130 "*Primary analysis at 24 weeks (by treatments), sensitivity analysis was conducted at 12 weeks including data on 12 weeks or closest time point after 12 weeks*."	This is an incorrect statement. The UCB submission has included NMA results for data at both 12 weeks and 24 weeks. The summary and presentation include the NMA results in parallel for both timepoints. Table 35 on page 135 clearly states both timepoints were considered as base-case analyses. Sensitivity analyses for those studies evaluate outcomes at times other than 12 weeks (i.e., 14 or 16 weeks).	Not a factual inaccuracy. See general response to UCB's comments on "Comparison of NMA/evidence synthesis"
324	Table 130 Data regarding subpopulation 2 included in the NMA "*ADEPT, Genovese 2007, GO-REVEAL, IMPACT, IMPACT 2, Mease 2000, Mease 2004, RAPID-PsA*	This is not an accurate summary. The UCB NMA includes ADEPT Genovese 2007, GO-REVEAL, IMPACT, IMPACT 2, Mease 2000, Mease 2004, PALACE 1, PALACE 3, PSUMMIT 1, SPIRIT-P1, RAPID-PsA	Not a factual inaccuracy. In AG report, the included studies were summarised based on UCB submission, Table 36, pg.136, where it was noted that PALACE1, PALACE2, and SPIRIT-P1

	(12-16 weeks analysis)"		were not included for PsARC outcome analysis for biologic naïve subpopulation. Although, the PSUMMIT 1 trial were considered for NMA (Table 36, pg.136), however, the results of NMA was presented for anti-TNFs (pg. 139 and Table 38, pg. 142 in UCB main submission; and Table 40, pg. 97 in UCB appendix document). Therefore, it was considered that PSUMMIT 1 trial was not included in the main analysis for biologic naïve subpopulation.
324	Table 130 Data regarding subpopulation 3 included in the NMA: study used in the analyses and drugs evaluated "*not clear*"	Table 36 (page 136) and figure 41 (page 129) in the UCB submission clearly note the studies contributed data from patients with prior TNF exposure to the NMA.	Not a factual inaccuracy. The studies included in the Figure 41 (page 129) and Table 36 (page 136) in the UCB submission contradict with each other. Figure shows four trials were included in the analysis, but table presents only RAPID-PsA trial was included in PsARC outcome analysis for biologic experienced subgroup. Therefore, it is not clear which studies and drugs were included for analysis of this subpopulation.
325 342	Table 131, "*Fixed effects on studies (for both biologic naïve and experienced subpopulation)"* The Assessment Group reports that AG and Rodgers et al. consider fixed effects on studies, whereas "*UCB and Novartis consider random effect on studies for biologic naïve subgroup and fixed effect on studies for biologic experienced subgroup analysis*."	This is an incorrect statement. Table 35 (page 135) in the UCB submission clearly notes both random and fixed-effect model NMAs were conducted for subpopulation 2, for both probit and univariate Bayesian NMAs.	Not a factual inaccuracy. See general response to UCB's comments on "Comparison of NMA/evidence synthesis"
325	Table 131 "*For biologic naïve subpopulation: treatment effects are exchangeable within classes (anti-TNFs=ADA, IFX, ETN, GOL)*"	This is an inaccurate statement. The treatments included in the NMA include agents within anti-TNFs as well as agents from other classes (i.e., ustekinumab and apremilast). For subpopulation 2, the statement on page 132 of the UCB submission clarifies the	Not a factual inaccuracy. AG acknowledges that the statement on page 132 of the UCB submission clarifies the approaches were taken for the analyses. However, it contradicts with the results presented in the table 38, page

		approach. In the unadjusted NMA, treatments were assumed to be independent of each other for subpopulation 2.	142, where only anti-TNFs results was presented. Additionally, it is noted that PALACE1 and PALACE-3 were not included for the PsARC (Table 36, pg. 136, UCB submission).
325	Table 131 UCB NMA model "*Adjusted for biologic naïve subpopulation, but unadjusted biologic experienced subpopulation*" Assessment Group NMA model "*Independent treatment effects models was unadjusted; but analysis assuming exchangeable class effects model was adjusted for the placebo response*"	Both the UCB and AG NMA included adjusted and unadjusted models for subpopulation 2, and are not able to have adjusted models due to sparse data. The statement in table 131 could mislead readers on the real difference.	Not a factual inaccuracy. See general response to UCB's comments on "Comparison of NMA/evidence synthesis"
333	Table 139 For median conditional on response HAQ change, timepoint considered in UCB NMA "*at 24 week*"	This is an incorrect statement. In Table 35 (page 135) of UCB submission, the analyses for HAQ-DI change by PsARC response include both 12 and 24 weeks.	Not a factual inaccuracy. See general response to UCB's comments on "Comparison of NMA/evidence synthesis"
343	For PASI response, Table 147 NMA Model of UCB "*conditional multinomial probit model*" Results report "*probability of PASI response in three categories 50/75/90*" Studies used in the analyses for subpopulation 2 *"... (12-16 weeks analysis)"*	It is an incorrect statement. UCB submission document, Table 35 (page 135), and statements on page 132 clearly note that three different NMA models are employed for the analyses for PASI response for both 12 and 24 weeks. Results of those analyses include both probability and odds ratios, and presented in table 39, 40 (page 143 and 144) in the submission document and in table 41 (page 98) in the appendices for subpopulation 2, in table 43 (page 147) of the UCB submission for subpopulation 3.	Not a factual inaccuracy. See general response to UCB's comments on "Comparison of NMA/evidence synthesis"
344	For PASI response, Table 148 NMA Model of UCB "*conditional multinomial probit model*" Fixed or random effects between studies "*Random effect on studies for biologic naïve subpopulation analysis and fixed effect for biologic experienced subpopulation analysis*" Model adjusted for the	This is an incorrect statement. Three difference NMA models are employed for the PASI response at both 12 and 24 weeks for subpopulation 2, including adjusted and unadjusted for placebo effect. Again, the table 35 (page 135) in the UCB submission clearly notes both random and fixed-effect model NMA conducted for subpopulation 2, for both probit and univariate Bayesian NMA	Not a factual inaccuracy. See general response to UCB's comments on "Comparison of NMA/evidence synthesis"

