NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
SINGLE TECHNOLOGY APPRAISAL

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

Contents:

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

NICE National Institute for Health and Care Excellence

Certolizumab pegol for treating moderate to severe plaque psoriasis

Pre-meeting briefing

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

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

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

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

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

NICE 2

Abbreviation	In full
ADA	Adalimumab
AE	Adverse events
BNF	British National Formulary
BROD	Brodalumab
BSC	Best Supportive Care
CZP	Certolizumab pegol
DLQI	Dermatology Life Quality Index
ETN	Etanercept
EQ-5D	EuroQol five dimensions questionnaire
GUS	Guselkumab
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
IFX	Infliximab
IXE	Ixekizumab
PAS	Patient Access Scheme
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PsA	Psoriatic arthritis
SD	Standard deviation
SEC	Secukinumab
TNF	Tumour Necrosis Factor
QALY	Quality Adjusted Life Year
UST	Ustekinumab

Key issues – clinical effectiveness

1. What it the likely position of certolizumab pegol in the treatment pathway?
   - Is there evidence that certolizumab pegol can be used earlier in the treatment pathway that other biologic therapies?
2. Are the results from the clinical trials generalisable to the eligible population in the NHS in terms of:
   - DLQI score?
   - Previous treatment with biologic therapies?
3. Do the pooled efficacy results from the overall trial population reflect the pooled results of the subgroups where certolizumab pegol would be used in the NHS?
4. Is the network meta analysis appropriate?
5. Is there evidence that certolizumab pegol is of additional benefit during pregnancy/breastfeeding?

4

Note:

The company has presented updated data relating to the meta analysis and an updated base case partially based on these data. The ERG has not had sufficient time to critique these analyses ahead of publication of the PMB so they are not presented here, but these may be presented at the committee meeting.

Key issues – cost effectiveness

1. Is analysis of treatment sequences using ICERs or individual treatments using a net monetary benefit framework preferred?
2. What is the most appropriate comparator?
3. Is the assumption of an equivalent discontinuation rate of 20% for all biologics appropriate?
4. How should the costs of biosimilars to adalimumab be accounted for?
5. Should cost of best supportive care be modelled updated prices?
6. Should utility values be modelled by limiting population to DLQI>10 and assuming biologic utility values are the same as best supportive care?
7. Is the dose escalation strategy for certolizumab pegol cost effective?
8. Is certolizumab pegol cost effective for candidates for systemic therapy?

5

Note:

The company has presented new base case analyses which alter the considerations in some of these issues, the ERG has not had sufficient time to critique these analyses ahead of publication of the PMB, so they are not presented here, but these may be presented at the committee meeting.

Disease background

- Chronic inflammatory condition characterised by flaky, scaly, itchy and red plaques on skin
- May affect scalp, elbows, knees, lower back and sometimes face, groin, armpits and behind the knees
- Unpredictable, relapsing and remitting course
- Associated with comorbidities such as depression, anxiety, arthritis, cardiovascular disease
- Graded as mild, moderate or severe (based on location, area affected, severity of lesions and impact on individual)
- Population:

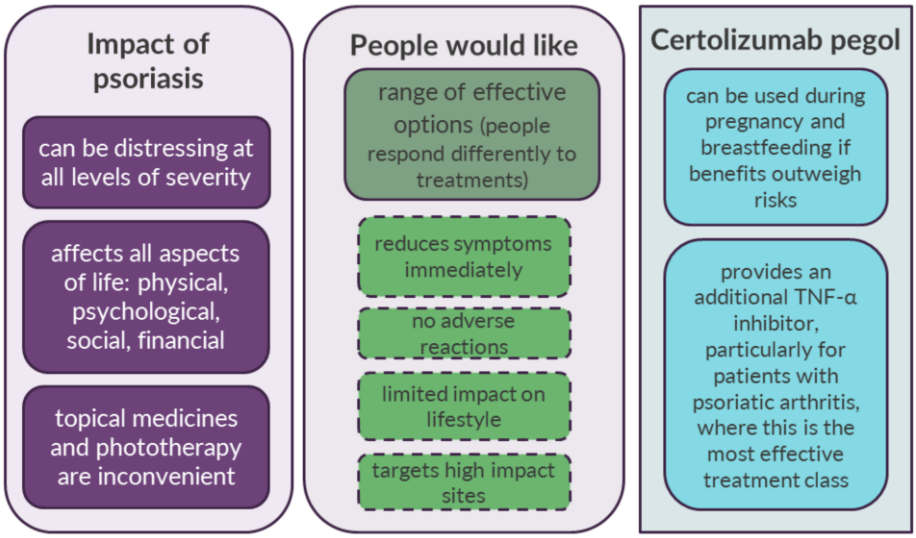
NICE

6

Source; Company submission p21-24

Patient and clinical perspective – summary

Distressing and debilitating, need for a range of highly effective convenient treatments with minimal adverse reactions and impact on lifestyle



7

Comments from patient groups

- Psoriasis can affect every stage of life to varying degrees – from bullying in school, through to difficulty writing in exams, choice of career, having children, holidays and long-term relationships. Access to treatments that are appropriate, suitable and reliable is vital
- Although there are a number of anti-TNF agents available, there will be a cohort of patients who have lost long-term efficacy on the available anti-TNFs but for whom the newer interleukin inhibitors are not suitable. This group in particular would benefit from a new anti-TNF agent
- Certolizumab pegol is the only biologic treatment licensed for use in women during pregnancy and breastfeeding, making it a much-needed option for women of childbearing age with moderate to severe psoriasis
- Nail psoriasis, which can be a huge issue for people with psoriasis, appears to be recorded as improved in trial. Nail psoriasis is an important disease domain with an unmet need
- Psoriatic arthritis needs to be considered as potentially benefiting, when skin psoriasis is treated.

NICE 8

Source: Patient group submissions from the Psoriasis and Psoriatic Arthritis Alliance (PAPAA) and the Psoriasis Association

Comments from professional organisations

- An additional TNF inhibitor available for use in people with severe psoriasis will be a helpful intervention in the psoriasis treatment pathway in the following scenarios:
  - Use in in women of child bearing potential planning conception or who are pregnant
    - lack of placental transfer, important in pregnant patients with severe psoriasis in whom ciclosporin has not been efficacious
  - Patients developing anti-TNF failure due to antidrug antibody (ADA) formation (common with adalimumab and infliximab)
  - Patients with a poor (primary) response to another TNF inhibitor

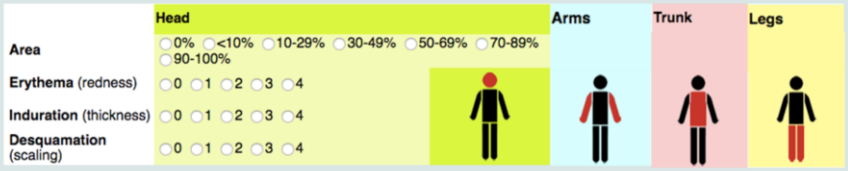
NICE 9

Source: Professional group submissions from the British Association of Dermatologists (BAD) and the British Society for Rheumatology (BSR) endorsed by the Royal College of Physicians.

Measuring psoriasis severity and response

Psoriasis Area and Severity Index (PASI)

- Weighted score (0 to 72) of 4 affected areas (Head, Arms, Trunk, Legs)
  - 0 (no psoriasis); 10 (moderate); >10 (severe)
- Clinically important response defined as a 75% reduction in PASI score from baseline (PASI 75), (PASI 50, 90 and 100 are also considered in this appraisal)



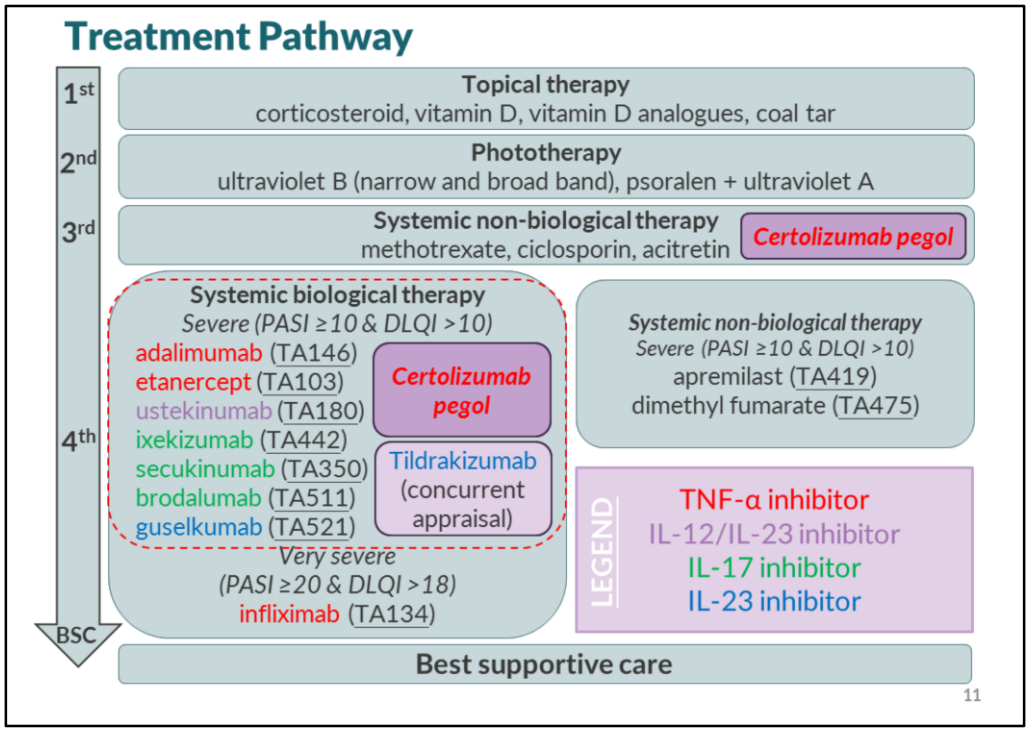
Physician Global Assessment (PGA)

- Scored physician's impression of psoriasis severity – 0 (clear) to 5 (severe)
- Clinically important response defined as a reduction to 'clear' (0) or 'minimal' (1)

Dermatology Life Quality Index (DLQI)

- 10 questions about how psoriasis affects quality of life: symptoms, feelings, daily activities, treatment etc.
  - Each question receives a response of 0-3 (3 is the worst impact); >10 DLQI (severe)
- Clinically important response defined as a 5 point reduction in DLQI

10



Source: NICE Psoriasis guideline (CG153; https://www.nice.org.uk/guidance/cg153). NICE technology appraisals (TA146, TA103, TA442, TA350, TA180, TA134, TA419, TA475, TA511, TA521).

Stopping criteria for treatments recommended by NICE for severe psoriasis

TA number	technology	Assessment made at:	Adequate response defined as:
103	Etanercept	12 weeks	• PASI 75 (75% reduction in PASI score from baseline) Or • PASI 50 + 5 point reduction in DLQI
350	Secukinumab		
442	Ixekinumab		
511	Brodalumab		
146	Adalimumab	16 weeks	
180	Ustekinumab		
419	Apremilast		
475	Dimethyl fumarate		
521	Guselkumab		

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PASI: Psoriasis Area and Severity index; DLQI dermatology life quality index

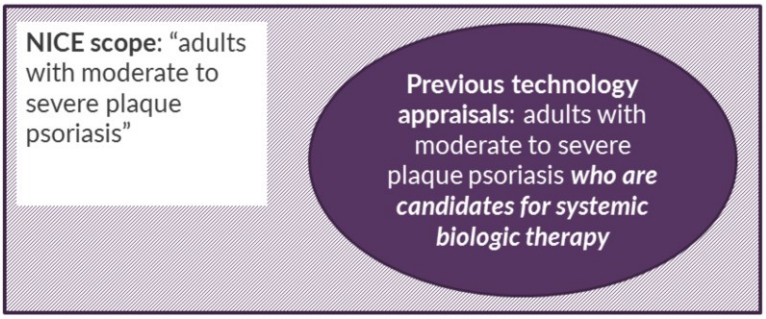
Certolizumab pegol (Cimzia®)

Mechanism	PEGylated TNF-α inhibitor
Marketing authorisation	Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy
Administration and dose	*Loading dose:* The recommended starting dose of certolizumab pegol is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. *Maintenance dose:* After the starting dose, the recommended maintenance dose of certolizumab pegol is 200 mg every 2 weeks. A dose of 400 mg every 2 weeks can be considered in patients with insufficient response.
List price	£357.50 per 200 mg pre-filled pen or syringe
Patient access scheme	First 12 weeks of CZP are provided free of charge

NICE 13

Source: Company submission, table 2, p17-18

Decision problem – population



- **Comparison to other biological treatments reflects likely position within UK clinical practice**
- Effectively limits decision problem to adults with severe plaque psoriasis (PASI ≥ 10 and DLQI > 10)
- The inclusion criteria of clinical trials specified PASI score ≥ 12

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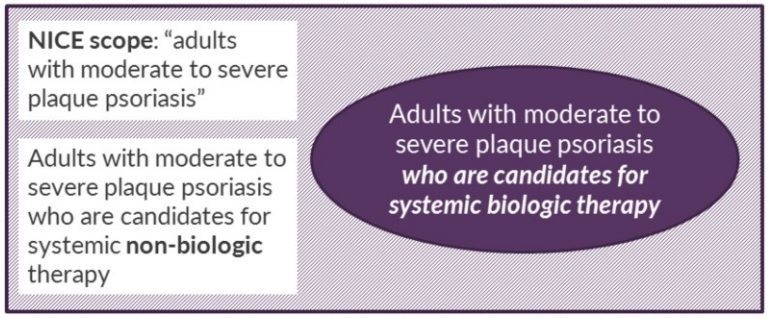
14

Source: brodalumab (TA511) appraisal committee slides

Company decision problem – population



- In contrast to previous appraisals company decision problem includes patients with moderate to severe plaque psoriasis if systemic **non-biological** therapy is suitable (in line with NICE scope)
- Company state this is with British Association of Dermatologists guidelines suggesting biologics may used earlier in treatment pathway if patients have severe or extensive psoriasis **and** active psoriatic arthritis or persistent psoriasis
  - Guideline describes "earlier" as "if methotrexate has failed, is not tolerated or is contra-indicated" in contrast to the criteria for biological therapy which require both methotrexate and ciclosporin to have failed – i.e. does not support use in treatment-naïve population

Source: company submission p13 and 27

BAD guidelines p15 R4 and R5, available at http://www.bad.org.uk/shared/get-file.ashx?id=5835&itemtype=document

Company decision problem - comparators

	Final scope issued by NICE	Decision problem addressed in the company submission
Comparator(s)	If systemic non-biological treatment or phototherapy is suitable: • Systemic non-biologic therapies (including methotrexate, ciclosporin, acitretin) • Phototherapy with or without psoralen If conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated: • Anti-TNFs (ADA, ETN, IFX) • IL-17 inhibitors (BROD, IXE, SEC) • IL-23 inhibitor (GUS) • IL-12/IL-23 inhibitor (UST) • APR • DMF • Best supportive care	If systemic non-biological treatment or phototherapy is suitable: • Systemic non-biologic therapies, including methotrexate, ciclosporin, acitretin If conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated: • Anti-TNFs (ADA, ETN) • IL-17 inhibitors (BROD, IXE, SEC) • IL-23p19 inhibitor (GUS) • IL-12/IL-23 inhibitor (UST) • Best supportive care

Source: Company submission, table 1 p13-16

Notes:

Company's rationale for

1) Not including phototherapy +/- psoralen (PUVA) as comparator: not expected to be used in clinical practice in same position as systemic non-biological or systemic biological therapies. Cited British association of dermatologists: PUVA not routinely used because of risk of skin cancer particularly when followed by immunosuppression. CG153 noted number of populations in which PUVA not recommended, PUVA should only be used when other options have been offered and cannot be used or are inappropriate
2) Not including infliximab (IFX): only recommended for very severe psoriasis and is a more restricted population than considered in the submission for certolizumab pegol
3) Not including dimethyl fumarate or apremilast. In clinical practice would only be considered for use in patients unsuitable for

biologic treatment or unwilling to receive biologics. Therefore would be used before or after biologics. BAD guidelines “other non-biologic systemic therapies (e.g. acitretin, apremilast) may be appropriate prior to using biologic therapy but not mandatory, given their unpredictable and lower overall efficacy.” Previous NICE TAGs have stated that apremilast and DMF would not displace biological therapies during their recent appraisals (NICE TA419, TA475). It was also accepted in the recent appraisal of guselkumab (TA521) that apremilast and DMF would not be comparators for this new biologic therapy.

Company decision problem - outcomes

	Final scope issued by NICE	Decision problem addressed in the company submission
Outcomes	• Severity of psoriasis • Psoriasis symptoms on the face, scalp, nails and joints • Mortality • Response rate • Duration of response • Relapse rate • Adverse effects of treatment • Health-related quality of life (HRQoL)	This submission includes a range of outcome measures to assess the clinical effect of CZP, including: • Severity of psoriasis, measured using the PASI, including PASI75/90/100 responder rates, PGA 0/1 response, and BSA affected by psoriasis. PASI75 responder rate was the co-primary endpoint in the clinical studies included in this submission and is the measure of clinical response used by NICE. PGA was a co-primary endpoint in two of the clinical studies included in this submission. • Improvement in symptoms on the nails, measured by mNAPSI • Improvement in symptoms in the joints, measured by data from the PsA clinical programme • Relapse rate, measured by time to not achieving PASI50 response • Adverse events • HRQoL, measured using the DLQI, SF-36, HADS-A and HADS-D, and EQ-5D • Work productivity and social activities, measured by WPAI-SHP

Source: Company submission, table 1 p13-16

ERG comments – decision problem

Population

- Clinical advice to ERG states that clinical advice confirmed that generally biologic therapies are used after non-biological systemic therapy in the treatment pathway because non-biologic therapies are less costly (approach used in previous appraisals) → most relevant population patients for whom standard systemic treatment or phototherapy is inadequately ineffective, not tolerated or contraindicated

Comparators

- Agree that phototherapy is not used in the same position in the treatment pathway → exclusion from comparators appropriate
- Clinical advice to ERG states dimethyl fumarate and apremilast would not displace biological therapies → exclusion from comparators appropriate

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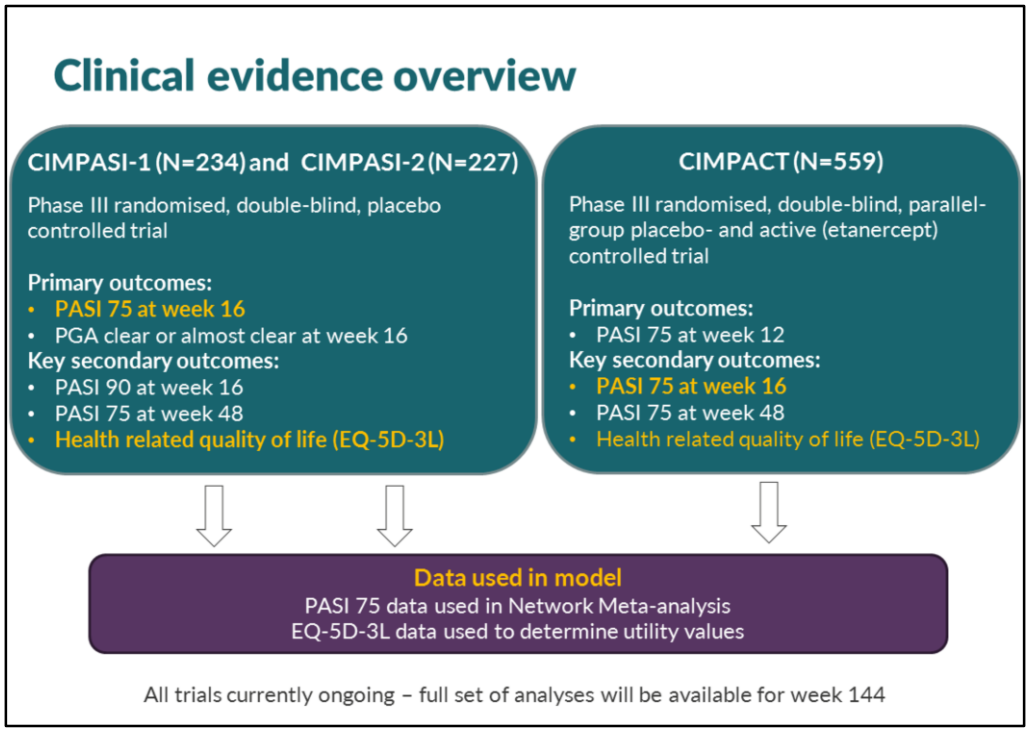
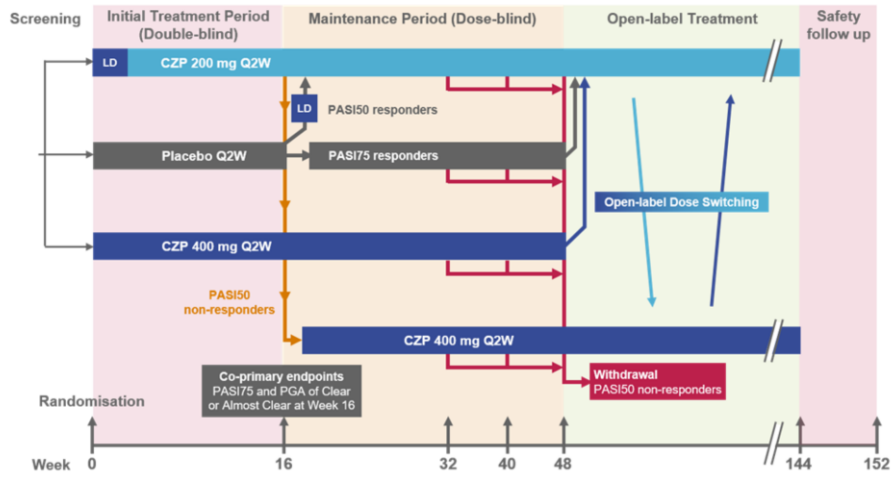
18

Source: ERG report p27-29



Source: Company submission table 8, p39-40 and table 9, p44-48

CIMPASI-1 and CIMPASI-2 trial design



NICE

20

Source: Company submission p41

Notes:

Randomisation 2:2:1 to CZP 200 mg:CZP 400 mg:placebo

Week 16: Co-primary endpoints measured

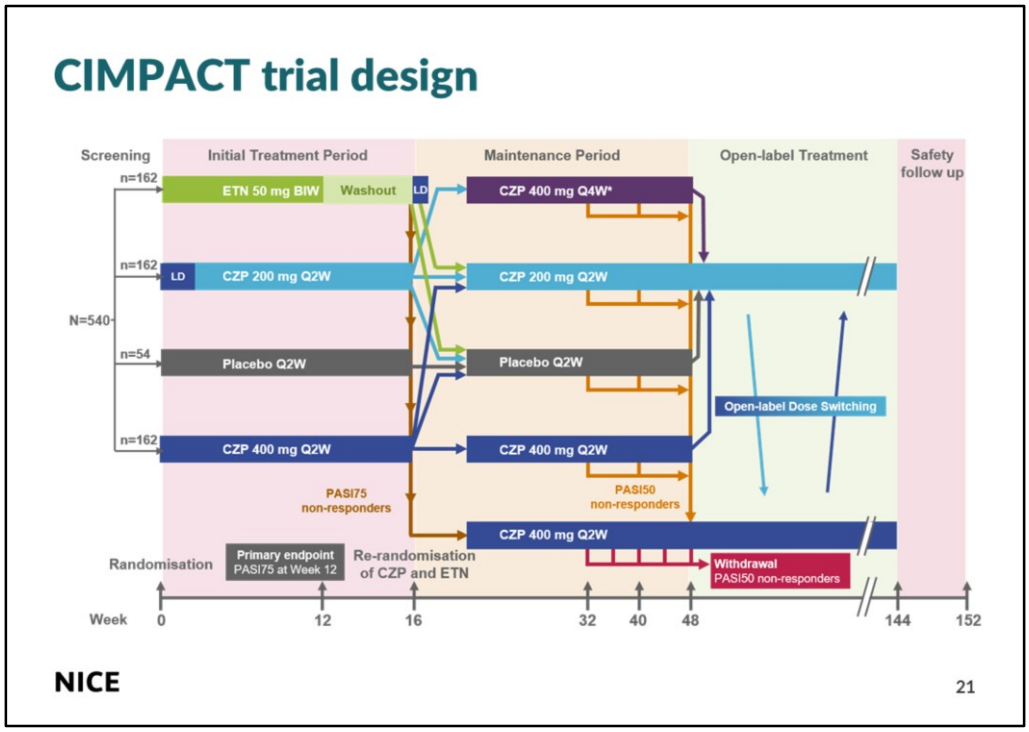
Week 16: responders (PASI 50 for CZP, PASI 75 for placebo) continue on therapy

Week 16: placebo non responders (PASI 50-75) receive 3 x 400 mg CSP loading dose then CZP 200 mg

Week 16: All non-responders (PASI <50) receive open label CZP 400 mg

Week 32: All non responders (PASI <50) withdrawn from study

Week 48: Open label phase with dose switching between CZP 200 mg and CZP 400 mg. Non responders withdrawn



Source: Company submission p42-43

Notes:

Randomisation 3:3:3:1 CZP 200 mg:CZP 400 mg:Etanacerpt:Placebo

Week 12: Primary endpoint measured, etanercept washout period

Week 16: All non responders (PASI<75) escape to CZP 400 mg

Week 16: Responders to etanercept re-randomised 2:1 to CZP 200 mg (with 3x loading dose CZP 400 mg)

Week 16: Responders to CZP 200 mg re-randomised 2:2:1 to CZP 200 mg:CZP 400 mg:placebo

Week 30: All non responders (PASI<50) withdrawn from study

Baseline characteristics

Characteristic	CIMPASI-1			CIMPASI-2			CIMPACT			
	Placebo (n=51)	CZP 200 mg (n=95)	CZP 400 mg (n=88)	Placebo (n=49)	CZP 200 mg (n=91)	CZP 400 mg (n=87)	Placebo (n=57)	ETN (n=170)	CZP 200 mg (n=165)	CZP 400 mg (n=167)
Male, n (%)	35 (68.6)	67 (70.5)	60 (68.2)	26 (53.1)	58 (63.7)	43 (49.4)	34 (59.6)	127 (74.7)	113 (68.5)	107 (64.1)
PASI, mean (SD)	19.8 (7.5)	20.1 (8.2)	19.6 (7.9)	17.3 (5.3)	18.4 (5.9)	19.5 (6.7)	19.1 (7.1)	21.0 (8.2)	21.4 (8.8)	20.8 (7.7)
DLQI, mean (SD)	13.9 (8.3)	13.3 (7.4)	13.1 (6.5)	12.9 (7.3)	15.2 (7.2)	14.2 (7.2)	13.2 (7.6)	14.1 (7.4)	12.8 (7.0)	15.3 (7.3)
Concomitant psoriatic arthritis, n (%)	4 (7.8)	10 (10.5)	15 (17.0)	9 (18.4)	22 (24.2)	26 (29.9)	12 (21.1)	27 (15.9)	27 (16.4)	24 (14.4)
Previous systemic therapy, n (%)	36 (70.6)	66 (69.5)	61 (69.3)	36 (73.5)	65 (71.4)	63 (72.4)	[redacted]	[redacted]	[redacted]	[redacted]
Previous biologic therapy, n (%)										
1 therapy	13 (25.5)	22 (23.2)	22 (25.0)	11 (22.4)	22 (24.2)	21 (24.1)	[redacted]	[redacted]	[redacted]	[redacted]
2 therapies	2 (3.9)	8 (8.4)	7 (8.0)	3 (6.1)	10 (11.0)	8 (9.2)	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company submission table 10, p50-53

Notes:

Higher proportion of males and patients with concomitant psoriatic arthritis in CIMPASI 2.

Trials include patients with no previous systemic therapy who currently would only be treated with biologics in NHS practice if they were contraindicated to all non-biologic systemic therapies.

Results – Response rates at week 16

- Both doses of certolizumab pegol resulted in statistically significant response rates compared with placebo unless otherwise stated

Responder rate, (%)	CIMPASI-1			CIMPASI-2			CIMPACT		
	Placebo (n=51)	CZP 200 mg (n=95)	CZP 400 mg (n=88)	Placebo (n=49)	CZP 200 mg (n=91)	CZP 400 mg (n=87)	Placebo (n=57)	CZP 200 mg (n=165)	CZP 400 mg (n=167)
PASI 75	6.5	66.5	75.8	11.6	81.4	82.6	3.8	68.2	74.7
PASI 90	0.4	35.8	43.6	4.5	52.6	55.4	0.3	39.8	49.1
PASI 100	0.2	13.7	12.7	1.8	15.4*	18.8	[redacted]	[redacted]	[redacted]
PGA 1/0	4.2	47.0	57.9	2.0	66.8	71.6	3.4	48.3	58.4

*p=[redacted]

NICE

23

Source: ERG report table 2, p43 (adapted from company submission, figures 5, 6 and 11)

Note: Primary endpoint for CIMPACT was response rate a week 12, week 16 results resented as these are used in the network meta analysis and model.

Comparison with etanercept (CIMPACT)

- Both doses of certolizumab pegol resulted in statistically significant response rates compared with placebo
- 400 mg dose showed statistically significant improvement in PASI 75 response rate compared with etanercept

Response rates at week 12

Responder rate, (%)	Placebo (n=57)	Etanercept (n=170)	CZP 200 mg (n=165)	CZP 400 mg (n=167)
PASI 75, p vs etanercept	5.0	53.3	61.3 0.1523	66.7 0.0152
PASI 90	0.2	27.1	31.2	34.0
PGA 0/1	1.9	39.2	39.8	50.3

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24

Source: Company submission p96

Note: Formal statistical test for significance for certolizumab pegol compared with etanercept only conducted for PASI 75 outcome.

ERG critique of clinical trials

- All trials of relatively good quality with low risk of bias
- ERG considers biologic exposed and systemic non-biologic therapy inadequate responders to be most relevant populations
- Trials contained [redacted] patients with a DLQI score <10 (below threshold recommended by NICE in previous appraisals) → results may not be fully generalisable to patient population
- Higher proportion of responders in CIMPASI-2 trial, may be explained by lower proportion of males and/or higher proportion of patients with psoriatic arthritis (who typically have poorer treatment outcomes) in this trial
  - Company stated in response to clarification that there is no clear evidence to indicate that differences in proportion of males and proportion of patients with psoriatic arthritis had any effect on clinical outcomes across the 3 trials → ERG considers reason for the difference in response rates to be unclear
  - ERG uncertain whether pooling of results appropriate because of this heterogeneity

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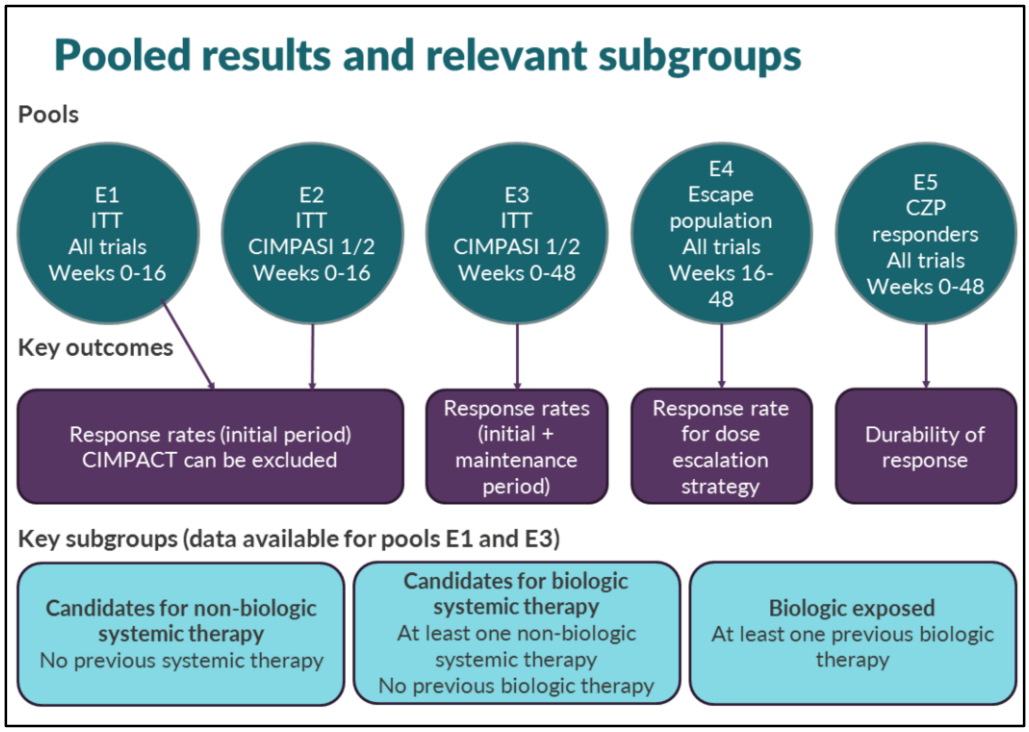
25

Source: ERG report p44, p60-62



Notes:

Candidates for non-biologic systemic therapy and candidates for biologic systemic therapy are post-hoc subgroups considered for the purpose of the appraisal. Results are also presented in the company submission for the pre-specified subgroups of biologically naïve and biologically exposed patients (see company submission p102-105)

The biologic exposed subgroup may or may not have had systemic therapy (see company submission appendices for baseline characteristics of subgroups).

Pooled results – response rates at week 16

Outcome	E1 pool – ITT population (CIMPASI 1/2 and CIMPACT)		
	Placebo (N = 157)	Certolizumab pegol 200 mg (N = 351)	Certolizumab pegol 400 mg (N = 342)
PASI 75, %	7.5	74.5	80.1
PASI 90, %	1.6	44.5	52.2
PASI 100, %	[redacted]	[redacted]	[redacted]
PGA clear/almost clear, %	2.8	54.6	63.7
DLQI score (change from baseline)	-2.4	-9.1	-10.4

All results were statistically significant comparing either dose of certolizumab pegol with placebo

Abbreviations: DLQI, Dermatology Life Quality Index; ITT, intention-to-treat; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment.

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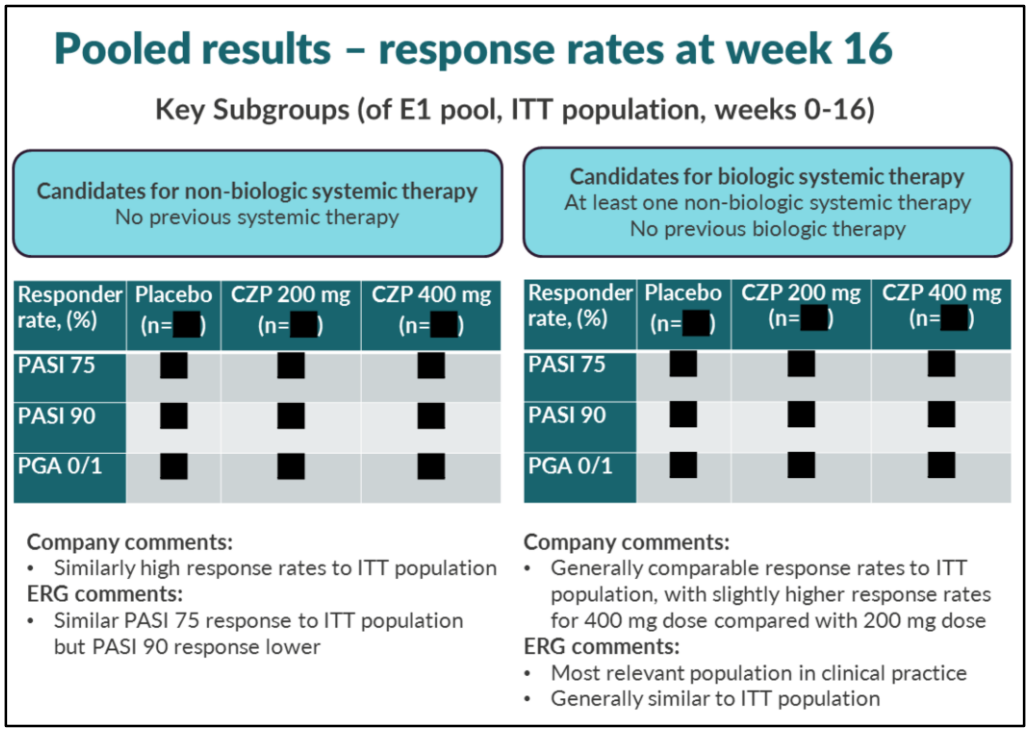
27

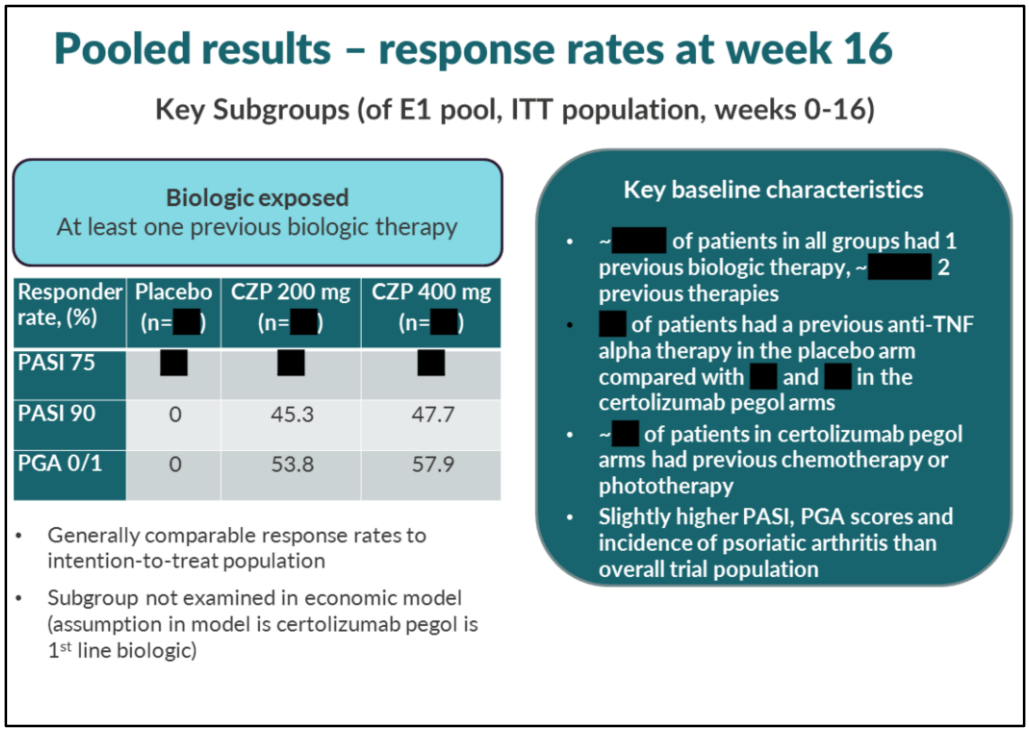
Source: adapted from ERG report table 6, p53 (data from company submission Figures 5, 6 and 11 and Tables 19 and 29)



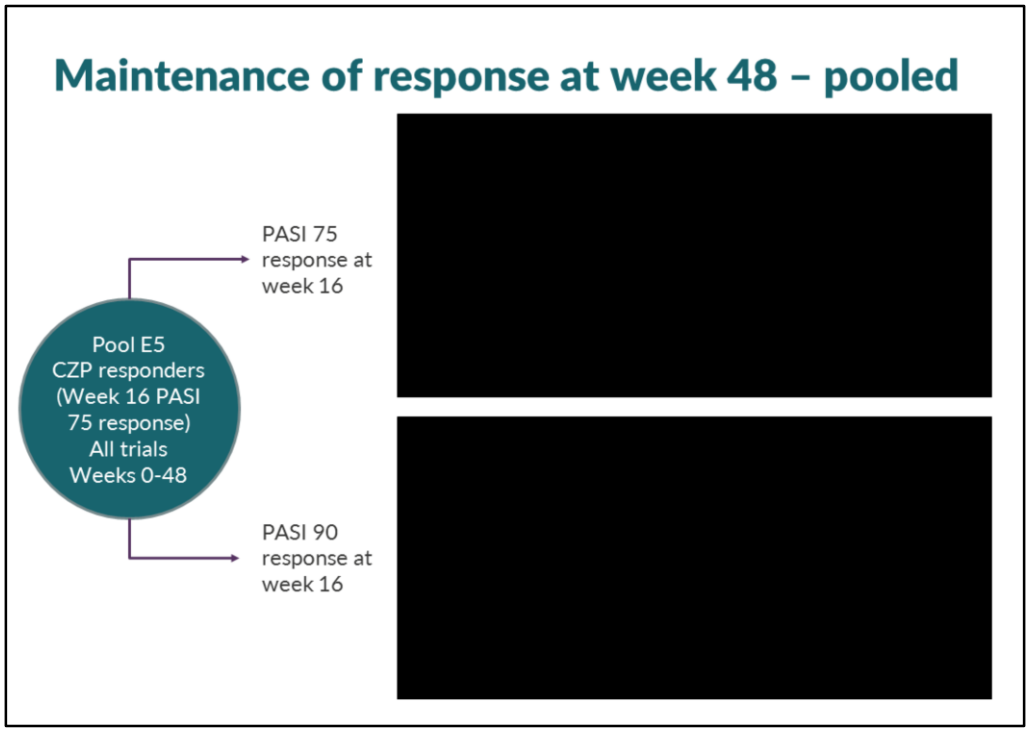
Source: Company submission table 41, p97 and table 46, p101

Note: Company stated in response to clarification that subgroup results should be interpreted with caution due to small sample size in many of the categories

Response rates in biologic-exposed population slightly higher for CZP 200 mg and slightly lower for CZP 400 mg.



Source: Company submission table 48, p103 and appendix M9, table 95, p209-211



Source: company submission: figure 9, p71

Light blue lines shows response rates over 48 weeks among patients who achieved a PASI 75 response at week 16. Almost [redacted]% of patients with PASI 75 response at week 16 and continued of CZP 200 mg Q2W maintain this response at week 48. The proportion of patients with a PASI 90 response increases from [redacted] between week 16 and week 48.

Pooled results – response rate weeks 0-48

Key Subgroups (of E3 pool, ITT population CIMPASI 1/2, weeks 0-48)

Candidates for non-biologic systemic therapy
No previous systemic therapy

Responder rate, (%)	CZP 200 mg (n=[redacted])	CZP 400 mg (n=[redacted])
PASI 75	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]
PGA 0/1	[redacted]	[redacted]

Company comments:
- Response maintained from week 16 for both doses of certolizumab pegol

ERG comments:
- PASI 75 rate decreases slightly from week 16 for the 400 mg dose

Candidates for biologic systemic therapy
At least one non-biologic systemic therapy
No previous biologic therapy

Responder rate, (%)	CZP 200 mg (n=[redacted])	CZP 400 mg (n=[redacted])
PASI 75	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]
PGA 0/1	[redacted]	[redacted]

Company comments:
- Increase in PASI 90 and PGA 0/1 response from rates at week 16 → clinical response improved or maintained

Source: Company submission figure 16, p98 and table 47, p101-102

Note: Company stated in response to clarification that subgroup results should be interpreted with caution due to small sample size in many of the categories

- Stopping criteria in trial was PASI<50 at weeks 16, 32 and 40. Adequate response in NICE recommendations for other biologic therapies defined is "PASI 75 (75% reduction in PASI score from baseline OR PASI 50 + 5 point reduction in DLQI" therefore may be some patients in company's analysis who would not continue treatment in NHS practice.