	placebo response "*unadjusted*"		
344	The Assessment group report states: '*In UCB submission, the estimated probabilities are much lower for etanercept compared to the result of previous and current assessment. The difference is largely because UCB used different PASI50 response data in the analysis.*'	The NMA data input for one of etanercept study are collected from graph presented in the Mease 2000 (Lancet, trial noted as University of Washington in UCB submission document). The difference in data is driven by the lack of direct reporting of proportion patients who achieved PASI response. Specifically, the figure 3 in the publication indicates an approximate little less than 40% patients treated with etanercept had PASI50 at week 12 in 19 patients who had concomitant psoriasis. The round up or down process along with small sample size lead to the difference of estimate on probability of etanercept in the NMA.	The AG acknowledges the differences, however it is not a factual error in the AG report. The AG included etanercept data from the previous MTA (Rodgers et al. 2010) which is correct and robust as it was provided by the etanercept manufacturer during the previous assessment.
346	The Assessment Group states that the PASI results are not comparable between the Assessment Group and UCB analyses as probabilities were estimated at two different time points (12 weeks and 24 weeks)	Week 12 data was also submitted by UCB	Not a factual inaccuracy. Probability of achieving PASI responses in three categories at 24 weeks were presented for biologic experienced subpopulation in Table 43, pg. 147 of UCB submission. However, the results at 12 weeks were not presented for this subpopulation in UCB submission.
358	Table 161 states UCB used a conditional multinomial probit model	The binary/binomial model was also submitted for ACR	Not a factual inaccuracy. See general response to UCB's comments on "Comparison of NMA/evidence synthesis"
358	For ACR response, Table 161 NMA Model of UCB "*conditional multinomial probit model*" Results report "*Probability of ACR response in three categories 20/50/70 for experienced subpopulation, but did not present probabilities for biologic naïve subpopulation*" Drug evaluated in subpopulation 2 "*Adalimumab 40mg; apremilast 20mg and*	It is an incorrect statement. Table 35 (page 135), and statements on page 132 of the UCB submission clearly note that three different NMA models are employed for the analyses for ACR response for both 12 and 24 weeks. Results of those analyses include both probability and odds ratios, and presented in table 37 (page 141) in the submission document and in table 38 (page 95) in the appendices for subpopulation 2, in table 42 (page 146) of the submission document, and in table 39 (page 96) in the appendices for subpopulation 3.	Not a factual inaccuracy. See general response to UCB's comments on "Comparison of NMA/evidence synthesis". Additionally, none of these mentioned tables presents probability of achieving ACR response in three categories for biologic naïve subpopulation [table 37 (pg. 141) and table 42 (pg. 146) in the submission document; table 38 (pg. 95) and table 39 (pg. 96) in the appendices].

	30mg; certolizumab pegol; etanercept 25mg; golimumab 50mg; infliximab: 5mg mg/kg"	Treatment evaluated in the subpopulation also include secukinumab for analyses of 24 week data, which is not included for 12 week data as such data are not available in public domain.	
358	For ACR response, Table 162 NMA Model of UCB "*conditional multinomial probit model*" Fixed or random effects between studies "*Random effect on studies for biologic naïve subpopulation analysis and fixed effect for biologic experienced subpopulation analysis*" Baselines "*common effect model was used to estimate baseline*" Model adjusted for the placebo response *"unadjusted"*	This is an incorrect statement. Three difference NMA models are employed for the ACR response at both 12 and 24 weeks for subpopulation 2, including adjusted and unadjusted for placebo effect. Again, the table 35 (page 135) in the UCB submission clearly notes both random and fixed-effect model NMA conducted for subpopulation 2, for both probit and univariate Bayesian NMA.	Not a factual inaccuracy. See general response to UCB's comments on "Comparison of NMA/evidence synthesis"
359	Table 162 states UCB used a conditional multinomial probit model	The binary/binomial model was also submitted for ACR	Not a factual inaccuracy. See general response to UCB's comments on "Comparison of NMA/evidence synthesis"
359	Table 162 states UCB used an unadjusted model for placebo response	An adjusted model was also submitted by UCB	Not a factual inaccuracy. See general response to UCB's comments on *"Comparison of NMA/evidence synthesis"*
332-333	For median conditional on response HAQ change, the Assessment Group states "*detailed information about evidence synthesis was not provided.*" Table 139 Key assumption for Model "*not clear from the submission*"	This is an incorrect statement. On page 133 of 289 of UCB submission document, the source of the data is stated, with Rodger 2010 HTA report cited as reference #136. The analyses method is noted on page 132 of 289 in the submission document. Results were presented in cost effectiveness section 5. "Specifically to support the economic model development, meta-analyses for HAQ-DI change in PsARC responders and non-responders were conducted with data extracted from a formal HTA report, and assumed an additive effect for the effect of treatment in treatment responders versus that for placebo responders, as has been done in the HTA report. Specific results	Not factual inaccuracy. AG acknowledges that pg. 132 of UCB submission specifies a very brief description of approaches were taken for the HAQ-DI outcome analysis; and pg. 133 of UCB submission specifies the source of data and an adopted approach of data analysis. However, detailed information about analysis and key model assumptions were not clearly mentioned in page 132-133 of 289 in UCB submission document. Therefore, comparison of methods and key assumptions were not plausible for HAQ changes conditional on PsARC response/non-

		are presented in Section 5.”	response.

Executive summary

Statement of the decision problem

The decision problem is to determine the clinical and cost effectiveness of secukinumab, within its marketing authorisation, for treating active psoriatic arthritis (PsA) in adults whose disease has not responded adequately to previous disease-modifying anti-rheumatic drug (DMARD) therapy. Clinical trial and network meta-analyses (NMA) data are presented for patients with active PsA (≥3 swollen and ≥3 tender joints) despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or DMARD therapy (see Section **Error! Reference source not found.**). In line with the NICE scope, the economic model is designed to allow consideration of three subgroups:

- Those who have failed one prior DMARD (termed 'biologic-naïve [1 prior DMARD]')
- Those who have failed two or more prior DMARDs (termed 'biologic-naïve [≥2 prior DMARDs]')
- Those who have failed one or more anti-tumour necrosis factor (TNF) therapies (hereafter termed 'biologic-experienced')

A more detailed summary of how the decision problem has been addressed in relation to the final scope issued by NICE is presented in Appendix 1.

Summary of the health condition and technology

Psoriatic arthritis and the current treatment pathway

PsA is a chronic, progressive, inflammatory arthropathy, related to psoriasis, which is characterised by both joint and skin manifestations (1-3). If left untreated, PsA can be highly debilitating and cause irreversible joint damage and disability. The severity of skin lesions has also been shown to significantly affect patient health-related quality of life (HRQoL), particularly in terms of psychosocial impact (4); it is therefore expected that PsA patients with concomitant moderate-to-severe psoriasis would have worse HRQoL compared to patients with milder psoriasis involvement.

Current biologic therapies recommended by NICE for the treatment of active PsA in adult patients whose disease has not responded adequately to previous DMARD therapy include agents targeting tumour necrosis factor (anti-TNF therapies): etanercept, infliximab, adalimumab and golimumab (5, 6). Ustekinumab, an interleukin (IL)-12/13 inhibitor, is also recommended by NICE but only for patients for whom treatment with anti-TNF therapies is contraindicated but would otherwise be considered, or patients who have received prior treatment with one or more anti-TNF therapies (7). These biologics, in addition to certolizumab pegol (another anti-TNF therapy), are included as relevant comparators in this submission.

Secukinumab for the treatment of PsA

Secukinumab is a fully-human, anti-IL-17A monoclonal antibody and therefore offers a novel mechanism of action to existing biologic therapies. In addition to the PsA indication under consideration in this submission, secukinumab also has marketing authorisation from the European Medicines Agency (EMA) for the treatment of moderate to severe plaque psoriasis and for ankylosing spondylitis (8). A Patient Access Scheme (PAS) is included in this submission whereby secukinumab is provided at a simple confidential discount, as applied in the previous appraisal of secukinumab in the psoriasis indication (TA350) (9).

Summary of clinical effectiveness

Clinical evidence base for secukinumab

The efficacy of secukinumab versus placebo has been studied in two pivotal phase III randomised controlled trials (RCTs; FUTURE 2 and FUTURE 1), including a total of 1,003 patients with active PsA (≥3 swollen and ≥3 tender joints) despite NSAID, corticosteroid or DMARD therapy (see Section **Error! Reference source not found.**) (10, 11). FUTURE 2 provides efficacy data for the licensed dosing regimen (10); FUTURE 1 used the licensed maintenance dose with an unlicensed intravenous loading dose (10 mg/kg), and provides further supportive efficacy data, including radiographic outcomes (11).

Clinical efficacy results from FUTURE 2 and FUTURE 1

In both FUTURE trials the primary endpoint was met (see Sections 4.5.1.1 and 4.5.2.1); a significantly higher proportion of patients receiving secukinumab achieved an American College of Rheumatology **(ACR) 20 response** at Week 24 versus placebo ($p<0.0001$ for both doses) (10, 11). Significant improvements in ACR 20 response with secukinumab were observed as early as Week 3 in both trials, with responses sustained up to the latest available time points, Week 52 (FUTURE 2) and Week 104 (FUTURE 1) (10-14). Superior responses versus placebo were also observed with secukinumab using the more stringent **ACR 50** (secondary endpoint) and **ACR 70** (exploratory analyses) response criteria in both FUTURE trials (10, 11).

In FUTURE 2, the licensed dose for patients with concomitant moderate to severe psoriasis (secukinumab 300 mg), was associated with significant improvements in skin psoriasis versus placebo at Week 24, as measured by Psoriasis Area Severity Index **(PASI) 75** ($p<0.0001$) and **PASI 90** ($p=0.0005$) (see Section **Error! Reference source not found.**) (10). Furthermore, as part of exploratory analyses, a significantly higher proportion of patients achieved a Psoriatic Arthritis Response Criteria **(PsARC)** response with secukinumab compared to placebo at Week 24 ($p<0.0001$ for both doses in FUTURE 2 and $p<0.0001$ for both doses in FUTURE 1) (12, 13). In FUTURE 1, in each dose arm 84.6% and 83.9% of patients with an X-ray reading at Week 104 had **no radiographic progression** (see Section **Error! Reference source not found.**) (14).

In both FUTURE trials, randomisation was stratified by prior anti-TNF treatment (naïve or inadequate responder); secukinumab 300 mg (FUTURE 2) demonstrated significant improvements in ACR 20/50/70 response versus placebo, irrespective of anti-TNF status (10). Secukinumab has also been shown to be effective versus placebo in patients who have only received one prior DMARD and separately in those with moderate to severe psoriasis (see Section **Error! Reference source not found.**).

Network meta-analysis results

A NMA was conducted to assess the relative efficacy of secukinumab compared to relevant comparators in terms of ACR, PASI and PsARC outcomes (see Section **Error! Reference source not found.**) in patients with active PsA despite treatment with DMARDs, NSAIDs and/or previous anti-TNF therapy and/or previous biologic therapy. Secukinumab performed equally well to all other active comparators in terms of ACR response (no significant differences) and ranked among the best of the treatments examined in terms of PASI response, with secukinumab being statistically superior to etanercept and certolizumab pegol. Once between-trial differences in placebo effects are accounted for, secukinumab was also found to be associated with higher PsARC responses relative to any of the other active comparators. Similar results were obtained from biologic-naïve and biologic-experienced subgroups, but the networks for these analyses were much sparser.

Safety and tolerability of secukinumab

Secukinumab was well tolerated by patients with active PsA in FUTURE 2 and FUTURE 1, with a low incidence of serious adverse events (SAEs) and discontinuations due to adverse events (AEs) observed in a pooled safety analysis of these trials (see Section **Error! Reference source not found.**) (15). The safety of secukinumab has been assessed extensively in various auto-immune indications, with over 12,000 patient years of exposure in clinical trials and more than 9,000 patient years post-authorisation (16). The results of a pooled analysis across FUTURE 2, FUTURE 1 and five plaque psoriasis trials, comprising a large cohort of 3,928 patients, demonstrated that secukinumab is well tolerated as a therapy for PsA and the related plaque psoriasis indication (see Section **Error! Reference source not found.**) (17), with no new safety concerns arising from the FUTURE 2 and FUTURE 1 PsA trials.

Summary of cost-effectiveness

A *de novo* cost-utility model was developed to evaluate the cost-effectiveness of secukinumab versus relevant comparators in adult patients with active PsA despite current or previous treatment with DMARDs, and/or anti-TNF therapies. Three patient populations were considered in the analysis:

- Patients who have failed one prior DMARD (biologic-naïve [1 prior DMARD]) compared to Standard of Care (SoC; methotrexate [MTX] 25 mg per week)
- Patients who have failed two or more prior DMARDs (biologic-naïve [≥2 prior DMARDs]) compared to certolizumab pegol, adalimumab, etanercept, infliximab, golimumab and SoC
- Patients who have failed one or more anti-TNF therapies (biologic-experienced) compared to certolizumab pegol, ustekinumab and SoC

The model structure was based on that developed for TA199 by the University of York. The model incorporates a short-term (3-month) decision-tree leading into a long-term (lifetime) Markov model. Patients enter the model at the start of treatment and are defined as responders if both a PsARC and PASI 75 response are achieved at 3 months, and as non-responders if these criteria are not met.

In the biologic-naïve (1 prior DMARD) population, secukinumab achieved a greater quality-adjusted life-year (QALY) gain over the lifetime time horizon when compared with SoC (7.5 *vs* 6.7). Moreover, secukinumab was associated with an incremental cost-effectiveness ratio **(ICER) of £12,189 *vs* SoC**, which is well below the standard NICE thresholds for cost-effectiveness. In the biologic-naïve (≥2 prior DMARDs) population, **secukinumab was found to be dominant (less costly and more effective) when compared with certolizumab pegol, etanercept, golimumab, and adalimumab**. Only infliximab was associated with greater benefits when compared with secukinumab; however, the ICER for infliximab versus secukinumab was well over £200,000 per QALY gained, and therefore considerably beyond standard NICE thresholds for cost-effectiveness. Despite greater uncertainty in the biologic experienced population, **secukinumab extendedly dominated certolizumab pegol and ustekinumab**. Compared with SoC, secukinumab was associated with an **ICER of £27,562**.

Results were robustly tested in deterministic, probabilistic and structural sensitivity analyses; the probabilistic results were in line with the deterministic results for all three populations. In the biologic-naïve (≥2 prior DMARDs) population secukinumab dominated all biologics except infliximab which was itself not cost-effective compared to secukinumab. The probability of secukinumab being the cost-effective option amongst all the comparators (including versus SoC) was 95.1% at a willingness-to-pay threshold of £20,000/QALY and 99.9% at £30,000/QALY.