Dose escalation strategy

Pool E4
Inadequate responders
(PASI <50)
re-randomised to CZP
400 mg, all trials

- Company consider effectiveness of certolizumab dose escalation strategy from 200 mg to 400 mg for people with an inadequate response in initial period
- Light blue line shows improvement in PASI 75 and PASI 90 response rates for patients in the clinical trials who were treated according to this dose escalation approach
- Improvement in response observed over time:
  - PASI 75 response at week 32 approximately [redacted]%
  - PASI 75 response at week 48 [redacted]%

32

Source: Company submission figure 10, p72

Note: Placebo with escape to 400 mg dose and re-treatment with 400 mg dose as shown in other series in graph do not reflect the intended use of certolizumab pegol in the NHS.

Other outcomes

- Reduction in mean psoriasis body surface area for both 200 mg and 400 mg doses of certolizumab pegol compared with placebo in all trials
- Majority of patients treated with certolizumab pegol in CIMPASI 1 and 2 with nail psoriasis at baseline achieved resolution of nail psoriasis by week 48 ([redacted]% of patients on 200 mg dose and [redacted]% of patients on 400 mg dose)
- Response rates generally comparable in patients with less severe (DLQI <10) and more severe (DLQI ≥10) psoriasis
  - For patients with less severe psoriasis response rates similar between 200 mg and 400 mg dose
  - For patients with more severe psoriasis response rates higher for 400 mg dose compared with 200 mg dose

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33

Source: Company submission p77, 81-82, 105-106

Network meta-analysis (NMA)

- 83 studies identified in systematic literature review, 62 included in NMA (alongside the 3 Phase III certolizumab pegol studies)
- [redacted]
- Analysis conducted for initial treatment period of 10-16 weeks
- Generates results for probability of PASI 50, 75 and 90 response
  - Used in economic model

ERG comments

- ERG unable to validate NMA due to not having required code to re-run the analysis

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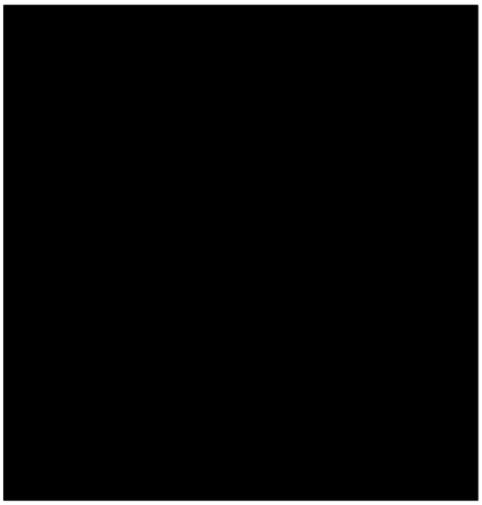
34

Source: Company submission p108-110

Note: Company provided updated code to run NMA. The ERG did not have sufficient time to validate this code prior to publication of the PMB but may report on this in an addendum to the ERG report available prior to the committee meeting.

Network meta-analysis: results

PASI 75 response rate



- Treatment of psoriasis with biologics is superior to placebo or standard of care (methotrexate, ciclosporin, acitretin)
- Certolizumab pegol has similar PASI 50/75/90 response rate vs most of the biologics considered
- PASI results similar comparable to ixekizumab NICE submission

ERG comments

- Ranking of treatments consistent with NMA undertaken by guideline development group for the British Association of Dermatologists guidelines
- Results similar to ixekizumab submission but effect estimates lower for each PASI outcome in this NMA

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35

Source: Company submission, figure 19, p 110-113

Note: Company provided updated results of NMA in relation to ERG comment that response rates for guselkumab were lower than expected. The ERG did not have sufficient time to critique these results prior to publication of the PMB but may report on this in an addendum to the ERG report available prior to the committee meeting

Network meta-analysis: ERG comments

- NMA shows that all biologic therapies are more effective than non-biologics and certolizumab has comparable efficacy to most other biologics → ERG does not agree that certolizumab should be the only biologic available for use before non-biologic therapies

36

Note: Company provided updated analysis related to the NMA. The ERG did not have sufficient time to provide critique of this analysis prior to publication of the PMB but may report on this in an addendum to the ERG report available prior to the committee meeting.

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Safety data

- Pooled initial phase and long-term safety summary

Adverse event, No. of patients (%)	Initial 16 week treatment phase				Initial, maintenance and open label extension phases
	Placebo (n=157)	CZP 200 mg (n=350)	CZP 400 mg (n=342)	All CZP (n=692)	All CZP (n=[redacted])
With TEAEs	97 (61.8)	197 (56.3)	217 (63.5)	414 (59.8)	[redacted]
With serious TEAEs	7 (4.5)	5 (1.4)	16 (4.7)	[redacted]	[redacted]
Drug-related TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With severe TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs associated with permanent discontinuation	0	4 (1.1)	4 (1.2)	8 (1.2)	[redacted]
Deaths	-	-	-	-	[redacted]

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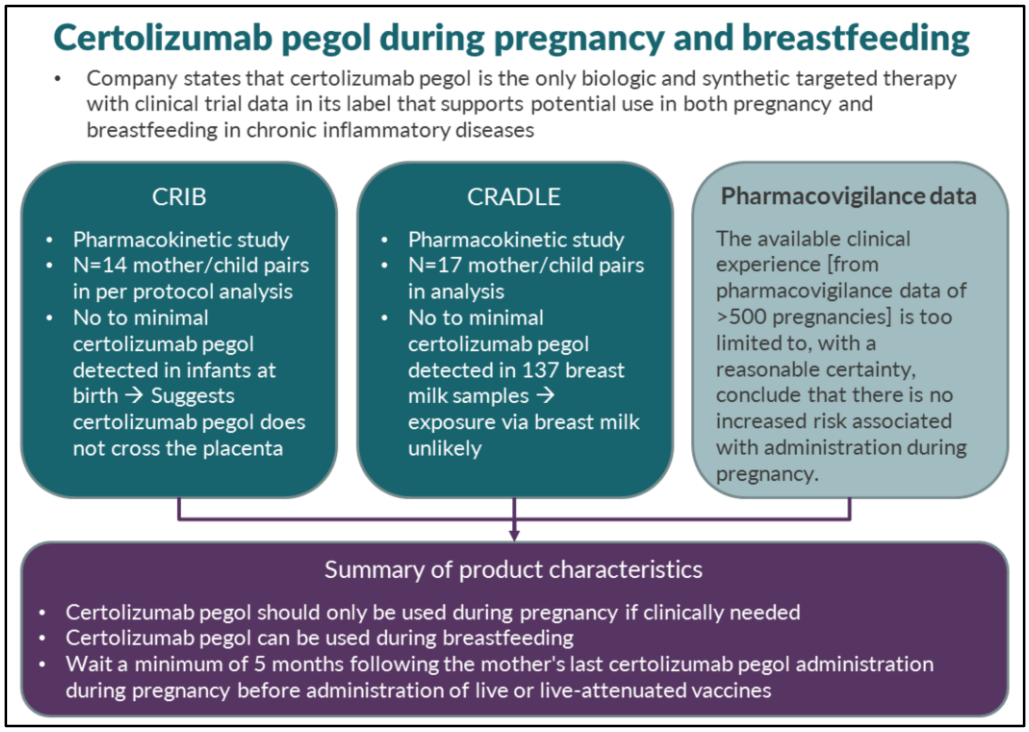
37

Source: Company submission table 55, p116 table 60, p122-123



Data from company submission (p130-131) and referenced studies

CRIB: https://ard.bmj.com/content/77/2/228
CRADLE: https://ard.bmj.com/content/76/11/1890

Note: 3 of 137 samples in CRADLE were not reportable

Summary of SmPC recommendations for biologics in pregnancy and breastfeeding

Treatment	Pregnancy		Breastfeeding	
	If clinically needed	Preferable to avoid	Can be used	Decide whether to discontinue treatment or breastfeeding
Certolizumab pegol	✓		✓	
Adalimumab	✓		✓	
Etanercept		✓ (not recommended)		✓
Ustekinumab		✓		✓
Ixekizumab		✓		✓
Secukinumab		✓		✓
Brodalumab		✓		✓
Guselkumab		✓		✓
Infliximab	✓			✓

Source: SmPCs

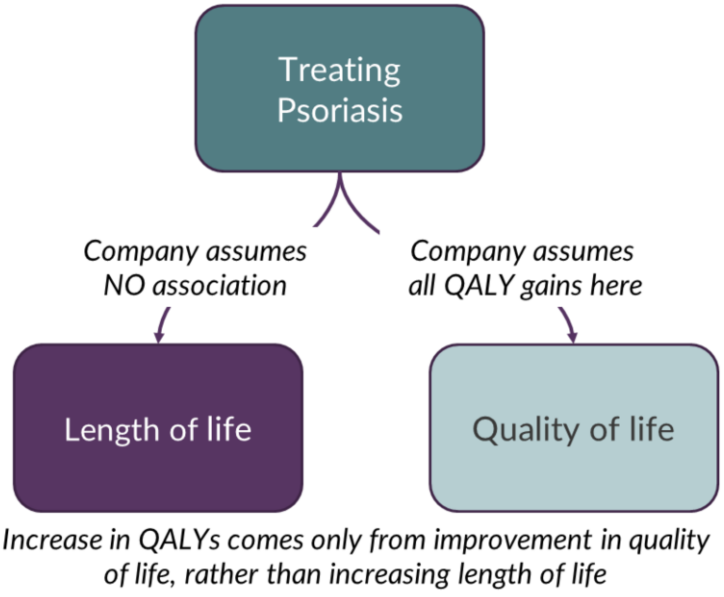
Notes:

Conclusions for adalimumab/infliximab based on registry data (pregnancy) and “limited information from the published literature” (breastfeeding for adalimumab).

Etanercept explicitly not recommended in pregnancy rather than being worded as “preferable to avoid.”

Cost-effectiveness

Where do QALY gains come from?



Increase in QALYs comes only from improvement in quality of life, rather than increasing length of life

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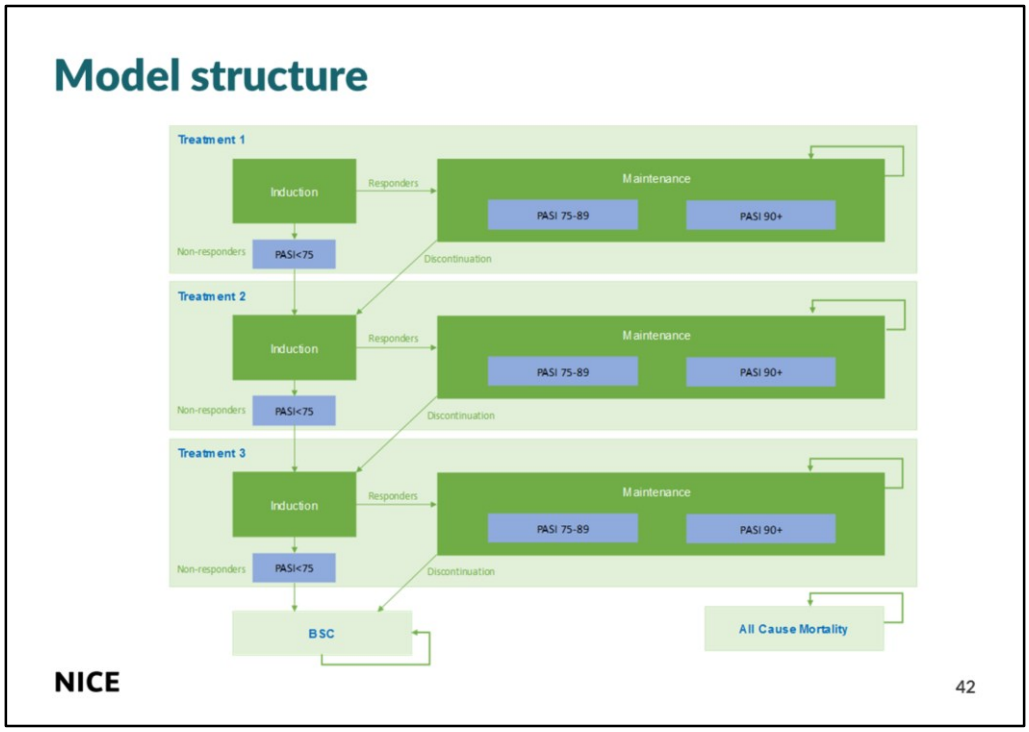
41



Source: Company submission p148

Notes:

State transition Markov model.

Two-week cycle length

Considered two key phases: induction and maintenance therapy. Movement between phases dependent on response to treatment (response defied as PASI>75 response). Non responders move to next treatment in sequence, responders move to maintenance phase until discontinuation due to loss of response or death.

Treatment sequences

- Company base case included treatment sequences for candidates for biological systemic therapy based on clinical expert opinion
- Scenario analyses compared single treatments followed by best supportive care

Sequence	1st line	2nd line	3rd line	4th line	5th line
A	CZP 200 mg	UST 90 mg	IFX	BSC	BSC
B	ADA	UST 90 mg	IFX	BSC	BSC
C	BROD	UST 90 mg	IFX	BSC	BSC
D	ETN	UST 90 mg	IFX	BSC	BSC
E	GUS	UST 90 mg	IFX	BSC	BSC
F	IXE	UST 90 mg	IFX	BSC	BSC
G	SEC	UST 90 mg	IFX	BSC	BSC
H	UST 45 mg	ADA	IFX	BSC	BSC
I	UST 90 mg	ADA	IFX	BSC	BSC

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43

Source: Company submission page 156

Treatment sequences – ERG comments

- Sequences proposed by company are unlikely to reflect current practice
  - majority of patients receive either adalimumab or secukinumab as their first line biologic
  - infliximab not funded for those with moderate to severe disease → unlikely to be used frequently in this population
  - adalimumab and secukinumab dominant the market and adalimumab biosimilars launch soon → positioning of certolizumab pegol as first-line biologic therapy unlikely
- Modelling selective sequences could provide misleading cost-effectiveness estimates, especially if there are treatments in the sequences that are not cost effective
- **No comparators are cost-effective versus best supportive care** → QALYs gained on BSC are cheaper → sequence of drugs with lower response rates will appear more cost-effective, as patients get to BSC more quickly
- Most relevant comparison may be between certolizumab pegol and other TNF-α inhibitors, most notably adalimumab
- ERG alternative approach uses comparison of single lines of therapy with a net monetary benefit framework (see later slides)
- Modelling single lines of therapy followed by BSC instead of treatment sequences (used by ERG) more appropriately reflects clinical practice
  - consistent with modelling approaches used in recent appraisals, and was used to inform decision-making

Source: ERG report p87-88

See slides 51-52 for further discussion on cost-effectiveness compared to best supportive care

Modelling assumptions

Assumption	Justification	ERG comments
Lifetime time horizon	Psoriasis is a chronic disease	Meets reference case but results in patients spending longer in BSC state → drugs with low response rates could appear more cost-effective. Shorter time horizons explored in scenario analysis
Treatment effect assumed to be maintained with ongoing treatment	Clinical trial data indicates a high durability of response into the long-term with CZP. Patients not responding to treatment have been captured within the maintenance discontinuation rate	Consistent with previous appraisals and acceptable given the availability of evidence to perform a robust network meta-analysis
Position of treatment does not impact on effectiveness	Subgroup analysis of the CZP phase III trials has shown that the efficacy benefit of CZP is similar in the biologic naïve and biologic exposed subgroups	
Long-term discontinuation is fixed at 20% for all treatment options	Long-term discontinuation was poorly reported by the captured clinical trials, therefore discontinuation during the maintenance treatment phase is based on real-world evidence from BADBIR	Assumptions in base case analysis more appropriate than alternative discontinuation rates in company scenario analysis

Source: Company submission table 86, p175. ERG report p79, 92-96

Treatment discontinuation

- Company base case assumes a flat discontinuation rate of 20% for all biologics in maintenance period
- Consistent with approach in previous appraisals
- Company explores differential discontinuation rates (discontinuation rate higher for adalimumab/etanercept than other biologics) in scenario analyses
  - ERG consider assumption in base case more justifiable as there is no biological explanation put forward as to why certolizumab pegol would have a substantially lower discontinuation rate than other TNF-alpha inhibitors
- Data on drug survival rates from BADBIR registry (non-randomised) does not yet include all available biologic therapies and has no data for certolizumab pegol

Drug survival rate, (%)	As 1st line biologic therapy			As 2nd line biologic therapy		
	1 year	2 year	3 year	1 year	2 year	3 year
Adalimumab	79	67	59	74	59	50
Etanercept	70	51	40	49	36	25
Ustekinumab	89	82	75	85	77	73

Source: company submission p161-162

BADBIR data from:

https://www.sciencedirect.com/science/article/pii/S0022202X15418494 for first line biologics

https://www.sciencedirect.com/science/article/pii/S0022202X17330683 for second line biologics

Note: A recent study based on data from BADBIR showed no significant difference in discontinuation rates between registry patients who would have been eligible or ineligible for clinical trials (or have unknown PASI at baseline or insufficient PASI at baseline). However differences in absolute PASI response and incidence of AEs were noted between the trial eligible and ineligible populations: https://jamanetwork.com/journals/jamadermatology/article-abstract/2674865

ERG notes that: “there exists significant uncertainty concerning both the rate of discontinuation and whether there are important treatment or class specific differences.” (ERG report p94-95)

Model inputs – proportion of responders

- PASI response derived from network meta analyses
  - Adalimumab 80 mg derived from CHAMPION study
  - BSC is a 45:55 mixture of placebo:methotrexate

	Response			
Treatment	PASI <50	PASI 50–<75	PASI 75–<90	PASI 90+
ADA 40 mg				
ADA 80 mg				
BROD				
BSC				
CZP 200 mg				
CZP 400 mg				
ETN				
GUS				
IFX				
IXE				
SEC				
UST 45 mg				
UST 90 mg				

Source: company submission, table 73, p159

Model inputs – source of utility values

State	Utility value: mean	95% confidence interval	Justification
No treatment effect: BSC and standard of care for candidates for systemic non-biologics			
Baseline PASI	[redacted]	NR	Derived from EQ-5D data from the CZP Phase III trials,
PASI <50	[redacted]	NR	
PASI 50–75	[redacted]	NR	
PASI 75–90	[redacted]	NR	
PASI 90–100	[redacted]	NR	
Treatment effect: All biologics			
Baseline PASI	[redacted]	NR	Derived from EQ-5D data from the CZP Phase II trials,. These values have been selected to also apply to all other biologics.
PASI <50	[redacted]	NR	
PASI 50–75	[redacted]	NR	
PASI 75–90	[redacted]	NR	
PASI 90–100	[redacted]	NR	

48

Source: Company submission table 76, p163

ERG comments – utility values

- In response to clarification company provided utility values for population with DLQI score >10
  - ERG considers this restriction to be more appropriate as they reflect the group of patients eligible for treatment

State	Prior biologics use (DLQI >10)	
	Utility value: BSC	Utility value: biologics
Baseline PASI	[redacted]	[redacted]
PASI <50	[redacted]	[redacted]
PASI 50–75	[redacted]	[redacted]
PASI 75–90	[redacted]	[redacted]
PASI 90–100	[redacted]	[redacted]

- Noted in previous appraisals that a possible effect on HRQoL associated with treatment with biologics over that of non-biologic systemic therapies may be plausible. Minimal evidence has been provided to substantiate this → a common utility set across both groups was used. ERG explore this approach in scenario analyses

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49

Source: ERG report table 23, p98

Model inputs – costs and resource use

Cost/Resource use	Source
Drug acquisition costs	List prices from BNF, confidential discount prices included in ERG analysis. Use of biosimilars for infliximab and etanercept included in scenario analyses
Administration costs	Include cost of training for subcutaneous injections and NHS reference costs for intravenous treatments
Monitoring costs and resource use	NHS reference costs
Best supportive care costs and utilities	Secondary care costs from Fonia et al, cost of non-biologic treatment from BNF, proportions of patients on each non-biologic treatment based on clinical export opinion
Non-responder costs	Fonia et al applied in initial treatment sequence, apart from in BSC where also applied in maintenance period – consistent with previous appraisals
Adverse event costs and resource use	None modelled – consistent with previous appraisals

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50

Source: Company submission p164-170

ERG comments – best supportive care costs

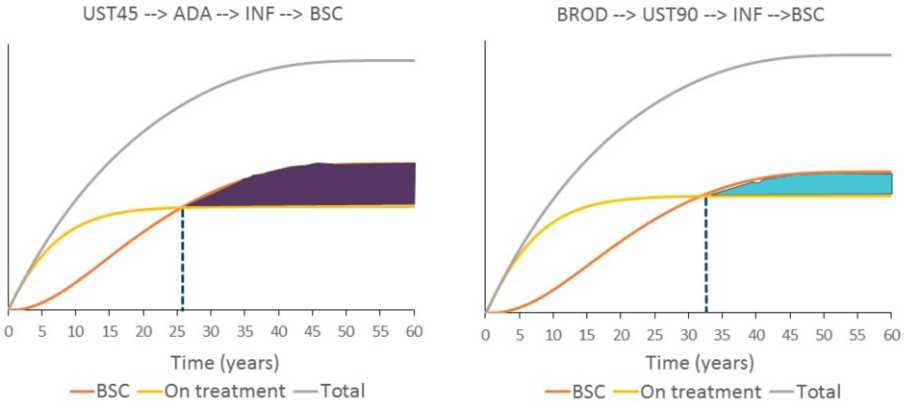
- Total annual costs of best supportive care in company's model lower than in previous appraisals – annual cost of **£3,672** compared with **£5,283** in TA511 (brodalumab)
  - Driven by large difference in drug acquisition costs (based on BNF prices and mean duration of treatment in Fonia instead of annual cost derived from Fonia)
- ERG considers estimates calculated by company appropriate as Fonia may overestimate costs
  - 41% of costs from Fonia from fumaric acid esters, which are not considered alongside BSC in this appraisal
  - Fonia likely overestimates cost of ciclosporin
- Has significant impact on cost-effectiveness of biologics vs BSC
  - BSC more cost effective → sequences that reach BSC sooner become more cost effective
- ERG implements drug costs from Fonia in line with previous appraisals in a scenario analysis

Source: ERG report p106-107

ERG comments – Best supportive care costs

- **No comparators are cost-effective versus best supportive care** → QALYs gained on BSC are **cheaper** → sequence of drugs with lower response rates will appear more cost-effective, as patients get to BSC more quickly
- Charts compare a sequence with low response rates on left with higher on right
  - Shaded area indicates time where majority of QALYs are gained on BSC

Cumulative QALYs over time horizon



Source: Generated by NICE technical team from ERG amended model

Notes: Majority of QALYs gained on best supportive care when treatment and BSC lines cross, occurs several years earlier for sequence where 1st two treatments have lower response rate.

ERG comments – biosimilar costs

- Considers company has underestimated the uptake of biosimilars of infliximab and etanercept (in April 2017 the uptake of biosimilar infliximab was 80%, rather than 20%, as assumed in company submission)
  - ERG explores scenarios assuming full uptake of biosimilars
- A number of adalimumab biosimilars have launched, with further launches anticipated
  - Clinical expert opinion suggests a reduction in current list price of 30-40%
  - ERG explores scenarios with various levels of discount to account for adalimumab biosimilars

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Source: ERG report p103

Note: In updated analysis presented by the company 100% uptake of biosimilars was assumed

NHS England adalimumab commissioning

- Aim: At least 90% of new patients will be prescribed the best value biological medicine (either biosimilar or reference product) within 3 months of launch of a biosimilar medicine, and at least 80% of existing patients within 12 months, or sooner if possible
- Framework agreement in place by Regional Medicines Optimisation Committee allocating adalimumab and biosimilars in regional lots – size and shape of lots dependent on offer received and relative prices
  - Duration of agreement Dec 2018 to Nov 2019
  - NHS England intends to set interim reference price for this period
- National reference price for adalimumab to be set by April 2019 – commissioning arrangements expected to reflect reference price

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Sources:

Commissioning intentions: adalimumab: https://www.sps.nhs.uk/wp-content/uploads/2018/09/20180925-Contractual-Commissioning-Intentions-Adalimumab_corporate-template.pdf

RMOC briefing on adalimumab: https://www.sps.nhs.uk/wp-content/uploads/2018/10/Adalimumab-RMOC-Briefing-Final-October.docx

Economic analysis overview

- Company presents three sets of base case analyses
  - Candidates for systemic biologic therapy (contraindicated, intolerant or non-responsive to systemic non-biologic therapy)
  - Candidates for non-biologic therapy
  - Dose escalation (partial response to initial biologic therapy)

Cost-effectiveness results for candidates for systemic biological therapy are confidential due to use of comparator patient access scheme information. Results of the company's and ERG's cost-effectiveness analyses in this population are presented in a confidential appendix to the PMB

Company's sensitivity and scenario analyses

- Certolizumab pegol cost-effective in company base-case analysis (fully incremental analysis with etanercept as baseline)
- Probabilistic sensitivity analyses results support conclusions of the base case analysis
- Scenario analyses show results are robust to altering time horizon and discontinuation rates
- Results generally robust to altering utility values, with exception of utility values from the ustekinumab appraisal, where etanercept was more cost-effective than certolizumab pegol

ERG corrections to company model

- ERG made several corrections to the companies model, including the corrections of
  - costs of administration, training and monitoring
  - inconsistencies in the calculation of drug administration costs
  - an error leading to an underestimation in costs for certolizumab in the first year
  - errors leading to an overestimation in the acquisition costs of guselkumab and infliximab
  - miscalculations in the incremental QALYs accrued on a number of treatment sequences

Incremental cost-effectiveness ratios (ICERs) vs net monetary benefit framework (NMB)

ICER: What is the extra cost per unit of extra benefit?

ICER decision rule: recommend technology if

Δ Costs/ Δ QALYs < threshold

But, ICER > 0 can mean:

NMB

- Value of an intervention in monetary terms at a willingness-to-pay threshold (NHS opportunity cost)
- For NMB, ICER decision rule is rearranged:

(Δ QALYs * threshold) – Δ Costs > 0

- Incremental NMB: difference in NMB between alternative interventions
- Positive incremental NMB: intervention is cost-effective compared with alternative at given willingness-to-pay threshold

58

Source: https://resource-allocation.biomedcentral.com/articles/10.1186/1478-7547-10-8. https://www.ncbi.nlm.nih.gov/books/NBK99711/ http://www.yhec.co.uk/glossary/net-monetary-benefit/

ERG base case – systemic biological therapy

- All ERG single-line head to head comparisons use a net monetary benefit framework, in contrast to company's approach of treatment sequences and fully incremental analysis compared to a baseline
- ERG base case also includes following scenarios
  - equal utilities applied to biologics and BSC with population limited to DLQI <10
  - biosimilar costs for etanercept and infliximab, adalimumab at list price
- ERG also presents alternative base case including
  - BSC costs, utility values and time horizon in line with assumptions from TA511 (brodalumab, most recent psoriasis appraisal)
  - Range of price reductions for adalimumab to account for introduction of biosimilar alternatives

Cost-effectiveness results for candidates for systemic biological therapy confidential due to use of comparator PAS information. Please see confidential appendix accompanying this PMB

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59

Source: ERG report p134-137

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Dose escalation strategy

- Most relevant comparator for escalation of certolizumab pegol from 200 mg dose to 400 mg dose is increasing dose of adalimumab from 40 mg to 80 mg
  - Only similar dose escalation strategy per label and British Association of dermatologists guidelines
- Explored scenario analysis using discount of [redacted]
  - Certolizumab 'dominates' adalimumab in this scenario

Sequence	Total costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	ICER)
CZP 200 mg → CZP 400 mg	[redacted]	[redacted]	[redacted]	[redacted]	£37,054
ADA 40 mg → ADA 80 mg	[redacted]	[redacted]			

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60

Source: Company submission table 88, p177 and table 93, p189

Note: Company presented an updated base case analysis for this strategy. This updated analyses has not been presented here as the ERG have not provided a critique at the time of publication of the PMB. The ERG may present their critique in an addendum and the new base case presented at the committee meeting.

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Dose escalation strategy – ERG analysis

- Consider that the appropriate comparator to certolizumab pegol dose escalation is certolizumab pegol without dose escalation
  - Under this approach patients on certolizumab would switch to the next biologic in the treatment pathway, in this case ustekinumab
- ERG base case also incorporates following scenarios;
  - dose escalation only in patients with PASI response 50-74 at 16 weeks
  - where equal utilities applied to biologics and BSC with population limited to DLQI <10
- ERG also explored [redacted]
  - certolizumab pegol escalation ICER compared with switching to ustekinumab is £22,618 per QALY gained under this scenario

Sequence	Total costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	ICER
CZP 200 mg → CZP 400 mg	[redacted]	[redacted]	[redacted]	[redacted]	£508,833
CZP 200 mg → UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	

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61

Source: ERG report page 88-89, 132-133 and 137

Note: Company presented an updated base case analysis for this strategy. This updated analyses has not been presented here as the ERG have not provided a critique at the time of publication of the PMB. The ERG may present their critique in an addendum and the new base case presented at the committee meeting.

G report page 88-89, 132-133 and 137

Scenario analysis did not include ERG scenario 7 (Equal utilities applied to biologics and BSC with population limited to DLQI≥10), ICER is likely to increase if this scenario is also incorporated.

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Candidates for systemic therapy

- Company's base case compares treatment sequences judged most likely to be used in clinical practice
- Clinical data for standard of care for non-biological therapy derived from pooled data from the placebo arms of the certolizumab trials

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
Company base case (candidates for non-biologics)						
Standard of care	ADA, UST 90, IFX, BSC	[redacted]	[redacted]	-	-	-
CZP 200	UST 90, IFX, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£3,650

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Source: Company submission: table 70 page 157 and table 88, p177

Candidates for systemic therapy – ERG analyses

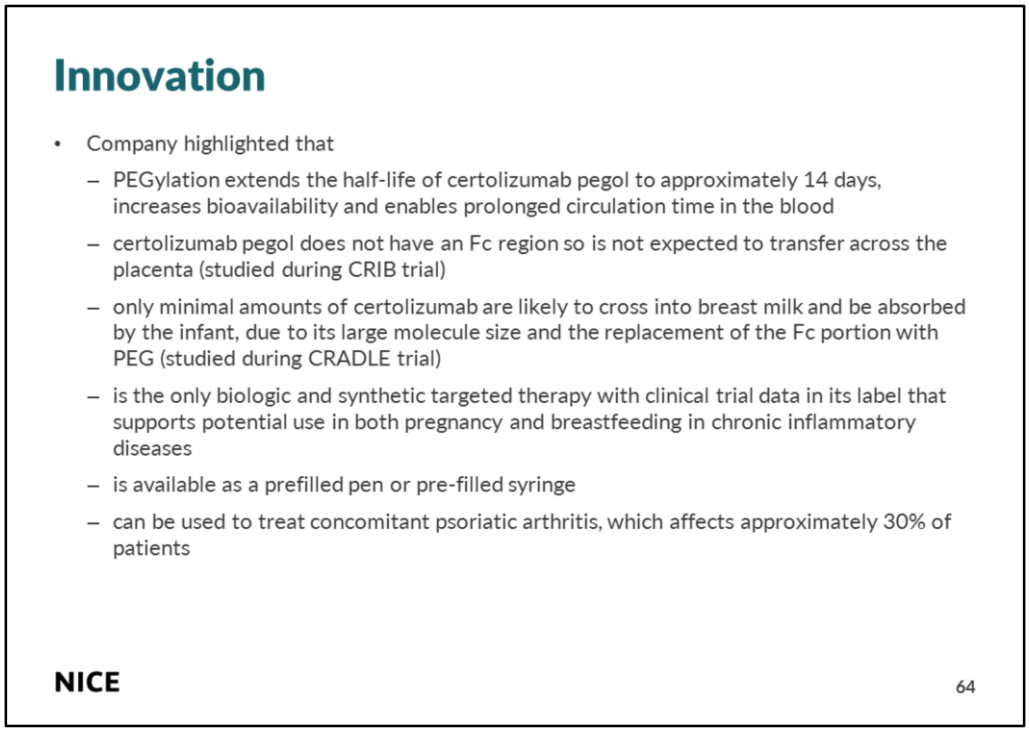
- ERG does not consider positioning of certolizumab pegol in this population appropriate
- Use of pooled placebo response rate as proxy for supportive care inappropriate as reflects no therapy rather than standard of care → used methotrexate response rate data provided by company in response to clarification as proxy for supportive care
- For consistency with other scenarios compare certolizumab as a first-line treatment with certolizumab second-line, followed by best supportive care
- Certolizumab pegol is also cost ineffective in sequences where certolizumab pegol is followed by ustekinumab, infliximab and best supportive care

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
ERG Alternative base-case (candidates for non-biologics): ERG Scenario 7 + 18						
BSC	CZP200, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
CZP 200	BSC, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

63

Source: ERG report p133-138

See clinical section for ERG comments on positioning of certolizumab pegol at this place in the treatment pathway



Source: Company submission p130-132

Note: Adalimumab can also be used in pregnancy and breastfeeding, this is supported by data from prospective cohort registries and literature reports in contrast to clinical trials,

Submission notes that the available evidence from CRIB is “is too limited to, with a reasonable certainty, conclude that there is no increased risk associated with CZP administration during pregnancy”

Submission notes that in a survey of pre-filled pens 59% of 76 patients preferred the certolizumab pegol device compared with adalimumab, etanercept and golimumab auto-injectors

Equality

- Pregnancy
  - Submission from Psoriasis Association noted that "Women of childbearing age deserve to have effective treatments available to them in order to manage their chronic condition without compromising their family plans."
- Issues raised in previous guidance
  - When using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate.
  - When using the DLQI, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI and make any adjustments they consider appropriate.

NICE 65

Notes:

Certolizumab pegol SPC states "Cimzia should only be used during pregnancy if clinically needed." and "Cimzia can be used during breastfeeding." See SPC section 4.6 for further information - https://www.medicines.org.uk/emc/product/4450/smpc

Adalimumab has similar SPC wording so can also potentially be used by women of childbearing age. Other biological therapies are not recommended during pregnancy and consideration should be given to stopping treatment during breastfeeding.

Submission from the British Association of Dermatologists states that certolizumab pegol may have additional advantages as it is not thought to cross the placenta.

Summary of key issues – clinical effectiveness

1. What it the likely position of certolizumab pegol in the treatment pathway?
   - Is there evidence that certolizumab pegol can be used earlier in the treatment pathway that other biologic therapies?
2. Are the results from the clinical trials generalisable to the eligible population in the NHS in terms of:
   - DLQI score?
   - Previous treatment with biologic therapies?
3. Do the pooled efficacy results from the overall trial population reflect the pooled results of the subgroups where certolizumab pegol would be used in the NHS?
4. Is the network meta analysis appropriate?
5. Is there evidence that certolizumab pegol is of additional benefit during pregnancy/breastfeeding?

66

Note:

The company has presented updated data relating to the meta analysis and an updated base case partially based on these data. The ERG has not had sufficient time to critique these analyses ahead of publication of the PMB so they are not presented here, but these may be presented at the committee meeting.

Summary of key issues – cost effectiveness

1. Is analysis of treatment sequences using ICERs or individual treatments using a net monetary benefit framework preferred?
2. What is the most appropriate comparator?
3. Is the assumption of an equivalent discontinuation rate of 20% for all biologics appropriate?
4. How should the costs of biosimilars to adalimumab be accounted for?
5. Should cost of best supportive care be modelled updated prices?
6. Should utility values be modelled by limiting population to DLQI>10 and assuming biologic utility values are the same as best supportive care?
7. Is the dose escalation strategy for certolizumab pegol cost effective?
8. Is certolizumab pegol cost effective for candidates for systemic therapy?

67

Note:

The company has presented new base case analyses which alter the considerations in some of these issues, the ERG has not had sufficient time to critique these analyses ahead of publication of the PMB, so they are not presented here, but these may be presented at the committee meeting.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Certolizumab pegol for treating moderate to severe plaque psoriasis [ID1232]

UCB Pharma Ltd

Document B

Company evidence submission

August 2018

File name	Version	Contains confidential information	Date
ID 1232 Certolizumab Pegol **Form B FINAL**	**1.0**	**Yes** AIC: Highlighted in yellow and underlined CIC: Highlighted in turquoise and underlined	**09.08.2018**

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Contents

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

Certolizumab pegol

- Certolizumab pegol (Cimzia®, CZP) is the only fragment-crystallizable-(Fc)-free, PEGylated, anti-TNF. It has a high affinity to both membrane-associated and soluble TNF and, therefore, selectively neutralizes TNF and the downstream pro-inflammatory cytokines and disease processes involved in many chronic inflammatory diseases. CZP has a unique and innovative structure, consisting of a recombinant, humanized antibody fragment antigen-binding (Fab') against TNFα, conjugated to polyethylene glycol (PEG). PEGylation extends the half-life of CZP to approximately 14 days, increases bioavailability and enables prolonged circulation time in the blood. Unlike all other biologics, CZP does not contain a fragment crystallisable (Fc) region, which is normally present in a monoclonal antibody. As CZP lacks an Fc region, it does not bind neonatal Fc receptor (FcRn), and is consequently not expected to undergo FcRn mediated transfer across the placenta.
- Certolizumab pegol is licensed in the European Union (EU) and recommended by NICE for the treatment of rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis. Certolizumab pegol was granted marketing authorisation for the use in the EU on 8 June 2018 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. The licensed starting dose of CZP is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. After the starting dose, the recommended maintenance dose of CZP is 200 mg Q2W. A dose of 400 mg Q2W can be considered in patients with insufficient response.

Psoriasis

- Psoriasis is a chronic inflammatory skin condition; in England and Wales, it is reported to affect ~1.75% of the population, equating to approximately 1.02 million people. Psoriasis is equally prevalent in males and females, and whilst onset may occur at any age, approximately 75% of patients present with psoriasis before the age of 40 years.
- The physical burden of psoriasis includes pain, itching and bleeding arising from the presence of skin lesions. Patients with psoriasis also face a higher risk of developing mental health problems such as anxiety, depression and suicidal ideation, and appear to be more likely to face difficulty in gaining employment. In addition to the dermatologic manifestations of psoriasis, patients may experience an additional burden as a result of nail and joint disease, as well as a broad spectrum of co-morbidities. Psoriasis is associated with a high burden of disease. The humanistic burden of psoriasis is substantial and comparable to conditions such as diabetes mellitus, cardiovascular disease and some cancers.[1]
- More than one-third of adults with chronic plaque psoriasis who initiate a biologic will require treatment modifications within the first year (switching, discontinuing, restarting therapy, dose escalation or reduction), according to UK British Association of Dermatologists Biologic Intervention Register (BADBIR) data from 2007–2014.

- Despite existing treatment options available, significant unmet medical need remains for effective and long-lasting therapies for moderate to severe PSO patients who experience inadequate response to treatment and require a change of therapy, patients with psoriasis who have, or are at risk of developing, PsA or axSpA, or for women of childbearing potential.

Clinical pathway of care

- Current NICE clinical guidelines (CG153) recommend topical therapy in the first-line, followed by systemic non-biologic therapies (e.g. ciclosporin, methotrexate [MTX] and acitretin) or phototherapy. Biologic therapies are recommended for patients based on individual NICE guidance: all technologies (except infliximab) are recommended in patients with severe disease (PASI score ≥10 and a DLQI score >10), and who have not responded to, or have an intolerance or contraindication to standard systemic therapies.
- In patients with moderate-to-severe plaque psoriasis, CZP demonstrated clinically meaningful improvements and durability of response, with long-term maintenance of clinical response, nail psoriasis and patient relevant outcomes. Efficacy with CZP was similarly high across a broad spectrum of patients, including candidates for systemic non-biologics, patients who are biologic-naïve or previously exposed to biologics. Similar improvements were seen with both CZP doses, with higher responses in CZP 400mg Q2W. The safety profile of CZP remains consistent with other TNFs.
- The proposed positioning of certolizumab pegol (CZP) is in line with its marketing authorisation, that is, for the treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy.

B.1.1 *Decision problem*

The submission covers the clinical efficacy and cost-effectiveness of certolizumab pegol (CZP) in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy. A summary of the decision problem for this technology appraisal is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Intervention	Certolizumab pegol (CIMZIA®, CZP)	Certolizumab pegol (CIMZIA®): CZP 200 mg SC injection comprising a CZP loading dose of 400 mg at weeks 0, 2 and 4, followed by CZP 200 mg Q2W. A maintenance dose of CZP 400 mg Q2W can be considered in patients with insufficient response.	As per final SmPC
Population	Adults with moderate to severe plaque psoriasis	Adults with moderate to severe plaque psoriasis	As per reference case and final SmPC
Comparator(s)	If systemic non-biological treatment or phototherapy is suitable: • Systemic non-biologic therapies (including MTX, ciclosporin, acitretin) • Phototherapy with or without psoralen If conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated: • Anti-TNFs (ADA, ETN, IFX) • IL-17 inhibitors (BROD, IXE, SEC) • IL-23 inhibitor (GUS) • IL-12/IL-23 inhibitor (UST) • APR • DMF • Best supportive care	If systemic non-biological treatment or phototherapy is suitable: • Systemic non-biologic therapies, including MTX, ciclosporin, acitretin If conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated: • Anti-TNFs (ADA, ETN) • IL-17 inhibitors (BROD, IXE, SEC) • IL-23p19 inhibitor (GUS) • IL-12/IL-23 inhibitor (UST) • Best supportive care	Phototherapy is not considered to be an appropriate comparator, as it is not expected to be used in clinical practice at the same position as these systemic non-biological therapies or biologics. It is the opinion of the British Association of Dermatologists (BAD) that it is appropriate not to include PUVA (i.e. phototherapy with psoralen) as a comparator in NICE appraisals for biologics for psoriasis. BAD has previously stated that PUVA is no longer used routinely in people with psoriasis due to its propensity to cause skin cancer, particularly when followed by immunosuppression.[2] Furthermore, in the NICE clinical guideline for psoriasis (CG153) there are a broad number of populations who are not recommended to receive PUVA and BAD indicated that PUVA should only be used when other options have been offered and cannot be used or are inappropriate.[2]

			IFX is not considered to be a first-line biologic as it is recommended for patients considered to have “very severe” psoriasis (PASI ≥20 and DLQI >18) and therefore would be used in a more restricted patient population than considered in this submission for CZP. IFX has been used as a third-line biologic in the treatment sequences employed within the cost-effectiveness analyses. Neither DMF nor apremilast are considered to be appropriate comparators as these therapies do not displace biologics. In clinical practice, these treatments would only be considered for use in patients unsuitable for biologic treatment or unwilling to receive biologic treatment. Clinical expert opinion indicated that apremilast and DMF would either be used in select patients prior to starting biologics or reserved for use after biologics, including CZP.[3] Furthermore, the BAD guidelines state that: “use of other non-biologic systemic therapies (e.g. acitretin, apremilast) may be appropriate prior to using biologic therapy but not mandatory, given their unpredictable and lower overall efficacy.”[4] Previous NICE TAGs have stated that apremilast and DMF would not displace biological therapies during their recent appraisals (NICE TA419, TA475). It was also accepted in the recent appraisal of guselkumab (TA521) that apremilast and DMF would not be comparators for this new biologic therapy. Consequently, DMF and apremilast will not be considered as comparators within this submission.