Considering all three populations, secukinumab offers the most cost-effective treatment option and its approval for use in PsA would result in significant QALY gains for patients.

Summary of budget impact

Secukinumab at the PAS price will provide cost savings to the NHS. It is estimated that **over five years the savings to the NHS will be substantial at £14,204,590**.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

ID579

Certolizumab pegol (Cimzia) for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs

1 July 2016

1 Executive summary

1.1 Introduction

Psoriatic arthritis (PsA) is a heterogeneous disease in terms of both presentation and severity. Patients experience chronic inflammatory peripheral arthritis in addition to other peri-articular sequelae. PsA is a progressive disease, with patients experiencing irreversible joint damage if left untreated.[1-4] PsA affects many aspects of a patient's life and is associated with high burden of disease due to the occurrence of pain, fatigue, impaired sleep patterns, limitations to physical ability and detriments to psychological, social and emotional well-being.[5-11] Moreover, PsA incurs a substantial economic impact on society and individual patients, resulting from the reduced capacity to work that is observed in patients who are typically of working age at disease presentation.

Despite existing treatment options, a substantial unmet need exists for PsA patients whose condition is uncontrolled, to rapidly improve all components of the disease and inhibit the progression of structural damage. There is a considerable need for a treatment that is efficacious across the various manifestations of disease, including proven efficacy on both joints and skin, as well as on extra-articular manifestations (i.e. skin and nail disease, axial disease, dactylitis and enthesitis), in a broad patient population that includes patients naïve or with prior exposure to tumour necrosis factor (TNF) inhibitors.

Certolizumab pegol (Cimzia®; CZP) is the only PEGylated TNF inhibitor that is indicated in Europe for the treatment of rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA).[12] CZP received its marketing authorisation for the treatment of active PsA in adults when the response to previous disease-modifying antirheumatic drug (DMARD) therapy has been inadequate in November 2013. CZP offers flexible dosing and has demonstrated a rapid improvement in the signs and symptoms of PsA, inhibition of structural damage, improvement in extra-articular manifestations and a broad spectrum of patient-relevant outcomes.[13] NICE currently recommends CZP for the treatment of patients with RA and axSpA.[14,15] This is the first time CZP is being appraised by NICE for the treatment of PsA.

1.2 Clinical effectiveness and safety of CZP

The RAPID-PsA (N=409) was a phase III placebo-controlled, multinational, multicentre, parallel-group trial which assessed the efficacy and safety of CZP in patients with adult-onset active and progressive PsA. The trial included a large number of outcomes that were clinically meaningful and relevant to patients. This study uniquely included pre-specified analyses of patients with prior exposure to TNF inhibitors.[13]

The RAPID-PsA study results showed that CZP is an effective treatment for the signs and symptoms of active PsA, across the breadth of disease manifestations regardless of prior treatments.

Both CZP maintenance dosing regimens (i.e. 200 mg every two weeks and 400 mg every 4 weeks) provided significant and rapid improvement in the signs and symptoms of disease, across the spectrum of joint, physical functioning, skin and extra-articular disease manifestations, in the overall population compared to placebo.[13] The co-primary endpoints of the trial were successfully met, whereby treatment with CZP resulted in statistically significantly higher ACR20 response rates at Week 12 and significant inhibition of radiographic progression at Week 24 versus placebo ($p<0.001$ and $p=0.007$, respectively).[13]

Substantial changes in outcomes were observed with CZP as early as the first assessment (e.g. Week 1 for ACR20 and pain, Week 2 for PASI and physical function).[13] Significantly greater improvements with CZP were also seen in terms of extra-articular manifestations of disease, including skin and nail disease, axial involvement, enthesitis and dactylitis. Patients treated with either CZP dosing regimen also reported significant and rapid improvement in a broad spectrum of patient-relevant outcomes (including pain, fatigue and health-related quality of life [HRQoL]) and also greater improvements in work and household productivity versus placebo at Week 24.[16,17] The initial improvements in clinical and patient-relevant outcomes following treatment with CZP during RAPID-PsA were maintained on long term, to Week 216.[18]

The rapid and long-term benefits following treatment with CZP were similarly high in all three subpopulations that were defined according to the final scope of this submission – i.e. TNF inhibitor naïve patients who have only received 1 prior cDMARD, TNF inhibitor naïve patients and patients with prior TNF inhibitor exposure.

Rates of adverse events (AEs), serious AEs, and infections were similar between treatment groups through Week 24 of the study. Moreover, no new safety signals were observed in the RAPID-PsA study up to Week 96[19] compared with the use of CZP in other indications and compared with other TNF inhibitor therapies both within PsA and in other indications.

1.3 Mixed treatment comparison

A systematic literature review and a mixed treatment comparison (MTC) were undertaken, to assess the relative efficacy of CZP compared to selected biological DMARDs, including TNF inhibitors, in PsA patients who had experienced previous failure of at least one DMARD (conventional and/or biologic).

The SLR identified 29 trials, out of which 15 were deemed feasible to be included in a Bayesian MTC for TNF inhibitor naïve and four of them were also feasible to be analysed for TNF inhibitor exposed subpopulations. No RCTs were identified that reported patients who were TNF inhibitor naïve and received only 1 prior cDMARD, except RAPID-PsA. The analysis was performed for a number of key outcomes, such as ACR 20/50/70, PsARC and PASI 50/75/90 responses and physical function (HAQ-DI).

In TNF inhibitor naïve PsA patients (subpopulation 2), the primary analysis at Week 24 showed that CZP has similar efficacy (with no significant difference on the vast majority of outcomes) when compared to adalimumab (ADA), etanercept (ETA), golimumab (GOL), infliximab (IFX) and secukinumab (SEC). The only exception was PASI75 at 24 weeks, for which CZP had a significantly higher response compared to ETA. There were no large differences in the results between the primary analyses and the sensitivity analysis for most interventions considered.

In TNF inhibitor exposed PsA patients (subpopulation 3), the primary analysis indicated that CZP has significantly or numerically better efficacy when compared to ustekinumab (UST) and SEC at Week 24. The difference in HAQ-DI improvement was statistically significant in favour of CZP when compared to SEC.

The findings of the NMA are consistent with the conclusions of the latest EULAR recommendations in PsA,[20] that noted the similar effect of CZP with the other TNF inhibitors, as well as the similar improvements of CZP in a broad population of patients who are naïve or exposed to TNF inhibitors, effect which was not seen in the UST and SEC studies.

1.4 Cost-effectiveness

A Markov model was developed to follow a cohort of patients with PsA, from the start of treatment through an initial response period and on to long-term follow-up until death. Two periods were considered: 1) short-term, in which the initial response to treatment is evaluated (corresponding to the clinical trials) and 2) long-term, during which responders remain on the initial treatment until they switch to the next line of treatment due to loss of efficacy or for other reasons. The model projected PsARC and PASI response, to estimate patients' health-related quality of life (HRQoL) and costs over their lifetime. Quality-adjusted life years (QALYs) were accrued based on the HAQ-DI score.