Outcomes	• Severity of psoriasis • Psoriasis symptoms on the face, scalp, nails and joints • Mortality • Response rate • Duration of response • Relapse rate • Adverse effects of treatment • Health-related quality of life (HRQoL)	This submission includes a range of outcome measures to assess the clinical effect of CZP, including: • Severity of psoriasis, measured using the PASI, including PASI75/90/100 responder rates, PGA 0/1 response, and BSA affected by psoriasis. PASI75 responder rate was the (co-)primary endpoint in the clinical studies included in this submission and is the measure of clinical response used by NICE. PGA was a co-primary endpoint in two of the clinical studies included in this submission. • Improvement in symptoms on the nails, measured by mNAPSI • Improvement in symptoms in the joints, measured by data from the PsA clinical programme • Relapse rate, measured by time to not achieving PASI50 response • Adverse events • HRQoL, measured using the DLQI, SF-36, HADS-A and HADS-D, and EQ-5D • Work productivity and social activities, measured by WPAI-SHP	Psoriasis symptoms of the face and scalp have not been included in this submission due to data limitations. These outcome measures have not been explicitly taken into account in the cost-effectiveness model which is based on the PASI response. Mortality was included in the reporting of AEs. However, treatment effect on mortality was not included due to data limitations.
Subgroups to be considered	Where the evidence allows, the following subgroups will be considered: • Previous use of phototherapy and	The following subgroup data were available from the trials and have been presented in the submission:	As per the reference case.

	systemic non-biological therapy • Previous use of biological therapy • Severity of psoriasis (moderate, severe) Where the evidence allows, sequencing of different drugs and the place of CZP in such a sequence in fully incremental analysis will be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	• Previous use of systemic non-biological therapy • Previous use of biologic therapy • Severity of psoriasis (by baseline DLQI)	

Abbreviations: ADA: adalimumab; AE: adverse event; APR: apremilast; BROD: brodalumab; CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; DMF: dimethyl fumarate; EQ-5D: EuroQol – 5 dimensions; ETN: etanercept; HADS-A: hospital anxiety and depression scale – anxiety; HADS-D: hospital anxiety and depression scale – depression; HRQoL: health-related quality of life; IXE: ixekizumab; mNAPSI: modified nail psoriasis severity index; MTX: methotrexate; NA: not applicable; NICE: National Institute for Health and Care Excellence; PASI: Psoriasis Area Severity Index; PGA: Physician's Global Assessment; PsA: psoriatic arthritis; SC: subcutaneous; SEC: secukinumab; SF-36: 36-item Short Form health survey; SmPC: Summary of Product Characteristics; TNF: tumour necrosis factor; UST: ustekinumab; WPAI-SHP: Work Productivity and Activity Impairment – Specific Health Problem.

B.1.2 *Description of the technology being appraised*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with CZP for moderate to severe plaque psoriasis is presented in Table 2. The summary of product characteristics (SmPC) and European public assessment report (EPAR) for CZP in this indication are presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Approved name: certolizumab pegol Brand name: Cimzia®
Mechanism of action	CZP is the only fragment-crystallizable-(Fc)-free, PEGylated, anti-TNF.[5] It has a high affinity to both membrane-associated and soluble TNF and therefore, selectively neutralises TNF and the downstream pro-inflammatory cytokines and disease processes involved in many chronic inflammatory diseases.[5, 6] CZP has a unique and innovative structure. CZP consists of a recombinant, humanized antibody Fab' against TNFα, conjugated to PEG. PEGylation extends the half-life of CZP to approximately 14 days, increases bioavailability and enables prolonged circulation time in the blood.[5] Unlike all other biologics, CZP does not contain an Fc region, which is normally present in a complete antibody.[5]
Marketing authorisation/CE mark status	CZP received the European Marketing Authorisation on 8 June 2018.[7]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Rheumatoid arthritis (RA) Cimzia, in combination with methotrexate (MTX), is indicated for: • The treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including MTX, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate • The treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with MTX. Axial spondyloarthritis (axSpA) Cimzia is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising: *Ankylosing spondylitis (AS)* Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs). *Axial spondyloarthritis without radiographic evidence of AS* Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein (CRP) and /or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs.

	Psoriatic arthritis Cimzia, in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Plaque psoriasis Cimzia is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.
Method of administration and dosage	CZP is administered by 200 mg subcutaneous injection. *Posology plaque psoriasis* *Loading dose:* The recommended starting dose of CZP for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. *Maintenance dose:* After the starting dose, the recommended maintenance dose of CZP for adult patients with plaque psoriasis is 200 mg Q2W. A dose of 400 mg Q2W can be considered in patients with insufficient response. Available data in adults with plaque psoriasis suggest that a clinical response is usually achieved within 16 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.
Additional tests or investigations	Certolizumab pegol has a similar administration profile to other biological treatments available to NHS England patients; no additional tests or investigations are required.
List price and average cost of a course of treatment	The list price of each 200 mg pre-filled pen or syringe is: £357.50. Without the patient access scheme (PAS) (see below), the cost of the first year of CZP is £10,367.50, which includes the loading dose at the start of treatment; with the patient access scheme, the cost of the first year is of £6,792.50. The cost of CZP in subsequent years is £9,295.00 per year.
Patient access scheme (if applicable)	Under the PAS agreed with the Department of Health for the use of CZP, the first 12 weeks of CZP are provided free of charge which is equivalent to 10 vials at a total cost saved of £3,575.00 in Year 1 of treatment.

Abbreviations: AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; CRP: C-reactive protein; CZP: certolizumab pegol; DMARD: disease-modifying anti-rheumatic drug; Fc: fragment crystallisable region; MRI: magnetic resonance imaging; MTX: methotrexate; NHS: National Health Service; NSAID: non-steroidal anti-inflammatory drug; PASLU: Patient Access Scheme Liaison Unit; PEG: polyethylene glycol; PsA: psoriatic arthritis; Q2W: every two weeks; Q4W: every four weeks; RA: rheumatoid arthritis; SmPC: Summary of Product Characteristics; TNFα: tumour necrosis factor alpha.
Source: CZP SmPC 2018.[5]

Recent update to the CZP SmPC across all indications[5]

Active transport of IgG across the placenta is mediated by the neonatal Fc receptor (FcRn).[8] Unlike all other anti-TNFs, CZP does not contain an Fc region, which is normally present in a complete antibody. As CZP lacks an Fc region, it does not bind FcRn, and is consequently not expected to undergo FcRn mediated transfer across the placenta.[9, 10]

The molecular structure of CZP, which translates into unique benefits supported by robust clinical data, are reflected in a label that allows potential use of CZP in pregnancy and breastfeeding in patients with chronic inflammatory diseases as per the licensed indications. Together, these factors have led to a recent change to the European Union (EU) label for CZP in which the key recommendations related to fertility, pregnancy and breastfeeding state that:[5]

- "The use of adequate contraception should be considered for women of childbearing potential. For women planning pregnancy, continued contraception may be considered for 5 months after the last CIMZIA® dose due to its elimination rate, but the need for treatment of the woman should also be taken into account."
- "CIMZIA® should only be used during pregnancy if clinically needed."
- "CIMZIA® can be used during breastfeeding."
- "It is recommended to wait a minimum of 5 months following the mother's last CIMZIA® administration during pregnancy before administration of live or live-attenuated vaccines (e.g. BCG vaccine), unless the benefit of the vaccination clearly outweighs the theoretical risk of administration of live or live-attenuated vaccines to the infants."

Further details are provided in Section B.2.12 of the submission.

Current UK HTA decisions for CZP

A summary of current UK HTA decisions for CZP across all indications is provided in Table 3.

Table 3: Summary of current recommendations for the use of CZP from UK HTA agencies

Agency	Appraisal	Recommendation
NICE	RA [TA375; January 2016]	CZP in combination with MTX is currently recommended as an option for the treatment of people with RA, if: • Disease is severe (i.e. disease activity score [DAS28] >5.1) • Disease has not responded to intensive therapy with a combination of cDMARDs • The manufacturer provides the first 12 weeks of CZP (10 pre-loaded 200 mg syringes) free of charge to all patients starting treatment. CZP monotherapy is also recommended by NICE as an option for treating rheumatoid arthritis in patients who cannot take MTX because it is contraindicated or because of intolerance, when the criteria above are met.
	AS and nr-axSpA [TA383; February 2016]	CZP is recommended by NICE within its marketing authorisation, as an option for the treatment of severe active AS in adult patients whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.

		CZP is also recommended by NICE within its marketing authorisation as an option for treating severe non-radiographic axSpA in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.
	RA [TA415; October 2016]	CZP, in combination with MTX, is recommended as an option for treating active RA in adults whose disease has responded inadequately to, or who cannot tolerate, other disease-modifying antirheumatic drugs (DMARDs) including at least 1 tumour necrosis factor‑alpha (TNF‑alpha) inhibitor, only if: • disease activity is severe and • rituximab is contraindicated or not tolerated and • the company provides certolizumab pegol with the agreed patient access scheme. CZP, as monotherapy, is also recommended as an option for treating active RA in adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNFα, only if: • disease activity is severe and • rituximab therapy cannot be given because MTX is contraindicated or not tolerated and • the company provides CZP with the agreed PAS. patient access scheme.
	PsA [TA445. May 2017]	CZP alone, or in combination with MTX, is recommended as an option for treating active PsA in adults only if: • it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis or • the person has had a TNFα inhibitor but their disease has stopped responding after the first 12 weeks. CZP is only recommended if the company provides it as agreed in the patient access scheme.
SMC	RA [drug ID: 590/09; October 2010]*	CZP is currently recommended by the SMC in combination with MTX for the treatment of moderate to severe active RA in adult patients when the response to DMARDs, including MTX, has been inadequate. CZP is also recommended as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. SMC advice was superseded by the NICE guidance (TA375) issued January 2016 (see above).
	AxSpA [drug ID: 960/14; May 2014]*	CZP is currently recommended by the SMC as an option for the treatment of adults with severe active axSpA comprising AS (adults with severe active AS who have had an inadequate response to, or are intolerant to NSAIDs) and axial spondyloarthritis without radiographic evidence of AS (nr-axSpA; adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to NSAIDs). SMC advice was superseded by the NICE guidance (TA383) issued February 2016 (see above).

	PsA [drug ID: 973/14; July 2014]*	CZP is currently recommended by the SMC in combination with MTX or as monotherapy as an option for the treatment of adults with active PsA whose disease has not responded to adequate trials of at least two standard DMARDs either individually or in combination. SMC advice was superseded by the NICE guidance (TA445) issued May 2017 (see above).
AWMSG	RA	Not assessed; product met AWMSG exclusion criteria due to NICE appraisal (originally NICE TA186 in February 2010; superseded by the NICE guidance TA375 in January 2016 [see above]).
	axSpA [Advice No: 3114; October 2014]	CZP is recommended by the AWMSG as an option for the treatment of adult patients with severe active axSpA, comprising: adults with severe active AS who have had an inadequate response to, or are intolerant to NSAIDs; and adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs. This recommendation applies only in circumstances where the approved Wales PAS is utilised. AWMSG recommendation superseded by the NICE guidance (TA383) issued February 2016 (see above).
	PsA [Advice No: 3214; October 2014]	CZP in combination with MTX is currently recommended by the AWMSG as an option for use within NHS Wales for the treatment of active PsA in adults when the response to previous DMARD therapy has been inadequate. CZP can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. This recommendation applies only in circumstances where the approved Wales PAS is utilised. AWMSG recommendation superseded by the NICE guidance (TA445) issued May 2017 (see above).

* SMC advice contingent upon the continuing availability of the patient access scheme (PAS) in NHS Scotland or a list price that is equivalent or lower.
Abbreviations: AS: ankylosing spondyloarthritis; axSpA: axial spondyloarthritis; AWMSG: All Wales Medicines Strategy Group; CRP: c-reactive protein; CZP: certolizumab pegol; cDMARD: conventional DMARD; DMARD: disease modifying anti-rheumatic drug; ID: identification; MRI: magnetic resonance imaging; MTX: methotrexate; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; nr-axSpA: non-radiographic axSpA; NSAID: nonsteroidal anti-inflammatory drug; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SMC: Scottish Medicines Consortium; TA: technology appraisal; TNFα: tumour necrosis factor alpha.

B.1.3 *Health condition and position of the technology in the treatment pathway*

B.1.3.1 Overview of the disease

Psoriasis

Psoriasis is a chronic inflammatory skin condition that affects more than two million people across the UK and Ireland.[11, 12] In England and Wales specifically, psoriasis is reported to affect ~1.75% of the population,[13] equating to approximately 1.02 million people.[14] It is equally prevalent in males and females.[15] Whilst onset may occur at any age, two peaks of incidence have been observed: before the age of 40 years (approximately 75% of patients present with

psoriasis during this timeframe) and in patients over the age of 40 years.[16, 17] It is estimated that approximately 20% of psoriasis is classed as moderate or severe, affecting more than 5% of the body surface area (BSA) or particularly troublesome body areas such as the hands, feet, face, or genitals.[18]

The disease is typified by red, scaly, often itchy and sometimes painful plaques,[19] which manifest predominantly on the elbows and knees, but also on the scalp, palms of the hands, soles of the feet, and the lumbosacral area.[20, 21] These psoriatic plaques are frequently accompanied by additional manifestations in the nails and joints.[19] Individuals with psoriasis often experience periods of remission and subsequent exacerbation.[11]

Plaque psoriasis

Plaque psoriasis is the most common form of psoriasis, constituting approximately 90% of all cases (equivalent to more than 900,000 people in England and Wales).[13, 14, 22] Of these, 20% are anticipated to have moderate to severe psoriasis (approximately 184,000 patients).[18] Plaque psoriasis is characterised by well-demarcated erythematous plaques with silvery scales; these lesions can present on any part of the skin, but are most commonly found on the scalp, back, elbows and knees.[19, 22] Lesions are usually round or oval and may begin as raised papules or flat erythematous regions less than 1 cm in diameter, which expand and coalesce to form larger plaques.[20]

As described above, plaque psoriasis is also marked by the formation of silvery-white scales, with fluctuating thickness; their removal can result in bleeding, a phenomenon described as the Auspitz sign.[20]

Burden of disease

Physical and psychological burden of disease

The physical burden of psoriasis includes pain, itching and bleeding arising from the presence of skin lesions.[22] These symptoms can have an impact on a patient's daily activities, sleep and physical functioning.[23] Whilst a number of topical treatments, phototherapies, and systemic agents are available, these may be inconvenient to apply, time-consuming, or fail to generate complete resolution of plaques.[22]

Patients with psoriasis face a higher risk of developing mental health problems such as anxiety, depression and suicidal ideation.[22] Psychological comorbidities such as anxiety and depression have been reported to increase in incidence with increasing disease severity and in turn may aggravate the physical symptoms of psoriasis. Furthermore, they have been linked to behavioural changes including alcoholism and non-adherence to treatment.[24] Beyond these formal psychological comorbidities, the impact of psoriasis on mental and emotional function manifests itself as an impairment of patient self-image, self-esteem and sense of well-being.[24] Patients reported that the disease affects their ability to carry out everyday activities as well as their interactions with other people, in part because of the reactions it can trigger.[22, 25, 26] For example:

- 74% of psoriasis patients prefer not to be seen in public,[25]
- 20% report being asked to leave public pools,[25] and
- 26% reported incidents in which others did not want to touch them.[25]

Additional impact of patient comorbidities

As well as the dermatologic manifestations of psoriasis, patients may also experience an additional physical burden, as a result of nail and joint disease. In a study of 949 psoriasis patients in Europe and North America, 30% were also diagnosed with PsA,[27] a disease characterised by symptoms including joint pain, swelling, tenderness and stiffness.[28] As well as reduced HRQoL, productivity and functionality, PsA has been linked to long-term work disability, loss of productivity and absenteeism.[28] Nail disease in patients with psoriasis has been reported to further exacerbate the reductions in quality of life. Symptoms of nail psoriasis include pitting, crumbling, the appearance of white spots in the nail plate, excessive growth of the nail bed (hyperkeratosis) and separation of the nail from the nail bed (onycholysis). Evidence suggests that, among psoriasis patients more generally, those with nail disease have the highest risk of developing PsA,[29] further compounding the burden for these patients.

Other diseases that occur with increased prevalence in psoriasis patients include cardiovascular disease (CVD) (odds ratio [OR] of 1.4; 95% CI: 1.2, 1.7),[30] metabolic syndrome (OR: 2.26; 95% CI: 1.70, 3.01)[31] and both Crohn's disease (CD) (OR: 2.49; 95% CI: 1.71, 3.62) and ulcerative colitis (OR: 1.64; 95% CI: 1.15, 2.33).[22, 32] This broad spectrum of co-morbidities contribute to morbidity and mortality among patients, with CVD in particular having been linked to a substantial reduction in the life expectancy of psoriasis patients.[22]

Economic impact

Individuals with psoriasis appear to be more likely to face difficulty in gaining employment. Twenty five percent of patients believe it is harder to get work, and they cannot choose the career they want;[26] in one study, almost half of 369 psoriasis patients were not in employment, of whom 34% attributed this to their disease.[24] For those who are employed, psoriasis may still negatively affect working life. A study of 150 patients with severe psoriasis found that 59% had lost a mean of 26 days from work during the preceding year because of their condition.[24] four percent of patients have also reported taking early retirement as a result of psoriasis.[24] The disease can therefore be life-ruining for those who are affected,[33] and the above factors (physical burden, impact on patient well-being, psychological comorbidities, and impact on relationships and employment) may explain the lower HRQoL scores among psoriasis patients compared to the general population.[34]

Unmet need

Treatment dissatisfaction, switching and discontinuation

Low treatment adherence rates and moderate levels of patient satisfaction have been reported for patients treated for their psoriasis.[35] The lack or loss of efficacy experienced by some patients whilst receiving treatment, as well as limited treatment durability, are suggestive of an unmet need in the treatment of psoriasis.[36] A study of 169 patients initiating biologic treatment at six dermatology clinics in England found that, after the first year, only 64% of patients were persistent on the therapy they had originally initiated. The patients who had not persisted on their initial biologic therapy comprised those who had:[37]

- Discontinued biologic therapy (18% of all patients)
- Switched biologic therapies (12%)
- Increased the dose of biologic therapy (7%)

More than one-third of adults with chronic plaque psoriasis who initiate a biologic will require treatment modifications within the first year (switching, discontinuing, restarting therapy, dose escalation or reduction), according to UK British Association of Dermatologists Biologic Intervention Register (BADBIR) data from 2007–2014.[38] More than half (52%) of patients with moderate-to-severe psoriasis are dissatisfied with their treatment, according to analysis of 5,604 patient responses to the NPF biannual surveys (2003–2011), primarily because of inefficacy or adverse effects.[39]

Data are also available from the international Psoriasis Longitudinal Assessment and Registry (PSOLAR) for 1,115 patients starting a first biologic, 1,436 patients starting a second-line biologic, and 922 patients starting a third-line biologic. Regardless of whether patients were initiating first-, second- or third-line therapy, the most common reason for discontinuation was lack of efficacy. However, the proportion discontinuing treatment due to lack of efficacy was numerically higher during second- and third-line therapy compared to first-line, for each of ustekinumab (UST), infliximab (IFX), adalimumab (ADA) and etanercept (ETN).[36]

These data highlight the importance of long-lasting treatments and suggest that alternative therapy options are therefore necessary to ensure that the treatment needs of patients with psoriasis are met. A range of agents is also required, to allow treatment switching when an initial biologic is not effective.

Treatment of patient comorbidities

Treatment guidelines from NICE,[40] the European Academy of Dermatology and Venereology (EADV),[41] and the BAD[42] recommend consideration of patient comorbidities when choosing and initiating psoriasis treatment. As discussed above, patients with psoriasis often have increased prevalence of comorbidities including psoriatic arthritis and nail disease. Therefore, there is a clear need for a variety of treatment options for patients with moderate to severe psoriasis, particularly ones that can also improve symptoms of comorbid conditions.

Impact of psoriasis treatment on family planning

Since 50% of pregnancies are reported to be unplanned, male and female patients may be taking medication at the time of conception.[43] There is therefore a clear unmet need for patients who are considering family planning, as well as those with the potential for an unplanned pregnancy, to have treatment options available during this time.

In 10–20% of women, psoriasis may worsen and require more intensive treatment during pregnancy.[44] In addition, more than half of patients report a psoriasis flare within the six weeks following delivery. The 2017 ‘British Association of Dermatologists guidelines for biologic therapy for psoriasis’ highlight the importance of controlling psoriasis activity during conception and pregnancy to maintain maternal health and that the risks and benefits of continuing versus stopping biologic therapy must be considered.[42] Despite the need for effective treatment throughout the pregnancy journey, clinical trial data during pregnancy and in breastfeeding women are limited and some treatments are unsuitable for use throughout pregnancy and breastfeeding leading to disruption in treatment.[43, 45]

B.1.3.2 Clinical pathway of care

NICE clinical guidelines [CG153]

Currently in England and Wales, psoriasis treatment is informed by the National Institute for Health and Care Excellence (NICE) "Psoriasis: Assessment and Management" Clinical Guideline Document, 2012 (CG153).[40] According to these guidelines, the first-line treatment is topical therapy; phototherapy and systemic non-biologic therapy (e.g. ciclosporin, MTX and acitretin) constitute second-line treatments; and the third-line therapies refer to biologics such as ADA, ETN, IFX and UST.[40] However, where topical therapy alone is unlikely to be adequate for disease control (in patients with body surface area [BSA] >10%, a Physician's Global Assessment [PGA] score of at least moderate, or with nail disease) it is recommended that phototherapy and systemic therapy are also offered in the first instance.[40] Specific instances in which systemic non-biologic therapy is recommended include for patients in whom:[40]

- The disease cannot be controlled with topical therapy, and
- The disease has a significant impact on physical, psychological or social wellbeing, and
- One or more of the following apply:
    - Psoriasis is extensive (e.g. more than 10% of body surface area affected or a psoriasis area and severity index (PASI) score greater than 10) or
    - Psoriasis is localised and associated with significant functional impairment and/or high levels of distress (e.g. severe nail disease or involvement at high-impact sites) or
    - Phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as >50% of baseline disease severity within 3 months).

The NICE clinical guidelines state that biologic treatments should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of psoriasis, and state that guidance for use is based on recommendations from the technology appraisal process. Furthermore, for patients with psoriasis and PsA, both should be taken into account prior to initiating or changing biologic therapy.[40] However, the current clinical guideline does not include explicit recommendations for when biologic therapy should be used, which agents are preferred, or the order in which they should be initiated.

Patients have the option to switch biologic treatment, and this may be considered in adults if:[40]

- They do not respond adequately to a first biological drug as defined in NICE technology appraisals (primary failure), or
- They initially respond adequately but subsequently lose this response (secondary failure), or
- The first biological drug cannot be tolerated or becomes contraindicated.

The NICE guideline refers to the individual technology appraisals for ADA, ETN, IFX, ixekizumab (IXE), secukinumab (SEC) and UST.[40] The guidance issued within these technology appraisals, as well as those for brodalumab (BROD) and guselkumab (GUS), both of which have been approved by NICE since the clinical guidelines were published, are summarised in Table 4.

Biosimilar versions of ETN and IFX are currently available within the UK.[46]

Table 4: Summary of NICE Technology Appraisal guidance for biologic and small molecule therapies for psoriasis

NICE guideline or guidance	Population	Stopping Rule
ADA **TA146 (2017)[47]**	Adult patients for whom anti-TNFs are being considered, and who have: • Severe disease, defined as a total PASI of ≥10 and DLQI of >10. • Psoriasis that has not responded, or has an intolerance or contraindication, to standard systemic therapies including ciclosporin, MTX and PUVA (psoralen and long-wave ultraviolet radiation)	Should be discontinued if an adequate response is not achieved at 16 weeks. An adequate response is defined as either: • A PASI75 response from when treatment started, or • A PASI50 response and a five-point reduction in DLQI from start of treatment
BROD **TA511 (2018)[48]**	Adult patients in whom: • The disease is severe (PASI ≥10 and a DLQI >10) • The disease has not responded to other systemic therapies, including ciclosporin, MTX and PUVA, or these options are contraindicated or not tolerated	Should be discontinued if an adequate response is not achieved at 12 weeks. An adequate response is defined as either: • A PASI75 response, or • A PASI50 response and a 5-point reduction in DLQI from when treatment started
ETN **TA103 (2017)[49]**	Within its licensed indications and at a dose not exceeding 25 mg twice weekly, for adult patients only when: • The disease is severe (PASI ≥10 and a DLQI >10) • The disease has not responded to standard systemic therapies, including ciclosporin, MTX and PUVA, or the person is intolerant or has a contraindication to these treatments	Should be discontinued if an adequate response is not achieved at 12 weeks. An adequate response is defined as either: • A PASI75 response, or • A PASI50 response and a 5-point reduction in DLQI from when treatment started
GUS **TA521 (2018)[50]}**	For adults, only if: • The disease is severe (PASI ≥10 and DLQI >10) • The disease has not responded to other systemic therapies, including ciclosporin, MTX and PUVA, or these options are contraindicated or not tolerated	Should be discontinued if an adequate response is not achieved at 16 weeks. An adequate response is defined as: • A PASI75 response • A PASI 50 response and a 5-point reduction in DLQI from when treatment started
IFX **TA134 (2017)[51]**	Adult patients with: • Very severe disease (PASI ≥20 and DLQI >18) • Psoriasis that has failed to respond to standard systemic therapies such as ciclosporin, MTX or PUVA or intolerance or contraindication to these treatments	Should be continued beyond 10 weeks only if an adequate response to treatment is achieved within 10 weeks. An adequate response is defined as either: • A PASI75 response, or • A PASI50 response and a 5-point reduction in the DLQI from when treatment started.

	Infliximab biosimilars also apply to this recommendation if their marketing authorisation covers psoriasis.	
IXE **TA442 (2017)[52]**	For adults, only if: • Psoriasis is severe (PASI ≥10 and a DLQI >10) • The disease has not responded to standard systemic therapies, e.g. ciclosporin, MTX and PUVA, or these treatments are contraindicated or not tolerated	Treatment should be stopped at 12 weeks if an adequate response is not achieved. An adequate response is defined as: • A PASI75 response from when treatment started, or • A PASI50 response and a 5-point reduction in DLQI from when treatment started
SEC **TA350 (2017)[53]**	Within its marketing authorisation, for adult patients only when: • Their disease is severe, as defined by a total PASI ≥10 or a DLQI >10 • Their disease has failed to respond to standard systemic therapies, for example, ciclosporin, MTX and PUVA, or these treatments are contraindicated or cannot be tolerated	Treatment should be stopped if an adequate response is not achieved at 12 weeks. An adequate response is defined as either: • A PASI75 response, or • A PASI50 response and a 5-point reduction in DLQI from when treatment started
UST **TA180 (2017)[54]**	Adult patients with: • Severe psoriasis (PASI ≥10 and a DLQI >10) • Psoriasis that has not responded to standard systemic therapies, including ciclosporin, MTX and PUVA, or an intolerance of or contraindication to these treatments	Treatment should be stopped if an adequate response is not achieved by 16 weeks after starting treatment. An adequate response is defined as either: • A PASI75 response from when treatment started, or • A PASI50 response and a 5-point reduction in the DLQI score from when treatment started

Abbreviations: ADA: adalimumab; APR: apremilast; BROD: brodalumab; DLQI: Dermatology Life Quality Index; DMF: dimethyl fumarate; ETN: etanercept; GUS: guselkumab; IFX: infliximab; IXE: ixekizumab; MTX: methotrexate; PASI: Psoriasis Area and Severity Index; PUVA: psoralen and ultraviolet A; SEC: secukinumab; TNF: tumour necrosis factor alpha; UST: ustekinumab

Other relevant treatment guidelines include those issued by the BAD and the EADV. These are summarised below in terms of their guidance for biologic therapies.

British Association of Dermatology (BAD) Psoriasis Guidelines

According to BAD, to be eligible for biologic therapy, patients must:[42]

- Require systemic therapy, and have failed, be intolerant to or have a contraindication for MTX and ciclosporin.
- Have disease that has a large impact on physical, psychological or social functioning.
- Have extensive disease and/or severe disease at localised sites, which is associated with significant functional impairment and/or high levels of distress.

However, BAD also suggests that patients may be eligible for biologic therapy earlier in the treatment pathway (i.e. if MTX has failed, is not tolerated or is contraindicated) if they:

- Fulfil the disease severity criteria and have active PsA (indicating that BAD, like NICE, consider the presence of absence of PsA to be an important factor in treatment decisions), or

- Have psoriasis that is persistent, i.e. that relapses rapidly upon discontinuation of a therapy that cannot be continued long-term (>50% baseline disease severity within 3 months).

However, in contrast to the guidance available from NICE, BAD specify the therapies that should be used first-line within the context of biologic treatment for psoriasis. These include ADA and SEC, regardless of whether patients also have PsA, as well as UST for psoriasis patients without PsA. When patients fail to respond to the chosen first-line therapy, it is suggested that any of the currently licensed biologics may be tried.[42]

The BAD guidelines also apply to treatment with biosimilars, subject to recommendations issued within the EMA guidelines,[42] and the BAD position statement on biosimilars, which states that the reference product and its biosimilars are not considered interchangeable.[55]

European Academy of Dermatology and Venereology (EADV) Psoriasis Guidelines

The European S3 guidelines were issued by the European Dermatology Forum (EDF) in conjunction with the European Association for Dermatology and Venereology (EADV) and the International Psoriasis Council (IPC) in 2015.[41] The guidelines were updated in 2017 with the addition of APR and SEC; further revisions will include recommendations for IXE (date not specified).[56] The recommendations are summarised in Table 5. Other special patient populations and considerations mentioned in the 2015 guidelines but not included in the table are tuberculosis, hepatitis/other hepatological dysfunctions, human immunodeficiency virus (HIV), malignancies including lymphoma and skin cancer, neurological disease, ischemic heart disease and congestive heart failure, diabetes mellitus, kidney failure/renal impairment, and vaccination.

Table 5: EADV treatment recommendations (2015)

Drug or patient group	Recommendation	Level	Strength of consensus	Comment
ADA	We recommend ADA as second line[a] medication for the induction and long-term treatment.	↑↑	Strong consensus	Evidence and consensus based
	We recommend using ADA with an initial loading dose of 80 mg, week 1 40 mg followed by 40 mg every other week.	↑	Strong consensus	Expert opinion
APR	We suggest APR as second-line medication for the induction and long-term treatment.	↑	Strong consensus	Evidence and consensus based
ETN	We recommend ETN as second line[a] medication for the induction and long-term treatment.	↑↑	Strong consensus	Evidence and consensus based
	In general, a starting dose of 50 mg once or twice weekly is used depending on individual factors.	Statement	Strong consensus	Expert opinion
	For maintenance therapy 50 mg once weekly is a commonly used dose.	Statement	Strong consensus	Expert opinion
IFX	We recommend IFX as second line[a] medication for the induction and long-term treatment.	↑↑	Strong consensus	Evidence and consensus based
	We recommend using IFX 5 mg/kg bodyweight continuously every eight weeks during long-term treatment.	↑↑	Strong consensus	Evidence and consensus based
SEC	We recommend SEC for the induction and long-term treatment.	↑↑	Consensus	Evidence and consensus based
	The use as first- or second-line[a] medication should be performed taking individual factors and regional regulations into account.	None	Consensus	None
UST	We recommend UST as second line[a] medication for the induction and long-term treatment.	↑↑	Strong consensus	Evidence and consensus based
	We suggest using 45 mg for patients with a bodyweight of ≤100 kg and 90 mg UST for patients with a body weight of >100 kg.	↑	Strong consensus	Evidence and consensus based
Psoriatic arthritis (PsA)	For inadequately responding patients after at least one synthetic DMARD, we recommend the use of biological DMARDs in combination with synthetic DMARDs or as monotherapy.	↑↑	Consensus	Expert opinion
	SEC is recommended for patients with psoriatic arthritis and an inadequate response to at least one	↑↑	Consensus	Expert opinion

	csDMARD, in whom TNF inhibitors are not appropriate.			
	APR is suggested for patients with psoriatic arthritis and an inadequate response to at least one csDMARD, in whom TNF inhibitors are not appropriate.	↑	Strong consensus	Expert opinion
Wish for pregnancy in near future	For pregnant women with severe psoriasis requiring systemic therapy for which the benefits outweigh the risk we suggest to consider ETN.	↑	Strong consensus	Expert opinion

Abbreviations: ADA: adalimumab; APR: apremilast; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; DMARD: disease-modifying anti-rheumatic drug; EADV: European Academy of Dermatology and Venereology; ETN: etanercept; IFX: infliximab; PsA: psoriatic arthritis; SEC: secukinumab; TNF: tumour necrosis factor; UST: ustekinumab.
[a]If phototherapy and conventional systemic agents are inadequate in response, or contraindicated, or not tolerated.
↑↑ strong recommendation for the use of an intervention; ↑ weak recommendation for the use of an intervention.
Source: Nast et al. (2015)[6]; Nast et al. (2017)[57].

Positioning of CZP relative to the current treatment pathway

The proposed positioning of CZP is in line with its marketing authorisation, that is, for the treatment of plaque psoriasis in adults who are candidates for systemic therapy. CZP will therefore be appraised as a treatment option for patients in the following populations, as specified by the NICE decision problem:

- Patients for whom systemic non-biological treatment or phototherapy is suitable (In the submission this is referred to as: “Candidates for systemic non-biologic therapy”)
- Patients in whom conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated (In the submission this is referred to as: “systemic non-biologic inadequate responders”)

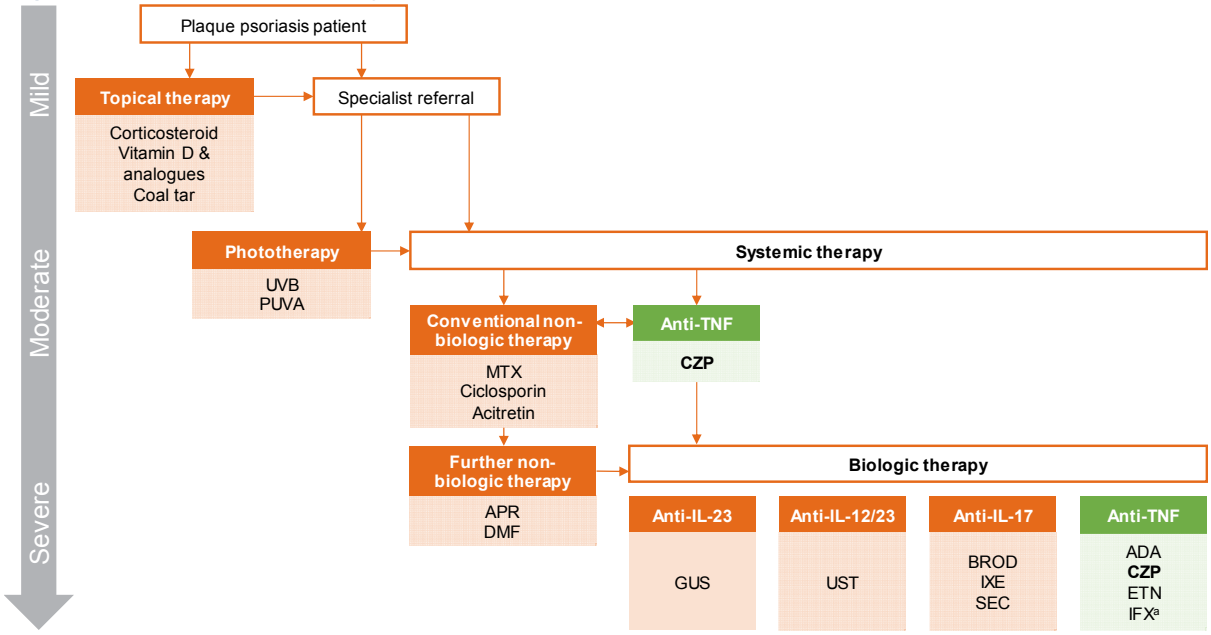
The current clinical pathway for the treatment of plaque psoriasis with systemic therapy (as defined by the NICE clinical guideline CG153 and the technology appraisals for the individual agents), is shown in Figure 1. Eligibility criteria for treatment with biologics, as defined by NICE, include a lack of response, intolerance or contraindication to standard systemic therapies, namely ciclosporin, MTX and PUVA. Patients with severe disease (PASI ≥10 and DLQI >10) are recommended by NICE to be treated with any of ADA, ETN, BROD, IXE, SEC, GUS or UST. IFX is recommended for patients with very severe disease (PASI ≥20 and DLQI >18).

In clinical practice, APR and DMF would only be considered for use in patients unsuitable for biologic treatment or unwilling to receive biologic treatment. Clinical expert opinion indicated that APR and DMF would either be used in select patients prior to starting biologics or reserved for use after biologics, including CZP.[3] Furthermore, previous NICE technology appraisals have stated that APR and DMF would not displace biological therapies during their recent appraisals (NICE TA419, TA475).[58, 59]

The recommendation from BAD that biologic therapies may be considered earlier in the treatment pathway in defined circumstances (as described above),[42] supports the further proposed positioning of CZP as a treatment option for patients who are candidates for systemic non-biologic therapy.

As is the case in the treatment of many diseases, the availability of multiple treatment options is beneficial to patients, allowing greater choice in therapy from the start and offering alternative options in the case of contraindication, intolerance or failure to the first treatment applied (see Section B.1.3.1).

Figure 1: Treatment pathway for patients with plaque psoriasis



Abbreviations: ADA: adalimumab; APR: apremilast; BROD: brodalumab; CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; DMF: dimethyl fumarate; ETN: etanercept; GUS: guselkumab; IFX: infliximab; IL: interleukin; IXE: ixekizumab; MTX: methotrexate; PASI: Psoriasis Area and Severity Index; PDE4: phosphodiesterase 4; PUVA: psoralen and ultraviolet A; SEC: secukinumab; TNF: tumour necrosis factor alpha; UST: ustekinumab.
CZP: Proposed positioning within current NICE pathway.
Source: NICE CG153;[40] adalimumab: TA146;[47] apremilast: TA419;[58] brodalumab: TA511;[48] etanercept TA103;[49] guselkumab: TA521;[50] infliximab: TA134;[51] ixekizumab: TA442;[52] secukinumab: TA350;[53] ustekinumab: TA180.[54]

B.1.4 *Equality considerations*

There are no equality issues arising in relation to this technology.

B.2 Clinical effectiveness

Clinical efficacy of CZP

- The efficacy and safety of CZP in adult patients with moderate-to-severe plaque psoriasis was evaluated in three Phase III trials, CIMPASI-1, CIMPASI-2, and CIMPACT, conducted in a total of 1,020 patients.
- CIMPASI-1 and CIMPASI-2 are two ongoing Phase 3, randomized, double-blind, PBO-controlled multicenter trials followed by an open-label follow up. CIMPACT is an ongoing Phase 3 multicenter, randomized, double blind, parallel group, PBO- and active-controlled trial followed by a PBO-controlled maintenance period and an open-label follow up. The overall duration of the three trials is 152 weeks. The three trials included a broad population of PSO patients, who were candidates for systemic non-biologic drugs, patients who were biologic naïve or biologic exposed. A large number of outcomes that are clinically meaningful and also relevant to patients were assessed in these trials.
- The efficacy of CZP in patients with moderate-to-severe plaque psoriasis has been demonstrated in all three trials, which successfully met their primary objectives, as supported by the hierarchical procedure testing.

Short-term efficacy

- The integrated analysis of the pooled populations of the three trials indicated that both dosing regimens (CZP 200 mg Q2W and CZP 400 mg Q2W) resulted in clinically meaningful and statistically significant clinical responses, as measured by PASI75 and PGA clear or almost clear at Week 16 (coprimary endpoints) versus placebo. CZP-treated patients also showed significantly higher PASI90 and PASI100 response rates and improvements in BSA versus placebo.
- At Week 16, CZP-treated patients reported clinically meaningful and statistically significant improvements versus placebo in a broad spectrum of patient-relevant outcomes, including health-related quality of life, anxiety and depression and work productivity and daily activity.
- In the CIMPACT trial, CZP 400 mg Q2W treatment resulted in statistically significant superior improvements in PASI75 at Week 12 (secondary endpoint) versus ETN. CZP 200 mg Q2W treatment demonstrated a numerically greater response versus ETN and was non-inferior to ETN for PASI75 at Week 12.
- Improvements with CZP were similar irrespective of prior treatment exposure, with similarly high improvements in patients who were candidates for systemic non-biologic treatments, patients who were biologic-naïve, or biologic-exposed.

Long-term maintenance and durability of response

- Maintenance and durability of response was demonstrated in the long-term, through to Week 48, for signs and symptoms of psoriasis and patient-relevant outcomes.
- The rapid and consistent increases in clinical response to Week 16, as measured through PASI75 response rates, were maintained over time through Week 48 of the maintenance treatment period in both CZP doses. Numerically higher responses were achieved for

patients receiving CZP 400 mg Q2W compared with CZP 200 mg Q2W, reaching 83.6% and 70.7% for PASI75 and 68.9% and 61.0% for PGA, respectively.

- A high durability of clinical response through to Week 48 was seen in patients who were Week 16 responders to CZP:
    - CZP-treated patients from the pooled CIMPASI trials who were PASI75, or PGA responders at Week 16 consistently maintained the improvements in efficacy to Week 48.
    - Of the CZP 400 mg Q2W treated patients who achieved a PASI75 response at Week 16 and continued with their original CZP dose, [redacted]% maintained their level of PASI75 response at Week 48, and [redacted]% and [redacted]% of these patients achieved PASI90 and PASI100 response, respectively, at Week 48.
    - Out of the CZP 200 mg Q2W treated patients who achieved a PASI75 response at Week 16 and continued with their original CZP dose, [redacted]% maintained their level of PASI75 response at Week 48, [redacted]% and [redacted]% of these patients achieved PASI90 and PASI100 response, respectively, at Week 48.
    - Clinically meaningful improvements in DLQI at Week 16 were maintained or improved through to Week 48 in patients receiving CZP 400 mg Q2W and CZP 200 mg Q2W, with 52.3% and 45.3% of patients in CIMPASI-1 and 50.6% and 38.5% of patients in CIMPASI-2 in DLQI remission at Week 48, respectively.
- Long-term maintenance of response with CZP was similar irrespective of prior treatment exposure, in patients who were candidates for systemic non-biologic treatments, and those who were biologic-naïve or biologic-exposed.

Extracutaneous manifestations

- Patients treated with both doses of CZP showed improvement in nail psoriasis (mNAPSI), at Week 48 (mean decrease from baseline of [redacted] and [redacted] for CZP 200 mg Q2W and CZP 400 mg Q2W, respectively).
- Complete resolution in psoriatic nail disease (mNAPSI score=0) was achieved in [redacted] and [redacted] of patients receiving CZP 200 mg Q2W and CZP 400 mg Q2W at Week 48, respectively.

Safety

The safety profile of CZP in patients with moderate-to-severe plaque psoriasis over a period of up to 144 weeks was comparable with that reported over shorter time periods and in other indications. Both doses, CZP 200 mg Q2W and CZP 400 mg Q2W, have similar and acceptable safety profiles, with a risk that does not increase with longer exposure.

- The safety profile of CZP treatment for up to 12 weeks, including the type and incidence of TEAEs, was comparable with treatment with Enbrel (ETN, with fewer discontinuations due to AEs vs ETN.
- No new previously unreported safety signals compared with the use of CZP in other indications occurred over the 144-week trial period.