The model accounted for multiple treatment sequences. The sequences considered vary by subpopulation. In subpopulation 1 (patients who received only one prior cDMARD), two sequences are compared: certolizumab pegol vs cDMARDs, each of them followed by a basket of TNF inhibitors, ustekinumab and a mix of cDMARDs. In subpopulation 2 (patients who are anti-TNF naïve) all sequences start with one anti-TNF (certolizumab pegol, etanercept, infliximab, adalimumab or golimumab) or secukinumab, followed by ustekinumab and then a mix of cDMARDs. Finally, in subpopulation 3 (patients who are anti-TNF experienced), certolizumab pegol is compared to secukinumab, ustekinumab and a mix of cDMARDs.

The base-case cost-effectiveness analysis accounted for the CZP Patient Access Scheme (PAS). Under the PAS agreed with the Department of Health for the use of CZP in the treatment of RA and axSpA, the first 12 weeks of CZP are provided free of charge, which is equivalent to 10 vials at a total cost saved of

£3,575 in Year 1 of treatment.[21] This approved PAS will be extended for the use of CZP in the treatment of PsA and has been submitted to the DoH. A Welsh PAS for CZP in this indication has already been accepted by the AWMSG.

Subpopulation 1 (patients who are anti-TNF naïve and had only one prior cDMARD)

The base case for subpopulation 1 relies entirely on the response data from the RAPID-PsA trial to compare CZP to cDMARD, due to lack of evidence for other comparators to inform the NMA. The base case analysis showed that, as a treatment option for patients naïve to TNF inhibitors who had only 1 cDMARD, CZP is cost-effective versus cDMARDs (ICER of £23,666 per QALY gained).

Subpopulation 2 (patients who are TNF inhibitor naïve)

The base case results indicated that, in patients who are TNF inhibitor naïve, CZP dominates all comparators considered (adalimumab, golimumab, etanercept, infliximab and secukinumab), as being more effective (greater QALYs) and less costly.

Subpopulation 3 (patients who are TNF inhibitor experienced)

In patients who are TNF inhibitor experienced, the basecase analysis indicated that CZP dominates both SEC and UST, as being more effective (greater QALYs) and less costly. CZP was cost effective versus cDMARDs (ICER of £8,894 per QALY gained).

The deterministic sensitivity analyses showed that the results were robust when varying parameters' estimates with outcomes being sensitive to shorter time horizons, discount rates for health and cost outcomes, and to the inclusion of indirect costs, which lowered the ICERs. Probabilistic sensitivity analyses (PSA) showed that, in subpopulation 1, CZP has 100% probability of being cost-effective at willingness-to-pay thresholds above £24,000 per QALY gained. In subpopulation 2, the PSA indicated that CZP has the highest probability of being the most cost-effective alternative at any willingness-to-pay threshold. Finally, with respect to subpopulation 3, the PSA indicated that CZP has the highest probability of being the most cost-effective alternative among available treatments at willingness-to-pay thresholds above £10,000 per QALY gained.

1.5 Budget impact

Under the base case assumption, the budget impact analysis indicated that the introduction of CZP with the PAS for the treatment of psoriatic arthritis, is expected to result in total net savings of £459,142. The introduction of CZP as the biologic treatment option for patients who are naive to TNF inhibitors and had only one prior cDMARD, is expected to incur an additional £51,258 over 5 years due to the displacement of cDMARDs towards CZP. This incremental budget is expected to be offset by the savings in the other subpopulations, patients who are TNF inhibitor naïve and TNF inhibitor experienced, who are expected to result in net savings of £163,777 and £346,622 respectively over 5 years.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]

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 (PAPAA)

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: *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 out an online survey between 29 Jan-29 Feb 2016 via the PAPAA website as free text form submissions, and promoted via social media. The mean age of responders was 46 years old (range 28- 64) with a split of male 49% female 51%. 55% respondents live in England.

We asked the following questions:

1. *What is it like to live with psoriatic arthritis?*
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.

What is it like to live with psoriatic arthritis?

"Day to day it's difficult ... I no longer plan long term. I haven't slept restfully in over a decade and now feel psoriatic arthritis is affecting my relationships. People don't take kindly to me cancelling on them so I just don't socialise anymore."

"It's very wearing living with chronic pain and stiffness. It is socially isolating. I had to give up working because it takes too long to see a rheumatologist, get diagnosed, start a treatment, fail a treatment, and start another...2 years later still suffering before failing another... equals job loss."

"Annoyingly painful, restrictive and tiring. Frustrating not to be able to chop food up or tie laces or wash your hair before work, as it's just too many jobs and you need to save your hands."

"I live with pain and horrendous fatigue on a daily basis. It is also depressing not being able to do the things I would love to do."

"Before treatment hard, disabling, depressing and painful. Trying to find treatment to suit."

"Ok, when ongoing treatment works, life is good but still with some pain."

"Worrying, stressful and frustrating - on top of the obvious pain. All forms of pain relief carry side effects. When my gastroenterologist tells me not to take the naproxen as it is destroying my stomach, but my rheumatologist tells me to take them to give me the mobility I need. I am fearful of what medication is doing to my stomach and what other medication may do if I change. The illness creates stress; stress increases flare-ups of the arthritis and the psoriasis."

"Difficult. I was very active before my diagnosis, a semi-competitive runner I ran 70-80 miles per week. I still try to run, I don't keep track of miles any longer, but I try to run 5-6 days a week, if even for a couple of miles. I also try to stay active by going to the gym, but there are few things I can do that don't inflame some joint or another. My hands, wrists, elbows, shoulder, hips, knee, and feet are all involved - sometimes seemingly randomly, and depending on how well my TNF-a, anti-inflammatory are working."

"Very difficult to live with psoriatic arthritis with constant pain. "

"In short good days bad days. As a carpenter joiner, I struggle most days to get a decent days work done so to be valuable to any employer. The fatigue that comes is the most debilitating as the pain can be reasonably controlled."

"Awful! Unpredictable. Exhausting. Frustrating. Upsetting. Life changing. Controlling of your life."

"Living with psoriatic arthritis is to have constant diffuse pain all the time to feel tired and exhausted at times when, sometimes, everything seems like a big effort. I also think that most rheumatologists are concerned with RA above all. It seems like many ideas are just extrapolated from findings for RA to PSA. I sometimes feel that I am not believed especially as I do not have swollen joints. My main problem is with enthesitis."

"Psoriatic arthritis affects my knees. During a flare - the pain is intense and disabling - it feels like having hot knives stabbed into your joints. Trying to walk was like dragging my legs through concrete. Not being able to walk was frightening."

"The disease is unpredictable - you don't know what it will do next and you can't control it - it's not easy to forget about having psoriatic arthritis - you cannot rely on your body any more. It was hard to do my job - I was so tired all the time. I went from being an enthusiastic 'workaholic' to being made redundant."

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?

"Relief from joint pain destruction, I want my life back "

"Quicker access to other medications. The process is too slow and leads to further deterioration making it even harder for new treatments to work. "

“Pain relief and inflammation control.”