Network meta-analysis (NMA)

- Following a systematic literature review, a network meta-analysis (NMA) was performed to evaluate the relative clinical effectiveness of CZP with its relevant active comparators as well as placebo. The main outcomes of interest were the PASI response rates at weeks 10–16. Analyses were conducted in the ITT population; due to lack of published evidence for comparators in the candidates for systemic non-biologic therapy population, no NMA could be conducted. The primary analysis considered was a placebo adjusted multinomial model, which allows the PASI response to be treated as a categorical variable, similarly to the approach adapted from the NICE Decision Support Unit.

[redacted]

Conclusion

- CZP offers an efficacious treatment for adult patients with moderate-to-severe chronic plaque psoriasis, across psoriasis signs and symptoms and extracutaneous manifestations, as well as a large spectrum of patient relevant outcomes. CZP demonstrates high durability of response, with long-term maintenance of clinical response, nail psoriasis and patient relevant outcomes. A similar effect with CZP was seen in a broad patient population, at all stages of the treatment pathway, including patients who are candidates for systemic non-biologics, are naïve to or have received prior therapy with biologics. Similar improvements were seen with both CZP doses, with higher responses in CZP 400 mg Q2W.
- Data from the overall clinical program demonstrates that CZP 200 mg Q2W is an effective treatment option for patients with moderate to severe plaque psoriasis. Furthermore, for some patients with insufficient response to CZP 200 mg Q2W, evidence shows that CZP 400 mg Q2W is an effective therapy. Escalation of the treatment dose in case of insufficient response is clinical practice in England, supported by the latest 2017 BAD guidelines and local treatment pathways in England.

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify relevant clinical evidence from RCTs on the efficacy and safety of certolizumab pegol, as well as licensed non-biologic and biologic therapies, for the treatment of moderate to severe plaque psoriasis. The SLR identified 83 RCTs from a total of 100 publication. Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

Table 6 provides a summary of all studies of CZP in moderate-to-severe plaque psoriasis, including those that were identified in the clinical SLR reported in Appendix D or from UCB data on file.

Table 6: Overview of relevant clinical evidence informing the submission

Study	Presentation in submission	Does the study inform the clinical evidence base for the economic model?	Primary study reference(s)
CIMPASI-1	Key evidence, presented in full in Section B.2	Yes	CIMPASI-1 CSR[60] Gottlieb et al., 2018[61]
CIMPASI-2	Key evidence, presented in full in Section B.2	Yes	CIMPASI-2 CSR[62] Gottlieb et al., 2018[61]
CIMPACT	Key evidence, presented in full in Section B.2	Yes	CIMPACT CSR[63] Lebwohl et al., 2018[64]
NCT00245765	Supportive study, not presented in the submission	Yes	Reich *et al.*(2012)[65]

B.2.2.1 Populations presented in the submission

A summary of the populations from the CZP clinical study programme in psoriasis that are presented in this submission and the rationale for their inclusion are provided in Table 7.

Table 7. Populations presented in the submission

NICE final scope	Referred to in UCB submission as:	UCB submission	Rationale
N/A	ITT population	ITT population	Presentation of the study results as per study protocol.
Patients for whom systemic non-biological treatment or phototherapy is suitable	Candidates for systemic non-biologic therapy	Patients who are naïve to both biologic and non-biologic systemic therapy	These patients are eligible for treatment with non-biologic systemic therapy in clinical practice. Within the biologic naïve subpopulation of the CZP clinical studies, the subset of patients who are naïve to non-biologic systemic therapy has been outlined in this submission for selected endpoints to reflect the NICE scope.
Patients for whom conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated	Systemic non-biologic therapy inadequate responders	Patients with exposure to at least 1 previous systemic non-biologic therapy and no previous biologic exposure	This subpopulation represents the patients who are eligible to start current biologics in clinical practice, as they have failed prior systemic non-biologic therapy and yet are biologic naïve. Historically, the precise number of prior systemic non-biologics has not been clearly reported in studies of patients with psoriasis. The inclusion and exclusion criteria in published studies indicate that the majority of psoriasis patients across trials receive ≥1 systemic non-biologic, but not all publications included further details on the percentage use or presentation of the results separately. As part of this submission, a systematic review of the literature for comparators (discussed in Appendix D) shows that this information is not consistently published. Most trials consider failure of systemic non-biologics as a 'yes/no' inclusion criteria rather than by number, and their use is variable between trials due in part to changes in treatment pathways over time. Therefore data for the ITT population are presented in the clinical effectiveness section of this submission (Section B.2.6; representative of the population in the NICE scope) as a conservative approach and to ensure consistency with the indirect comparisons to be made later in the submission.

			Due to the lack of published data for the systemic non-biologic therapy inadequate responders population specifically, an NMA was not possible to run. Therefore the ITT populations of the CZP and comparator trials have been used within the NMA and these results are used in the health economic model to represent the systemic non-biologic therapy inadequate responders. For completeness and to address the NICE scope, results for selected clinical outcomes for the population of patients who are systemic non-biologic therapy inadequate responders are presented in Section B.2.6.10.

Abbreviations: CZP: certolizumab pegol; ITT, intention to treat; NICE: National Institute for Health and Care Excellence.

B.2.2.2 CZP trial summary

CIMPASI-1 and CIMPASI-2 are two ongoing Phase III, randomised, placebo-controlled clinical trials of CZP for the treatment of chronic plaque psoriasis in adults (Table 8). CIMPACT is an ongoing Phase III, randomised, placebo- and active-controlled trial of CZP for the treatment of chronic plaque psoriasis (Table 9).

A Phase II study was also available; this study was a randomised, double-blind, placebo-controlled study in which patients were allocated to placebo, CZP 200 mg Q2W or CZP 400 mg Q2W, for 10 weeks during the 12-week treatment period.[66] Patients were then followed, without treatment, for a further 12 weeks (non-responders) or until relapse (responders). PASI75 responder rate and discontinuation rate data (for the licensed dose only) from this study were included in the network meta-analysis, which feeds into the cost-effectiveness analyses presented as part of this submisson.[66] Further details of this Phase II study, including relevant top-level efficacy results, are summarised in Appendix M.

Table 8: Clinical effectiveness evidence

Study	CIMPASI-1 (NCT02326298)	CIMPASI-2 (NCT02326272)	CIMPACT (NCT02346240)
Study design	Phase III, randomised, double-blind trial, placebo-controlled trial		Phase III, randomised, double-blind, parallel-group, placebo- and active-controlled trial
Population	Patients aged ≥18 years with chronic plaque psoriasis for ≥6 months Patients must have: • Baseline PASI ≥12 • Baseline BSA ≥10% • Baseline PGA score ≥3 Patients must also be candidates for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy		
Intervention(s)	Sc CZP 400 mg Q2W Sc CZP 400 mg at Weeks 0, 2 and 4; CZP 200 mg at Week 6 and Q2W thereafter (hereafter known as CZP 200 mg Q2W)		
Comparator(s)	Sc placebo Q2W		Sc placebo Q2W Sc ETN 50 mg BIW

Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X	Yes	X	**Indicate if trial used in the economic model**	Yes	X	Yes	X	**Indicate if trial used in the economic model**	Yes	X
	No			No		No			No		No			No	

Rationale for use/non-use in the model	CIMPASI-1, CIMPASI-2 and CIMPACT are the three pivotal trials for CZP in plaque psoriasis. They informed the marketing authorisation application and consider a population directly relevant to the decision problem addressed in the submission
Reported outcomes specified in the decision problem **(outcomes that are incorporated into the model**	• Severity of psoriasis o Measured by **PASI75**, PGA 0/1 response, BSA affected • Improvement in symptoms on the nails o Measured by change from baseline in mNAPSI response • Response rate o Measured by **PASI75**/90/100 and PGA 0/1 response rates • Duration of response

are marked in bold)	o Measured by **PASI75**/90 and PGA 0/1 response to Week 48 • Relapse rate o Measured by time to not achieving PASI50 response (CIMPACT only) • Adverse effects of treatment o Measured by adverse events • Health-related quality of life o Measured by DLQI, SF-36, HADS-A and HADS-D, and EQ-5D-3L
All other reported outcomes	• PASI50 • Absolute and percent change from baseline in PASI score • PGA score distribution • Time to onset of action (time to PASI50, PASI75, PASI90) • Change from baseline in WPAI-SHP v2.0 adapted to psoriasis scores CIMPASI-1 and CIMPASI-2 only: • Socio-professional status (educational level, professional status, and assistance in the usual activities) CIMPACT only: • Change from baseline in FASca

Abbreviations: BIW: twice a week; BSA: body surface area; CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; EQ-5D-3L™: EuroQoL – 5 dimensions, 3 levels; FASca: Fatigue Assessment Scale; HADS-A: hospital anxiety and depression scale for anxiety; HADS-D: hospital anxiety and depression scale for depression; mNAPSI: modified nail psoriasis severity index; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; PSO: psoriasis; Q2W: every two weeks; SF-36: 36-item Short Form health survey; WPAI-SHP: work productivity and activity impairment questionnaire–specific health problem;
Source: CIMPASI-1 Clinical Study Report;[60] CIMPASI-2 Clinical Study Report;[62] CIMPACT Clinical Study Report.[63]

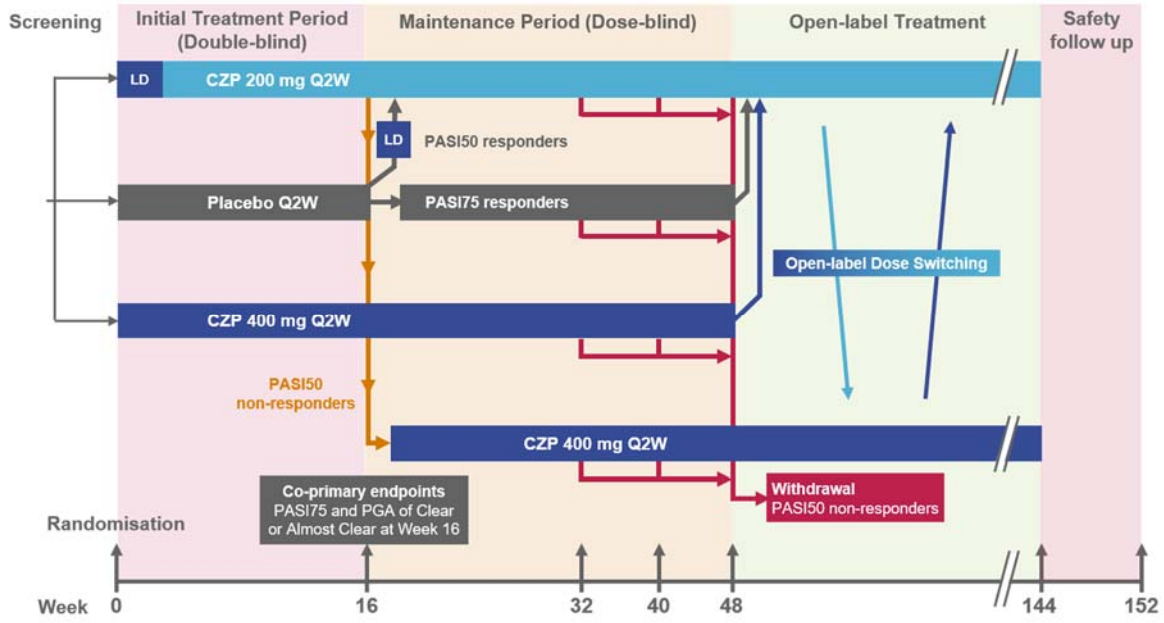
B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Summary of methodologies of studies for moderate to severe plaque psoriasis

The CIMPASI-1 and CIMPASI-2 trials consisted of the following periods: screening; initial, maintenance and open-label treatment; and safety-follow up (Figure 2). At the start of the initial treatment period, patients were randomised 2:2:1 to receive CZP 200 mg Q2W, CZP 400 mg Q2W or placebo. Week 16 responders (patients achieving a PASI50 if receiving CZP 200 mg or 400 mg, or PASI75 if receiving placebo) continued to receive the therapy to which they were randomised at baseline. Patients randomised to placebo at baseline who achieved a PASI50 response (but not a PASI75 response) at Week 16 crossed over, receiving three loading doses of CZP 400 mg followed by CZP 200 mg Q2W. Non-responders at Week 16 (patients not achieving a PASI50 response) escaped from blinded treatment and received open-label CZP 400 mg Q2W. Patients not achieving a PASI50 response at Week 32 or later were withdrawn from the study.

During the open-label treatment period, Week 48 PASI50 responders, and escape arm PASI75 responders at Week 48 (at the investigator's discretion), received CZP 200 mg Q2W. Failure to achieve a PASI50 response (or, at the investigator's discretion, achievement of a PASI50 response but not a PASI75 response) at Weeks 60, 72, 84, 96, 108, 120, or 132, resulted in patients switching to CZP 400 mg Q2W for a minimum of 12 weeks. Following 12 weeks of CZP 400 mg Q2W, PASI75 responders could be switched back to CZP 200 mg Q2W, while patients not achieving a PASI50 response were withdrawn.

Figure 2: CIMPASI-1 and CIMPASI-2 trial design



Abbreviations: CZP: certolizumab pegol; LD: loading dose; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
Source: CIMPASI-1 Clinical Study Report;[60] CIMPASI-2 Clinical Study Report.[62]

In the CIMPASI-1 study, the co-primary outcomes at Week 16 were the proportion of patients achieving a PASI75 response, and the proportion of patients achieving a PGA score of clear or almost clear (with at least a 2-category improvement). Secondary efficacy outcomes assessed disease severity at Weeks 16 and 48, and the impact on quality of life at Week 48. The other key outcomes assessed by CIMPASI-1 concerned time to onset of action, the severity of nail disease, and patient productivity and quality of life. Table 9 provides additional details relating to the study methodology. Eligible patients were aged 18 years or older, and had had chronic plaque psoriasis for at least 6 months.[60] Patients were also required to meet criteria relating to both disease severity and eligibility for systemic therapy, phototherapy, and/or chemotherapy. Further details of the inclusion and exclusion criteria can be found in Appendix N.

CIMPASI-2 was largely identical to CIMPASI-1 with regards to both study design (Figure 2 and Table 9) and the patient inclusion and exclusion criteria (Appendix N).[62] Differences between the two trials primarily related to the study locations involved (Table 9), and a small number of local inclusion and exclusion criteria requirements arising subsequent to this.[60, 62]

The CIMPACT study consisted of the same periods as CIMPASI-1 and CIMPASI-2 (screening; initial, maintenance and then open-label treatment; and safety-follow up; Figure 3:). However, in contrast to the CIMPASI trials, CIMPACT also included an active comparator, with patients randomised 3:3:3:1 at baseline to CZP 200 mg Q2W, CZP 400 mg Q2W, ETN 50 mg BIW or placebo. At Week 16, patients in the CIMPACT trial who did not achieve a PASI75 response escaped from blinded treatment to receive CZP 400 mg Q2W. Escape arm patients not achieving a PASI50 response at Week 32 or a subsequent timepoint were withdrawn from the study.

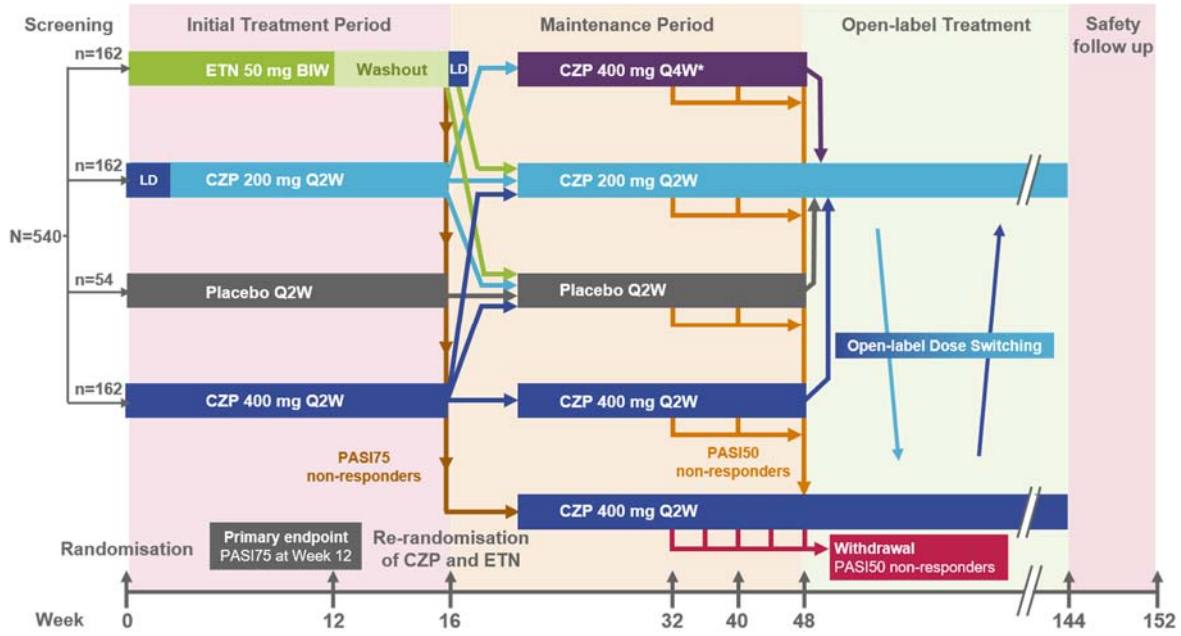
For patients who did achieve a PASI75 response at Week 16:

- Patients initially randomised to placebo continued to receive blinded placebo
- Patients initially randomised to ETN were re-randomised (2:1) to either CZP (loading dose of 400 mg at Weeks 16, 18, and 20 followed by 200 mg Q2W) or placebo
- Patients initially randomised to CZP 200 mg Q2W were re-randomised (2:2:1) to receive either CZP 200 mg Q2W or CZP 400 mg Q4W or placebo

Patients initially randomised to CZP 400 mg Q2W were re-randomised (2:2:1) to CZP 200 mg Q2W or CZP 400 mg Q2W or placebo. Patients who relapsed (<PASI50 response) during the maintenance treatment period were removed from the double-blind placebo-controlled maintenance treatment period and entered into the open-label extension (OLE), receiving CZP 400 mg Q2W. Patients entering the OLE from the escape arm of the initial treatment period continued to receive CZP 400 mg Q2W. All other patients entering the OLE (i.e. those completing the Week 48 visit of the maintenance treatment period without relapse) received CZP 200 mg Q2W.

Where patients receiving CZP 200 mg Q2W did not achieve a PASI50 response, individuals switched to CZP 400 mg Q2W. PASI50 non-responders at Week 32 or later, who had received CZP 400 mg Q2W for at least 12 weeks, were withdrawn from the study. At the investigator's discretion, patients in the escape arm who achieved a PASI75 could switch to the CZP 200 mg dose arm.

Figure 3: CIMPACT trial design



Abbreviations: BIW: twice a week; CZP: certolizumab pegol; ETN: etanercept; LD: loading dose; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
Source: CIMPACT Clinical Study Report[63]

The inclusion and exclusion criteria for the CIMPACT study were largely similar to those observed in CIMPASI-1 and CIMPASI-2, with the exception of requirements that were specific to individual countries involved (Appendix N). However, in contrast to CIMPASI-1 and CIMPASI -2, the key primary efficacy outcome was the proportion of patients achieving a PASI75 at Week 12. A summary of the trial methodology for CIMPASI-1, CIMPASI-2 and CIMPACT is presented in Table 9. The inclusion and exclusion criteria for CIMPASI-1, CIMPASI-2 and CIMPACT are presented in Appendix N.

Table 9: Summary of methodologies for CIMPACT, CIMPASI-1 and CIMPASI-2 studies

Trial number (acronym)	CIMPASI-1 (NCT02326298)	CIMPASI-2 (NCT02326272)	CIMPACT (NCT02346240)
Location	Conducted at 30 sites across the following countries: Canada, Czech Republic, Germany, Hungary, USA	Conducted at 23 sites across the following countries: Austria, Canada, Poland, USA	Conducted at 70 sites across the following countries: Bulgaria, Czech Republic, France, Germany, Hungary, Netherlands, Poland, UK ([redacted] sites), USA
Trial design	Randomised, double-blind, placebo-controlled Phase III trial		Randomised, double-blind, parallel-group, placebo- and active-controlled Phase III trial
Duration of study	• Screening period: up to 5 weeks of screening • Initial treatment period: baseline (Week 0) to Week 16 • Maintenance treatment period: Weeks 16–48 • Open-label extension period: Weeks 48–144 • Safety follow-up (10 weeks after final dose of trial medication): Weeks 144–152		
Method of randomisation	At baseline, eligible patients were randomised 2:2:1 to • CZP 200 mg Q2W • CZP 400 mg Q2W • Placebo Randomisation was achieved using IVRS/IWRS, based on a predetermined production randomisation and/or packaging schedule provided by the Sponsor Patient treatment assignment was stratified by site		At baseline, eligible patients were randomised 3:3:3:1 to • CZP 200 mg Q2W • CZP 400 mg Q2W • ETN 50 mg BIW • Placebo Randomisation was achieved using an IVRS/IWRS, based on a predetermined production randomisation and/or packaging schedule provided by the Sponsor
Method of blinding	Blinding for CZP/placebo was maintained throughout the initial and maintenance treatment phases (baseline to Week 48) This was achieved through the following: • Use of the IVRS/IWRS		Patients receiving ETN were not blinded to their treatment. However, all sites used a dedicated blinded assessor to perform the PASI, PGA and BSA assessments at each designated visit

	• The unblinded personnel who administered CZP and placebo were otherwise not involved in the study • Pharmacokinetic and antibody data were not provided to the blinded study team until the database had been locked once the last subject reached Week 48	Blinding for CZP/placebo was maintained through the following: • Use of the IVRS/IWRS • The unblinded personnel who administered CZP and placebo were otherwise not involved in the study • Pharmacokinetic and antibody data were not provided to the blinded study team until the database had been locked once the last subject reached Week 48
Trial drugs and method of administration	• Sc CZP 200 mg Q2W after a loading dose of CZP 400 mg at Week 0, 2 and 4 • Sc CZP 400 mg Q2W • Sc placebo Q2W	• Sc CZP 200 mg Q2W after a loading dose of CZP 400 mg at Week 0, 2 and 4. Patients could be re-randomised into CZP 400 mg at Week 16 • Sc CZP 400 mg Q2W • Sc placebo Q2W • Sc ETN 50 mg BIW
Permitted and disallowed concomitant medication	Permitted concomitant medications: • [redacted] • [redacted] Concomitant medications for psoriasis permitted during the open-label treatment period: • [redacted] • [redacted] • [redacted] Prohibited concomitant medications: • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]	

	• [redacted] • [redacted] [redacted] • [redacted] • [redacted] • [redacted] • [redacted] o [redacted] o [redacted] o [redacted] o [redacted] o [redacted]	
Primary outcomes (including scoring methods and timings of assessments)	• PASI75 at Week 16 • PGA clear or almost clear (with ≥2-category improvement) at Week 16	• PASI75 at Week 12
Secondary outcomes (including scoring methods and timings of assessments)	• PASI90 at Week 16 • PGA clear or almost clear (with ≥2-category improvement) at Week 48 • PASI75 at Week 48 • Change from baseline in DLQI at Week 16	• PASI75 at Week 16 • PASI90 at Week 12 and Week 16 • PGA clear or almost clear (with ≥2 category improvement) at Week 12 • PGA clear or almost (with ≥2 category improvement) at Week 16 • PASI75 at Week 48 for those achieving PASI75 at Week 16
Other key outcomes	• Time to onset of action (time to PASI50/75/90 response) • Change from baseline in mNAPSI	• Time to onset of action (time to PASI50/75/90 response) • Time to relapse (not achieving PASI50

	• Change from baseline in SF-36 • Change from baseline in HADS-A and HADS-D scores, • Change from baseline in WPAI-SHP v2.0 adapted to psoriasis scores • EQ-5D-3L and EQ-5D-3L VAS	response) for those achieving PASI75 at Week 16 • Change from baseline in DLQI • Change from baseline in WPAI-SHP v2.0 adapted to psoriasis scores • Health status as assessed by EQ-5D-3L and EQ-5D-3L VAS • Change from baseline in mNAPSI
Pre-specified subgroup analyses	PASI75 responder rate at Week 16, and PGA response at Week 16 analysed by: • Age (years) • Gender • Race • Ethnic origin • Psoriasis disease duration (years) • Geographical region • Baseline BMI (kg/m^2) • Baseline weight (kg) • Prior biologic exposure • Prior anti-TNF exposure • Prior systemic therapy (non-biologic) • Prior systemic chemophototherapy or phototherapy • Any prior systemic treatment for psoriasis • Previous exposure to at least 2 systemic treatments out of phototherapy, MTX, and ciclosporin (with no previous biologic exposure) • Anti-CZP antibody status • Baseline PASI score • Baseline psoriasis BSA (%)	PASI75 responder rate at Week 12 by: • Age (years) • Gender • Race • Ethnic origin • Psoriasis disease duration (years) • Geographical region • Baseline BMI (kg/m^2) • Baseline weight (kg) • Prior biologic exposure • Prior anti-TNF exposure • Prior systemic therapy (non-biologic) • Prior systemic chemophototherapy or phototherapy • Any prior systemic treatment for psoriasis • Previous exposure to at least 2 systemic treatments out of phototherapy, MTX, and ciclosporin (with no previous biologic exposure), anti-CZP antibody status • Baseline PASI score • Baseline psoriasis BSA (%)

Duration of safety follow-up	All subjects, including those withdrawn from the study treatment, had a safety follow-up visit 10 weeks after their final dose of study medication.

Abbreviations: AE: adverse event; anti-TNF: anti-tumour necrosis factor alpha; BIW: twice weekly; BMI: body mass index; BSA: body surface area; CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; ETN: etanercept; EQ-5D-3L: EuroQoL – 5 dimensions – 3 levels; HADS-A: hospital anxiety and depression scale – anxiety; HADS-D: hospital anxiety and depression scale – depression; IVRS: interactive voice response system; IWRS: interactive web response system; mNAPSI: modified nail psoriasis severity index; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drugs; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; PsA: psoriatic arthritis; Q2W: every two weeks; sc: subcutaneous; SF-36: 36-item Short Form health survey; TNF: tumour necrosis factor; UK: United Kingdom; USA: United States of America; VAS: visual analogue scale; WPAI: work productivity and activity impairment questionnaire.
Source: ClinicalTrials.gov (CIMPASI-1);[67] ClinicalTrials.gov (CIMPASI-2);[68] ClinicalTrials.gov (CIMPACT);[69] CIMPASI-1 Clinical Study Report;[60] CIMPASI-2 Clinical Study Report;[62] CIMPACT Clinical Study Report.[63]

Psoriasis was assessed using PASI, a tool to assess the severity of psoriasis. This was used to measure the co-primary endpoint for CIMPASI-1 and CIMPASI-2, and the primary endpoint for CIMPACT. PGA response was also used to measure changes in severity of psoriasis and was the other co-primary endpoint in CIMPASI-1 and CIMPASI-2. The response criteria for PASI, PGA and the other outcomes reported by CIMPASI-1, CIMPASI-2 and CIMPACT are detailed in Appendix O.

B.2.3.2 Baseline characteristics for psoriasis patients in pivotal trials

The baseline patient demographics and clinical characteristics are reported below for each of the studies (Table 10). Demographic characteristics were generally well balanced across groups and across trials. The only notable exception was that there were fewer males overall in CIMPASI-2 (127 patients [55.9%]) compared with CIMPASI-1 (162 patients [69.2%]) and CIMPACT (381 patients [68.2%]).

Baseline disease characteristics were generally well balanced across trials and were reflective of a population with moderate to severe psoriasis. Notable differences between the trials were observed for prior anti-TNF therapy, prior chemotherapy or phototherapy use, and geographical region. A lower percentage of patients used prior anti-TNF therapy in CIMPACT (21 patients [3.8%]) compared with CIMPASI-1 (46 patients [19.7%]) and CIMPASI-2 (53 patients [23.3%]). This difference in prior anti-TNF therapy is likely due to the fact that prior ETN use was not permitted in CIMPACT. A higher percentage of patients used chemotherapy or phototherapy in CIMPACT ([redacted] patients [redacted]) compared with CIMPASI-1 ([redacted] patients [redacted]), and CIMPASI-2 ([redacted] patients [redacted]). Additionally, a higher percentage of patients were from Europe in CIMPACT (approximately 83.5%) compared with CIMPASI-1 (48.7%) and CIMPASI 2 (30.8%).

The baseline characteristics were validated by the clinical trial investigators as part of the internal study programme as being suitable to pool across the CZP studies. UK clinical expert opinion further agreed that the small differences between the baseline characteristics of the trials would not affect outcomes.[3]

Patient disposition for CIMPASI-1, CIMPASI-2 and CIMPACT is reported in Appendix D.

Table 10: Baseline characteristics in the randomised treatment group population for the initial treatment period

	CIMPASI-1			CIMPASI-2			CIMPACT			
Characteristic	**Placebo (n=51)**	**CZP 200 mg (n=95)**	**CZP 400 mg (n=88)**	**Placebo (n=49)**	**CZP 200 mg (n=91)**	**CZP 400 mg (n=87)**	**Placebo (n=57)**	**ETN (n=170)**	**CZP 200 mg (n=165)**	**CZP 400 mg (n=167)**
Age, years										
Mean (SD)	47.9 (12.8)	44.5 (13.1)	43.6 (12.1)	43.3 (14.5)	46.7 (13.3)	46.4 (13.5)	46.5 (12.5)	44.6 (14.1)	46.7 (13.5)	45.4 (12.4)
Gender, n (%)										
Male	35 (68.6)	67 (70.5)	60 (68.2)	26 (53.1)	58 (63.7)	43 (49.4)	34 (59.6)	127 (74.7)	113 (68.5)	107 (64.1)
Female	16 (31.4)	28 (29.5)	28 (31.8)	23 (46.9)	33 (36.3)	44 (50.6)	23 (40.4)	43 (25.3)	52 (31.5)	60 (35.9)
Racial group, n (%)										
White	45 (88.2)	87 (91.6)	79 (89.8)	44 (89.8)	86 (94.5)	81 (93.1)	57 (100)	163 (95.9)	158 (95.8)	162 (97.0)
Black	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographical region, n (%)										
North America	26 (51.0)	49 (51.6)	45 (51.1)	35 (71.4)	61 (67.0)	61 (70.1)	10 (17.5)	29 (17.1)	26 (15.8)	27 (16.2)
Europe	25 (49.0)	46 (48.6)	43 (48.9)	14 (28.6)	30 (33.0)	26 (29.9)	[redacted]	[redacted]	[redacted]	[redacted]
Central/East Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36 (63.2)	111 (65.3)	107 (64.8)	109 (65.3)
Western Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11 (19.3)	30 (17.6)	32 (19.4)	31 (18.6)
Weight, kg										
Mean (SD)	95.2 (19.5)	92.6 (21.0)	92.2 (21.7)	87.1 (26.4)	97.8 (25.6)	91.8 (27.7)	93.7 (29.7)	88.6 (20.7)	89.7 (20.6)	86.3 (20.0)

Characteristic	CIMPASI-1			CIMPASI-2			CIMPACT			
	Placebo (n=51)	CZP 200 mg (n=95)	CZP 400 mg (n=88)	Placebo (n=49)	CZP 200 mg (n=91)	CZP 400 mg (n=87)	Placebo (n=57)	ETN (n=170)	CZP 200 mg (n=165)	CZP 400 mg (n=167)
BMI, kg/m^2										
Mean (SD)	32.2 (6.8)	31.1 (7.3)	30.7 (6.7)	30.2 (8.0)	32.8 (8.3)	31.7 (8.9)	31.2 (8.5)	29.5 (6.3)	29.8 (6.1)	28.9 (5.9)
Baseline clinical characteristics										
PASI score										
Mean (SD)	19.8 (7.5)	20.1 (8.2)	19.6 (7.9)	17.3 (5.3)	18.4 (5.9)	19.5 (6.7)	19.1 (7.1)	21.0 (8.2)	21.4 (8.8)	20.8 (7.7)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA score, n (%)										
3	35 (68.6)	62 (65.3)	65 (73.9)	37 (75.5)	66 (72.5)	61 (70.1)	40 (70.2)	115 (67.6)	114 (69.1)	113 (67.7)
4	16 (31.4)	33 (34.7)	23 (26.1)	12 (24.5)	25 (27.5)	26 (29.9)	17 (29.8)	55 (32.4)	51 (30.9)	54 (32.3)
BSA affected by psoriasis										
Mean (SD)	26.1 (16.1)	25.4 (16.9)	24.1 (16.6)	20.0 (9.5)	21.4 (12.2)	23.1 (11.6)	24.3 (13.8)	27.5 (15.5)	28.1 (16.7)	27.6 (15.3)
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI total score										
Mean (SD)	13.9 (8.3)	13.3 (7.4)	13.1 (6.5)	12.9 (7.3)	15.2 (7.2)	14.2 (7.2)	13.2 (7.6)	14.1 (7.4)	12.8 (7.0)	15.3 (7.3)
Duration of disease, years										
Mean (SD)	18.5 (12.9)	16.6 (12.3)	18.4 (12.9)	15.4 (12.2)	18.8 (13.5)	18.6 (12.4)	18.9 (12.9)	17.4 (12.0)	19.5 (13.2)	17.8 (11.5)

	CIMPASI-1			CIMPASI-2			CIMPACT			
Characteristic	**Placebo (n=51)**	**CZP 200 mg (n=95)**	**CZP 400 mg (n=88)**	**Placebo (n=49)**	**CZP 200 mg (n=91)**	**CZP 400 mg (n=87)**	**Placebo (n=57)**	**ETN (n=170)**	**CZP 200 mg (n=165)**	**CZP 400 mg (n=167)**
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous biologic therapy, n (%)										
Never used	36 (70.6)	65 (68.4)	59 (67.0)	35 (71.4)	59 (64.8)	57 (65.5)	46 (80.7)	119 (70.0)	121 (73.3)	119 (71.3)
1 therapy	13 (25.5)	22 (23.2)	22 (25.0)	11 (22.4)	22 (24.2)	21 (24.1)	[redacted]	[redacted]	[redacted]	[redacted]
2 therapies	2 (3.9)	8 (8.4)	7 (8.0)	3 (6.1)	10 (11.0)	8 (9.2)	[redacted]	[redacted]	[redacted]	[redacted]
≥3 therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous anti-TNF therapy, n (%)[c]										
Yes	10 (19.6)	19 (20.0)	17 (19.3)	9 (18.4)	22 (24.2)	22 (25.3)	5 (8.8)	8 (4.7)	4 (2.4)	4 (2.4)
No	41 (80.4)	76 (80.0)	71 (80.7)	40 (81.6)	69 (75.8)	65 (74.7)	52 (91.2)	162 (95.3)	161 (97.6)	163 (97.6)
Any previous systemic treatment for psoriasis, n (%)[b]										
Yes	36 (70.6)	66 (69.5)	61 (69.3)	36 (73.5)	65 (71.4)	63 (72.4)	[redacted]	[redacted]	[redacted]	[redacted]
No	15 (29.4)	29 (30.5)	27 (30.7)	13 (26.5)	26 (28.6)	24 (27.6)	[redacted]	[redacted]	[redacted]	[redacted]
Previous chemophototherapy or phototherapy, n (%)										
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant PsA, n (%)[d]										

	CIMPASI-1			CIMPASI-2			CIMPACT			
Characteristic	**Placebo (n=51)**	**CZP 200 mg (n=95)**	**CZP 400 mg (n=88)**	**Placebo (n=49)**	**CZP 200 mg (n=91)**	**CZP 400 mg (n=87)**	**Placebo (n=57)**	**ETN (n=170)**	**CZP 200 mg (n=165)**	**CZP 400 mg (n=167)**
Yes	4 (7.8)	10 (10.5)	15 (17.0)	9 (18.4)	22 (24.2)	26 (29.9)	12 (21.1)	27 (15.9)	27 (16.4)	24 (14.4)
No	47 (92.2)	85 (89.5)	73 (83.0)	40 (81.6)	69 (75.8)	61 (70.1)	45 (78.9)	143 (84.1)	138 (83.6)	143 (85.6)

Abbreviations: anti-TNF: anti-tumour necrosis factor alpha; BMI: body mass index; BSA: body surface area; CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; ETN: etanercept; MTX: methotrexate; NR: not reported; PASI: Psoriasis Area and Severity Index; PGA: Physicians' Global Assessment; PsA: psoriatic arthritis; RS: randomised set; SD: standard deviation.
[a]**CIMPACT:** Other/mixed
[b]**Any systemic treatment for psoriasis:** any of previous biologic therapy, previous systemic non-biologic therapy, or previous systemic chemophototherapy or phototherapy.
[c]**Prior anti-TNF therapy:** any of etanercept, infliximab, golimumab, and adalimumab, including biosimilar versions of each.
[d]PsA diagnosis was not confirmed by a rheumatologist.
Source: Gottlieb AB *et al.* (2018)[61]; Lebwohl M *et al.* (2018)[64]; CIMPASI-1 Clinical Study Report;[60] CIMPASI-2 Clinical Study Report;[62] CIMPACT Clinical Study Report[63].

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

B.2.4.1 Statistical analysis in CIMPASI-1 and CIMPASI-2

A total of 234 and 227 patients were randomised to the initial treatment period in CIMPASI-1 and CIMPASI-2, respectively. The trial populations used in the analysis of outcomes are presented in Table 11. CONSORT diagrams of the population flow, and reasons for study drug discontinuation and discontinuation from CIMPASI-1 and CIMPASI-2 are given in full in Appendix D.

Table 11: Trial populations for CIMPASI-1 and CIMPASI-2

Analysis	Trial population	
	CIMPASI-1	CIMPASI-2
Randomised set (RS)	All patients randomised into the study. Used for baseline characteristics and efficacy endpoint summaries, including subgroup analyses.	
	N=234	N=227
Safety set (SS)	All patients in the RS who received ≥1 dose of study medication. Used for safety summaries.	
	N=[redacted]	N=[redacted]
Maintenance set (MS)	All patients who completed the Week 16 visit and had ≥1 efficacy assessment in the maintenance treatment period. Used for efficacy endpoint summaries that only included the maintenance treatment period.	
	N=[redacted]	N=[redacted]
Maintenance safety set (MSS)	Patients in the RS who received ≥1 dose of study medication during the maintenance treatment period (i.e., started on/after Week 16). Used for safety summaries that only included the maintenance treatment period.	
	N=[redacted]	N=[redacted]

Abbreviations: CZP: certolizumab pegol; RS: randomised set. TCS: treated with CZP set.
Source: Gottlieb AB *et al.* (2018)[61]; CIMPASI-1 Clinical Study Report;[60] CIMPASI-2 Clinical Study Report[62].

Interim analyses

This analysis included data for patients who completed up to the Week 48 visit, when the interim database lock and interim analysis were conducted. Safety follow-up data are included for patients who withdrew and whose safety follow-up occurred before Week 48, whilst the final analysis will include data from safety follow-up visits occurring after Week 48. This submission presents the described interim efficacy analysis, with a maximum treatment period of 48 weeks for each patient.

Study treatment discontinuation

Patients were free to withdraw consent and discontinue from the study at any time. Withdrawals could also be requested by the Sponsor or regulatory agency; reasons for mandated withdrawal included the following: non-compliance with the study procedures or medications; development of an illness that would interfere with participation; development of erythrodermic, guttate or generalised pustular psoriasis; or pregnancy.

Statistical tests

The co-primary endpoints in CIMPASI-1 and CIMPASI-2 were PASI75 and PGA clear or almost clear (with at least a 2-category improvement) responder rates at Week 16. The primary analysis of the co-primary efficacy endpoints consisted of comparisons of CZP 200 mg Q2W versus placebo and CZP 400 mg Q2W versus placebo. Further details of the hierarchical testing methods can be found in Appendix N.

A summary of the statistical tests used in the primary analysis is presented in Table 12 alongside sample size calculations and methods for handling missing data.

Table 12: Statistical tests for the primary analysis of CIMPASI-1 and CIMPASI-2

Trial number (acronym)	NCT02326298 (CIMPASI-1)	NCT02326272 (CIMPASI-2)
Hypothesis objective	The statistical objectives were to test whether: • The CZP 400 mg Q2W responder rate was equal to the placebo responder rate • The CZP 200 mg Q2W responder rate was equal to the placebo responder rate	
Statistical tests	The co-primary objectives were analysed using a logistic regression analysis (MCMC method for multiple imputation) with factors for treatment, region, study (pooled analysis only), prior biologic exposure (yes/no), study*region, (pooled analysis only), and study*prior biologic exposure (yes/no; pooled analysis only) on the multiple-imputed data sets where missing data were imputed using the MCMC method. The responder rates were the adjusted predicted probabilities from the logistic regression model. The fixed-sequence testing procedure accounted for multiplicity and controlled the familywise type I error rate at a 2-sided alpha level of 0.05. The co-primary endpoints were assessed at baseline and Weeks 2, 4, 8, 12 and 16.	
Sample size, power calculation	The planned sample size was 225 patients, randomised in a 2:2:1 ratio to: CZP 400 mg Q2W; CZP 200 mg Q2W (after a loading dose of CZP 400 mg Q2W at Weeks 0, 2 and 4); or placebo. A 2-sided test at the 0.025 level was used. Both studies had >99% power to detect a statistically significant difference in PGA response between either CZP dose or and placebo. This relied on the following assumed PASI75 response rates at Week 16: • CZP 400 mg Q2W: 80% • CZP 200 mg Q2W: 75% • Placebo: 10% And the following assumed PGA response rates at Week 16: • CZP 400 mg Q2W: 70% • CZP 200 mg Q2W: 50% • Placebo: 5%	
Data management, patient withdrawals	Initial treatment period: • Missing data for the co-primary variables and other key efficacy variables were handled using the MCMC method for multiple imputation. • Other binary efficacy variables were imputed using NRI. Missing continuous variables were imputed using the LOCF approach. Missing post-baseline values were imputed using the most recent previous value available for a given subject (including baseline).	

	Maintenance treatment period: • Blinded groups: Patients who escaped at Week 16 were treated as non-responders from Week 16 onwards. Patients who should have withdrawn at Week 32 or 40 for not achieving PASI50 were treated as non-responders at subsequent visits. Other missing data were handled using the MCMC method for multiple imputation for PASI and PGA outcomes. Other binary efficacy variables that were summarised without statistical modelling were imputed using NRI. This was done only for the patients randomised to CZP. For missing continuous efficacy variables, the LOCF approach was used. • Escape arm: Missing data were not imputed, and summaries were based on OC data over time.

Abbreviations: CZP: certolizumab pegol; LOCF: last observation carried forward; MCMC: Markov chain Monte Carlo; NRI: non-responder imputation; OC: observed case; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
Source: CIMPASI-1 Clinical Study Report[60]

Methods for additional analyses: subgroup analysis

Subgroup analyses were conducted for age, gender, race, duration of disease, geographic region, body mass index (BMI), weight, prior systemic chemophototherapy or phototherapy, prior systemic therapy (non-biologic), prior biologic exposure, prior anti-TNF exposure, any systemic treatment for psoriasis, previous exposure to at least 2 systemic treatments out of phototherapy, MTX, and ciclosporin (with no previous biologic exposure), disease severity, and overall anti-CZP antibody status. These subgroup analyses were performed on the co-primary efficacy variables using the RS and contained only descriptive statistics for Week 16.

B.2.4.2 Statistical analysis in CIMPACT

A total of 559 patients were randomised to the initial treatment period in CIMPACT. The trial populations used in the analysis of outcomes are presented in Table 13. CONSORT diagrams of the population flow, and reasons for study drug discontinuation and discontinuation from CIMPASI-1 and CIMPASI-2 are given in full in Appendix D.

Table 13: Trial populations for CIMPACT

Analysis	Trial population
Initial treatment period randomised set (RS)	**(N=559)** - All patients randomised during the study. Used for baseline characteristics and efficacy endpoint summaries, including subgroup analyses.
Safety set (SS)	**(N=[redacted])** - All patients in the RS who had received ≥1 dose of study medication. Used for safety summaries.
Week 16 randomised set	**(N=310)** – All patients who achieved a PASI75 response at Week 16 and were re-randomised into the double-blind, placebo-controlled maintenance treatment period. Used for efficacy endpoint summaries for the maintenance treatment period.
Maintenance set (MS)	**(N=[redacted])** - All patients who completed the Week 16 visit and had ≥1 efficacy assessment in the maintenance treatment period. Used for efficacy endpoint summaries that only included the maintenance treatment period.
Maintenance safety set (MSS)	**(N=[redacted])** - All patients in the RS who received ≥1 dose of study medication during the maintenance treatment period (i.e., starting on/after Week 16). Used for summaries of safety that only include the maintenance treatment period.

Abbreviations: RS: randomised set.
Source: Lebwohl M *et al.* (2018)[64]; CIMPACT Clinical Study Report[63]

Interim analyses

The interim database was locked after the last patient completed the Week 48 visit, in order for interim data analyses to be conducted. For patients who completed up to the Week 48 visit, data through Week 48 were included in this analysis. The interim efficacy analysis data is presented in this submission, with a maximum treatment period of 48 weeks for each patient.

Study treatment discontinuation

In CIMPACT, study treatment was discontinued if the sponsor requested that the patient be withdrawn for reasons relating to the safety risk to the patient. Discontinuation was also required if a patient developed an illness that would interfere with participation, withdrew informed consent, was non-compliant with study procedures or medications, or pregnant. Additionally, if a patient developed the erythrodermic, guttate, or generalised pustular form of psoriasis, then treatment was discontinued.

Statistical tests

The primary endpoint in CIMPACT was PASI75 responder rate at Week 12. A summary of the statistical tests used in the primary analysis is presented in Table 14 alongside sample size calculations and methods for handling missing data. The fixed sequence testing procedure for the CZP versus placebo comparisons began with the primary efficacy variable. First, the PASI75 at Week 12 was tested comparing CZP 400 mg Q2W verusus placebo at a two-sided alpha level of 0.05. If the result was significant in favor of CZP, then the PASI75 at Week 12 was tested comparing CZP 200 mg Q2W versus placebo. Further details regarding the hierarchical analysis can be found in Appendix N.

Table 14: Statistical tests for the primary analysis of CIMPACT

Trial number (acronym)	NCT02346240 (CIMPACT)
Hypothesis objective	The statistical objectives were to test whether: • The CZP 400 mg Q2W responder rate was equal to the placebo responder rate • The CZP 200 mg Q2W responder rate was equal to the placebo responder rate
Statistical tests	The primary efficacy variable was analysed using a logistic regression analysis (MCMC method for multiple imputation) with factors for treatment, region, study (pooled analysis only), prior biologic exposure (yes/no), study*region, (pooled analysis only), and study*prior biologic exposure (yes/no; pooled analysis only) on the multiply-imputed data sets where missing data were imputed using the MCMC method. The responder rates were the adjusted predicted probabilities from the logistic regression model. The fixed-sequence testing procedure accounted for multiplicity to control for the overall type I error. The primary endpoint was assessed at baseline and Weeks 2, 4, 8, 10 and 12.

Sample size, power calculation	The planned sample size was 540 patients, randomised in a 3:3:3:1 ratio during the initial treatment period to: CZP 200 mg Q2W; CZP 400 mg Q2W, ETN 50 mg BIW; or placebo. A 2-sided test at the 0.05 level was used. The CIMPACT study had 91% power to test for a significant difference in PASI75 response between the CZP 200 mg Q2W and ETN treatment arms at Week 12. This relied on the following assumed PASI75 response rates: • CZP 400 mg Q2W: 80% • CZP 200 mg Q2W: 75% • ETN: 57% • Placebo: 5%
Data management, patient withdrawals	Initial treatment period: • Missing data for the primary and secondary endpoints and selected additional efficacy variables (e.g., PASI50, PASI90, PASI100, PGA) were handled using the MCMC method for multiple imputation. Maintenance treatment period: • In some analyses, missing data were imputed using the NRI method; other analyses were conducted without imputation, using OC only. • Patients in the blinded maintenance groups who relapsed (no longer achieved a PASI50) and were therefore withdrawn from the maintenance treatment period, or who withdrew for any other reason, were non-responders for all subsequent timepoints in the NRI analyses. • Patients in the escape arm who should have been withdrawn from study treatment at Week 32 or later due to not achieving a PASI50 response or any other reason were considered non-responders for all subsequent timepoints in the NRI analyses.

Abbreviations: BIW: twice a week; CZP: certolizumab pegol; ETN: etanercept; MCMC: Markov Chain Monte Carlo; NRI: non-responder imputation; OC: observed case; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks; sc: subcutaneous.
Source: CIMPACT Clinical Study Report[63]

Methods for additional analyses: subgroup analysis

Subgroup analyses were conducted for age; gender; duration of disease; geographic region; BMI; weight; prior systemic chemotherapy and/or photochemotherapy; prior systemic therapy (nonbiologic); prior biologic exposure; prior anti-TNF exposure; any prior systemic treatment for psoriasis; previous exposure to at least 2 systemic treatments out of phototherapy, MTX, and ciclosporin (with no previous biologic exposure); PASI score at baseline; BSA at baseline; and overall anti-CZP antibody status.

B.2.4.3 Pooling of studies: efficacy

Efficacy data from the CIMPASI-1, CIMPASI-2 and CIMPACT studies have been pooled to provide more precise estimates of the effect of treatment with CZP. The treatment pools are outlined in Table 15.

Table 15: Treatment efficacy pools

Pool	Studies included	Treatment groups included	Treatment periods included
E1	CIMPASI-1 CIMPASI-2 CIMPACT	Placebo (N=157) CZP 200 mg Q2W (N=351) CZP 400 mg Q2W (N=342)	Initial treatment period (Weeks 0–16)
E2	CIMPASI-1	Placebo (N=100)	Initial treatment period

	CIMPASI-2	CZP 200 mg Q2W (N=186) CZP 400 mg Q2W (N=175)	(Weeks 0–16)
E3	CIMPASI-1 CIMPASI-2	Placebo (N=100) CZP 200 mg Q2W (N=186) CZP 400 mg Q2W (N=175)	Combined initial and maintenance treatment period (Weeks 0–48)
E4	CIMPASI-1 CIMPASI-2 CIMPACT	Placebo/Esc CZP 400 mg Q2W (N=[redacted]) CZP 200 mg Q2W/Esc CZP 400 mg Q2W (N=[redacted]) CZP 400 mg Q2W/Esc CZP 400 mg Q2W (N=[redacted])	Maintenance treatment period (Weeks 16–48)
E5	CIMPASI-1 CIMPASI-2 CIMPACT	CZP 200 mg Q2W/CZP 200 mg Q2W • PGA responders (N=[redacted]) • PASI75 responders (N=[redacted]) • PASI90 responders (N=[redacted]) • PASI100 responders (N=[redacted]) CZP 400 mg Q2W/ CZP 400 mg Q2W • PGA responders (N=[redacted]) • PASI75 responders (N=[redacted]) • PASI90 responders (N=[redacted]) • PASI100 responders (N=[redacted])	Maintenance treatment period (Weeks 16–48)

Abbreviations: CZP: certolizumab pegol; Esc: escape; Q2W: every two weeks; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment.
Source: Gottlieb AB *et al.* (2018)[61]; Blauvelt A *et al.* (2018)[70]; Certolizumab Pegol 2.7.3 Summary of Clinical Efficacy[71]; UCB Data on File (2017–2018)[72].

B.2.4.4 Pooling of studies: safety

Safety data from the CIMPASI-1, CIMPASI-2 and CIMPACT studies were pooled in order to summarise the safety of CZP more precisely. The treatment pools are outlined in Table 16.

Table 16: Treatment safety pools

Pool	Studies included	Treatment groups included	Treatment periods included
S1	CIMPASI-1 CIMPASI-2 CIMPACT	Patients exposed to: CZP 400 mg Q2W CZP 200 mg Q2W Placebo	Initial treatment period (Weeks 0–16)
S3[a]	CIMPASI-1 CIMPASI-2 CIMPACT	Patients exposed to: CZP 400 mg Q2W CZP 200 mg Q2W CZP 400 mg Q4W	Initial, maintenance and OLE treatment periods (Weeks 0–144)

Abbreviations: CZP: certolizumab pegol; Q2W: every two weeks; Q4W: every four weeks.
[a]This pool also included patients from studies C87040 (NCT00245765) and C87044 (NCT00329303). However, data presented in this submission only includes patients from CIMPASI-1, CIMPASI-2 and CIMPACT.
Source: Certolizumab pegol 2.7.4 Summary of Clinical Safety[73]

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

CIMPASI-1 and CIMPASI-2

CIMPASI-1 and CIMPASI-2 were well-designed, with appropriate randomisation and adequate concealment of treatment allocation. At screening, each patient was assigned a unique identification number by an IVRS/IWRS. Subsequent randomisation at baseline was based on a predetermined schedule and executed using the central response system. Both studies were double-blind, with participants and outcome assessors blinded to treatment allocation, and were funded by UCB Biopharma S.P.R.L.

CIMPACT

CIMPACT was well-designed, with appropriate randomisation and adequate concealment of treatment allocation. At screening, each patient was assigned a unique identification number by an IVRS/IWRS. Participants receiving CZP or placebo, and outcome assessors were blinded to treatment allocation. However, ETN could only be procured in a commercial presentation, therefore, patients randomised to ETN received unblinded study medication. This study was sponsored by UCB Biopharma S.P.R.L.

A summary of the quality assessment for CIMPASI-1, CIMPASI-2 and CIMPACT is provided in Table 17. Full quality assessments for these studies are available in Appendix D.

Table 17: Summary of quality assessment for Phase III trials of CZP

Trial number (acronym)	CIMPASI-1 (NCT02326298)	CIMPASI-2 (NCT02326272)	CIMPACT (NCT02346240)
Was randomisation carried out appropriately?	Yes		
Was the concealment of treatment allocation adequate?	Yes		
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Participants and outcome assessors were blinded.		Participants receiving CZP or placebo, and outcome assessors, were blinded.
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[74]
Source: CIMPASI-1 Clinical Study Report;[60] CIMPASI-2 Clinical Study Report;[62] CIMPACT Clinical Study Report;[63] ClinicalTrials.gov (CIMPASI-1);[67] ClinicalTrials.gov (CIMPASI-2);[68] ClinicalTrials.gov (CIMPACT).[69]

B.2.6 *Clinical effectiveness results of the relevant trials*

Short-term efficacy

- The integrated analysis of the pooled population in the three trials indicated that both dosing regimens (CZP 200 mg Q2W and CZP 400 mg Q2W) resulted in clinically meaningful and statistically significant clinical responses, as measured by PASI75 and PGA clear or almost clear at Week 16 ([co-]primary endpoints) versus placebo. CZP-treated patients also showed significantly higher PASI90 and PASI100 response rates and improvements in BSA versus placebo.
- In the CIMPACT trial, CZP 400 mg Q2W treatment resulted in statistically significantly superior improvements in PASI75 at Week 12 (secondary endpoint) versus ETN, and CZP 200 mg Q2W treatment demonstrated a numerically greater response versus ETN and was non-inferior to ETN for PASI75 at Week 12.
- Improvements with CZP were similar in patients with moderate-to-severe chronic plaque psoriasis irrespective of prior treatment exposure, with similarly high improvements in patients who were candidates for systemic non-biologic treatments, patients who were biologic naïve, or biologic exposed.

Long-term maintenance and durability of response

- Maintenance and durability of response was demonstrated in the long-term, through to Week 48, for signs and symptoms of psoriasis, based on data from the pooled CIMPASI-1 and CIMPASI-2 population and from CIMPACT.
- The rapid and consistent increases in clinical response to Week 16, as measured through PASI75 response rates, were maintained over time through Week 48 of the maintenance treatment period in CZP 400 mg Q2W and CZP 200 mg Q2W. Numerically higher responses were achieved for patients receiving CZP 400 mg Q2W compared with CZP 200 mg Q2W, reaching 83.6% and 70.7% for PASI75 and 68.9% and 61.0% for PGA, respectively.
- A high durability of clinical response through to Week 48 was seen in patients who were Week 16 responders to CZP. CZP-treated patients from the pooled CIMPASI-1 and CIMPASI-2 trials who were PASI75, or PGA responders at Week 16 consistently maintained the improvements in efficacy to Week 48 (i.e. 32 weeks of the maintenance treatment period).

- CZP-treated patients from the pooled CIMPASI trials who were PASI75, or PGA responders at Week 16 consistently maintained the improvements in efficacy to Week 48.
- Of the CZP 400 mg Q2W treated patients who achieved a PASI75 response at Week 16 and continued with their original CZP dose, [redacted]% maintained their level of PASI75 response at Week 48, and [redacted]% and [redacted]% of these patients achieved PASI90 and PASI100 response, respectively, at Week 48.
- Out of the CZP 200 mg Q2W treated patients who achieved a PASI75 response at Week 16 and continued with their original CZP dose, [redacted]% maintained their level of PASI75 response at Week 48, [redacted]% and [redacted]% of these patients achieved PASI90 and PASI100 response, respectively, at Week 48.
- Clinically meaningful improvements in DLQI at Week 16 were maintained or improved through to Week 48 in patients receiving CZP 400 mg Q2W and CZP 200 mg Q2W, with 52.3% and 45.3% of patients in CIMPASI-1 and 50.6% and 38.5% of patients in CIMPASI-2 in DLQI remission at Week 48, respectively.

- Improvements with CZP were similar in patients with moderate-to-severe chronic plaque psoriasis irrespective of prior treatment exposure, with similarly high improvements in patients who were candidates for systemic non-biologics, who were biologic-naïve or who were previously exposed to biologics.

Extracutaneous manifestations

- Patients treated with both doses of CZP showed improvement in nail psoriasis (mNAPSI), at Week 48 (a mean decrease from baseline of [redacted] and [redacted] for CZP 200 mg Q2W and CZP 400 mg Q2W, respectively, in the pooled CIMPASI-1 and CIMPASI-2 population).
- Complete resolution in psoriatic nail disease (defined as mNAPSI score=0) was achieved in [redacted] of patients receiving CZP 200 mg and [redacted] of patients receiving CZP 400 mg Q2W at Week 48 in the pooled CIMPASI-1 and CIMPASI-2 population.

Patient-relevant outcomes

- At Week 16, CZP-treated patients reported clinically meaningful and statistically significant improvements versus placebo in a broad spectrum of patient-relevant outcomes, including HRQoL, anxiety and depression and work productivity and daily activity.
- Numerically higher responses were also achieved for other HRQoL measures (including SF-36 MCS and PCS score) and work productivity and social activities, in patients receiving CZP 400 mg Q2W compared with those receiving CZP 200 mg Q2W.
- Maintenance of improvements in patient-relevant outcomes was demonstrated in the long-term, through to Week 48.
- Clinically meaningful changes in DLQI at Week 16 were maintained or improved through to Week 48 in patients receiving CZP 400 mg Q2W and CZP 200 mg Q2W. Numerically higher improvements were seen at Week 48 for patients receiving CZP 400 mg Q2W versus CZP 200 mg Q2W in terms of change from baseline in DLQI score (-9.8 versus -8.8 in CIMPASI-1, and −10.9 versus -10.7 in CIMPASI-2) and the proportion of patients in DLQI remission (52.3% versus 45.3% in CIMPASI-1, and 50.6% versus 38.5% in CIMPASI-2), respectively.

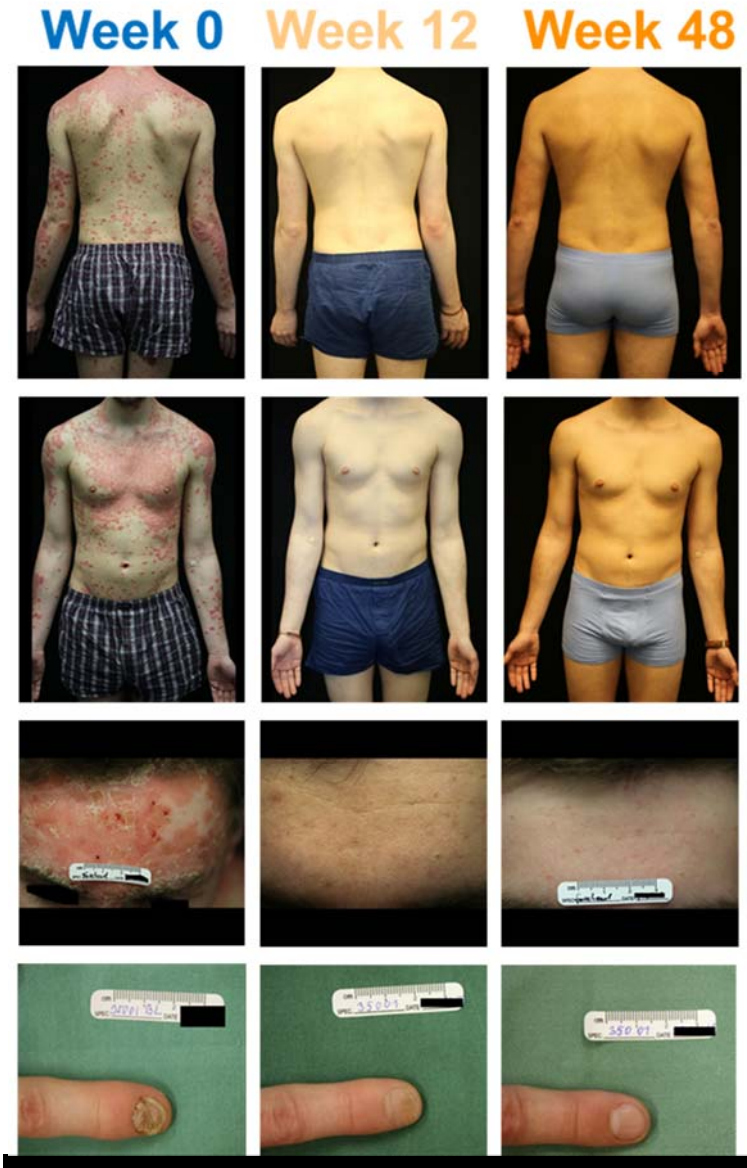
B.2.6.1 Overview of clinical effectiveness in CZP (ITT population)

Clinical effectiveness in the intention-to-treat (ITT) population

CIMPASI-1 and CIMPASI-2 both achieved their co-primary efficacy endpoints (PASI75 and PGA clear or almost clear response rates at Week 16). The key efficacy endpoint was also achieved in CIMPACT (PASI75 response at Week 12).

Images showing the improvement of a patient over the course of treatment with CZP is presented in Figure 4. This highlights the substantial change for patients when they achieve a treatment response.

Figure 4: Psoriasis improvements from Week 0–48



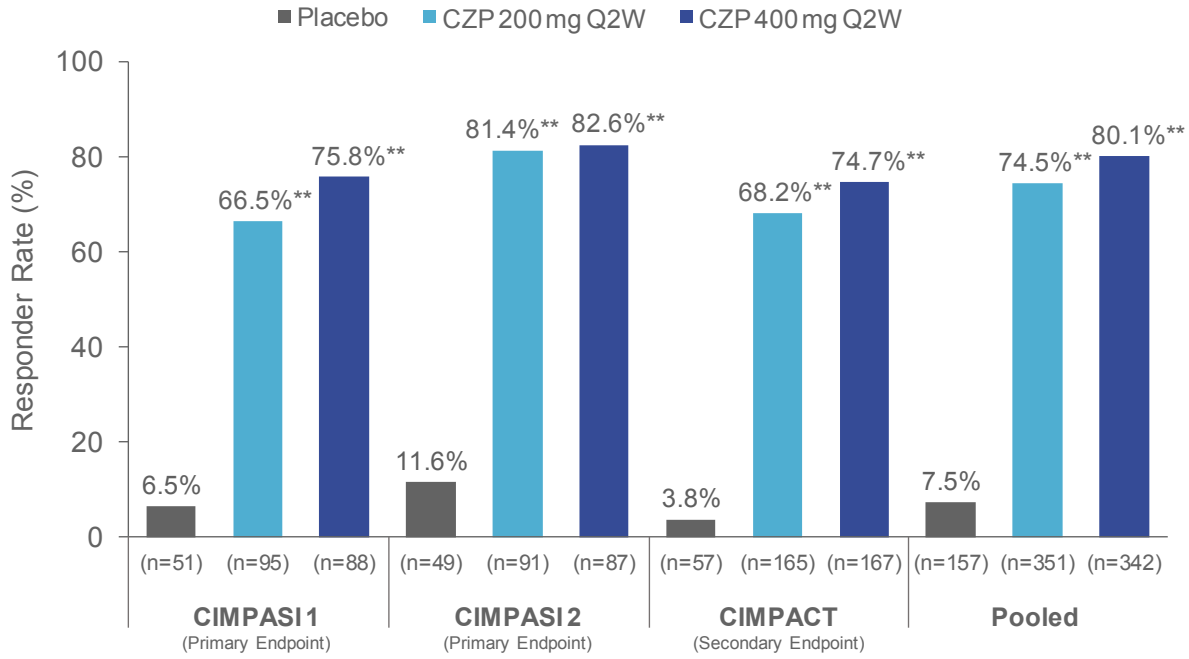
[redacted]

B.2.6.2 PASI results

PASI75 responder rate at Week 16

At Week 16, all three trials showed that CZP was significantly greater than placebo (p<0.0001) at achieving a PASI75 response (Figure 5), meeting the co-primary endpoint for CIMPASI-1 and CIMPASI-2. This was also observed in the results from the pooled analysis E1. The PASI75 responder rate was numerically higher in the CZP 400 mg Q2W compared to the CZP 200 mg Q2W group across all three trials and the pooled analysis. These results indicate that patients on CZP in all three studies reported clinically meaningful improvements in the severity of psoriasis compared with placebo. The odds ratios for being a responder versus placebo for all three studies, and for Pool E1, are reported in Table 18.

Figure 5: PASI75 responder rate at Week 16 in CIMPASI-1, CIMPASI-2, CIMPACT and pooled analysis E1 – ITT population



Abbreviations: CZP: certolizumab pegol; MCMC: Markov chain Monte Carlo; Q2W: every two weeks.
**p<0.0001 vs placebo.
Based on logistic regression model with factors for treatment group, region, prior biologic exposure (yes/no), study (pooled only), and interaction terms for study by region (pooled only) and study by prior biologic exposure (pooled only) using MCMC method for multiple imputation. Pool E1: the responder rates are the adjusted predicted probabilities from the logistic regression model.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1)
Source: Gottlieb AB *et al.* (2018)[61]; Lebwohl M *et al.* (2018)[64]; Blauvelt A *et al.* (2018).[70]

Table 18: Odds ratios for being a PASI75 responder versus placebo at Week 16 – ITT population

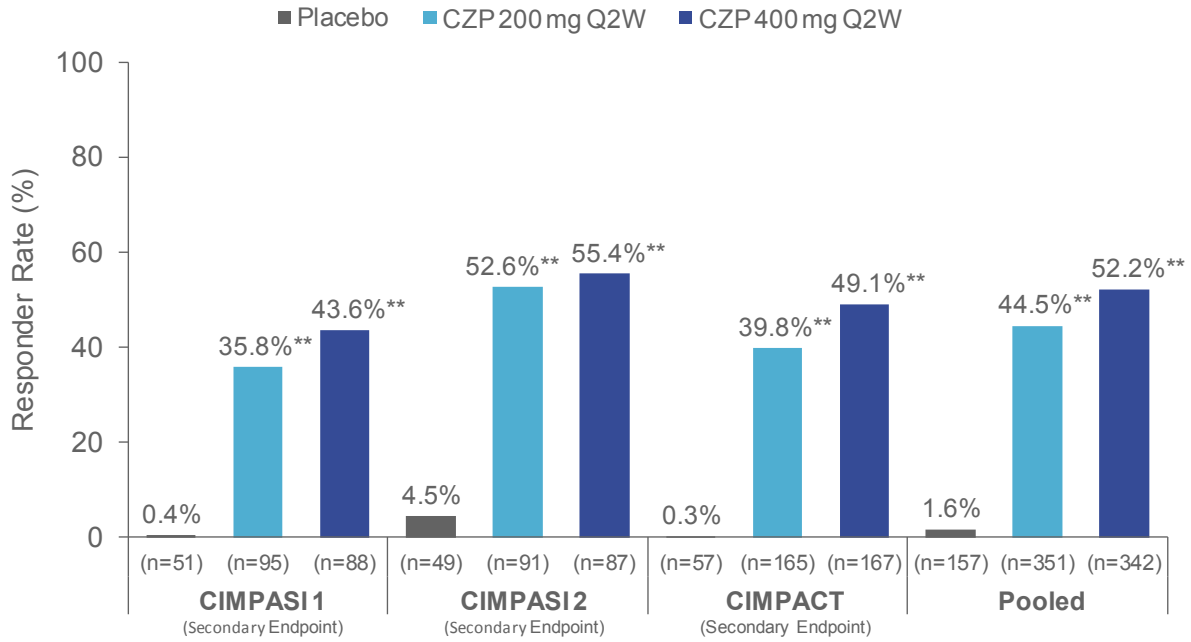
	Odds ratio (97.5% CI; p value)	
	CZP 200 mg Q2W	**CZP 400 mg Q2W**
CIMPASI-1	n=95	n=88
	29.0 (7.0, 120.4; p<0.0001)	45.7 (10.7, 195.6; p<0.0001)
CIMPASI-2	n=91	n=87
	33.4 (10.0, 112.0; p<0.0001)	36.2 (10.7, 122.7; p<0.0001)
CIMPACT[a]	n=165	n=167
	55.4 (13.1, 233.8; p<0.0001)	76.3 (18.0, 324.1; p<0.0001)
Pool E1	n=351	n=342
	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CZP: certolizumab pegol; MCMC: Markov chain Monte Carlo; Q2W: every two weeks.
[a]97.5% CIs were not available for the CIMPACT trial, therefore 95% CIs are presented here.
Based on logistic regression model with factors for treatment group, region, prior biologic exposure (yes/no), study (pooled only), and interaction terms for study by region (pooled only) and study by prior biologic exposure (pooled only) using MCMC method for multiple imputation. Pool E1: the responder rates are the adjusted predicted probabilities from the logistic regression model.
Pooled data is from Pool E1 (CIMPASI-1, CIMPASI-2 and CIMPACT)
Source: Gottlieb AB *et al.* (2018)[61]; Lebwohl M *et al.* (2018)[64]; UCB Certolizumab Pegol 2.7.3 Summary of Clinical Efficacy (Pool E1)[71]

PASI90 responder rate at Week 16

The improved results with CZP versus placebo extended to the PASI90 response at Week 16, further demonstrating the rapid and extensive improvements in disease severity possible with CZP. All three studies reported that significantly more patients in the CZP 200 mg Q2W arm and the CZP 400 mg Q2W arm achieved a PASI90 response during the initial treatment period compared to the placebo arm (Figure 6). This result was echoed when the results from each trial were pooled in the pool E1 results. Consistent with the results for PASI75, there was a numerical increase in the proportion of responders in the CZP 400 mg Q2W arm versus CZP 200 mg Q2W.

Figure 6: PASI90 responder rate at Week 16 in CIMPACT, CIMPASI-1, CIMPASI-2 and pooled analysis E1 – ITT population



Abbreviations: CZP: certolizumab pegol; MCMC: Markov chain Monte Carlo; Q2W: every two weeks.
**p<0.0001 vs placebo.
Based on logistic regression model with factors for treatment group, region, prior biologic exposure (yes/no), study (pooled only), and interaction terms for study by region (pooled only) and study by prior biologic exposure (pooled only) using MCMC method for multiple imputation. Pool E1: the responder rates are the adjusted predicted probabilities from the logistic regression model.
Pooled data is from Pool E1 (CIMPASI-1, CIMPASI-2, CIMPACT).
Source: Gottlieb AB *et al.* (2018)[61]; Lebwohl M *et al.* (2018)[64]; Blauvelt A *et al.* (2018).[70]

PASI100 responder rate at Week 16

In Pool E1, clinically meaningful differences in PASI100 responder rate were observed from Week 4 in the CZP 200 mg Q2W group (p[redacted]) and at Week 8 in the CZP 400 mg Q2W group (p[redacted]). At Week 16, PASI100 responder rates were [redacted]% in the CZP 200 mg Q2W group and [redacted]% in the CZP 400 mg Q2W group compared with [redacted]% in the placebo group (Table 19). The odds of being a PASI100 responder at Week 16 compared to placebo was statistically significant for both the CZP 200 mg Q2W and CZP 400 mg Q2W treatment arms ([redacted] and [redacted] respectively).

Table 19: PASI100 responder rate at Week 16 in Pool E1 – ITT population

	Placebo (n=157)	CZP 200 mg Q2W (n=351)	CZP 400 mg Q2W (n=342)
Week 16 responder rate, %	[redacted]	[redacted]	[redacted]
P value vs placebo	[redacted]	[redacted]	[redacted]
Odds ratio (97.5% CI; p-value)	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; MCMC: Markov chain Monte Carlo; N/A: not applicable; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks.
Based on logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), and interaction terms for study by region and study by prior biologic exposure using MCMC method for multiple imputation. The responder rates are the adjusted predicted probabilities from the logistic regression model.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1)
Source: UCB Cimzia Plaque Psoriasis Integrated Summary of Efficacy.[75]

Absolute PASI scores

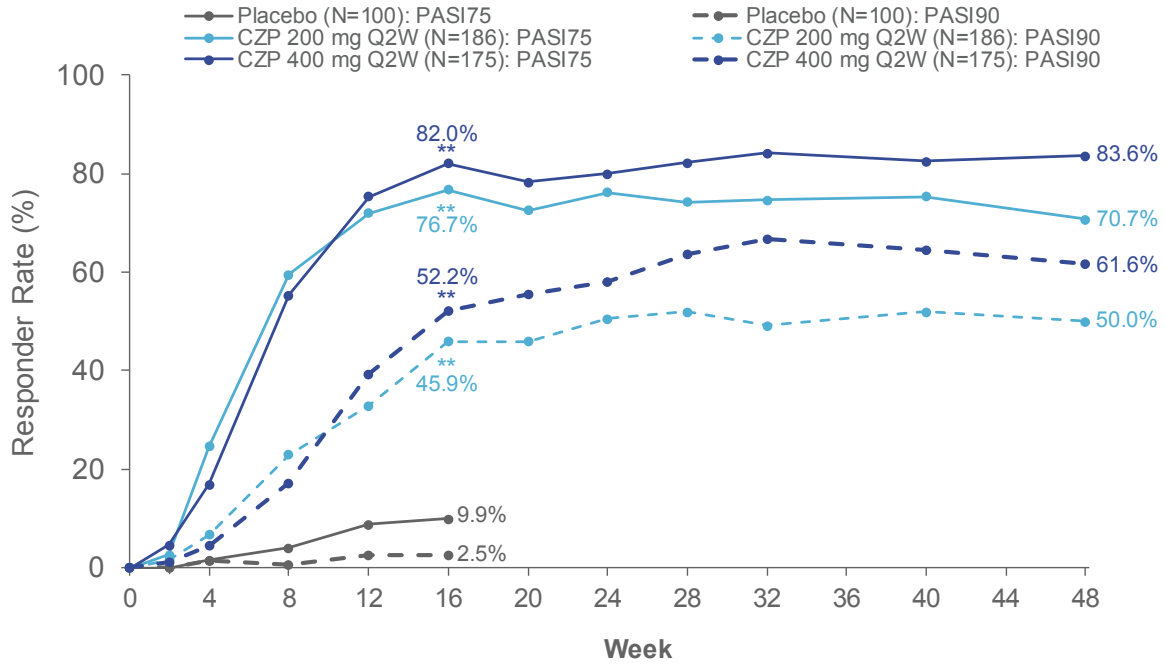
Across all three studies, the mean PASI scores at baseline were similar between the CZP 200 mg Q2W and CZP 400 mg Q2W groups. By Week 16, the mean absolute PASI scores across all three studies had considerably decreased in the CZP 200 mg Q2W and CZP 400 mg Q2W groups (Appendix M).

Long-term maintenance and durability of response to Week 48 (PASI75 and PASI90 responder rates)

In Pool E3, the rapid and consistent increases in PASI75 responder rates through Week 16 of the initial treatment period (in Pool E2 [CIMPASI-1 and CIMPASI-2 only]) were maintained through Week 48 of the maintenance treatment period in both the CZP 200 mg Q2W and CZP 400 mg Q2W groups. As in the initial treatment period, PASI75 responder rates were numerically higher in the CZP 400 mg Q2W group compared with the CZP 200 mg Q2W group throughout the maintenance period. By Week 48, PASI75 responder rates were 70.7% in the CZP 200 mg Q2W group and 83.6% in the CZP 400 mg Q2W group (Figure 7).

In Pool E3, consistent increases in PASI90 responder rates through Week 16 of the initial treatment period (in Pool E2) continued to increase through Week 28 and were then maintained through Week 48 in both the CZP 200 mg Q2W and CZP 400 mg Q2W groups. Again, the PASI90 responder rates were numerically higher in the CZP 400 mg Q2W group compared with the CZP 200 mg Q2W group throughout the maintenance period. By Week 48, PASI90 responder rates were 50.0% in the CZP 200 mg Q2W group and 61.6% in the CZP 400 mg Q2W group (Figure 7). This demonstrates that the effect of CZP is continued throughout treatment, meaning that patients sustain their response to treatment.

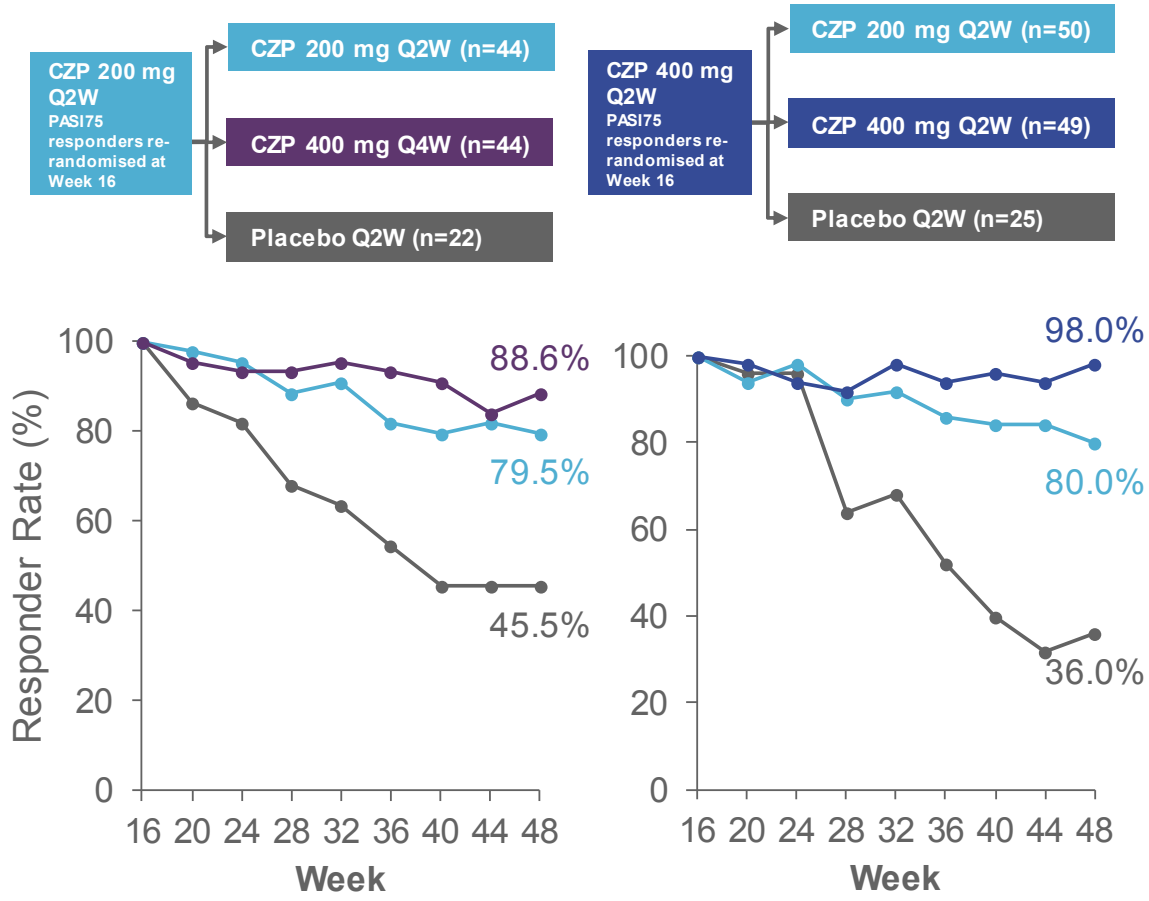
Figure 7: Maintenance of PASI75 and PASI90 responder rate to Week 48 – ITT population (Pool E2 and E3)



Abbreviations: CZP: certolizumab pegol; MCMC: Markov chain Monte Carlo; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks.
**p<0.0001 vs placebo.
Based on logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no) and interaction terms for study by region and study by prior biologic exposure using MCMC method for multiple imputation. The responder rates are the adjusted predicted probabilities from the logistic regression model. Only patients achieving PASI50 at Week 16 continued into the maintenance period of the study (Week 16–48).
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E2 and E3).
Source: Gottlieb AB *et al.* (2018)[61].

Patients were required to achieve a PASI75 response at Week 16 in the blinded maintenance groups in order to enter the maintenance treatment period in CIMPACT; at Week 48, the majority of patients receiving CZP 200 mg Q2W or CZP 400 mg Q2W continued to be PASI75 responders (Figure 8). These results highlight the durability of response with continuous treatment with CZP.

Figure 8: PASI75 responder rates during Weeks 16–48 by re-randomised blinded treatment group in CIMPACT – ITT population



Abbreviations: CZP: certolizumab pegol; NRI: non-responder imputation; PASI: Psoriasis Area Severity Index; Q2W: every two weeks; Q4W: every four weeks.
Using NRI.
Source: Lebwohl M *et al.* (2018)[64]; CIMPACT Clinical Study Report[63].

In the CIMPACT study, the PASI90 responder rate was greater or similar at all timepoints within each group compared with Week 16 in the groups that continued to receive CZP (either 200 mg Q2W or 400 mg Q2W) after the initial treatment period. The blinded maintenance group treated with CZP 400 mg Q2W through both the initial and maintenance periods achieved the best response at Week 48 with 87.8% of patients achieving PASI90. For patients who received placebo during the maintenance treatment period, the PASI90 responder rate considerably decreased from Week 16 to Week 48 (Table 20).

Table 20: PASI90 responder rate at Week 48 by re-randomised blinded treatment group in CIMPACT – ITT population

Treatment group	Responder rate, % (95% CI)
CZP 200 mg Q2W/placebo (n=22)	18.2 [redacted]
CZP 200 mg Q2W/ CZP 200 mg Q2W (n=44)	61.4 [redacted]
CZP 200 mg Q2W/CZP 400 mg Q4W (n=44)	68.2 [redacted]
CZP 400 mg Q2W/placebo (n=25)	12.0 [redacted]
CZP 400 mg Q2W/ CZP 200 mg Q2W (n=50)	60.0 [redacted]
CZP 400 mg Q2W/ CZP 400 mg Q2W (n=49)	87.8 [redacted]

Abbreviations: CI: confidence interval; CZP: certolizumab pegol; ETN: etanercept; NRI: non-responder imputation; PASI: Psoriasis Area Severity Index; Q2W: every two weeks; Q4W: every four weeks.
*Patients receiving placebo during the initial treatment period were required to achieve a PASI75 response at Week 16 to continue receiving placebo during the maintenance treatment period.
Using NRI.
Source: Lebwohl M *et al.* (2018)[64]; CIMPACT Clinical Study Report[63]

During the maintenance treatment period in both CIMPASI-1 and CIMPASI-2, decreases from baseline in PASI score were similar between the CZP 200 mg Q2W and CZP 400 mg Q2W groups and were consistently maintained for the duration of the maintenance treatment period. Mean decreases from baseline in PASI score were comparable between the two studies (Appendix M). In CIMPACT, in the blinded maintenance groups in which patients received CZP treatment during the maintenance treatment period, mean decreases from baseline at Week 16 were generally maintained within each group through Week 48 (Appendix M).

Long-term maintenance and durability of response to Week 48 in Week 16 responders

In Pool E5, out of the CZP 400 mg Q2W treated patients who achieved a PASI75 response at Week 16 and continued with their original CZP dose, [redacted] maintained their level of PASI75 response at Week 48, and [redacted] of these patients achieved a PASI90 response at Week 48 (Figure 9). Out of the CZP 200 mg Q2W treated patients who achieved a PASI75 response at Week 16 and continued with their original CZP dose, [redacted] maintained their level of PASI75 response at Week 48; [redacted] of these patients achieved PASI90 response at Week 48. Similar trends were seen in each of the individual trials.

Figure 9: Durability of PASI75 response and PASI90 response in Week 16 PASI75 responders – ITT population (Pool E5)

A) PASI75 response

B) PASI90 response

Abbreviations: CZP: certolizumab pegol; MCMC: Markov chain Monte Carlo; PASI: psoriasis area and severity index; Q2W: every two weeks.
Patients who received escape treatment starting at Week 16 (regardless of PASI50/PASI75 response at Week 16) were excluded from this analysis.
Observed case results.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E5).
Source: UCB Data on File (2018)[76].

Improvements in clinical response to Week 48 in patients with insufficient response to CZP 200 mg Q2W at Week 16 and who were re-randomised to CZP 400 mg Q2W

For patients initially treated with CZP 200 mg Q2W who were PASI50 non-responders at week 16 and who escaped to CZP 400 mg Q2W treatment, notable improvements in PASI75 and PASI90 responder rates were observed at Week 48 (Figure 10).

Figure 10: Improvements in clinical response (PASI75: left; PASI90: right) to Week 48 in patients with insufficient response to CZP 200 mg Q2W at Week 16 and who were re-randomised to CZP 400 mg Q2W – ITT population (Pool E4)

Abbreviations: CZP: certolizumab pegol; Esc: escape; NRI: non-responder imputation; Q2W: every two weeks.
Using NRI.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E4).
Source: UCB Cimzia Plaque Psoriasis Integrated Summary of Efficacy[75].