“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.”

“Take away pain and inflammation to stop joints from getting worse.”

“To relieve pain obviously. At this moment in time, I just want to stay mobile for as long as I possibly can. So reduction of the inflammation is as important as pain relief.”

“A normal life. I don't mind modifying my expectations, but pain management is difficult, and fatigue is a real problem. I have always led an active life with a high impact (unfortunately high stress) job - and it is difficult to modify my lifestyle to accommodate the unexpected trajectories of this disease.”

“Pain relief and better mobility”

“Aches and pains to go without any side effects!”

“Less stiffness and tackle the fatigue, if possible”

“I would like to be pain free because it restricts my daily life”

“A treatment which doesn't require frequent visits to a GP or the hospital.”

“A better quality of life. I understand that we will never be pain free but I would like treatment to be able to control the unpredictable flares, the fatigue and the damage done to joints etc.”

“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.”

‘‘*To give me mobility and flexibility in my joints - to be able to walk and run normally. To enjoy walking. To feel energetic again.”*

“Most important is feeling well in 'myself' - feeling like a person - not a zombie, sleepwalking through life getting every infection going around and feeling sick and tired for several days a week.”

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”

“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. It enabled me to walk properly again without pain - but meant I had no energy to want to walk anywhere. It was hard to go to work as I had been used to doing - I didn't have enough energy to put into my job.”

”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.”

“So far so good but it's not widely understood. It varies from hospital to hospital and there are just as many uninformed rheumatologists as there are amazing ones. Pot luck.”

“Nothing has worked so far, but sulfasalasine is the only one so far that hasn't given me horrible side effects.”

“For me, they have not helped at all. I have been on methotrexate tabs then injections, leflunomide, which I took a bad reaction to and now on sulfasalasine. Nothing has worked so far. I am due to start Cimzia Feb 2016.”

"Very good lots of options but I had to suffer for at least two and half years before being allowed to take Humira. "

"Restricting."

"I think they are helpful, and I can't imagine no treatment, or methotrexate and NSAIDs alone. But none of them have been 90-100% for me."

"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"

"Not many that I can have, definitely should be more"

"The DMARD seems to have had no effect"

"As very good my rheumatology team are always trying new drugs but nothing seems to work for me"

"I am currently unaware of any other drug(s) than those I'm on. I'm constantly told by the GP that there's not much more can be done. So in a word... frustrated."

"They are reasonable; however, I don't always feel that psoriatic arthritis is taken as seriously as other illnesses. I would like to see more widely available treatments for those people who are either trying to conceive or who are pregnant as there only seems to be one, sulfasalasine. Also, I'd like to see more dietary, exercise and pain management advice/sessions available."

How acceptable are these different treatments and which do you prefer and why?

"Methotrexate is the only treatment that has had any effect on, me apart from vioxx (now banned in the UK) "

"I've been on azathioprine, methotrexate and now leflunomide. More hoops to jump through before finally accessing something that might give me some sort of life back. In the meantime joints are deteriorating."

"They are all worth a try but high risk. I'm on methotrexate shortly to add sulfasalasine. Hopefully won't have to progress to a biological."

"Acceptable, but have to wait too long before being offered biologics"

"I don't know enough about the range of medication available."

"I don't mind auto-inject medications, really don't like syringes. I loved Humira but I was allergic to something in the solution - caused moderately severe hives. Otherwise, worked the best so far (Enbrel -> Humira -> Simponi -> Cimzia)"

"Enbrel worked for 6 months then stopped; Humira = allergic reaction; Simponi worked for 21 days but not 28; Cimzia moderately works, frequent breakthrough flares"

"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 very, as I no one seems to know whether they are having an effect or not. if I stop we have to wait months to find out"

"I have tried : hydroxychloroquine sulphate, sulphasalasine, methotrexate., golimumab."

"The only treatment that worked for me was golimumab. All the others were ineffective and lowered my white cell and neutrophil count to dangerous levels. The golimumab also lowers my white cell counts and so I also have GCSF injections to remedy this."

"I couldn't say I had a preferred treatment. I tried COX-2 inhibitors and they did not work at all. I also had a corticosteroid injection which did nothing either. Methotrexate did work - but made me feel terrible."

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.

People want pain relief, reduction in symptoms such as swollen joints and reduced fatigue. These also want minimal side-effects or at least the ability to manage those adverse events.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

Wider access, choice and options appear to be important as many people seem to move through the pathway quickly if there is no response to current treatment.

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.

No comments to make.

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.

No comments to make.

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.

The use of secukinumab in a population who have extensive psoriasis might see a greater combined benefit, if they also have psoriatic arthritis.

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.

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.

The few that responded to the survey offered similar experiences to those in the trials.

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?

The problem with the trial is that the standard measure and outcomes are ACR20, ACR50, ACR70, these reflect percentage improvement, which is OK as a measure for trial purposes against placebo and active comparator. Pain, swollen joints and fatigue are the main issues that people have, therefore in reality praising a 20% improvement (ACR20) from base is hardly going to make people with psoriatic arthritis feel significantly better as they will still have significant disease.

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?

The side-effects in the trial appear to match those which we have heard about from people on these therapies.

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.

No

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.

There is always a suggestion around self-injecting and those with phobias, or poor hand mobility, which this group often have, but looking at the responses we received, people appear to cope with the therapies and methods of administration, or find ways to cope, as long as there is a treatment benefit.

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.)

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.

- *Reduction in pain, inflammation and fatigue.*
- *Avoid disabling consequences of psoriatic arthritis by maintaining mobility, stopping further deterioration and joint destruction.*
- *Reduced drug adverse events, without loss of efficacy.*
- *Access and choice to a wide range of therapies*
- *Halt progression and reverse disease effects.*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]

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. Due to the close association psoriatic arthritis shares with psoriasis, the work of the Psoriasis Association over the years has come to encompass this condition as well. 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?

Psoriatic arthritis can affect people of any age, and it often affects people in young or 'mid' adulthood who should, otherwise, be 'in their prime', pursuing careers, relationships and families. Psoriatic arthritis causes inflammation in

the joints and areas where tendon join to bone, which creates symptoms such as pain, stiffness and swelling. As with many types of musculoskeletal conditions, these symptoms impair function, and make it difficult to carry out normal everyday tasks. Psoriatic arthritis can flare up and subside unpredictably. This unpredictable nature, along with the physical symptoms, impacts greatly on the ability of people with the condition to work or study consistently, or make future commitments. This can have permanent effects on long-term career prospects. Psoriatic arthritis can have an adverse impact on relationships – one Psoriasis Association member in her 20s stated that her relationship broke down after her diagnosis of psoriatic arthritis, as it left her too tired and in pain to pursue the activities that her and her partner enjoyed doing. The described losses in quality of life, coupled with having to live long-term with pain, fatigue, immobility and uncertainty mean that psoriatic arthritis can have a significant impact on mental wellbeing. Crucially, without timely and effect treatment, the damage –and associated symptoms and impacts – caused by psoriatic arthritis can be permanent.

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.

Psoriatic arthritis is a condition that is unique to each individual, and it is important for clinicians to discuss the condition, its symptoms and impacts thoroughly with each patient/carer, and note what would be a successful treatment outcome for them. Important treatment outcomes may not be the same for every patient.

However, many patients with diagnosed or suspected psoriatic arthritis express worries regarding long term outlook and their future. Keeping disease activity to a minimum could indicate a positive long term outlook, and would offer stability and predictability to patients, which may result in increased quality of life and mental wellbeing.

In the shorter term, a reduction in pain and other immobility-causing symptoms (stiffness, for example) would be favoured by many patients, as it

would allow them to go about a more ‘normal’ life. Additionally, fatigue is not to be under-considered. It is common for patients to complain of fatigue and the adverse effect it has on their lives, and so an improvement here would be welcome.

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?

Non-Steroidal Anti-Inflammatory Drugs are often prescribed in primary care, and steroid injections are a common initial treatment in secondary care. Whilst these often improve symptoms, they are short-term and do nothing to tackle the actual condition itself. NSAIDs and steroids can be useful supportive treatments as part of a larger treatment ‘package’, but they will not prevent long-term irreversible damage from occurring or do anything to improve the long-term outlook of the condition. Additionally, steroids can cause associated psoriasis to flare, which will likely have further adverse impacts on the patients’ quality of life, mental wellbeing and general health.

There are a number of biologic and non-biologic ‘Disease-Modifying’ treatments available, which often do have a beneficial impact on the condition and can prevent progression and irreversible damage. However, every psoriatic arthritis patient is unique and it is often a process of trial and error to find the treatment, or combination of treatments, that works for each individual. This is hampered greatly when individual CCGs limit the number of Disease Modifying treatments a patient can access (usually biologics).

Additionally, not every Disease-Modifying drug works well on ‘extra-articular’ symptoms of the condition, such as enthesitis, fatigue and skin psoriasis itself. In patients where these symptoms are of particular concern, it may be that one Disease-Modifying treatment is more appropriate than another, or that more than one needs to be tried to achieve the optimal outcome for the patient. Limits on numbers of biologics per patient can seriously hamper or prevent this from being achieved.

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.

Both certolizumab pegol and secukinumab are Disease-Modifying treatments, and therefore patients or their carers would expect that these treatments would slow down or stop the progression of the psoriatic arthritis, resulting in a better long-term outlook, reduction of symptoms and stability – allowing them to plan ahead and look forward to the future. This may also lead to an improvement in mental health and quality of life, allowing patients to carry out activities that they were able to do before the onset of the disease.

Both of these treatments offer a different option for those who have tried the currently-available Disease-Modifying treatments and not had acceptable results. Secukinumab in particular is a novel treatment that works in a different way to all currently available treatments.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

Secukinumab in particular is a novel treatment that works in a different way to all currently available treatments.

Certolizumab pegol has a good track record in rheumatoid arthritis, and therefore may suggest that it will have positive benefits on other types of inflammatory arthritis, including psoriatic arthritis.

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.

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.

Many people do worry about the side effects/potential toxicity of Disease-modifying treatments, and long-term safety in particular is not yet certain. However, many people will be willing to tolerate a certain level of side effect for an improvement in their quality of life, related to improving their psoriatic arthritis.

Psoriatic arthritis often affects people who are at the age where they are considering starting a family, and these treatments are usually contraindicated in pregnancy or breastfeeding. However, severe psoriatic arthritis may in itself

prevent pregnancy for a number of reasons. Therefore, treatment with these drugs for a time, to attain stability, may be beneficial.

Please list any concerns patients or carers have about the treatment(s) being appraised.

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.

These treatments may be of particular benefit to patients who have tried other currently-available Disease-Modifying drugs and not had acceptable results. Psoriatic arthritis is a disease that can behave uniquely to each individual and, therefore, the widest possible range of treatments gives patients the most options for results.

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 Somewhat familiar☐ 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.

The patient experiences of using these treatments that we are aware of have been mainly positive.

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?

It is pleasing to see that clinical trials of both treatments considered secondary outcomes including the effect on dactylitis, enthesitis, skin and nail psoriasis, as well as the primary outcomes on joint symptoms. This is extremely important as, to patients, the 'extra-articular' symptoms can be just as debilitating as the specific articular symptoms.

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?

As far as we are aware, the side effects are as described in clinical trial outcomes.

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.

Chisolm, A., et al. **Distress, misperceptions, poor coping and suicidal ideation in psoriatic arthritis: a qualitative study**. Rheumatology (2016) doi:10.1093/rheumatology/kew009 First published online: March 8, 2016.

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.

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.)

The IL-17A action of secukinumab is entirely different to anything that is currently available.

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.

- Psoriatic arthritis causes considerable life impact to relatively young and healthy people. Its symptoms and capacity for irreversible damage can prevent people from pursuing work and careers, relationships, and a

satisfying family life. The effects of this on mental health and quality of life cannot be understated.

- Psoriatic arthritis is unpredictable without effective management. Without the stability that Disease-Modifying treatments can provide, the short, mid and long-term future for a person with psoriatic arthritis is unknown.
- Non-Disease-Modifying treatments (such as non-steroidal anti-inflammatories, painkillers and steroid injections) do not treat the condition. They have a place in treating the symptoms, but the only way to ensure longer-term management and stability, and to prevent irreversible joint damage, is to use Disease-Modifying treatments.
- The two treatments being considered in this MTA are different from those that are currently available, and therefore provide additional options which may be of particular benefit to people whose options for treating and managing their psoriatic arthritis are running out.
- Every person with psoriatic arthritis is different, and what works for one will not necessarily work for another. Therefore, the Psoriasis Association supports the availability of the widest possible range of effective treatments.

British Association of Dermatologists
Comments on Multiple Technology Appraisal ID579:
Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs
April 2016

The scope makes no mention of people with concurrent skin disease. As per NICE CG153, before making changes to biological therapy, for patients with psoriatic arthritis and psoriasis, both compartments should be considered. Where available outcomes on skin disease (e.g. PASI, DLQI) should be included. There is mention of looking at PASI scores in outcomes, and we advise looking at DLQI also.

For the same reasons, the sequences of drugs may be influenced by whether or not skin disease is present, given that some biologics are either not as effective as others or have different dosing schedules for psoriatic arthritis and psoriasis (e.g. secukinumab) or where there is a differential response in either compartment (e.g. responding in joints but not skin).