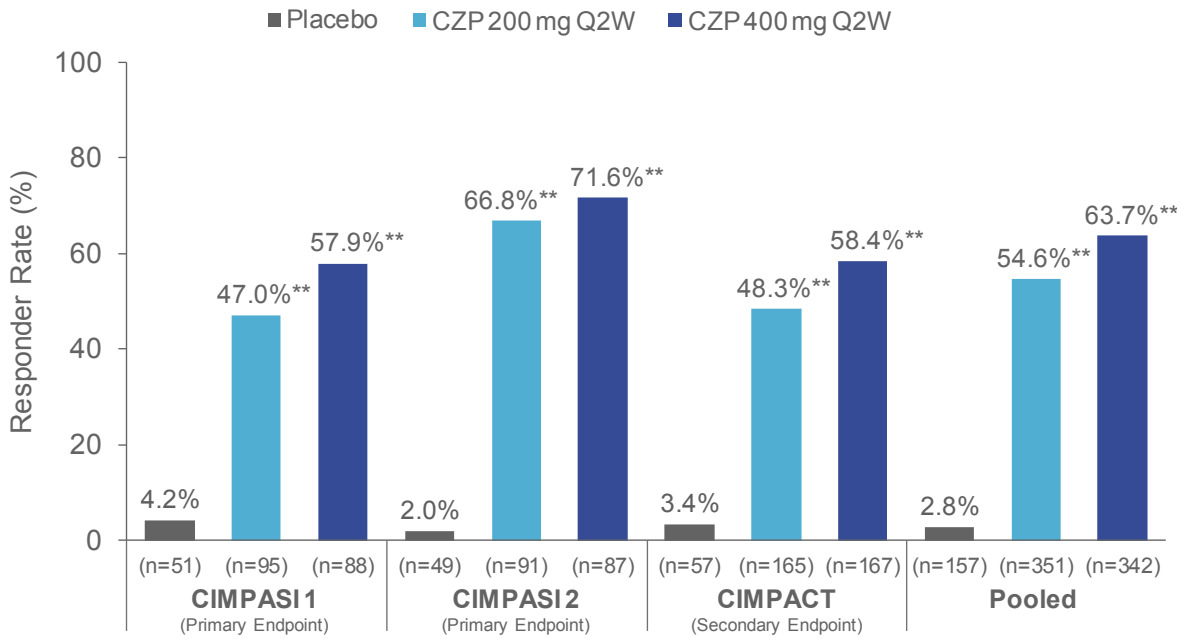
B.2.6.3 PGA results

PGA clear/almost clear at Week 16

Across all three trials, there was a statistically significant and clinically meaningful difference in being classified as a PGA responder for patients treated with either CZP 200 mg Q2W or CZP 400 mg Q2W versus placebo at Week 16 (Figure 11; Table 21). This can be observed in Pool E1, where the PGA responder rates were significant greater in both the CZP 200 mg Q2W arm (54.6%) and the CZP 400 mg Q2W arm (63.7%; p<0.0001). The odds ratio of being a PGA responder versus placebo were [redacted] (97.5% CI: [redacted]) for the CZP 200 mg Q2W arm and [redacted] (97.5% CI: [redacted]) for the CZP 400 mg Q2W arm ([redacted]) in Pool E1. These results further reinforce that CZP has a rapid onset of action in patients with psoriasis, showing a clear improvement in psoriasis severity by Week 16.

PGA responder rates were higher in CIMPASI-2 compared with CIMPASI-1 and CIMPACT in both CZP arms, particularly in the CZP 200 mg Q2W group. In both CIMPASI-1 and CIMPACT, PGA responder rates and odds ratios for being a PGA responder at Week 16 were numerically higher in the CZP 400 mg Q2W group compared with the CZP 200 mg Q2W group (31.1 [97.5% CI: 5.7, 170.5] versus 20.1 [97.5% CI: 3.7, 109.4] for CIMPASI-1 and 40.7 [97.5% CI: 9.7, 170.2] versus 27.2 [97.5% CI: 6.5, 113.5] for CIMPACT; Table 21). This was also observed in CIMPASI-2, but the difference between the doses was not as large (133.2 [97.5% CI: 11.9, 1489.6] versus 106.2 [97.5% CI: 9.6, 1178.8], for CZP 400 mg Q2W and CZP 200 mg Q2W, respectively).

Figure 11: PGA responder rates at Week 16 in CIMPASI-1, CIMPASI-2, CIMPACT and Pool E1 – ITT population



Abbreviations: CZP: certolizumab pegol; MCMC: Markov chain Monte Carlo; PGA: Physician's Global Assessment; Q2W: every two weeks.
**p<0.0001 vs placebo.
Based on logistic regression model with factors for treatment group, region, prior biologic exposure (yes/no), study (pooled only), and interaction terms for study by region (pooled only) and study by prior biologic exposure (pooled only) using MCMC method for multiple imputation. Pool E1: Responder rates are the adjusted predicted probabilities from the logistic regression model.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1)
Source: Gottlieb AB *et al.* (2018)[61]; Lebwohl M *et al.* (2018)[64]; Blauvelt A *et al.* (2018)[70].

Table 21: Odds ratios for being a PGA responder versus placebo at Week 16 – ITT population

	Odds ratio (97.5% CI; p value)	
	CZP 200 mg Q2W	**CZP 400 mg Q2W**
CIMPASI-1	n=95	n=88
	20.1 (3.7, 109.4; p<0.0001)	31.1 (5.7, 170.5; p<0.0001)
CIMPASI-2	n=91	n=87
	106.2 (9.6, 1178.8; p<0.0001)	133.2 (11.9, 1489.6; p<0.0001)
CIMPACT[a]	n=165	n=167
	27.2 (6.5, 113. 5; p<0.0001)	40.7 (9.7, 170.2; p<0.0001)

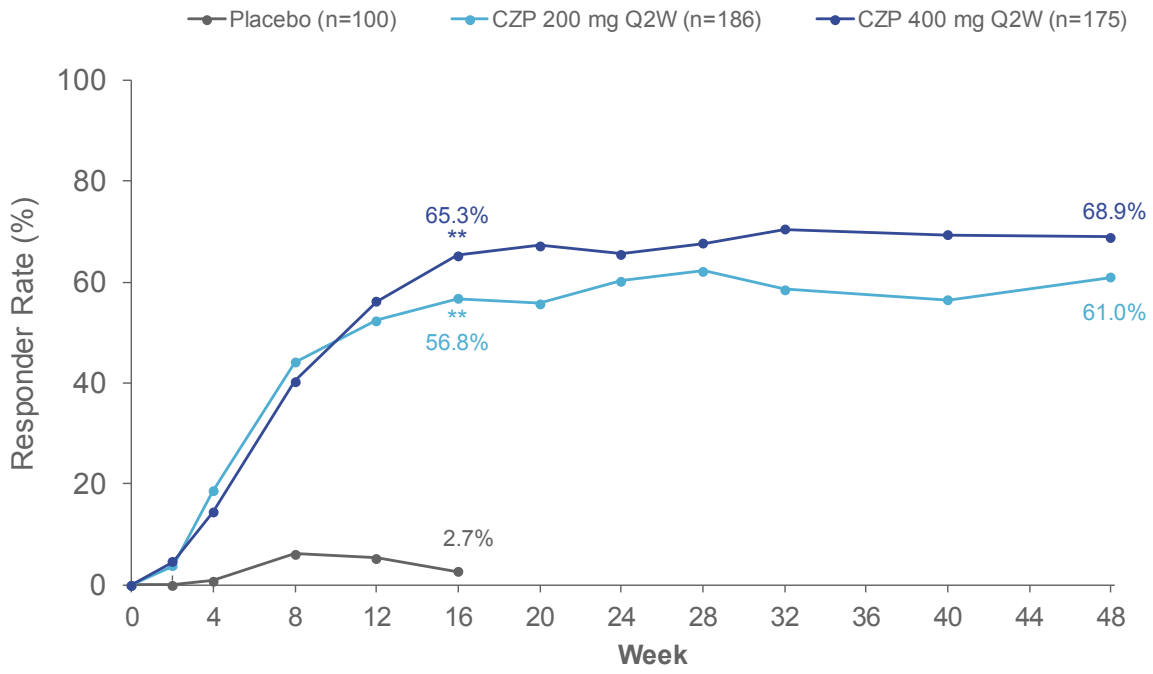
Pool E1	n=351	n=342
	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CZP: certolizumab pegol; MCMC: Markov chain Monte Carlo; PGA: Physician's Global Assessment; Q2W: every two weeks.
[a]97.5% CIs were not available for the CIMPACT trial, therefore 95% CIs are presented here.
Based on logistic regression model with factors for treatment group, region, prior biologic exposure (yes/no), study (pooled only), and interaction terms for study by region (pooled only) and study by prior biologic exposure (pooled only) using MCMC method for multiple imputation. Pool E1: the responder rates are the adjusted predicted probabilities from the logistic regression model.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).
Source: Gottlieb AB *et al.* (2018)[61]; Lebwohl M *et al.* (2018)[64]; UCB Certolizumab Pegol 2.7.3 Summary of Clinical Efficacy (Pool E1)[71]

Long-term maintenance and durability of response to Week 48 (PGA clear/almost clear)

In Pool E3, the rapid and consistent increases in PGA responder rates through Week 16 of the initial treatment period (in Pool E2) were maintained through Week 48 of the maintenance treatment period in both the CZP 200 mg Q2W and CZP 400 mg Q2W groups. PGA responder rates were numerically higher in the CZP 400 mg Q2W group compared with the CZP 200 mg Q2W throughout the maintenance period, and by Week 48, PGA responder rates were 61.0% in the CZP 200 mg Q2W group and 68.9% in the CZP 400 mg Q2W group (Figure 12).

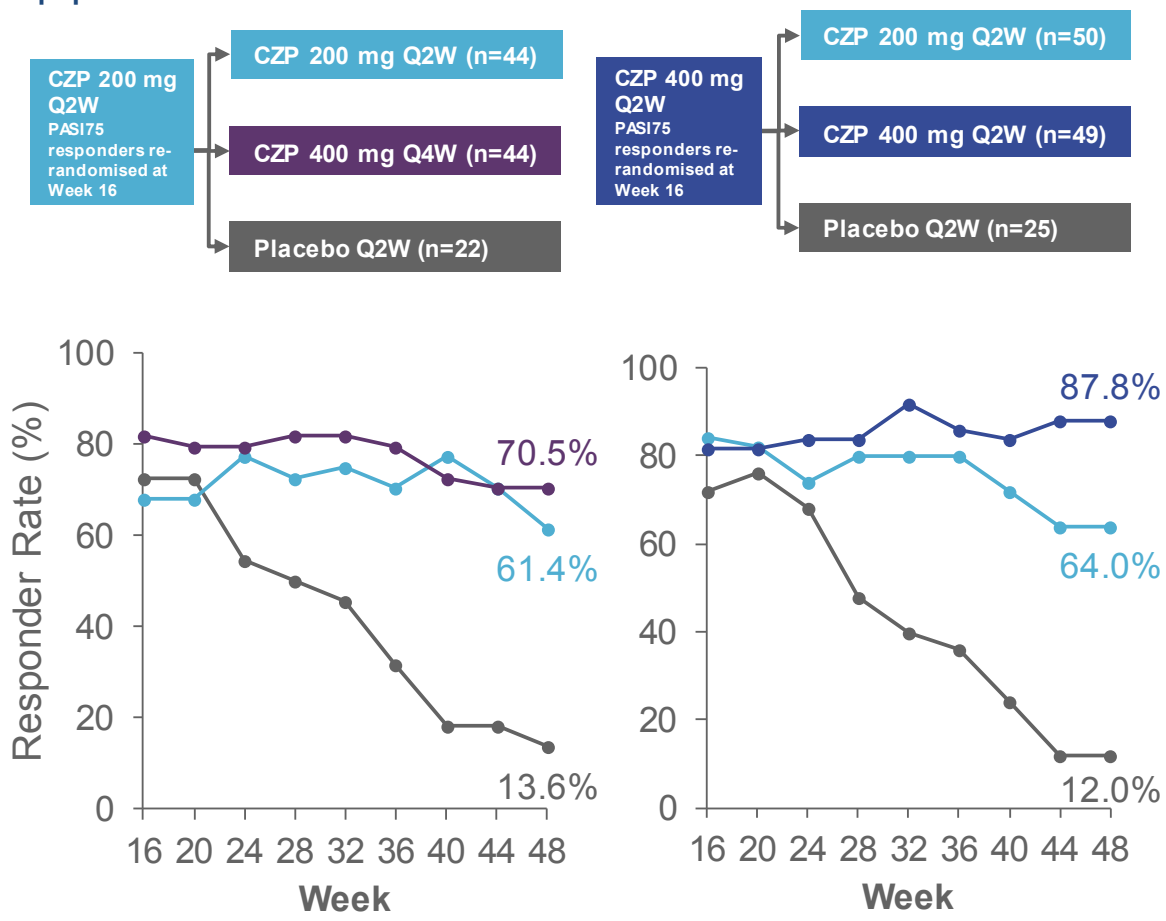
Figure 12: PGA clear or almost clear to Week 48 – ITT population (Pool E2 and E3)



Abbreviations: CZP: certolizumab pegol; MCMC: Markov chain Monte Carlo; PGA: Physician's Global Assessment; Q2W: every two weeks.
**p<0.0001 vs placebo; P-values are not adjusted for multiplicity.
Based on logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no) and interaction terms for study by region and study by prior biologic exposure using MCMC method for multiple imputation. The responder rates are the adjusted predicted probabilities from the logistic regression model. Patients not achieving PASI50 at Week 16, 32 or 40 were treated as non-responders for all subsequent timepoints. Only patients achieving PASI50 at Week 16 continued into the maintenance period of the study (Week 16–48).
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E2 and E3)
Source: Gottlieb AB *et al.* (2018)[61].

In CIMPACT, the majority of patients (≥61.4%) in the blinded maintenance groups for patients initially randomised to CZP, in each group that received CZP treatment during the maintenance treatment period achieved a PGA response at each visit. For patients who received placebo, the mean PGA responder rate decreased from Week 16 to Week 48. In the blinded maintenance group that received CZP 400 mg Q2W in both the initial and maintenance treatment periods, the PGA responder rate increased from Week 16 through Week 32 (81.6% to [redacted]%) and then was generally maintained through Week 48 (87.8%). In the group initially treated with CZP 400 mg Q2W that received a reduced dose during the maintenance treatment period and the groups treated with CZP 200 mg Q2W (or the same cumulative monthly dose, 400 mg Q4W), the PGA responder rate was generally maintained from Week 16 through Week 36 or 40 and then decreased through Week 48 (Appendix M; Figure 13).

Figure 13: PGA clear or almost clear responder rates from Weeks 0–48 (initial and maintenance treatment periods) by re-randomised blinded treatment group in CIMPACT – ITT population



Abbreviations: CZP: certolizumab pegol; NRI: non-responder imputation; PGA: Physician's Global Assessment; Q2W: every two weeks; Q4W: every four weeks.
Note: Patients who escaped at Week 16 were treated as non-responders at all subsequent timepoints, and imputation using NRI methodology was used for all other missing data.
Source: Lebwohl M *et al.* (2018)[64]; CIMPACT Clinical Study Report[63].

Improvements in clinical response to Week 48 in patients with insufficient response to CZP 200 mg Q2W at Week 16 that were re-randomised to CZP 400 mg Q2W (PGA response)

For the treatment groups initially treated with CZP 200 mg Q2W who escaped to CZP 400 mg Q2W treatment, notable improvements in PGA responder rate were observed at Week 48 (Figure 14).

Figure 14: Improvements in clinical response to Week 48 in patients with insufficient response to CZP 200 mg Q2W at Week 16 that were re-randomised to CZP 400 mg Q2W (PGA response)

Abbreviations: CZP: certolizumab pegol; Esc: escape; NRI: non-responder imputation; Q2W: every two weeks.
Using NRI.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E4).
Source: UCB Cimzia Plaque Psoriasis Integrated Summary of Efficacy[75].

B.2.6.4 Psoriasis body surface area

In each of the CIMPASI-1, CIMPASI-2 and CIMPACT trials, clinically meaningful and notably larger mean decreases from baseline at Week 16 in psoriasis percentage BSA affected were observed in the CZP 200 mg Q2W and 400 mg Q2W groups compared with placebo. In CIMPASI-1 and CIMPASI-2, these decreases from baseline were generally similar between the CZP 200 mg Q2W and CZP 400 mg Q2W groups, while in CIMPACT the decreases from baseline were slightly greater in the CZP 400 mg Q2W group than the CZP 200 mg Q2W group (Table 22).

Table 22: Change from baseline in psoriasis percentage BSA affected in CIMPASI-1, CIMPASI-2 and CIMPACT at Week 16 – ITT population

	CIMPASI-1			CIMPASI-2			CIMPACT		
	Placebo (n=51)	CZP 200 mg Q2W (n=95)	CZP 400 mg Q2W (n=88)	Placebo (n=49)	CZP 200 mg Q2W (n=91)	CZP 400 mg Q2W (n=87)	Placebo (n=57)	CZP 200 mg Q2W (n=165)	CZP 400 mg Q2W (n=167)
Psoriasis BSA, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 16									
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSA: body surface area; CZP: certolizumab pegol; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks; SD: standard deviation.
Source: CIMPASI-1 Data Tables[77]; CIMPASI-2 Data Tables[78]; CIMPACT Data Tables[79].

Among the blinded maintenance groups in both CIMPASI-1 and CIMPASI-2, decreases from baseline in psoriasis percentage BSA affected CZP-treated patients who remained on their randomised treatment were greater at Week 48 compared with Week 16; in CIMPASI-1, this was particularly true for the CZP 400 mg Q2W group (Table 23). In CIMPACT, in the blinded maintenance groups receiving CZP treatment during the maintenance treatment period, mean decreases (i.e. improvements) from baseline in psoriasis percentage BSA affected at Week 16 were further improved at Week 48. For patients receiving placebo, smaller mean changes from baseline in psoriasis percentage BSA affected were observed from Week 16 to Week 48 (Table 24).

Table 23: Change from baseline in psoriasis percentage BSA affected at Week 48 in CIMPASI-1 and CIMPASI-2 by blinded maintenance treatment group – ITT population

	CZP 400 mg Q2W/ CZP 400 mg Q2W	Placebo/ Esc CZP 400 mg Q2W	CZP 200 mg Q2W/ Esc CZP 400 mg Q2W	CZP 400 mg Q2W/ Esc CZP 400 mg Q2W
CIMPASI-1				
n	[redacted]	[redacted]	[redacted]	[redacted]
Week 48 n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 48				
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
CIMPASI-2				
n	[redacted]	[redacted]	[redacted]	[redacted]
Week 48 n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 48				
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSA: body surface area; CZP: certolizumab pegol; Esc: escape; ETN: etanercept; Q2W: every two weeks; SD: standard deviation.
Source: CIMPASI-1 Data Tables[77]; CIMPASI-2 Data Tables[78].

Table 24: Change from baseline in psoriasis percentage BSA affected at Week 48 in CIMPACT by maintenance treatment group – ITT population

	CZP 200 mg Q2W/ placebo (n=22)	CZP 200 mg Q2W/ CZP 200 mg Q2W (n=44)	CZP 200 mg Q2W/ CZP 400 mg Q4W (n=44)	CZP 400 mg Q2W/ placebo (n=25)	CZP 400 mg Q2W/ CZP 200 mg Q2W (n=50)	CZP 400 mg Q2W/ CZP 400 mg Q2W (n=49)
Psoriasis BSA, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 48						
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSA: body surface area; CZP: certolizumab pegol; ETN: etanercept; Q2W: every two weeks; SD: standard deviation.
Source: CIMPACT Data Tables[79].

B.2.6.5 Time to relapse

Relapse rate data was assessed in the CIMPACT study as time to not achieving a PASI50 response for those who achieved PASI75 at Week 16. During the maintenance treatment period, time to relapse among patients achieving a PASI75 response at Week 16 was longer for those receiving CZP compared with those receiving placebo in the blinded treatment groups ([redacted] across all CZP maintenance groups versus placebo). No difference in time to relapse was observed for patients in the CZP 200 mg Q2W/CZP 200 mg Q2W versus CZP 200 mg Q2W/CZP 400 mg Q4W group. There was a trend towards a difference in time to relapse among patients in the CZP 400 mg Q2W/CZP 400 mg Q2W group versus the CZP 400 mg Q2W/CZP 200 mg Q2W group ([redacted]), suggesting a trend towards longer time to relapse among patients remaining on CZP 400 mg Q2W. A table reporting the proportion of patients who relapsed between Weeks 16 and 48 by re-randomised blinded maintenance treatment group is included in Appendix M; Figure 15 shows the time to relapse by re-randomised blinded maintenance treatment group.

Figure 15: Time to relapse among patients achieving a PASI75 response at Week 16 in CIMPACT – ITT population

A) CZP 200 mg Q2W/placebo, CZP 200 mg Q2W/CZP 200 mg Q2W and CZP 200 mg Q2W/CZP 400 mg Q4W treatment arms

B) CZP 400 mg Q2W/placebo, CZP 400 mg Q2W/CZP 200 mg Q2W and CZP 400 mg Q2W/CZP 400 mg Q2W treatment arms

Abbreviations: CZP: certolizumab pegol; Q2W: every two weeks; Q4W: every four weeks; PASI: Psoriasis Area and Severity Index; PBO: placebo.
Source: UCB CIMPACT Clinical Study Report[63]

B.2.6.6 mNAPSI results

mNAPSI change from baseline and nail psoriasis resolution at Week 48

In Pool E3, at Week 48, the mean mNAPSI scores for the groups receiving CZP 200 mg Q2W or CZP 400 mg Q2W in both study periods were [redacted] and [redacted], representing a mean change from baseline of [redacted] and [redacted], respectively. The majority of patients with psoriatic nail disease at baseline achieved an absence of nail disease (i.e., mNAPSI score of 0) at Week 48 in the CZP 200 mg Q2W and CZP 400 mg Q2W groups ([redacted]% and [redacted]%, respectively; Table 25).

Table 25: Change from baseline in mNAPSI score and nail psoriasis resolution (mNAPSI=0) at Week 48 in Pool E3 – ITT population

	Placebo [redacted]	CZP 200 mg Q2W [redacted]	CZP 400 mg Q2W [redacted]
mNAPSI change from baseline at Week 48			
n	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]
Nail psoriasis resolution at Week 48			
n	[redacted]	[redacted]	[redacted]
Patients, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; mNAPSI: Modified Nail Psoriasis Severity Index; N/A: not applicable; NR: not reported; Q2W: every two weeks; SD: standard deviation.
Patients who remained on the treatment to which they were randomised at baseline.
Source: UCB Cimzia Plaque Psoriasis Integrated Summary of Efficacy[75].

In CIMPACT, the mean decrease (i.e., improvement) from baseline in mNAPSI score was generally numerically greater in those groups that remained on CZP for 48 weeks (range of mean changes from baseline: [redacted] to [redacted]) compared with those groups re-randomised to placebo at Week 16 (range of mean changes from baseline: [redacted] to [redacted]; Table 26).

Table 26: Change from baseline in mNAPSI score at Week 48 in CIMPACT – ITT population

	CZP 200 mg Q2W/ placebo [redacted]	CZP 200 mg Q2W/ CZP 200 mg Q2W [redacted]	CZP 200 mg Q2W/ CZP 400 mg Q4W [redacted]	CZP 400 mg Q2W/ placebo [redacted]	CZP 400 mg Q2W/ CZP 200 mg Q2W [redacted]	CZP 400 mg Q2W/ CZP 400 mg Q2W [redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; ETN: etanercept; mNAPSI: modified nail psoriasis severity index; N/A: not applicable; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation.
Source: CIMPACT Clinical Study Report[63].

B.2.6.7 Patient-relevant outcomes

Fatigue: FASca

Baseline mean FASca scores were low and similar across the 4 treatment groups, ranging from [redacted] to [redacted] on a scale of 0 to 10. Mean changes from baseline were slightly greater for the CZP 200 mg Q2W (range of means: [redacted] to [redacted]) and CZP 400 mg Q2W groups (range of means: [redacted] to [redacted]) compared to the placebo group (range of means: [redacted] to [redacted]).

Table 27: Change from baseline in FASca score at Week 16 in CIMPACT – ITT population

	Placebo (n=57)	ETN (n=170)	CZP 200 mg Q2W (n=165)	CZP 400 mg Q2W (n=167)
n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 16				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; ETN: etanercept; FASca: Fatigue Assessment Scale; SD: standard deviation.
Source: CIMPACT Data Tables[79].

For the blinded treatment groups, mean improvements from baseline at Week 16 in FASca were consistently maintained or improved through Week 48 in groups that received CZP treatment during the maintenance treatment period. For groups receiving placebo, a loss of improvement from baseline at Week 16 was observed over time (Table 28).

Table 28: Change from baseline in FASca score at Week 48 by re-randomised blinded maintenance treatment group for patients initially randomised to CZP in CIMPACT – ITT population

	CZP 200 mg Q2W/placebo (n=22)	CZP 200 mg Q2W/CZP 200 mg Q2W (n=44)	CZP 200 mg Q2W/CZP 400 mg Q4W (n=44)	CZP 400 mg Q2W/ placebo (n=25)	CZP 400 mg Q2W/CZP 200 mg Q2W (n=50)	CZP 400 mg Q2W/CZP 400 mg Q2W (n=49)
Week 48 n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Change from baseline at Week 48						
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; FASca: Fatigue Assessment Scale; LOCF: last observation carried forward; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation.
Using LOCF imputation.
Source: CIMPACT Data Tables[79].

Disease-specific quality of life: DLQI

CZP demonstrated rapid and clinically meaningful improvements in HRQoL, measured as change from baseline in DLQI, compared to placebo. In Pool E1, rapid and clinically meaningful improvements were observed in both the CZP 200 mg Q2W and CZP 400 mg Q2W groups beginning at Week 2 through Week 16 ([redacted] at all timepoints for both doses). No apparent dose response was observed (Table 29; Appendix M). Generally similar and increasingly larger percentages of patients in both the CZP 200 mg Q2W and CZP 400 mg Q2W groups achieved DLQI remission compared with placebo at each timepoint. At Week 16, 42.7% of patients in the CZP 200 mg Q2W group and 47.1% of patients in the CZP 400 mg Q2W group had achieved DLQI remission compared with 8.3% of patients in the placebo group (Table 29).

The rapid and clinically meaningful mean change from baseline in DLQI observed during the initial treatment period in CIMPASI-1 and CIMPASI-2 was maintained through Week 48 in both CZP treatment groups (Table 30). The percentage of patients who were in DLQI remission was maintained through Week 48 in the CZP 200 mg Q2W group in CIMPASI-1 (Week 16: 47.4%; Week 48: 45.3%) and decreased slightly in CIMPASI-2 (Week 16: 46.2%; Week 48: 38.5%). In the CZP 400 mg Q2W group, the percentage of patients who were in DLQI remission increased from Week 16 to Week 48 in CIMPASI-1 (Week 16: 45.5%; Week 48: 52.3%) and was maintained in CIMPASI-2 (Week 16: 50.6%; Week 48: 50.6%; Table 30).

Table 29: Change from baseline in DLQI score and DLQI remission rate (0/1) at Week 16 – ITT population (Pool E1)

	Placebo (n=157)	CZP 200 mg Q2W (n=351)	CZP 400 mg Q2W (n=342)
Change from baseline to Week 16			
Baseline mean (SD)	13.4	13.6	14.5
Mean (SD)	-2.4 [redacted]	-9.1 [redacted]	-10.4 [redacted]
P-value		<0.0001	<0.0001
Remission rate at Week 16			

Remission rate, %	8.3	42.7	47.1

Based on ANCOVA model with factors for treatment group, region, study, prior biologic exposure (yes/no) and interaction terms for study by region and prior biologic exposure (yes/no) and baseline DLQI score as a covariate using LOCF imputation.
Abbreviations: ANCOVA: analysis of covariance; CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; LOCF: last observation carried forward; SD: standard deviation.
Source: Blauvelt A *et al.* (2018);[70] UCB Certolizumab Pegol 2.7.3 Summary of Clinical Efficacy (Pool E1)[71].

Table 30: Change from baseline in DLQI score and DLQI remission rate (0/1) by randomised treatment group at Week 48 in CIMPASI-1 and CIMPASI-2 – ITT population

	CIMPASI-1		CIMPASI-2	
	CZP 200 mg Q2W (n=95)	**CZP 400 mg Q2W (n=88)**	**CZP 200 mg Q2W (n=91)**	**CZP 400 mg Q2W (n=87)**
Change from baseline at Week 48				
Week 48 n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	13.3	13.1	15.2	14.2
Change from baseline mean (SD)	-8.8 [redacted]	-9.8 [redacted]	-10.7 [redacted]	-10.9 [redacted]
DLQI remission rate at Week 48				
Responder rate, n (%)	43 (45.3)	46 (52.3)	35 (38.5)	44 (50.6)

Using LOCF imputation.
Abbreviations: CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; LOCF: last observation carried forward; Q2W: every two weeks; SD: standard deviation.
Source: Gottlieb AB *et al.* (2018)[61]; CIMPASI-1 Clinical Study Report[60]; CIMPASI-2 Clinical Study Report[62].

In CIMPACT, patients in the CZP 200 mg Q2W and CZP 400 mg Q2W groups had clinically meaningful improvements in patients' HRQoL (as assessed by the mean change from baseline in the DLQI) compared with the placebo group, beginning as early as Week 8 and continuing through Week 16. Consistently larger mean decreases from baseline in the DLQI score were observed over time from Weeks 2 through 12 and subsequently maintained at Week 16 for the CZP 200 mg Q2W group, whereas the DLQI score continued to improve through Week 16 for the CZP 400 mg Q2W group. Mean decreases from baseline in the DLQI score at Week 16 were -8.1 in the CZP 200 mg Q2W group and -11.0 in the CZP 400 mg Q2W group compared with -1.1 in the placebo group (see Appendix M). At Week 12, the change from baseline in DLQI (SD) was numerically comparable

between ETN and CZP 200 mg Q2W ([redacted] [redacted] and [redacted] [redacted], respectively), with a slightly greater change from baseline in the CZP 400 mg Q2W arm ([redacted] [redacted]).

Improvements in DLQI at Week 16 were generally maintained through Week 48 by patients receiving CZP treatment in the maintenance treatment period. For the treatment groups initially treated with CZP 200 mg Q2W, the mean change from baseline in DLQI score from Week 16 to Week 48 in the treatment group receiving CZP 400 mg Q4W improved slightly over time, and the treatment group continuing on CZP 200 mg Q2W maintained over time. Similar patterns were seen in the treatment groups initially treated with CZP 400 mg Q2W (Table 31).

With regard to DLQI remission, the percentage of patients who were in DLQI remission was maintained or increased in groups that received CZP treatment during the maintenance treatment period. Among patients initially treated with CZP 200 mg Q2W, the percentage in DLQI remission generally increased from Week 16 to Week 48 with no notable differences observed between those receiving CZP 400 mg Q4W in the maintenance period, and those continuing on CZP 200 mg Q2W. For patients initially treated with CZP 400 mg Q2W, the percentage in DLQI remission was maintained from Week 16 to Week 48 in those receiving CZP 200 mg Q2W in the maintenance treatment period, whereas the percentage increased in those continuing on CZP 400 mg Q2W (Table 31). For groups receiving placebo, the percentage of patients who were in DLQI remission dramatically decreased from Week 16 to Week 48.

Table 31: Change from baseline in DLQI score at Week 48 by re-randomised blinded maintenance treatment group for patients initially randomised to CZP in CIMPACT – ITT population

	CZP 200 mg Q2W/placebo (n=22)	CZP 200 mg Q2W/CZP 200 mg Q2W (n=44)	CZP 200 mg Q2W/CZP 400 mg Q4W (n=44)	CZP 400 mg Q2W/placebo (n=25)	CZP 400 mg Q2W/CZP 200 mg Q2W (n=50)	CZP 400 mg Q2W/CZP 400 mg Q2W (n=49)
Change from baseline at Week 48						
Week 48 n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI remission rate at Week 48						

Remission rate, n (%)	[redacted] (13.6)	[redacted] (54.5)	[redacted] (59.1)	[redacted] (4.0)	[redacted] (50.0)	[redacted] (77.6)

Abbreviations: CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; LOCF: last observation carried forward; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation.
Using LOCF imputation.
Source: Piguet V *et al.* (2017)[80]; CIMPACT Clinical Study Report[63].

Generic health-related quality of life: SF-36

An improvement in HRQoL among patients treated with CZP was also demonstrated through change from baseline in SF-36 score in both CIMPASI-1 and CIMPASI-2. Greater reductions from baseline in the MCS and PCS at Week 16 were reported for patients in both CZP treatment arms compared to placebo ([redacted]; Table 32).

In the blinded maintenance group in both CIMPASI-1 and CIMPASI-2, increases from baseline in PCS score at Week 48 were clinically meaningful. In CIMPASI-1, increases from baseline in PCS score were generally maintained in patients who remained on their randomised CZP treatment through Week 48 and in CIMPASI-2 were maintained in patients who remained on their randomised CZP treatment through Week 48 and were PASI50 responders at Week 16. In terms of MCS scores in CIMPASI-1, in patients who remained on their randomised treatment of CZP 200 mg Q2W through Week 48, increases from baseline were clinically meaningful at all timepoints but were lower at Week 48 ([redacted]) compared with Week 16 ([redacted]). In patients who remained on their randomised treatment of CZP 400 mg Q2W through Week 48, increases from baseline in the MCS score were clinically meaningful at all timepoints and were generally maintained (Week 48: [redacted]; Week 16: [redacted]). In CIMPASI-2, increases from baseline in the MCS score were also clinically meaningful and were consistently maintained in patients who remained on their randomised CZP 200 mg Q2W treatment through Week 48. In the CZP 400 mg Q2W/CZP 400 mg Q2W, in patients who completed the maintenance treatment period, increases from baseline in the MCS score were larger at Week 48 ([redacted]) compared with Week 16 ([redacted]; **Error! Reference source not found.**).

Table 32: Change from baseline in SF-36 score in CIMPASI-1 and CIMPASI-2 at Week 16 – ITT population

	CIMPASI-1			CIMPASI-2		
	Placebo (n=51)	CZP 200 mg Q2W (n=95)	CZP 400 mg Q2W (n=88)	Placebo (n=49)	CZP 200 mg Q2W (n=91)	CZP 400 mg Q2W (n=87)
PCS, baseline n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 16						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P-value		[redacted]	[redacted]		[redacted]	[redacted]
MCS, baseline n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 16						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P-value		[redacted]	[redacted]		[redacted]	[redacted]

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; CZP: certolizumab pegol; LOCF: last observation carried forward; MCS: mental component summary; PCS: physical component summary; Q2W: every two weeks; SD: standard deviation; SF-36: 36-item Short Form health survey.
Based on ANCOVA model with treatment group, region and prior biologic exposure (yes/no) as factors and baseline SF-36 PCS or MCS as a covariate using LOCF imputation.
Source: CIMPASI-1 Clinical Study Report[60]; CIMPASI-2 Clinical Study Report[62].

Table 33: Change from baseline in SF-36 score in CIMPASI-1 and CIMPASI-2 at Week 48 – ITT population

	CIMPASI-1		CIMPASI-2	
	CZP 200 mg Q2W/CZP 200 mg Q2W (n=74)	CZP 400 mg Q2W/CZP 400 mg Q2W (n=77)	CZP 200 mg Q2W/CZP 200 mg (n=76)	CZP 400 mg Q2W/CZP 400 mg Q2W (n=69)
PCS baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 48				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MCS baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 48				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; MCS: mental component summary; PCS: physical component summary; Q2W: every two weeks; SD: standard deviation.
Source: CIMPASI-1 Data Tables[77]; CIMPASI-2 Data Tables[78].

Anxiety and depression: HADS-A and HADS-D

Treatment with either of CZP 200 mg Q2W or CZP 400 mg Q2W resulted in numerically greater reductions from baseline compared to placebo in HADS-A scores at weeks 12 and 16, in both CIMPASI-1 and CIMPASI-2. Treatment with either of CZP 200 mg Q2W or CZP 400 mg Q2W resulted in statistically significantly ([redacted]) greater reductions from baseline in the HADS-D score at weeks 12 and 16 compared to placebo in CIMPASI-1. In CIMPASI-2, treatment with CZP 200 mg Q2W resulted in statistically significantly ([redacted]) greater reductions from baseline in the HADS-D score at Weeks 12 and 16 compared to placebo (Table 34). For both trials, among patients who remained on randomised treatment up to Week 48, decreases from baseline (improvements) in HADS-A and HADS-D scores were generally maintained at Week 48 relative to Week 16 (Table 35).

Table 34: Change from baseline in HADS-A and HADS-D score in CIMPASI-1 and CIMPASI-2 at Week 16 – ITT population

	CIMPASI-1			CIMPASI-2		
	Placebo (n=51)	CZP 200 mg Q2W (n=95)	CZP 400 mg Q2W (n=88)	Placebo (n=49)	CZP 200 mg Q2W (n=91)	CZP 400 mg Q2W (n=87)
HADS-A						
Baseline n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 16						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P-value		[redacted]	[redacted]		[redacted]	[redacted]
HADS-D						
Baseline, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 16						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P-value		[redacted]	[redacted]		[redacted]	[redacted]

Abbreviations: ANCOVA: analysis of covariance; CZP: certolizumab pegol; HADS-A: hospital anxiety and depression score – anxiety; HADS-D: hospital anxiety and depression score – depression; LOCF: last observation carried forward; SD: standard deviation.
Based on ANCOVA model with treatment group, region and prior biologic exposure (yes/no) as factors and baseline HADS-A or HADS-D score as a covariate using LOCF imputation.
Source: CIMPASI-1 Clinical Study Report[60]; CIMPASI-2 Clinical Study Report[62].

Table 35: Change from baseline in HADS-A and HADS-D score in CIMPASI-1 and CIMPASI-2 at Week 48 – ITT population

	CIMPASI-1		CIMPASI-2	
	CZP 200 mg Q2W/CZP 200 mg Q2W (n=74)	CZP 400 mg Q2W/CZP 400 mg Q2W (n=77)	CZP 200 mg Q2W/CZP 200 mg Q2W (n=76)	CZP 400 mg Q2W/CZP 400 mg Q2W (n=69)
HADS-A				
Baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to week 48				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
HADS-D				
Baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to week 48				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; HADS-A: hospital anxiety and depression score – anxiety; HADS-D: hospital anxiety and depression score – depression; N/A: not applicable; SD: standard deviation.
Source: CIMPASI-1 Data Tables[77]; CIMPASI-2 Data Tables[78].

Workplace productivity and daily activities: WPAI-SHP

During the initial treatment period, no consistent trends over time were seen in absenteeism in the three studies following treatment with CZP 200 mg Q2W or CZP 400 mg Q2W. The median score at baseline was [redacted] for all treatment groups in all three studies, therefore, the subjects included in this analysis had no/low absenteeism at baseline, and there was little room for improvement in this domain in any of the treatment groups (Table 36).

Regarding presenteeism, across the studies, differences from placebo were observed as early as Week 4 for both the CZP 200 mg Q2W and CZP 400 mg Q2W groups. Decreases from baseline were numerically larger in the CZP 400 mg Q2W group compared with the CZP 200 mg Q2W group at all timepoints in CIMPASI-2 and CIMPACT and at Weeks 12 and 16 in CIMPASI-1.

In terms of overall work impairment due to psoriasis, across three studies, differences from placebo were observed as early as Week 4 for both the CZP 200 mg Q2W and CZP 400 mg Q2W groups. Decreases from baseline were numerically larger in the CZP 400 mg Q2W group compared with the CZP 200 mg Q2W group at all timepoints in CIMPASI-2 and CIMPACT and at Weeks 12 and 16 in CIMPASI-1.

During the initial treatment period, improvements versus placebo in daily activity impairment due to psoriasis were observed as early as Week 4 for both the CZP 200 mg Q2W and CZP 400 mg Q2W groups across CIMPASI-1, CIMPASI-2 and CIMPACT. In CIMPASI-1, the decreases from baseline were larger in the CZP 400 mg Q2W group compared with the CZP 200 mg Q2W group at timepoints, in particular at Weeks 12 and 16.

In both CIMPASI-1 and CIMPASI-2 studies, improvements in workplace productivity and activities were consistently maintained from Weeks 16 to 48 for both the CZP 200 mg 200 mg Q2W and CZP 400 mg Q2W/CZP 400 mg Q2W groups (Table 37). Similar results were seen in the CIMPACT study. For patients who were randomised to placebo after receiving either CZP or ETN during the initial treatment period, trends toward smaller decreases from baseline over time were observed (

Table 38).

Table 36: Change from baseline in WPAI-SHP scores in CIMPASI-1, CIMPASI-2 and CIMPACT at Week 16 – ITT population

	CIMPASI-1			CIMPASI-2			CIMPACT		
	Placebo (n=51)	CZP 200 mg Q2W (n=95)	CZP 400 mg Q2W (n=88)	Placebo (n=49)	CZP 200 mg Q2W (n=91)	CZP 400 mg Q2W (n=87)	Placebo (n=57)	CZP 200 mg Q2W (n=165)	CZP 400 mg Q2W (n=167)
Percent work time missed due to problem									
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49	117	123
Mean CfB (SD)	7.1 [redacted]	4.1 [redacted]	5.5 [redacted]	-1.8 [redacted]	-3.2 [redacted]	3.7 [redacted]	4.6 [redacted]	-3.3 [redacted]	-1.5 [redacted]
p value		NS	NS		NS	NS		<0.05	<0.05
Percent impairment while working due to problem									
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49	117	123
Mean CfB (SD)	-0.8 [redacted]	-8.0 [redacted]	-13.0 [redacted]	2.5 [redacted]	-11.5 [redacted]	-12.8 [redacted]	3.5 [redacted]	-10.4 [redacted]	-18.4 [redacted]
p value		<0.05	<0.05		<0.05	<0.05		<0.05	<0.0001
Percent overall work impairment due to problem									
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49	117	123
Mean CfB (SD)	7.8 [redacted]	-4.7 [redacted]	-8.9 [redacted]	1.5 [redacted]	-13.8 [redacted]	-9.1 [redacted]	7.4 [redacted]	-13.3 [redacted]	-18.3 [redacted]
p value		<0.05	<0.05		NS	NS		<0.0001	<0.0001
Percent activity impairment due to problem									
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57	164	167
Mean CfB (SD)	-0.6 [redacted]	-15.8 [redacted]	-24.4 [redacted]	-2.4 [redacted]	-26.4 [redacted]	-23.4 [redacted]	2.8 [redacted]	-17.1 [redacted]	-21.4 [redacted]
p value		<0.0001	<0.0001		<0.0001	<0.0001		<0.0001	<0.0001

Abbreviations: ANCOVA: analysis of covariance; CfB: change from baseline; CZP: certolizumab pegol; LOCF: last observation carried forward; NS: not significant; Q2W: every two weeks; SD: standard deviation; WPAI-SHP: Work Productivity and Activity Impairment – Specific Health Problem.
Based on ANCOVA model with treatment group, region and prior biologic exposure (yes/no) as factors and baseline WPAI-SHP score as a covariate using LOCF imputation.
Source: Thaçi D *et al.* (2017)[81]; Piguet V *et al.* (2017)[80]; CIMPASI-1 Data Tables[77]; CIMPASI-2 Data Tables[78]; CIMPACT Data Tables[79].