[redacted], Therapy & Guidelines Sub-Committee

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]

Thank you for agreeing to give us a statement on your 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 statement, 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:

Philip Helliwell

Name of your organisation

British Society for Rheumatology
(University of Leeds and Bradford Hospitals NHS Trust)

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)? YES
- 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, member
- 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: None

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Psoriatic arthritis is a heterogeneous disease with diverse clinical manifestations. From a rheumatologic point of view it is appropriate to consider the condition as peripheral and axial arthritis. The peripheral arthritis can be usefully considered either oligoarticular (less than 4 joints) or polyarticular, although it should be accepted that this division is somewhat arbitrary. It is likely that the response to treatment differs between these sub-grouos. For this reason it is difficult to design a single treatment algorithm to cover all aspects of the disease. The situation is complicated by the lack of evidence supporting the use of many of the so called ‘disease modifying drugs’ for use in psoriatic arthritis. Indeed, the drug that is the mainstay of treatment of psoriatic arthritis and the one that most rheumatologists first turn at disease onset, methotrexate, has little support from randomised controlled trials. Further, methotrexate has no efficacy on axial disease. Nevertheless,

there is sufficient evidence from both observational studies, uncontrolled trials and physicians own experience for methotrexate to maintain a pivotal role in the treatment of peripheral psoriatic arthritis, and it remains the first line drug in this condition. Methotrexate is not without problems: patients often complain of nausea, hair thinning and both physicians and patients worry about hepatotoxicity, particularly in the overweight patients and those who consume moderate amount of alcohol. If methotrexate fails many physicians will be looking to use anti-TNF drugs, particularly if there are adverse prognostic factors. However, many European countries, including the UK as part of the British Society Guidelines, advise the use of a second agent, such as sulfasalazine or leflunomide, before moving onto biologics.

Within the last 12 months two sets of international treatment recommendations have been published. Both groups performed a similar systematic literature review, including published abstracts, up to autumn 2015 (EULAR recommendations: Gossec et al., Ann Rheum Dis, 2016;75:499-510. GRAPPA recommendations: Coates et al. Arthr Rheum, 2016:68:1060-1075). Both now include the new technologies under consideration here: certolizumab pegol (a TNF inhibitor) and secukinumab (an antibody directed against IL-17). Differences between the different recommendations include differences in methodology (The GRAPPA recommendations used the GRADE methodology) and in the treatment algorithms (GRAPPA developed algorithms according to disease domain whereas EULAR developed a single algorithm). At the time data for secukinumab were in abstract form only but have since been published as full papers. Certolizumab pegol, as a TNF inhibitor (TNFi) was grouped with the other TNFi as there is no reason to believe it differs in its efficacy from the other members of this class of drugs. Thus TNFi are the biologic drugs of choice when conventional DMARDs have failed and have shown efficacy against all the different manifestations of this disease. The emerging data on secukinumab show very effective suppression of skin disease and efficacy equivalent to TNFi in the musculoskeletal

domains of this disease. Inhibitors of IL-17, including seculinumab, were therefore recommended *after* TNFi in the EULAR recommendations, whereas GRAPPA made *provisional* recommendations *alongside* TNFi for most domains of disease. Both groups recommended IL-17 inhibitors when TNFi drugs had failed, or there was intolerance, or contraindication.

From the point of view of the NHS these are different technologies. Certolizumab pegol is another in the class of TNFi. It may have some advantages in terms of adverse events, and possibly tissue penetration, but the evidence to support this is not substantial. Therefore the place of this drug in the treatment of psoriatic arthritis, after the decision to use a TNFi, will depend on factors such as cost and dosing convenience.

Secukinumab represents a new class of biologic drug for treating psoriasis and psoriatic arthritis. It is currently available for the treatment of psoriasis. With trial data suggesting improved efficacy against psoriasis it is now being used as the first biologic in this condition. At this stage I can't see this being the case for the treatment of psoriatic arthritis, unless the skin disease is particularly severe, and with time this position may change. However, secukinumab will offer an alternative for people who do not respond to TNFi (about 30%) and for people who have failed, or become intolerant, or who can't take TNFi for other reasons. Long term familiarity and safety concerns will also play a part in prescribing patterns.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Certolizumab pegol, another in the class of TNFi, in clinical trials has shown efficacy in all clinical domains of psoriatic arthritis as well as inhibiting radiographic damage. As far as can be seen, the adverse event profile is similar to other members of this class of drugs. It's use in clinical practice will depend on cost and dosing schedules.

From the data available so far secukinumab may be a valuable addition the psoriasis and psoriatic arthritis treatment portfolio. However, although drugs such as secukinumab seem to have a favourable side effect profile, both direct comparison with other drugs and long term studies are needed to complete the picture. In particular more information is needed on people with liver disease, heart disease and in pregnancy. There is a note of caution with

this class of drugs in people with psoriatic arthritis: psoriatic arthritis is a member of the spondyloarthropathy group of diseases in which there is a higher prevalence of both clinical and sub-clinical inflammatory bowel disease and IL-17 inhibitors may exacerbate inflammatory bowel disease. Therefore, in some people, this class of drug may be contraindicated.

Equality and Diversity

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

As far as I am aware there are no data on the response of different ethnic groups to this drug.

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.

I know of no other data. Since the drug has only recently been licensed data are not yet available on its efficacy and safety in a practice setting, nor from Registries.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government 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)?

As with other biologic drugs these technologies are administered parentally. The infrastructure to support the delivery and administration of these drugs already exists in the UK NHS.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]

Thank you for agreeing to give us a statement on your 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 statement, 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: Dr Ellie Korendowych

Name of your organisation
Royal National Hospital for rheumatic Diseases, RUHFT, Bath

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)? YES
- 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.)? NO
- 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: none

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Multiple Technology Appraisal (MTA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

It would be anticipated that certolizumab would be used alongside currently approved TNFi (etanercept, adalimumab, golimumab and infliximab). There is no evidence to expect the response to this TNFi to be significantly different to the other TNFi which are used in patients who have failed 2 DMARDS and have 3 or more tender and swollen joints.

Sekukinumab offers an alternative pathway via IL17 inhibition which is welcomed for those patients who have contra-indications to TNFi or previous inefficacy to TNFi and could be used as an alternative to TNFi first line after DMARD failure.

Both medications have proven efficacy in treating psoriasis, with sekukinumab having a proven track record in psoriasis treatment following NICE guidance for Dermatologists. Sekukinumab may be particularly attractive in patients where psoriasis is a significant factor.

Both medications would be restricted in use to secondary care.

There are published BSR, EULAR and GRAPPA guidelines for treatment of PsA.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for

example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The advantage of certolizumab is that it is an established TNFi used in RA under NICE guidelines. It should sit alongside the other TNFi for patient choice whilst considering availability and pricing of biosimilars. There are some patients who have side effects or inefficacy to other TNFi where certolizumab would be helpful. As it is pegolated it is especially attractive in pregnancy due to its limited movement across the placenta.

Sekukinumab offers a completely different pathway and is therefore a very attractive option for PsA treatment. It would be particularly beneficial for patients with severe psoriasis and has a rapid onset of action. There are limited agents available that have such efficacy that are not TNFi (ustekinumab is the only available agent approved by NICE as an alternative agent for TNFi failures)

It is advantageous that methotrexate is not necessarily required as some patients are unable to tolerate methotrexate.

The trials would largely reflect the population these medications would be used in, although in reality both agents are likely to be used after failure of several other agents eg other TNFi and ustekinumab which is not necessarily reflected in the clinical trials.

Equality and Diversity

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Multiple Technology Appraisal (MTA)

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- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

No identified issues

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No additional information that should not already be available for consideration.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government 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)?

No additional resources required