Table 37: Change from baseline in WPAI-SHP scores in CIMPASI-1 and CIMPASI-2 at Week 48 – ITT population

	CIMPASI-1		CIMPASI-2	
	CZP 200 mg Q2W/ CZP 200 mg Q2W (n=74)	CZP 400 mg Q2W/ CZP 400 mg Q2W (n=77)	CZP 200 mg Q2W/ CZP 200 mg Q2W (n=76)	CZP 400 mg Q2W/ CZP 400 mg Q2W (n=69)
Percent work time missed due to problem				
n	47	54	42	42
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	5.9 [redacted]	0.3 [redacted]	-1.2 [redacted]	-0.6 [redacted]
Percent impairment while working due to problem				
n	47	54	42	42
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	-7.7 [redacted]	-18.1 [redacted]	-12.4 [redacted]	-15.5 [redacted]
Percent overall work impairment due to problem				
n	47	54	42	42
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	-3.7 [redacted]	-17.6 [redacted]	-12.9 [redacted]	-15.0 [redacted]
Percent activity impairment due to problem				
n	68	68	64	61
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	-19.7 [redacted]	-31.2 [redacted]	-28.3 [redacted]	-25.7 [redacted]

Abbreviations: CZP: certolizumab pegol; NR: not reported; Q2W: every two weeks; SD: standard deviation; WPAI-SHP: Work Productivity and Activity Impairment – Specific Health Problem.
Source: Thaçi D *et al.* (2017)[81]; CIMPASI-1 Data Tables[77]; CIMPASI-2 Data Tables[78].

Table 38: Change from baseline in WPAI-SHP scores in CIMPACT at Week 48 – ITT population

	CZP 200 mg Q2W/ placebo (n=22)	CZP 200 mg Q2W/ CZP 200 mg Q2W (n=44)	CZP 200 mg Q2W/ CZP 400 mg Q4W (n=44)	CZP 400 mg Q2W/ placebo (n=25)	CZP 400 mg Q2W/ CZP 200 mg Q2W (n=50)	CZP 400 mg Q2W/ CZP 400 mg Q2W (n=49)
Percent work time missed due to problem						
n	6	27	27	10	27	38
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean CfB (SD)	2.6 [redacted]	-2.5 [redacted]	-12.6 [redacted]	3.1 [redacted]	-4.2 [redacted]	1.5 [redacted]
Percent impairment while working due to problem						
n	6	27	27	10	27	38
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean CfB (SD)	-5.0 [redacted]	-8.5 [redacted]	-18.5 [redacted]	-22.0 [redacted]	-20.7 [redacted]	-26.8 [redacted]
Percent overall work impairment due to problem						
n	6	27	27	10	27	38
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean CfB (SD)	-5.4 [redacted]	-10.9 ([redacted])	-28.8 [redacted]	-13.0 [redacted]	-22.1 [redacted]	-24.9 [redacted]
Percent activity impairment due to problem						
n	12	36	40	15	41	48
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean CfB (SD)	-32.5 [redacted]	-18.9 [redacted]	-21.3 [redacted]	-4.7 [redacted]	-24.4 [redacted]	-30.2 [redacted]

Abbreviations: CfB: change from baseline; CZP: certolizumab pegol; NR: not reported; Q2W: every two weeks; SD: standard deviation; WPAI-SHP: Work Productivity and Activity Impairment – Specific Health Problem.
Source: Piguet V *et al.* (2017)[80]; CIMPACT Data Tables[79].

B.2.6.8 Comparative efficacy of CZP versus ETN (CIMPACT)

Both dosing regimens (CZP 200 mg Q2W and CZP 400 mg Q2W) resulted in a significantly greater PASI75 response rate at Week 12, when compared to placebo (p<0.0001 for both CZP groups). The CZP 400 mg Q2W dosing regimen also showed a statistically significant improvement when compared to the active comparator ETN (p=0.0152), indicating that CIMPACT met its primary endpoint. This is indicative of an additional benefit of CZP compared to ETN, in terms of rapid onset of treatment efficacy. No other formal statistical comparisons between CZP and ETN were conducted as part of the CIMPACT study, however the comparative PASI75, PASI90 and PASI100 data is presented below (Table 39).

Table 39: PASI 75, PASI 90 and PASI 100 responder rate at Week 12 in CIMPACT – ITT population

	Placebo (n=57)	ETN (n=170)	CZP 200 mg Q2W (n=165)	CZP 400 mg Q2W (n=167)
PASI75	5.0%	53.3%	61.3%*	66.7%†
PASI90	0.2%	27.1%	31.2%‡	34.0%‡
PASI100	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; ETN: etanercept; MCMC: Markov chain Monte Carlo; PASI: Psoriasis Area Severity Index; Q2W: every two weeks.
*p<0.0001 versus placebo, p=0.1523 versus ETN; †p<0.0001 versus placebo, p=0.0152 versus ETN. ‡p<0.0001 versus placebo; [redacted]
Based on logistic regression model with factors for treatment, region and prior biologic exposure (yes/no) using MCMC method for multiple imputation.
Source: Lebwohl M *et al.* (2018)[64]; CIMPACT Clinical Study Report[63].

PGA responder rate versus etanercept was numerically increased in the CZP 400 mg Q2W arm at Week 12 in CIMPACT

A summary of the PGA responder rates at Week 12 for CZP versus etanercept from the CIMPACT trial is presented in Table 40. Compared with patients receiving placebo, those in both CZP treatment arms were more likely to achieve a PGA clear or almost clear response (p=0.0004 for CZP 200 mg Q2W, p<0.0001 for CZP 400 mg Q2W). No formal statistical comparisons were made between CZP and ETN with regards to the PGA responder rate at Week 12, however, numerically this was comparable for ETN versus CZP 200 mg Q2W, with CZP 400 mg Q2W showing an increased response compared to ETN (Appendix M). These results are demonstrative of an early and meaningful reduction in the visible severity of disease.

Table 40: Proportion of patients with a PGA response of clear or almost clear, and at least a two-category improvement, at Week 12 in CIMPACT – ITT population

	Placebo (n=57)	ETN (n=170)	CZP 200 mg Q2W (n=165)	CZP 400 mg Q2W (n=167)
PGA responder rate, %	1.9%	39.2%	39.8%	50.3%
Estimate for difference in proportion of	-	-	[redacted]	[redacted]

responders vs placebo, % (95% CI)				
p-value	-	-	0.0004	<0.0001

Abbreviations: CZP: certolizumab pegol; ETN: etanercept; MCMC: Markov chain Monte Carlo; PGA: Physician's Global Assessment; Q2W: every two weeks.
Based on logistic regression model with factors for treatment group, region and prior biologic exposure (yes/no) using MCMC method for multiple imputation.
Source: Lebwohl M *et al.* (2018)[64]; CIMPACT Clinical Study Report[63]

B.2.6.9 Clinical effectiveness in candidates for non-biologic systemic therapies

Baseline characteristics

In general, baseline characteristics were similar to those observed in the ITT populations for each trial (Section B.2.3.2). The baseline patient demographics and clinical characteristics among candidates for non-biologic systemic therapies in Pool E1 are reported in Appendix M.

Clinical response

CZP was found to be efficacious at Weeks 16 and 48 in patients who were candidates for non-biologic systemic therapies, with similarly high response rates as those observed in the ITT population. Clinically meaningful efficacy based on PASI75, PASI90 and PGA 0/1 responder rates was observed at Week 16 in patients without a history of prior systemic treatment of psoriasis (Table 41).

Table 41: PASI75, PASI90, PASI100 and PGA 0/1 responses at Week 16 – candidates for non-biologic systemic therapies (Pool E1)

	Placebo [redacted]	CZP 200 mg Q2W [redacted]	CZP 400 mg Q2W [redacted]
Responder rate at Week 16, %[a]			
PASI75	[redacted]	[redacted]	[redacted]
PASI90	[redacted]	[redacted]	[redacted]
PASI100	[redacted]	[redacted]	[redacted]
PGA 0/1 response	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
[a]Based on logistic regression model with factors for treatment, region and study using NRI (patients missing PASI or PGA response are considered to be non-responders). Responder rates are the adjusted probabilities from the logistic regression model.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).
Source: UCB Data on File (2017–2018)[72].

Long-term maintenance of efficacy

Efficacy in patients who were candidates for systemic non-biologic drugs was maintained through Week 48. Both CZP 200 mg Q2W and CZP 400 mg Q2W were effective over the longer-term in maintaining PASI and PGA 0/1 responder rates (Table 42). Among candidates for non-biologic systemic therapies, PASI75 and PASI90 responder rates at Week 48 were also numerically higher in the CZP 400 mg Q2W group compared with the CZP 200 mg Q2W at Week 48 (Figure 1617).

Table 42: PASI75, PASI90, PASI100 and PGA 0/1 responses and absolute PASI scores at Week 48 – candidates for non-biologic systemic therapies (Pool E3)

	CZP 200 mg Q2W [redacted]	CZP 400 mg Q2W [redacted]
Absolute PASI score at Week 48	[redacted]	[redacted]
Responder rate, n (%)		
PASI75	[redacted]	[redacted]
PASI90	[redacted]	[redacted]
PASI100	[redacted]	[redacted]
PGA 0/1 response, n (%)	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; NR: not reported; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
Patients who meet escape criteria at Week 16 (i.e., do not achieve a PASI50) or who meet criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 are treated as non-responders at subsequent visits. For patients who achieved a PASI50 response at Week 16 but were mistakenly put into the CZP 400 mg Q2W escape arm, all visits after Week 16 are imputed with the value observed at Week 16 (i.e., Week 16 carried forward). All other missing data are imputed using NRI methodology.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Source: UCB Cimzia Plaque Psoriasis Integrated Summary of Efficacy[75]; UCB Data on File (2017–2018)[72].

Figure 1617: PASI75 and PASI90 responder rate from baseline to Week 48 – candidates for non-biologic systemic therapies (Pool E2 and E3)

Abbreviations: CZP: certolizumab pegol; NRI: non-responder imputation; PASI: Psoriasis Area Severity Index;; Q2W: every two weeks.

PASI75: For week 2, 4 and 8, missing data were imputed using NRI method. Responder rates are based on the observed raw proportions from the input dataset. For week 12 and 16 estimates of responder rate are based on a logistic regression model with factors for treatment, region and study, where missing data were imputed using NRI (patients missing PASI response are considered to be non-responders). The responder rates are the adjusted probabilities from the logistic regression model; the model factor levels were weighted based on frequencies in the analysis population.
PASI90: Missing data were imputed using NRI method. Responder rates are based on the observed raw proportions from the input dataset.
PASI75 and PASI90: Week 20–48: Patients who met escape criteria at Week 16 (i.e., did not achieve a PASI50) or who met criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 were treated as non-responders at subsequent visits. For patients who achieved a PASI50 response at Week 16 but were mistakenly put into the CZP 400 mg Q2W escape arm, all visits after Week 16 were imputed with the value observed at Week 16 (i.e., Week 16 carried forward). All other missing data are imputed using NRI methodology.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E2 and Pool E3).
Source: UCB Data on File (2018)[76].

Body surface area

In patients who are candidates for non-biologic systemic therapies, substantial improvements in psoriasis percentage BSA were seen with both CZP doses at week 16 and at week 48 (Appendix M).

Extracutaneous manifestations

In patients who are candidates for non-biologic systemic therapies, improvements in extracutaneous manifestations seen with CZP were similarly high to those seen in the overall ITT population, with both CZP doses (Table 43).

Table 43: Change from baseline in mNAPSI score and nail psoriasis resolution (mNAPSI=0) at Week 48 – candidates for non-biologic systemic therapies (Pool E3)

	CZP 200 mg Q2W [redacted]	CZP 400 mg Q2W [redacted]
mNAPSI change from baseline at Week 48[a]		
n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
Nail psoriasis resolution at Week 48		
n	[redacted]	[redacted]
Patients, n (%)	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; mNAPSI: Modified Nail Psoriasis Severity Index; N/A: not applicable; NR: not reported; Q2W: every two weeks; SD: standard deviation.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Source: UCB Data on File (2017–2018)[72]; UCB Data on File (2018)[76].

Quality of life

Significant reductions in DLQI score were observed in both CZP arms compared to placebo at Week 16 in Pool E1 (Table 44). By Week 48, patients in the CZP 200 mg Q2W and CZP 400 mg Q2W arms maintained their reduction in DLQI in Pool E3. The results observed in the candidates for non-biologic systemic therapies are comparable to the ITT populations from CIMPASI-1, CIMPASI-2 and CIMPACT (see Section B.2.6.7). Improvement in the PCS and MCS domains of SF-36 were also observed by Week 16 in Pool E2, and further improved to Week 48 in the CZP

200 mg Q2W and CZP 400 mg Q2W arms, with similar improvements to the ITT populations (see Appendix M).

Table 44: Change from baseline in DLQI score and DLQI remission rate (0/1) at Week 16 – candidates for non-biologic systemic therapies (Pool E1)

	Placebo [redacted]	CZP 200 mg Q2W [redacted]	CZP 400 mg Q2W [redacted]
Change from baseline to Week 16			
n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
p value vs placebo[a]	[redacted]	[redacted]	[redacted]
Remission rate at Week 16[a]			
Remission rate, %	[redacted]	[redacted]	[redacted]
p value vs placebo[b]		[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; NRI: non-responder imputation; SD: standard deviation.
Based on a logistic regression model with factors for treatment, region and study, where missing data were imputed using NRI (patients missing DLQI response are considered to be non-responders). Responder rates are the adjusted probabilities from the logistic regression model; the model factor levels were weighted based on frequencies in the analysis population.
[a]p value for adjusted mean treatment differences. [b]p value for odds ratio versus placebo.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).
Source: UCB Data on File (2017–2018)[72].

Table 45: Change from baseline in DLQI score and DLQI remission rate (0/1) at Week 48 – candidates for non-biologic systemic therapies (Pool E3)

	CZP 200 mg Q2W [redacted]	CZP 400 mg Q2W [redacted]
Change from baseline at Week 48[a]		
n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
DLQI remission rate at Week 48[b]		
Remission rate, n (%)	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; LOCF: last observation carried forward; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks; SD: standard deviation.
[a]Using LOCF.
[b]Patients who meet escape criteria at Week 16 (i.e., do not achieve a PASI50) or who meet criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 are treated as non-responders at subsequent visits. For patients who achieved a PASI50 response at Week 16 but were mistakenly put into the CZP 400 mg Q2W escape arm, all visits after Week 16 are imputed with the value observed at Week 16 (i.e., Week 16 carried forward). All other missing data are imputed using NRI methodology.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Source: UCB Data on File (2017–2018)[72].

Among patients who were candidates for non-biologic systemic therapy, CZP also demonstrated improvements in HRQoL when measured as the change from baseline in SF-36 PCS and MCS. However, the change from baseline in HADS-A and HADS-D scores at Week 16 among candidates for non-biologic systemic therapies did not reach significance. Finally, regarding workplace productivity and daily activities, statistically significant improvements were reported at Week 16 compared to baseline in both the CZP 200 mg Q2W and CZP 400 mg Q2W treatment groups (Appendix M).

B.2.6.10 Clinical effectiveness in systemic non-biologic therapy inadequate responders

One of the populations stipulated in the NICE scope is patients for whom conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated ("candidates for biologic therapy"). In this submission, this population has been defined as patients who have had exposure to a previous non-biologic systemic therapy but are naïve to previous biologic therapy.

Baseline characteristics

The baseline patient demographics and clinical characteristics among systemic non-biologic therapy inadequate responders in Pool E1 are reported in Appendix M. In general, baseline characteristics were similar to those reported across all three trials in the ITT populations (Section B.2.3.2).

Clinical response

The PASI75/90 and PGA 0/1 responder rates for patients who were considered inadequate responders to systemic non-biologic therapy are presented in (Table 46). Results were generally comparable to the ITT population in Pool E1, with slightly higher response rates observed in patients who received CZP 400 mg Q2W compared to CZP 200 mg Q2W.

Table 46: PASI75, PASI90 and PGA 0/1 responder rates at Week 16 – systemic non-biologic therapy inadequate responders (Pool E1)

Responder rate, (%)	Placebo (n=[redacted])	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
PASI75	[redacted]	[redacted]	[redacted]
PASI90	[redacted]	[redacted]	[redacted]
PGA 0/1	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks.
Based on a logistic regression model with factors for treatment, region and study, where missing data were imputed using NRI (patients missing PASI or PGA response are considered to be non-responders). The responder rates are the adjusted probabilities from the logistic regression model; the model factor levels were weighted based on frequencies in the analysis population.
Source: UCB Data on File (2018)[76].

An increase in PASI90 and PGA 0/1 response rates was observed from Week 16 to Week 48 in patients who were considered inadequate responders to systemic non-biologic therapy (Table 47), demonstrating that CZP further improves or maintains clinical response rates over time.

Table 47: PASI75, PASI90 and PGA 0/1 responder rates at Week 48 – systemic non-biologic therapy inadequate responders (Pool E3)

Responder rate, n (%)	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
PASI75	[redacted]	[redacted]
PASI90	[redacted]	[redacted]
PGA 0/1	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
Patients who meet escape criteria at Week 16 (i.e., do not achieve a PASI50) or who meet criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 are treated as non-responders at subsequent visits. For patients who achieved a PASI50 response at Week 16 but were mistakenly put into the CZP 400 mg Q2W escape arm, all visits after Week 16 are imputed with the value observed at Week 16 (i.e., Week 16 carried forward). All other missing data are imputed using NRI.
Source: UCB Data on File (2018)[76].

B.2.7 *Subgroup analyses*

Pre-planned analyses were conducted for the prespecified subgroups listed in Section B.2.3.1. The Pool E1 and E3 data for the subgroups of patients with and without prior biologic exposure (i.e., biologic-naïve and biologic-exposed patients) are presented below. Results for the other pre-specified subgroup analyses are presented in Appendix E.

Pre-planned subgroup analyses were also conducted in CIMPACT for the stratifications listed in Section B.2.3.1. These subgroup analyses were performed on the primary efficacy endpoint of PAS75 at Week 12. The results from these subgroup analyses should be interpreted with caution due to the small sample sizes for many of the categories. Results for these subgroup analyses are provided in Appendix E.

B.2.7.1 Subgroup analyses in biologic-naïve and biologic-exposed patients

Baseline characteristics

Generally, patients in the biologic-exposed group had slightly more severe psoriasis, with slightly higher baseline PASI and PGA scores compared to biologic-naïve patients. Those patients classified as biologic-exposed also had a higher incidence of concomitant PsA. However, overall the characteristics were similar with those in the ITT populations for CIMPASI-1, CIMPASI-2 and CIMPACT. The baseline patient demographics and clinical characteristics among biologic-naïve and biologic-exposed patients in Pool E1 are reported in Appendix M.

Clinical response

Clinically meaningful responses were observed with CZP in patients with or without a history of prior biologic exposure. CZP 200 mg Q2W and CZP 400 mg Q2W were significantly more effective than placebo in treating psoriasis regardless of whether patients had previously received biologic therapies, in terms of:

- Clinical response as assessed by PASI75, PASI90, PASI100 and PGA 0/1 responder rates (Table 48)
- Quality of life, i.e. change from baseline in DLQI, and DLQI remission rate (Table 51)

Both CZP doses showed similarly high response rates in patients who were biologic-naïve and those who were biologic-experienced and were similarly high to those seen in the overall ITT population.

Efficacy in biologic-naïve and biologic-exposed patients was maintained through Week 48. CZP 200 mg Q2W and CZP 400 mg Q2W were effective over the longer-term in treating psoriasis regardless of whether patients were biologic-naïve or biologic-experienced in terms of

- Maintenance of the clinical response as measured by PASI75, PASI90, PASI100 and PGA 0/1 responder rates (Table 49)
- Extracutaneous manifestations, i.e. mNAPSI change from baseline and nail psoriasis resolution at Week 48 (Table 50)
- Maintenance of improvements in quality of life, i.e. change from baseline in DLQI and DLQI remission rate (Table 52)

Table 48: PASI75, PASI90 and PGA 0/1 responder rate at Week 16 – biologic-naïve and biologic-exposed patients (Pool E1)

	Biologic-naive			Biologic-exposed		
Responder rate, %	**Placebo (n=[redacted])**	**CZP 200 mg Q2W (n=[redacted])**	**CZP 400 mg Q2W (n=[redacted])**	**Placebo (n=[redacted])**	**CZP 200 mg Q2W (n=[redacted])**	**CZP 400 mg Q2W (n=[redacted])**
PASI75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI90	[redacted]	[redacted]	[redacted]	0	45.3	47.7
PGA 0/1	[redacted]	[redacted]	[redacted]	0	53.8	57.9

Abbreviations: CZP: certolizumab pegol; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
Based on logistic regression model with factors for treatment, region and study, where missing data were imputed using NRI (patients missing PASI or PGA response are considered to be non-responders). Responder rates are the adjusted probabilities from the logistic regression model; the model factor levels were weighted based on frequencies in the analysis population.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).
Source: Blauvelt A *et al.* (2018)[82]; UCB Data on File (2017–2018)[72].

Table 49: PASI75, PASI90 and PGA 0/1 responder rate at Week 48 – biologic-naïve and biologic-exposed patients (Pool E3)

	Biologic-naïve		Biologic-exposed	
Responder rate, n (%)	**CZP 200 mg Q2W (n=[redacted])**	**CZP 400 mg Q2W (n=[redacted])**	**CZP 200 mg Q2W (n=[redacted])**	**CZP 400 mg Q2W (n=[redacted])**
PASI75	[redacted]	[redacted]	[redacted]	[redacted]
PASI90	[redacted]	[redacted]	[redacted]	[redacted]
PGA 0/1	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; NRI: non-responder imputation; PASI50: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
Patients who meet escape criteria at Week 16 (i.e., do not achieve a PASI50) or who meet criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 are treated as non-responders at subsequent visits. For patients who achieved a PASI50 response at Week 16 but were mistakenly put into the CZP 400 mg Q2W escape arm, all visits after Week 16 are imputed with the value observed at Week 16 (i.e., Week 16 carried forward). All other missing data are imputed using NRI methodology.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Source: UCB Cimzia Plaque Psoriasis Integrated Summary of Efficacy[75]

Reduction in disease severity

In patients who were naïve or previously exposed to biologics, substantial improvements in psoriasis percentage BSA were seen with both CZP doses at Week 16 and at Week 48. Percent change from baseline in psoriasis BSA data among biologic-naïve and biologic-exposed patients, at Week 16 and Week 48, are presented in Appendix M.

Extracutaneous manifestations

Table 50: Change from baseline in mNAPSI score and nail psoriasis resolution (mNAPSI=0) at Week 48 – biologic-naïve and biologic-exposed patients (Pool E3)

	Biologic-naïve		Biologic-exposed	
	CZP 200 mg Q2W	CZP 400 mg Q2W	CZP 200 mg Q2W	CZP 400 mg Q2W
mNAPSI change from baseline at Week 48				
n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Nail psoriasis resolution at Week 48				
n	[redacted]	[redacted]	[redacted]	[redacted]
Patients, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; LOCF: last observation carried forward; mNAPSI: Modified Nail Psoriasis Severity Index; N/A: not applicable; NR: not reported; Q2W: every two weeks; SD: standard deviation.
One patient (CZP 200 mg Q2W) had a different nail location assessed at baseline (left hand, third finger) compared to Week 48 (right hand thumb). For the purposes of this summary, the difference in location has been ignored. For patients escaping at week 16, week 16 score has been used to impute all subsequent visits scores. For non-escaping patients LOCF imputation has been used to impute missing scores.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Source: UCB Data on File (2017–2018)[72]; UCB Data on File (2018)[76].

Quality of life

Table 51: Change from baseline in DLQI score and DLQI remission rate (0/1) at Week 16 – biologic-naïve and biologic-exposed patients (Pool E1)

	Biologic-naïve			Biologic-exposed		
	Placebo (n=[redacted])	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])	Placebo (n=[redacted])	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to Week 16						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p value vs placebo[a]		[redacted]	[redacted]		[redacted]	[redacted]
Remission rate at Week 16[a]						

Remission rate, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p value vs placebo[b]		[redacted]	[redacted]		[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; NRI: non-responder imputation; SD: standard deviation.
Based on logistic regression model with factors for treatment, region and study, where missing data were imputed using NRI (patients missing DLQI response are considered to be non-responders). Responder rates are the adjusted probabilities from the logistic regression model; the model factor levels were weighted based on frequencies in the analysis population.
[a]p value for adjusted mean treatment differences. [b]p value for odds ratio versus placebo.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).
Source: UCB Data on File (2017–2018)[72].

Table 52: Change from baseline in DLQI score and DLQI remission rate (0/1) at Week 48 – biologic-naïve and biologic-exposed patients (Pool E3)

	Biologic-naïve		Biologic-exposed	
	CZP 200 mg Q2W (n=[redacted])	**CZP 400 mg Q2W (n=[redacted])**	**CZP 200 mg Q2W (n=[redacted])**	**CZP 400 mg Q2W (n=[redacted])**
Change from baseline at Week 48[a]				
n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
DLQI remission rate at Week 48[b]				
Responder rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; LOCF: last observation carried forward; NRI: non-responder imputation; PASI50: at least 50% reduction from Baseline in Psoriasis Area and Severity Index; Q2W: every two weeks; SD: standard deviation.
[a]For patients escaping at Week 16, Week 16 score has been used to impute all subsequent visits scores. For non-escaping patients LOCF imputation has been used to impute missing scores.
[b]Patients who meet escape criteria at Week 16 (i.e., do not achieve a PASI50) or who meet criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 are treated as non-responders at subsequent visits. For patients who achieved a PASI50 response at Week 16 but were mistakenly put into the CZP 400 mg Q2W escape arm, all visits after Week 16 are imputed with the value observed at Week 16 (i.e., Week 16 carried forward). All other missing data are imputed using NRI methodology.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Source: UCB Data on File (2017–2018)[72].

B.2.7.2 Subgroup analyses based on severity of psoriasis

Key efficacy results for patients based on severity of psoriasis (DLQI <10 or DLQI ≥10) is provided in Table 53. Generally, patients with less severe psoriasis (DLQI <10) had comparable responder rates across both the CZP 200 mg Q2W and CZP 400 mg Q2W doses. In patients with more severe psoriasis (DLQI ≥10), responder rates were higher in the CZP 400 mg Q2W arm.

Table 53: PASI75/90/PGA responder rate by baseline DLQI at Week 16 – ITT population Pool E1

	DLQI <10			DLQI ≥10		
	Placebo (n=[redacted])	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])	Placebo (n=[redacted])	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
PASI75[a]						
Responder rate, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI90[a]						
Responder rate, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA 0/1[b]						
Responder rate, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Based on logistic regression model with factors for treatment, region and study, using NRI (patients missing PASI response are considered to be non-responders). The responder rates are the adjusted probabilities from the logistic regression; the model factor levels were weighted based on frequencies in the analysis population. [b]Based on logistic regression model with factors for treatment, region and study, where missing data were imputed using NRI (patients missing PGA response are considered to be non-responders). [a]The responder rates are the adjusted probabilities from the logistic regression; model factor levels were weighted based on frequencies in the analysis population. [b]The responder rates are the adjusted probabilities from the logistic regression model and exclude NRI effects; the model factor levels were weighted based on frequencies in the analysis population.
Abbreviations: CI: confidence interval; CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; NRI: non-responder imputation; PASI: Psoriasis Area Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
Source: UCB Data on File (2018)[76].

B.2.8 *Meta-analysis*

Head-to-head evidence is not available comparing CZP to its comparators, apart from ETN. Therefore, an NMA was conducted to estimate the relative efficacy of CZP versus all relevant comparators.

B.2.9 *Indirect and mixed treatment comparisons*

As the trials for CZP are all placebo-controlled, it was necessary to conduct an NMA to compare the relative efficacy of CZP versus other relevant treatment options. Whilst conventional pairwise meta-analysis is typically used to compare one intervention to a reference therapy from direct evidence (i.e. head-to-head trials), an NMA can be used to synthesise evidence indirectly (i.e. it allows treatments that have no head-to-head evidence to be compared) by the creation of a network of linked treatment arms.

The base case NMA was conducted using a multinomial model approach (with a bio-naïve sub-group population in sensitivity analysis [see Appendix D]). A secondary sensitivity analysis has been undertaken using a binomial model. Fixed effects, random effects and risk-adjusted random effects model have been further applied to all approaches to help determine the best fitting model.

B.2.9.1 Search strategy for the network meta-analysis

An overview of the SLR methods undertaken for this submission is provided in Section D. In summary, systematic searches were carried out in MEDLINE-, Embase-, and CENTRAL-indexed databases for RCTs that were published to December 11th, 2017, and evaluated the efficacy and safety of selective biologic therapies and non-biologic therapies in patients with moderate to severe plaque PSO. These searches also encompassed annual proceedings for scientific meetings held through (2015 and 2016). Comprehensive database search algorithms are provided in Appendix D. To present and describe the key evidence relevant to the final scope, networks that were dependent on the outcomes of interest were constructed by selecting only RCTs that evaluated CZP and the comparators of interest for the treatment of patients with moderate to severe plaque PSO.

B.2.9.2 Study selection for the network meta-analysis

Criteria for study inclusion/exclusion to define the NMA evidence base are described in Table 54.

Table 54: Criteria for study inclusion/exclusion used in selection of the NMA evidence base

	Inclusion criteria	Exclusion criteria
Population	Adult (≥18 years) patients with moderate to severe plaque PSO, who are candidates for systemic psoriasis therapy	Studies of non- moderate to severe plaque PSO patients, who are not candidates for systemic psoriasis therapy
Intervention	Certolizumab pegol (Cimzia®): 200mg every two weeks (with a loading dose of 400mg at weeks 0, 2 and 4) 400mg every two weeks	Studies that do not include a treatment arm with any of the selected comparators of interest
Comparators	• Tumour necrosis factor (TNF) alpha inhibitors: Etanercept, Infliximab, Adalimumab • IL-12/23 inhibitors: Ustekinumab, • IL-23p19 inhibitor: Tildrakizumab, Guselkumab, • IL-17 inhibitor: secukinumab, Ixekizumab, Brodalumab • Non-biologics: Apremilast, Dimethyl fumarate, Cyclosporin, Acitretin,	
Outcomes	The proportion of patients who achieve a Psoriasis Area and Severity Index response PASI 50, PASI 75, PASI 90,	Studies are lacking relevant data on any of the outcomes of interest (PASI 50, 75, 90, 100.
Study Design	Randomised Controlled Trials	Studies that are not randomised, reviews, commentaries, pharmacokinetic or pharmacodynamic studies, correction documents, with fewer than 10 patients, studies with only one treatment arm of interest

B.2.9.3 Methods of analysis used for the network meta-analysis

The analysis was used to synthesise outcomes PASI response based on an indirect treatment comparison. The main analysis considered was a multinomial model, which allows the PASI response to be treated as a categorical variable, similarly to the approach adapted from the NICE Decision Support Unit (DSU) technical support documents.[83-85] As sensitivity analysis, binomial models were used. For both models, fixed effects, random effects and baseline risk-adjusted (placebo adjusted) random effects were considered. The population of interest for the analysis was the Intention-To-Treat (ITT), with a bio-naïve sub-group population in sensitivity analysis [see Appendix D]

The multinomial ordered probit model has the advantage that it simultaneously considers evidence from all available PASI response categories; the model generates the absolute probabilities of achieving a PASI outcome (PASI 50, 75 or 90). Additional sensitivity analyses conducted using a binomial model for the PASI response outcomes were developed to validate the results from the multinomial model and quality assurance purposes.

The baseline risk-adjusted (placebo adjusted) random effects model for the multinomial analysis was considered the best fit based on Deviance Information Criterion (DIC), the between-study standard deviation and previously published literature. The placebo adjusted model was chosen as the preferred (primary) method for this analysis. Among the unadjusted FE and RE models, the fixed effects model assumed negligible between-study heterogeneity while the random effects model allowed for some between-study heterogeneity. These analyses were used as estimates for the main analysis reported for PASI response in the trial.

The analysis was conducted on the initial phase of treatment, which varied amongst treatments with the majority of initial treatments being 16 weeks although the range across studies was 10 to 16 weeks.

The baseline-risk adjusted NMA was designed to use Bayesian Markov Chain Monet Carlo (MCMC) methods to summarise the posterior distribution of the estimates for each intervention versus placebo. A minimum of 100,000 samples was used to summarise the posterior distribution of estimates of effect with at least 20,000 sample burn in to ensure convergence and that estimates had appropriately stabilised.

All NMAs were conducted in Winbugs (Version 1.4.3). The methodology for the meta-analysis was as per the recommended methods published by the NICE Decision Support Unit.

Full details of the methodology of the NMA are provided in Appendix D.

B.2.9.4 Summary of trials included in the NMA

A total of 83 trials reported by 100 publications were identified in the SLR (see Appendix D), providing results for 35 different comparisons. The sample sizes of the included studies ranged from 20 to 1,881 (median 287). The largest trials were AMAGINE-2 and AMAGINE-3, both of which assessed the efficacy and safety of BROD compared to UST. Seventy-five trials were double-blind, and eight were open-label. Within the quality assessment, many of the trials were judged to have an unclear risk of bias as authors failed to appropriately report the method of generating the sequence of randomisation and the method of blinding (see Appendix D).

Of the 83 trials, ten were in biologic-naïve patients. The remaining trials reported that a proportion of subjects had previous exposure to a biological treatment. The percentage of patients previously exposed to a biologic was 29.7% (median).

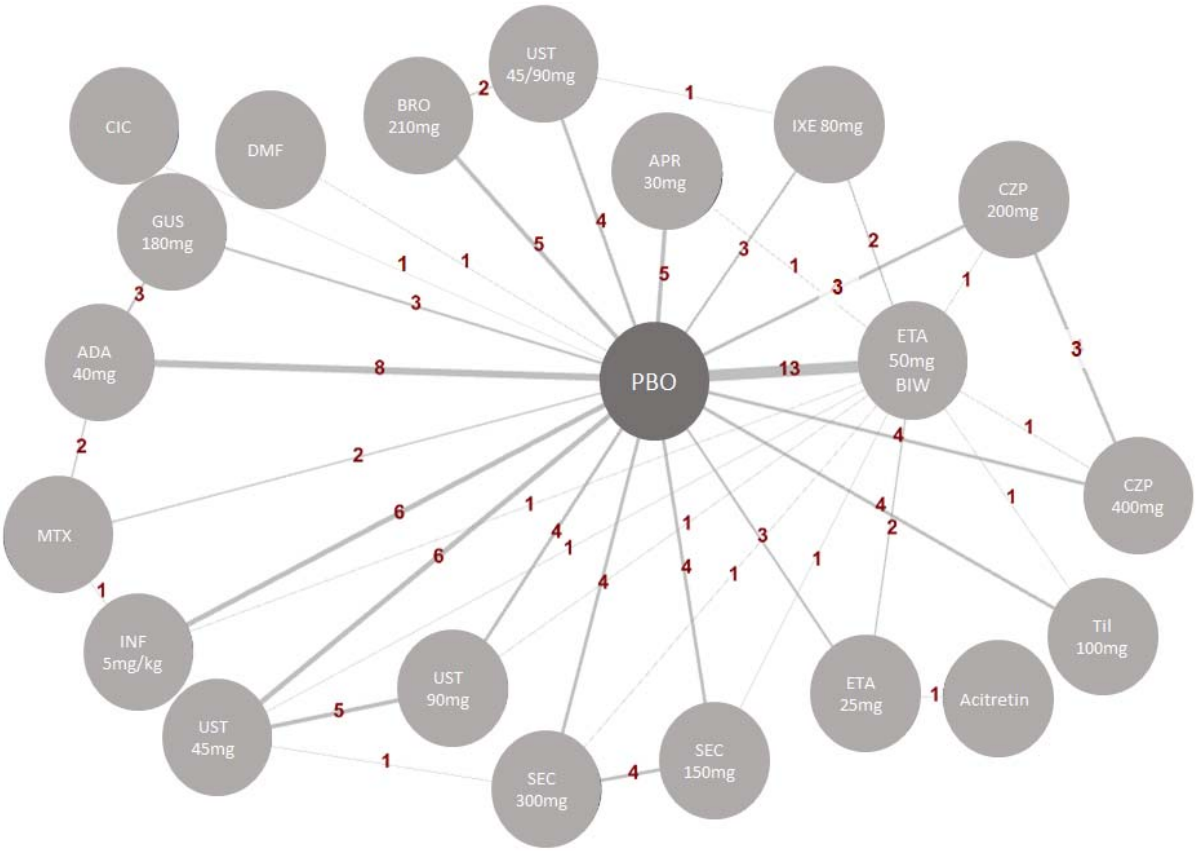
There is no formal consensus for a definition of mild, moderate or severe plaque psoriasis; however, the eligibility criteria in terms of severity of psoriasis was broadly consistent across the studies included in the SLR, with most trials defining moderate to severe psoriasis a PASI score ≥12 and involving at least 10% of BSA. Mean duration of PSO ranged from 11 to 26 years (median 18 years) for patients included in the trials identified. The mean baseline PASI score ranged from 10.4 to 33.1 (median 20). In the certolizumab pegol trials, moderate to severe PSO has been defined as a PASI score of at least 12, covering at least 10% of BSA and PGA score of more than three.

The SLR identified six studies evaluating MTX versus approved biologic therapies (infliximab and adalimumab) in patients with moderate to severe psoriasis patients. These studies have been included to provide proxy estimates of BSC (i.e. an estimate of effect for a commonly used systemic non-biologic therapy in a population eligible for treatment with biologic therapies). It was therefore anticipated that including MTX in the NMA would provide alternative estimates for BSC (i.e. not purely based on placebo data).

In total, 65 studies (62 studies identified in the SLR and three CZP trials) were included in the NMA. The base case analysis of PASI response outcomes included data from 65 RCTs involving 27,640 patients. The network diagram of included evidence in the base case analysis is presented in Figure 18. The 65 RCTs reported outcomes for 22 key therapies of interest including RIS 150 mg and placebo. The majority of trials compared to placebo (57/65). The remaining (8/65) studies compared therapies of interest to active comparators.

Full details of the methodology of the NMA are provided in Appendix D.

Figure 18: Network diagram for all studies identified in the SLR and included in the NMA, ITT population



B.2.9.5 Results of the NMA

[redacted]

[redacted]

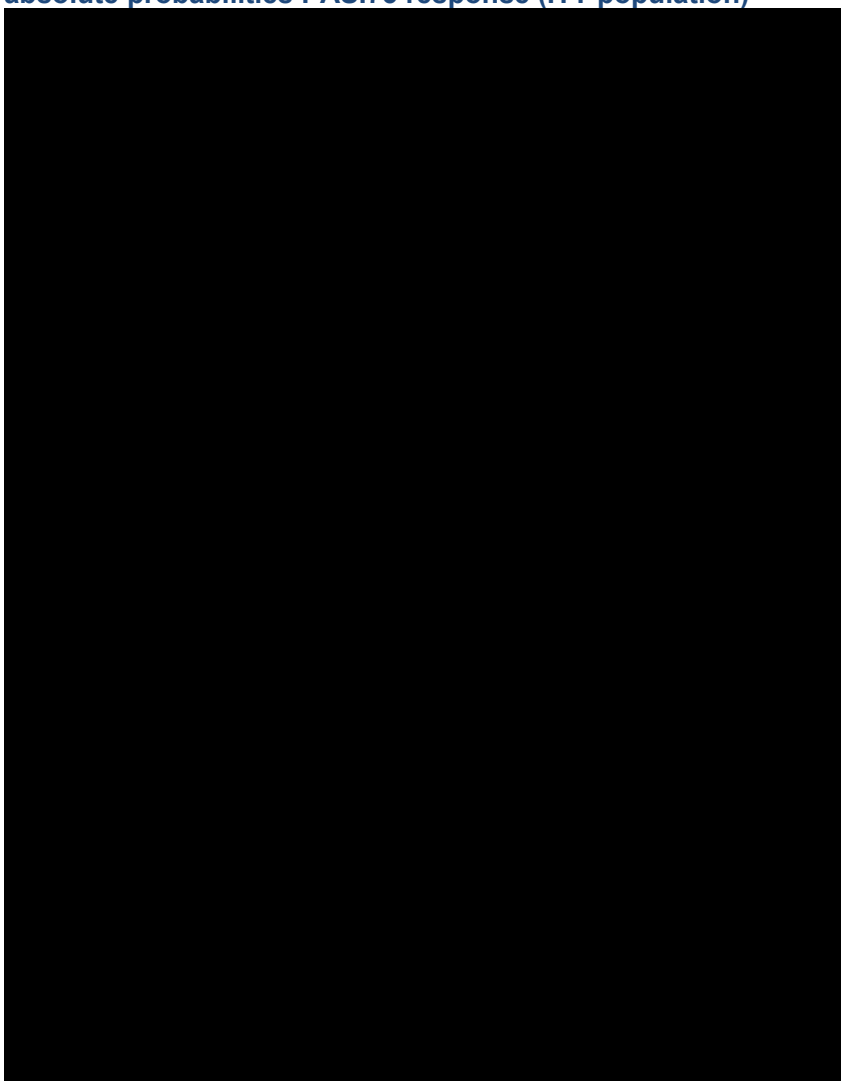
[redacted]

[redacted]

[redacted]

A forest plot of the NMA results is presented in Figure 19 (PASI75), Figure 20 (PASI90) and Figure 20 (PASI50).

Figure 19: Primary analysis (random effects placebo-adjusted multinomial model): absolute probabilities PASI75 response (ITT population)



Abbreviations: CZP: certolizumab pegol; ITT: intention-to-treat.

Figure 20: Primary analysis (random effects placebo-adjusted 21: Forest plot for multinomial model): absolute probabilities PASI90 response (ITT population)

Abbreviations: CZP: certolizumab pegol; ITT: intention-to-treat.

Figure 22: Primary analysis (random effects placebo-adjusted multinomial model): absolute probabilities PASI50 response (ITT population)

Abbreviations: CZP: certolizumab pegol; ITT: intention-to-treat.

B.2.9.6 Uncertainties in the indirect and mixed treatment comparisons

Whilst the conducting of an NMA allows for the indirect comparison of CZP versus the relevant comparators to this submission, limitations exist with the NMA approach and these are discussed here.

Specifically, the multinomial approach can present some challenges: it may need weakly informative priors to attain convergence for random effects (RE) models; its shared effect across outcomes may not hold; and there is potential for outcome reporting bias whereby some studies may have pooled PASI cut-offs (i.e. PASI 50-100) rather than reporting PASI cut-offs separately (i.e. PASI 50, PASI 75 etc.)

The multinomial model also assumes not only proportional odds (i.e. same relative treatment effect for each therapy), but also that the proportional odds assumption holds across all categories of PASI response (i.e. the same relative treatment effect is assumed for each PASI category). Cross-validation of the results from the binomial models with those predicted from the multinomial model indicated some evidence of proportional odds violation (across PASI

categories). The treatment effects of each therapy of interest do not appear to be consistent for PASI 50, PASI 75 and PASI 90. This is evidenced in the binomial model results, notably, the odds ratio estimates (and rankings) were not consistent across PASI 50, PASI 75 and PASI 90 endpoints. Nevertheless, there is strong precedence of using the multinomial approach given the nature of the outcomes addressed, an approach which was considered by the NICE DSU and in other independent published NMAs.

Finally, in the base case analysis, only treatments were fitted as variables and therefore an implicit assumption was made that any change in the outcome being measured was because of treatment only. Further details of the methodology of the NMA are presented in Appendix D.

B.2.9.7 Conclusions

In summary, the results of the NMA indicate that treatment of psoriasis with biologics is superior to placebo or standard of care. The results of the primary analysis showed that both CZP doses have similar efficacy in terms of PASI response rate (overlapping 95% CrIs) vs most of the biologics considered; [redacted]

B.2.10 *Adverse reactions*

Summary of adverse reactions

- The safety profile of CZP in patients with moderate-to-severe plaque psoriasis over a period of up to 144 weeks was comparable with that reported over shorter time periods and in other indications. Both dose regimens have an acceptable safety profile with a risk that does not increase with longer exposure.
- CZP safety profile for up to 12 weeks, including type and incidence of TEAEs, was comparable with ETN (CIMPACT trial), with fewer discontinuations due to AEs vs ETN.
- The incidences of TEAEs and SAEs were similar between the CZP 400 mg Q2W and placebo groups and were lower in the CZP 200 mg Q2W group during a 16-week initial treatment period. Four patients each in the CZP 400 mg Q2W and CZP 200 mg Q2W groups withdrew due to a TEAE; no patient in the placebo group withdrew due to a TEAE.
- Up to 144 weeks, the incidence of any TEAE was slightly higher in the CZP 400 mg Q2W group, however the incidences of SAEs, discontinuations due to TEAEs, drug related TEAEs and deaths were similar between the CZP 200 mg Q2W group and the CZP 400 mg Q2W.
- No new previously unreported safety signals compared with the use of CZP in other indications occurred over the 144-week trial period.

B.2.10.1 Overview

Data from the pooled analyses suggest that the safety profiles for CZP 200 mg Q2W and CZP 400 mg Q2W are comparable. The two dose regimens have an acceptable safety profile, and the risks of CZP treatment do not increase with longer exposure. Furthermore, no new safety signals were identified compared with previous studies of CZP in other indications [73, 86] and the safety profile remains consistent with other anti-TNFs.

Safety analyses were conducted using the safety analysis set, which consisted of all patients in the randomised set who had received at least one dose of study medication. AEs were recorded for the treatment received by patients, rather than the treatment to which they had been randomised (where different).

Initial treatment period

The incidences of TEAEs in Pool S1 (initial treatment period) were generally similar between the CZP 400 mg Q2W and placebo groups (63.5% and 61.8%, respectively) and were lower in the CZP 200 mg Q2W group (56.3%; Table 55). The data also revealed that the most frequently reported TEAEs (occurring in >5% of patients in any treatment group) were nasopharyngitis ([redacted] of patients in the 'all CZP' group) and upper respiratory tract infections ([redacted]; Table 56). This was consistent with the 'all CZP group' in both CIMPASI-1 and CIMPASI-2; in CIMPASI-1, headache was also included in this category.

Table 55: All causality treatment-emergent adverse events in the initial treatment phase (Pool S1)

Adverse event, No. of patients (%)	Placebo (n=157)	CZP 200 mg (n=350)	CZP 400 mg (n=342)	All CZP (n=692)
Number of patients:				
With TEAEs	97 (61.8)	197 (56.3)	217 (63.5)	[redacted]
With serious TEAEs	7 (4.5)	5 (1.4)	16 (4.7)	[redacted]
Drug-related TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
With severe TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
With AEs associated with:				
Permanent discontinuation	0	4 (1.1)	4 (1.2)	[redacted]

Abbreviations: AE: adverse event; CZP: certolizumab pegol; TEAE: treatment-emergent adverse event.
Source: Blauvelt *et al.* (2018)[70]; UCB Certolizumab pegol 2.7.4 Summary of Clinical Safety 2017[73]

Table 56: TEAEs occurring in >5% patients in any group in the initial treatment phase (Pool S1)

Adverse event, No. of patients (%)	Placebo (n=157)	CZP 200 mg (n=350)	CZP 400 mg (n=342)	All CZP (n=692)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Congenital, familial, and genetic disorders	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]

Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infections	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning, and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus NEC	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; NEC: not elsewhere classified; TEAE: treatment-emergent adverse event.
Source: UCB Certolizumab pegol 2.7.4 Summary of Clinical Safety 2017[73]

According to the Pool S1 data, the incidence of serious TEAEs was similar between the placebo group (4.5%) and CZP 400 mg Q2W group (4.7%) in the initial treatment period, but slightly lower in the CZP 200 mg Q2W group (1.4%; Table 57).

Table 57: Serious TEAEs in at least 2 subjects in any group in the initial treatment phase (Pool S1)

Adverse event, No. of patients (%)	Placebo (n=157)	CZP 200 mg (n=350)	CZP 400 mg (n=342)	All CZP (n=692)
Any serious TEAE	7 (4.5)	5 (1.4)	16 (4.7)	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	0	0	2 (0.6)	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]

Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; TEAE: treatment-emergent adverse event.
Source: Blauvelt *et al.* (2018)[70]; UCB Certolizumab pegol 2.7.4 Summary of Clinical Safety 2017[73]

When the data from the initial treatment period was pooled, the incidence of any TEAE leading to permanent study drug discontinuation was low and comparable between the CZP 400 mg Q2W and CZP 200 mg Q2W groups ([redacted] and [redacted], respectively; Table 58).

Table 58: AEs leading to permanent treatment discontinuation in the initial treatment phase (Pool S1)

Adverse event, No. of patients (%)	Placebo (n=157)	CZP 200 mg (n=350)	CZP 400 mg (n=342)	All CZP (n=692)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaphylactic responses	[redacted]	[redacted]	[redacted]	[redacted]
Anaphylactoid reaction	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Liver function analyses	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue pain and discomfort	[redacted]	[redacted]	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]

Neurological signs and symptoms NEC	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Depressive disorders	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dermal and epidermal conditions NEC	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis and eczema	[redacted]	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus NEC	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus generalised	[redacted]	[redacted]	[redacted]	[redacted]
Rashes, ruptions and exanthems NEC	[redacted]	[redacted]	[redacted]	[redacted]
Rash papular	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; TEAE: treatment-emergent adverse event.
Source: UCB Cimzia Plaque Psoriasis Integrated Summary of Safety[87]

Initial, maintenance and open-label extension treatment periods

Overall, the safety profile of CZP in moderate-to-severe plaque psoriasis up to 144 weeks was consistent with that previously reported for the CIMPASI and CIMPACT trials, with no new safety signals identified with increased exposure.

[redacted]
59
[redacted]

[redacted]
59

Table 59: Duration of exposure and patient exposure at risk during the initial, maintenance and OLE treatment period (Pool S3)

Variable	Statistic	CZP 200 mg Q2W	CZP 400 mg Q2W	All CZP
Duration of exposure (months)	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
>0 months	n (%)	[redacted]	[redacted]	[redacted]
≥3 months	n (%)	[redacted]	[redacted]	[redacted]
≥6 months	n (%)	[redacted]	[redacted]	[redacted]
≥12 months	n (%)	[redacted]	[redacted]	[redacted]
≥18 months	n (%)	[redacted]	[redacted]	[redacted]
≥24 months	n (%)	[redacted]	[redacted]	[redacted]
Duration of exposure (weeks)[a]				
>0 to 16	n (%)	[redacted]	[redacted]	[redacted]
>16 to 32	n (%)	[redacted]	[redacted]	[redacted]
>32 to 48	n (%)	[redacted]	[redacted]	[redacted]
>48	n (%)	[redacted]	[redacted]	[redacted]

>48 to 64	n (%)	[redacted]	[redacted]	[redacted]
>64 to 80	n (%)	[redacted]	[redacted]	[redacted]
>80[a]	n (%)	[redacted]	[redacted]	[redacted]
Number of doses received	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
Patient exposure days at risk	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
Patient exposure years at risk		[redacted]	[redacted]	[redacted]

Patients who received both CZP 200 mg Q2W and CZP 400 mg Q2W are included in the population count for both treatment groups.
Data collected during treatment with the CZP 400 mg Q4W dose in CIMPACT have been summarised under the Phase III CZP 200 mg Q2W treatment group as they are the same cumulative monthly dose.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool S3).
[a]The following duration of exposure categories were summarised >0 to 16 weeks, >16 to 32 weeks, >32 to 48 weeks, >48 weeks, >48 to 64 weeks, and >64 weeks.
Abbreviations: CZP: certolizumab pegol; max: maximum; min: minimum; OLE: open-label extension; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation.
Source: UCB, Data on File. Certolizumab pegol summary of clinical safety. D120 safety update. 2017[88].

An overall summary of TEAEs in patients during the initial, maintenance and OLE treatment period for Pool S3 are summarised in Table 60. The exposure-adjusted TEAE incidence rates do not indicate an increase in risks with longer or higher exposure to CZP. The safety profile was consistent with that expected in patients with moderate-to-severe plaque psoriasis receiving anti-TNF therapy (e.g. hypersensitivity and infections).

[redacted]

Table 60: Overall summary of TEAEs in the initial, maintenance and OLE treatment periods (Pool S3)

Incidence, n (%)	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])	All CZP (n=[redacted])
Exposure, 100 patient-years	[redacted]	[redacted]	[redacted]
Any TEAE	[redacted]	[redacted]	[redacted]
Serious TEAEs	[redacted]	[redacted]	[redacted]
Discontinuation due to TEAEs	[redacted]	[redacted]	[redacted]
Drug-related TEAEs	[redacted]	[redacted]	[redacted]
Severe TEAEs	[redacted]	[redacted]	[redacted]
All deaths (AEs leading to death)	[redacted]	[redacted]	[redacted]
Deaths (TEAEs leading to death)	[redacted]	[redacted]	[redacted]

n, number of patients who reported at least one TEAE in the category. Patients who received both CZP 200 mg Q2W and CZP 400 mg Q2W are included in the population count for both treatment groups. Data collected during treatment with the CZP 400 mg Q4W dose in CIMPACT has been summarised under the Phase III CZP 200 mg Q2W treatment group as they are the same cumulative monthly dose.
Abbreviations: AE: adverse event; CZP: certolizumab pegol; OLE: open-label extension; Q2W: every two weeks; TEAE: treatment-emergent adverse event.
Source: UCB, Data on File. Certolizumab pegol summary of clinical safety. D120 safety update. 2017[88].

Deaths

[redacted] deaths occurred during the initial treatment period. [redacted] treatment-emergent deaths were reported ([redacted] patients receiving CZP 400 mg Q2W and [redacted] patient receiving CZP 200 mg Q2W). [redacted] fatal events were considered not to be related to study medication. [redacted] additional treatment-emergent death was reported in the OLE treatment period (fatal TEAEs of disseminated intravascular coagulation, hemorrhagic necrotic pancreatitis, hepatic failure, distributive shock, and cardiac arrest). In addition, [redacted] non-treatment-emergent death was reported (blood count abnormal).

Serious adverse events

Serious AEs occurring in patients during the initial, maintenance and OLE treatment period for Pool S3 are summarised in Table 61 by system organ class (SOC) and preferred (PT) for events occurring in at least two patients in any treatment group. Overall, the pattern and incidence of SAEs were in line with those expected for this patient population treated with anti-TNF therapies. The SAE profile did not change with longer or higher exposure to CZP.

During the initial treatment period (up to Week 16), [redacted] SAEs were reported by [redacted] patients in the All CZP group; 7 patients (4.5%) patients in the placebo group reported [redacted] SAEs. The incidence of SAEs was similar in the CZP 400 mg Q2W and placebo groups; the incidence was slightly lower in the CZP 200 mg Q2W group. Up to Week 144 the incidence of SAEs continued to be low in both dose groups. An additional [redacted] patients ([redacted] patients in the Phase III CZP 400 mg Q2W group and [redacted] patients in the Phase III CZP 200 mg Q2W group, with [redacted] patient reporting at least one SAE in both dose groups) reported SAEs in the maintenance and OLE treatment periods. [redacted]

additional SAEs were reported in the maintenance and OLE treatment periods ([redacted] events in the Phase III CZP 400 mg Q2W group and [redacted] events in the Phase III CZP 200 mg Q2W group).

The difference in the percentage of patients reporting at least one SAE between the Phase III CZP 400 mg Q2W and Phase CZP 200 mg Q2W groups were similar up to Week 144 and during the placebo-controlled period. No individual SOC showed a difference (>5%) in incidence across the two dose groups, and no trend was identified.

Table 61: Summary of SAEs in all SOCs, including PTs with an incidence of at least two patients in any group, during the OLE treatment period (Pool S3)

System organ class Preferred term	CZP 200 mg Q2W (n=[redacted]) 100 patient-years=[redacted]		CZP 400 mg Q2W (n=[redacted]) 100 patient-years=[redacted]		All CZP (n=[redacted]) 100 patient-years=[redacted]	
	n (%)	IR	n (%)	IR	n (%)	IR
Any serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inguinal hernia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug-induced liver injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erysipelas	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concussion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radius fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wrist fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rib fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriatic arthropathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prostate cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Migraine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy, puerperium and perinatal conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ovarian cyst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; IR: incidence rate; PT: preferred term; Q2W: every two weeks; SAE: serious adverse event; SOC: system organ class; TEAE: treatment-emergent adverse event.
n: number of patients who reported at least one serious TEAE in the category.
IR: incidence of new cases per 100 patient years.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool S3).
Source: UCB, Data on File. Certolizumab pegol summary of clinical safety. D120 safety update. 2017[88].

Common treatment-emergent adverse events

TEAEs in all SOCs, including high level terms (HLTs) and PTs with an incidence ≥5% in any group for the initial, maintenance and OLE treatment periods are presented in

Table 62. The safety profile of CZP in patients with moderate-to-severe plaque psoriasis up to Week 144 is consistent with the initial treatment period. No new safety signals were identified with longer exposure to CZP at either dose; therefore, the benefit-risk balance for CZP at either dose remains favorable. The safety profile was consistent with that expected in patients with moderate-to-severe plaque psoriasis receiving anti-TNF therapy (e.g. hypersensitivity and infections).

The most frequently reported TEAEs (≥5%) in the two active CZP groups were in the SOC of Infections and infestations ([redacted]% for CZP 200 mg Q2W, [redacted]% for CZP 400 mg Q2W) and Musculoskeletal and connective tissue disorders ([redacted]% for CZP 200 mg Q2W, [redacted]% for CZP 400 mg Q2W). The incidences of TEAEs by SOC were similar between the CZP 400 mg Q2W and CZP 200 mg Q2W groups, with the exception of General disorders and

administration site conditions ([redacted]% versus [redacted]%); Investigations ([redacted]% versus [redacted]%); Nervous system disorders ([redacted]% versus [redacted]%); Respiratory, thoracic and mediastinal disorders ([redacted]% versus [redacted]%) and Skin and subcutaneous tissue disorders ([redacted]% versus [redacted]%).

Similar to the initial treatment period, the most frequently reported (>5%) TEAEs by PT in the CZP 400 mg Q2W and CZP 200 mg Q2W groups up to Week 144 were upper respiratory tract infection ([redacted]% and [redacted]%, respectively) and nasopharyngitis ([redacted]% and [redacted]%, respectively).

Table 62: Summary of all TEAES in all SOCs, including HLT and PTs with an incidence ≥5% in any group to Week 144 (Pool S3)

System organ class High level term Preferred term	CZP 200 mg Q2W (n=[redacted]) 100 patient-years=[redacted]		CZP 400 mg Q2W (n=[redacted]) 100 patient-years=[redacted]		All CZP (n=[redacted]) 100 patient-years=[redacted]	
	n (%)	IR	n (%)	IR	n (%)	IR
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infection and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower respiratory tract and lung infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Viral infections NEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver function analyses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue pain and discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache NEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Joint related signs and symptoms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis and eczema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriatic conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular hypertensive disorders NEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; HLT: high level term; IR: incidence rate; NEC: not elsewhere classified: PT: preferred term; Q2W: every two weeks; SOC: system organ class; TEAE: treatment emergent adverse event.
n: number of patients who reported at least one TEAE in the SOC/HLT/PT.
IR: incidence of new cases per 100 patient years.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool S3).
Source: UCB, Data on File. Certolizumab pegol summary of clinical safety. D120 safety update. 2017[88].

The safety profile of CZP is comparable to ETN

During the 16-week initial treatment period for the safety set, the mean duration of exposure was similar for the CZP 400 mg Q2W, 200 mg Q2W and PBO treatment groups (means: [redacted], [redacted], [redacted] days, respectively); mean duration of exposure for the ETN group was [redacted] days. The median number of days a trial medication dose was received was [redacted] days in the CZP and PBO treatment groups, as expected per the Q2W injection schedule, and [redacted] days in the ETN group, as expected for the biweekly schedule. The total patient exposure years at risk was [redacted] in the CZP 200 mg Q2W group, [redacted] in the CZP 400 mg Q2W group, [redacted] in the ETN group, and [redacted] in the placebo group.

The incidences of SAEs and discontinuations due to TEAEs were similar between all ETN, CZP 200 mg Q2W and CZP 400 mg Q2W treatment groups (<2% difference). The incidences of TEAEs were similar between the two CZP doses and between ETN and CZP 400 mg Q2W, however the incidence for ETN was slightly lower than CZP 200 mg Q2W (Table 63). The incidence of related TEAEs were similar between the ETN and CZP 400 mg Q2W treatment groups, related TEAEs were slightly higher in the ETN treatment group versus CZP 200 mg Q2W group and also slightly higher in the CZP 400 mg Q2W compared with the CZP 200 mg Q2W treatment group (Table 63). The incidence of severe TEAEs was similar between the two CZP doses and between the ETN and CZP 400 mg Q2W treatment groups, however the incidence of severe TEAEs was higher in the ETN group compared with the CZP 200 mg Q2W treatment group.

Table 63: All causality treatment-emergent adverse events with CZP versus ETN in the initial treatment period (CIMPACT)

Adverse event, No. of patients (%)	Placebo (n=57)	ETN (n=168)	CZP 200 mg (n=165)	CZP 400 mg (n=167)	All CZP (n=332)
Number of patient[redacted]					
With TEAEs	32 (56.1)	78 (46.4)	78 (47.3)	82 (49.1)	[redacted]
With serious TEAEs	5 (8.8)	1 (0.6)	1 (0.6)	4 (2.4)	[redacted]
Drug-related TEAESs	7 (12.3)	20 (11.9)	16 (9.7)	22 (13.2)	[redacted]
With severe TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
Permanent discontinuation	0	4 (2.4)	1 (0.6)	1 (0.6)	[redacted]

Abbreviations: AE: adverse event; CZP: certolizumab pegol; ETN: etanercept; TEAE: treatment-emergent adverse-events
Source: Lebwohl M *et al.* (2018)[64]; UCB CIMPACT Clinical Study Report[63]

B.2.10.2 Safety conclusions

The safety profile of CZP in patients with moderate-to-severe plaque psoriasis over a period of up to 144 weeks was comparable with that reported over shorter time periods and in other indications. Both dose regimens have an acceptable safety profile with a risk that does not increase with longer exposure.

The safety profile of CZP treatment for up to 12 weeks, including the type and incidence of TEAEs, was comparable with treatment with ETN.

The incidences of TEAEs and SAEs were similar between the CZP 400 mg Q2W and placebo groups and were lower in the CZP 200 mg Q2W group during a 16-week initial treatment period. Four patients each in the CZP 400 mg Q2W and CZP 200 mg Q2W groups withdrew due to a TEAE; no patient in the placebo group withdrew due to a TEAE.

Up to 144 weeks, the incidence of any TEAE was slightly higher in the CZP 400 mg Q2W group, however the incidences of SAEs, discontinuations due to TEAEs, drug-related TEAEs and deaths were similar between the CZP 200 mg Q2W group and the CZP 400 mg Q2W.

No new previously unreported safety signals compared with the use of CZP in other indications occurred over the 144-week trial period.

B.2.11 *Ongoing studies*

The CIMPASI-1, CIMPASI-2 and CIMPACT studies are all currently ongoing. In addition, the following study of CZP for the treatment of moderate to severe chronic plaque psoriasis is also ongoing. This multi-centre, double-blind, parallel-group RCT in 149 Japanese patients includes CZP 200 mg Q2W and CZP 400 mg Q2W treatment arms. The primary endpoint is the proportion of patients achieving a PASI75 response at Week 16, and the estimated study completion date is January 2019.[89]

B.2.12 *Innovation*

CZP is the only fragment-crystallizable-(Fc)-free, PEGylated, anti-TNF. It has a high affinity to both membrane-associated and soluble TNF and, therefore, selectively neutralizes TNF and the downstream pro-inflammatory cytokines and disease processes involved in many chronic inflammatory diseases.[5]

CZP has a unique and innovative structure. The structure of CZP consists of a recombinant, humanized antibody fragment antigen-binding (Fab') against TNFα, conjugated to polyethylene glycol (PEG). PEGylation extends the half-life of CZP to approximately 14 days, increases bioavailability and enables prolonged circulation time in the blood.[90]

Active transport of IgG across the placenta is mediated by the neonatal Fc receptor (FcRn).[8] Unlike all other biologics, CZP does not contain an Fc region, which is normally present in a complete antibody. As CZP lacks an Fc region, it does not bind FcRn, and is consequently not expected to undergo FcRn mediated transfer across the placenta.[9, 10]

Breast milk transfer of biologic molecules is driven by the size of the molecule and how lipophilic it is.[91] Although biologics generally have very low oral bioavailability due to their large molecular size and the proteolytic environment in the digestive system,[92] FcRn on human intestinal epithelial cells may promote uptake of undigested immunoglobulins. Physiologically, only minimal amounts of CZP are likely to cross into breast milk and be absorbed by the infant, due to its large molecule size and the replacement of the Fc portion with PEG.[91]

The UCB-sponsored CRIB trial is the only placental transfer study to date, and CRADLE was the first breast milk transfer study, conducted for biologics in chronic inflammatory diseases. They

are multicentre, prospective, pharmacokinetic studies that used a very specific and sensitive assay to assess transfer of CZP at the 200 mg Q2W and 400 mg Q4W maintenance dose in women suffering from chronic inflammatory diseases (including RA, axSpA, PsA and CD).[9, 91] Data from the CRIB trial indicate that there was no to minimal placental transfer of CZP from mothers to infants, suggesting a lack of in utero fetal exposure during the third trimester. The clinical significance of low levels of CZP for infants is unknown. The results of the CRADLE trial suggest that the level of CZP ingested by the suckling infant is minimal, indicating that continuation of CZP treatment is compatible with breastfeeding.[91]

No new safety signals for CZP were identified in mothers or infants in the CRIB[9] or CRADLE[91] trials. In addition, the latest review of the CZP pregnancy outcomes pharmacovigilance data (March 2017) of more than 500 prospectively collected pregnancies exposed to CIMZIA® with known pregnancy outcomes, including more than 400 pregnancies exposed during the first trimester, does not indicate a malformative effect of CZP.[93] However, the available clinical experience is too limited to, with a reasonable certainty, conclude that there is no increased risk associated with CZP administration during pregnancy.[5]

Results from the UCB CZP pregnancy outcomes, CRIB and CRADLE studies have also been incorporated into the US prescribing information. The unique molecular structure of CZP, which translates into unique benefits supported by robust clinical data, are reflected in a label that allows potential use of CZP in pregnancy and breastfeeding in patients with chronic inflammatory diseases as per the licensed indications. Together, these factors have led to a recent change to the European Union (EU) label for CZP in which the key recommendations related to fertility, pregnancy and breastfeeding state that:[5]

- "The use of adequate contraception should be considered for women of childbearing potential. For women planning pregnancy, continued contraception may be considered for 5 months after the last CIMZIA® dose due to its elimination rate, but the need for treatment of the woman should also be taken into account."
- "CIMZIA® should only be used during pregnancy if clinically needed."
- "CIMZIA® can be used during breastfeeding."
- "It is recommended to wait a minimum of 5 months following the mother's last CIMZIA® administration during pregnancy before administration of live or live-attenuated vaccines (e.g. BCG vaccine), unless the benefit of the vaccination clearly outweighs the theoretical risk of administration of live or live-attenuated vaccines to the infants."

CIMZIA® is the only biologic and synthetic targeted therapy with clinical trial data in its label that supports potential use in both pregnancy and breastfeeding in chronic inflammatory diseases (axSpA, PsA, RA and psoriasis) as indicated in the CIMZIA SmPC.[5] It should be noted that the CIMZIA® 400 mg Q2W maintenance dose was not studied in CRIB and CRADLE.[9, 91]

Ease of use through range of devices for administration

According to a study of 36 psoriasis patients, the burden of hospital-based administration (in terms of frequent hospital visits) could result in lower treatment persistence compared to self-administered SC injections.[94] CZP can be self-administered at home by patients with psoriasis, providing greater patient autonomy. The two options available for patient self-administration of CZP are the pre-filled pen and pre-filled syringe:

- Pre-filled pen (PFP): the CIMZIA® AutoClicks® PFP was developed in collaboration with OXO, and also designed with patient input.[95]
    - In a comparative usability analysis involving 76 RA patients without prior experience of an auto-injector device, 59% of patients ranked the CZP device as their most preferred device, compared to the ADA, ETA and golimumab auto-injectors.[96]
- Pre-filled syringe (PFS): an award-winning, ergonomically-designed PFS that was also designed in collaboration with OXO Good Grips® to ensure that it is easy to use.[97] The PFS offers key features in its mechanism of action and design to simplify the injection process for patients, including:[5]
    - A wide, latex-free, non-slip grip
    - A button-free injection, enabling the patient to use their whole arm to depress the device and actuate the injection, rather than relying on using digits

Treatment option for a spectrum of immunological diseases

CZP has previously been recommended by NICE in PsA, axial spondyloarthritis (axSpA) and RA.[98-102] CZP may therefore be a suitable treatment option for psoriasis patients with other comorbid immunological diseases; this is particularly important in the case of PsA, which has been reported to affect approximately 30% of patients.[27] Indeed, treatment guidelines from NICE,[40] EADV,[41] and BAD[42] recommend consideration of patient comorbidities when choosing and initiating psoriasis treatment. Furthermore, since TNFα can induce endothelial cell dysfunction, insulin resistance and atherosclerosis, it has been suggested that anti-TNF agents for the treatment of psoriasis may also have a beneficial effect on patient comorbidities.[103]

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Principle findings from the clinical evidence base

Efficacy and safety of CZP in plaque psoriasis

The clinical efficacy and safety of CZP has been demonstrated in three pivotal phase III studies, CIMPASI-1, CIMPASI-2 and CIMPACT, which successfully met their (co-) primary objectives, as supported by the hierarchical procedure testing.

These trials are large, international, multicentre, controlled pivotal Phase III studies, with an overall duration of 152 weeks. In total, CIMPASI-1, CIMPASI-2 and CIMPACT included a large cohort of 1,020 patients with moderate to severe psoriasis. CIMPASI-1 and CIMPASI-2 were placebo-controlled studies, with the addition of an active control in CIMPACT. The three trials included a broad population of PSO patients, who were candidates for systemic non-biologic drugs, patients who were biologic naïve or biologic exposed.

Short term clinical response

Across all three studies, CZP demonstrated a significant improvement in PASI75 responder rates compared to placebo at Week 16 ($p<0.0001$), meeting the (co-)primary endpoint for these studies. This suggests that CZP provides rapid clinically meaningful improvements in severity of psoriasis.

Across all three trials, there was a statistically significant and clinically meaningful difference in being classified as a PGA responder for patients treated with either CZP 200 mg Q2W or CZP 400 mg Q2W versus placebo at Week 16, meeting the co-primary endpoint for CIMPASI-1 and CIMPASI-2.

CZP-treated patients also showed significantly higher PASI90 and PASI100 response rates and improvements in Body Surface Area (BSA) vs PBO.

Improvements with CZP were similar irrespective of prior treatment exposure, with similarly high improvements in patients who were candidates for systemic non-biologic treatments, patients who were biologic-naïve, or biologic-exposed.

Long-term maintenance and durability of response with CZP

CZP demonstrated long-term maintenance and durability of response through to Week 48 of the maintenance period for signs and symptoms of psoriasis and patient relevant outcomes, based on data from the individual trials and also pooled analysis.

Rapid and consistent increases in clinical response to Week 16, as measured by PASI75 response rates and PGA, were maintained through to Week 48 of the maintenance treatment period in patients receiving CZP 400 mg Q2W and CZP 200 mg Q2W. Similarly, rapid and consistent responses in PASI90 and PASI100 were also maintained through to Week 48 of the maintenance treatment period in CZP 400 mg Q2W and CZP 200 mg Q2W arms, with numerically higher responses seen in the CZP 400 mg Q2W arm.

A high durability of clinical response through to Week 48 was seen in patients who were Week 16 responders to CZP: in the pooled analysis from the CIMPASI-1 and CIMPASI2 trials, CZP-treated patients who were PASI75 or PGA responders at Week 16 consistently maintained the improvements in efficacy to Week 48 (i.e., 32 weeks of the maintenance treatment period).

- CZP-treated patients from the pooled CIMPASI trials who were PASI75, or PGA responders at Week 16 consistently maintained the improvements in efficacy to Week 48.
- Of the CZP 400mg Q2W treated patients who achieved a PASI75 response at Week 16 and continued with their original CZP dose, [redacted]% maintained their level of PASI75 response at Week 48, and [redacted]% and [redacted]% of these patients achieved PASI90 and PASI100 response, respectively, at Week 48.
- Out of the CZP 200mg Q2W treated patients who achieved a PASI75 response at Week 16 and continued with their original CZP dose, [redacted]% maintained their level of PASI75 response at Week 48. [redacted]% and [redacted]% of these patients achieved PASI90 and PASI100 response, respectively, at Week 48.

Short term improvements with CZP were maintained to week 48 regardless of prior treatment, with similarly high improvements in patients who were candidates for systemic non-biologic drugs, were biologic-naïve, or were previously exposed to biologics.

Extracutaneous manifestations

As PSO is acknowledged to be a chronic systemic disease with skin as one of its manifestations, additional dimensions of the burden of disease were studied in the CIMPASI and CIMPACT program.

Patients treated with both doses of CZP showed improvement in nail psoriasis (mNAPSI), at Week 48, with complete resolution in psoriatic nail disease (mNAPSI score=0) being achieved in [redacted] and [redacted] of patients receiving CZP 200mg Q2W and CZP 400 mg Q2W at Week 48, respectively.

Patient-relevant outcomes

At Week 16, CZP-treated patients reported clinically meaningful and statistically significant improvements versus placebo in a broad spectrum of patient-relevant outcomes, including health-related quality of life, anxiety and depression and work productivity and daily activity.

Clinically meaningful improvements were seen as early as Week 2 in disease-specific quality of life, as measured by changes in DLQI scores. Generally similar and increasingly larger percentages of patients in both the CZP 200 mg Q2W and CZP 400 mg Q2W groups achieved DLQI remission compared with placebo at each timepoint. These improvements in DLQI were maintained or improved through to Week 48 in patients receiving CZP 400 mg Q2W and CZP 200 mg Q2W, with [redacted]% and [redacted]% of patients in DLQI remission at Week 48, respectively.

Clinically meaningful improvements were seen at Week 8 (first assessment) in generic health related quality of life (as indicated by the changes in SF-36 PCS and MCS scores) in the pooled CIMPASI-1 and CIMPASI-2 trials. Statistically significant improvements in anxiety and depression at Week 12, as assessed by HADS-A and HADS-D, were also seen in the CZP-treated arms compared to placebo, in pooled CIMPASI-1 and CIMPASI-2 trials. CZP-treated patients also reported statistically significant and clinically meaningful improvements in psoriasis-related work productivity and daily activity (measured by changes in WPAI-SHP score), with improvement seen as early as Week 4 (first assessment) through to Week 16, in the pooled analysis of the three trials.

Maintenance and durability of response was demonstrated in the long-term, through to Week 48, for all patient relevant outcomes, based on data from the pooled CIMPASI-1 and CIMPASI-2 population and from CIMPACT. [104] [101] [101] [100] [102] [101] [101] [96] [90] [90]

CZP in comparison to ETN

In CIMPACT, CZP was compared to ETN, up to Week 12. Formal comparisons were made for noninferiority and superiority for PASI75 responder rate at this timepoint.

CZP 400 mg Q2W demonstrated superiority over ETN at Week 12 (66.7% versus 53.3%; p=0.0152). This suggests that the higher dose of CZP provides a significantly higher response compared with ETN. There was a numerical increase in PASI75 responder rate in the CZP 200 mg Q2W arm versus ETN that did not reach statistical significance (61.3% vs 53.3%, respectively). CZP also consistently demonstrated similar or greater numerical improvements over the ETN group across a number of outcomes, including PGA and HRQoL, as well as EQ-5D.

Adverse events and overall safety profile

The safety of psoriasis therapies is an important consideration for physicians when making prescribing decisions, and the potential safety concerns with the biologic therapies in psoriasis are well documented. In order for a therapy to be considered appropriate it must have a benefit-risk profile that is acceptable to both the physician and the patient.

The safety profile of CZP in patients with moderate-to-severe plaque psoriasis over a period of up to 144 weeks was comparable with that reported over shorter time periods in PSO and in other indications. Both CZP dose regimens have an acceptable safety profile with a risk that does not increase with longer exposure.

The safety profile of CZP treatment for up to 12 weeks, including the type and incidence of TEAEs, was comparable with treatment with ETN in the CIMPACT trial, with fewer discontinuations due to AEs vs ETN.

The incidences of TEAEs and SAEs were similar between the CZP 400 mg Q2W and placebo groups and were lower in the CZP 200 mg Q2W group during the 16-week initial treatment period. Four patients each in the CZP 400 mg Q2W and CZP 200 mg Q2W groups withdrew due to a TEAE; no patient in the placebo group withdrew due to a TEAE.

Up to 144 weeks, the incidence of any TEAE was slightly higher in the CZP 400mg Q2W group, however the incidences of SAEs, discontinuations due to TEAEs and drug-related TEAEs were similar between the two CZP doses.

No new safety signals were identified over the 144-week trial period in psoriasis compared with what is known for CZP in other indications.

Indirect treatment comparison

The placebo-adjusted multinomial NMA conducted indicated that treatment of PSO with biologics is superior to placebo or standard of care and that among all biologics considered, IXE had the highest probability of achieving a PASI50/75/90 response, which is in line with findings from recent NICE appraisals.

The primary NMA results showed that both CZP doses have similar or higher efficacy in terms of PASI response rates vs the biologics considered. CZP 400 mg Q2W has a similar efficacy in terms of PASI75 response rate (overlapping 95% CrIs) vs IXE, BROD, IFX, GUS, SEC, UST (45mg or 90mg), with numerically higher response rates vs IFX, GUS, SEC, UST (45mg or 90mg). CZP 400 mg Q2W had significantly higher PASI75 response rates when compared to ADA, ETA, TIL and UST 45/90mg. Similar results were seen for the PASI 90 response rate. The probability of achieving a PASI 75 response was similar (overlapping 95% CrIs) for CZP 200mg Q2W vs all comparators considered, with numerically higher response rates than ADA, ETA, GUS, TIL and UST. When compared to ETA, CZP 200mg Q2W had a significantly higher response. Similar results were seen for the PASI 90 response rate.

Known long term safety profile of CZP from other indications: psoriatic arthritis, axial spondyloarthritis and rheumatoid arthritis

CZP has a known and established long term safety profile across other licensed indications in EU, PsA, axSpA and RA.[98-102] There are a considerable amount of long-term safety data available for CZP in other indications for clinicians to draw conclusions from.

Efficacy and safety of CZP in psoriatic arthritis

As previously described, psoriasis is frequently accompanied by additional manifestations in the joints, i.e. PsA.[19] CZP is indicated for the treatment of adult patients with active PsA (see Section B.1.2)[5] and is also recommended by NICE in this indication.[102]

RAPID-PsA was a Phase III, multinational, multicentre, randomised, placebo-controlled, registration study that examined the efficacy of CZP in PsA, and included a broad population of PsA patients, both anti-TNF naïve and anti-TNF exposed.[105] The RAPID-PsA study results showed that CZP is an effective treatment, across both CZP dosing regimens for PsA (CZP 200 mg Q2W and CZP 400 mg Q4W).

Treatment with CZP resulted in rapid improvements in the signs and symptoms of active PsA, inhibition of structural damage, improvements across the breadth of disease manifestations and a broad spectrum of patient-relevant outcomes, regardless of prior treatments.[86, 106, 107] The co-primary endpoints of the trial were 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).[107, 108] Substantial changes in outcomes with CZP were observed as early as the first assessment (e.g. Week 1 for ACR20 and pain, Week 2 for PASI and physical function).[107, 109]

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.[107] Of note, the latest 2015 GRAPPA update of treatment recommendations for PsA provided a “strong recommendation” based on the GRADE system for the significant improvements on dactylitis, enthesitis, nail psoriasis and skin manifestations for anti-TNFs, including certolizumab pegol.[110]

Furthermore, PsA 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 HRQoL) and also greater improvements in work and household productivity versus placebo at Week 24.[109]

The initial improvements in clinical and patient-relevant outcomes following treatment with CZP during RAPID-PsA were maintained to 4 years (Week 216).[86] The rapid and long-term benefits of CZP treatment were similarly high for anti-TNF-naïve patients who had received only 1 prior cDMARD, anti-TNF-naïve patients and anti-TNF-experienced patients.[86, 106, 107]

These data are supportive of CZP efficacy for joint manifestations in psoriasis patients, and consistent with the data from the Phase III trials in psoriasis demonstrating similar efficacy in biologic-naïve and biologic-exposed patients.

The 4 years data from RAPID-PsA trial indicated that there are no new safety signals, and long-term exposure did not increase the risk for AEs. The safety profile for patients with PsA treated with CZP is consistent with the safety profile in RA and previous experience with CZP.

B.2.13.2 Strengths and limitations of the clinical evidence base

The clinical evidence base for CZP in moderate to severe plaque psoriasis comes primarily from the three Phase III studies: CIMPASI (CIMPASI-1, CIMPASI-2) and CIMPACT. The three trials successfully met their (co-) primary objectives, as supported by the hierarchical procedure testing.

The three studies provide comparative evidence for CZP versus placebo, with CIMPACT also providing comparative evidence for CZP versus ETN. All three studies were well-designed, with appropriate randomisation and adequate concealment of treatment allocation, and all patients

were randomised following the appropriate double-blinding procedures. A large number of outcomes that are clinically meaningful and also relevant to patients were assessed in these trials. The clinical program allows an evaluation of short- and long-term (to 3 years) efficacy and safety of CZP.

The key clinical outcomes used in the three trials directly measure health benefits and are not surrogate endpoints. The co-primary endpoints in CIMPASI-1 and CIMPASI-2 (PASI75 and PGA clear/almost clear response rates at Week 16) and the primary endpoint in CIMPACT (PASI75 response rate at Week 16) are highly relevant to the UK clinical practice and the severity of psoriasis symptoms.

The CIMPASI and CIMPACT clinical program included a broad population of patients with moderate to severe plaque PSO, who were candidates or inadequate responders to systemic non-biologic drugs, as well as patients who were biologic naïve or biologic exposed. This would largely be reflective of the composition of the PSO population in England and Wales given that TNF inhibitors have been approved for treatment of PSO since 2006.

The CZP phase III clinical program was designed in line with the evolution of treatment management and treatment target guidelines with two doses of CZP being investigated, to allow greater flexibility for clinicians and patients. As per the label, the recommended maintenance dose is CZP 200mg Q2W (after the starting dose). For insufficient clinical response or patients who lose response on CZP 200mg Q2W, escalation to CZP 400mg Q2W is an option. Data from the overall clinical program demonstrated that CZP 200mg Q2W is an effective treatment option for patients with moderate to severe plaque psoriasis. Furthermore, for some patients with insufficient response to CZP 200mg Q2W, evidence shows that CZP 400mg Q2W is an effective therapy. Escalation of the treatment dose in case of insufficient response is clinical practice in England, supported by the latest 2017 BAD guidelines for biologic therapy for psoriasis and local treatment pathways in England. This avoids overtreatment for patients for whom CZP 200mg Q2W achieves the optimal outcome, while allowing the option for dose escalation for those patients who do not.

Considered together, these outcomes indicate that CZP provides patient benefit, where the reduction in signs and symptoms of psoriasis translates into measurable improvements in patients' lives, by improving health-related quality of life and workplace productivity and social activities. These benefits can be expected by patients in clinical practice.

A limitation of the evidence base from the CIMPASI and CIMPACT trials, is the lack of direct comparison with active comparators, other than ETN included in the CIMPACT trial. However, direct comparisons with all available comparators as per the NICE scope are not feasible in clinical trials and this has been a similar issue observed for other biologic therapies for psoriasis, previously assessed by NICE. To address this limitation, an NMA was conducted to allow indirect comparisons of CZP with all relevant comparators outlined in the NICE final scope. The primary NMA approach considered was in line with the methodology suggested by the NICE Decision Unit Support group.

The evidence base from CIMPASI-1, CIMPASI-2 and CIMPACT is highly relevant to the NICE decision problem. CIMPACT compared CZP to ETN, a relevant comparator in the decision problem and included patients recruited in five UK study centres. Baseline disease characteristics from the clinical trials were generally well balanced across trials. It would be expected that the characteristics of the patient population in England and Wales should largely

reflect that of other European countries in terms of age, disease burden, severity and demographics. The baseline characteristics of the CIMPASI and CIMPACT trials population are reasonably reflective of the typical cohort of moderate to severe psoriasis patients who are eligible for biologic treatment in clinical practice in England and Wales. The CIMPASI and CIMPACT trials included a broad patient population of patients with moderate to severe plaque PSO, who were candidates for or inadequate responders to systemic non-biologic drugs, as well as those who were biologic naïve or biologic exposed. This provides evidence for the populations and subgroups of patients relevant to the NICE decision problem.

B.3 Cost effectiveness

The cost-effectiveness analysis

- An adaption of the York Markov model was developed to compare the cost-effectiveness of CZP to the relevant comparators in this submission. A lifetime time horizon was used and the perspective taken was the NHS and Personal Social Services. The model structure and assumptions are in line with recent NICE technology appraisals in psoriasis.
- For the base case, the analysis was conducted in the overall patient populations included within the clinical trials, which should inform the decision for the population defined in the NICE scope as patients for whom conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated. For the overall patient population, clinical outcomes in the model (PASI75 responder rate and discontinuation at weeks 12/16) were informed by the network meta-analysis.
- Separate economic analysis has been conducted to investigate the population specified in the NICE scope as patients for whom systemic non-biological treatment or phototherapy is suitable. For this analysis, the model clinical outcomes were based on a subgroup of the pooled CZP Phase III trials, where patients at the start of the trial were naïve to both non-biologic and biologic systematic therapy.
- CZP 200 mg was compared to the comparators as part of treatment sequences, to reflect clinical practice. Separate analyses were conducted, to allow for escalation of the CZP dose from 200 mg to 400 mg in patients with insufficient response, it is assumed that this does not count as an additional line of treatment and therefore CZP is still followed by two subsequent biologics and then BSC, as per the other sequences.

Base case results

Systemic non-biologic inadequate responders

- The economic analysis demonstrated that the treatment sequences that started with CZP is cost-effective versus all other biologic comparator considered for systemic non-biologic inadequate responders.
- When compared against the ADA escalation strategy, CZP was more efficacious (incremental QALY of [redacted]), but more costly (incremental costs of [redacted]), leading to an ICER of £37,053.86.

Candidates for systemic non-biologics

- In the candidates for systemic non-biologic population, CZP is a cost-effective treatment option versus the standard of care treatment sequence (ICER for CZP 200 mg versus standard of care: £3,649.53/QALY).

Sensitivity analyses

Systemic non-biologic inadequate responders

- The probabilistic sensitivity analysis (PSA) results indicate that the CZP sequence is cost-effective versus all other treatments at a WTP threshold of £20,000/QALY.

- The main drivers of the model in the deterministic sensitivity analyses were the drug acquisition cost of CZP and the biologic comparators.

Candidates for systemic non-biologics

- The PSA results indicate the CZP sequence is cost-effective versus the standard of care sequence at a WTP threshold of £20,000/QALY.
- The main drivers in the deterministic sensitivity analysis were the acquisition cost of CZP, PASI health state utilities and the cost of non-responders.

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted to identify published data describing the cost-effectiveness of CZP relative to comparator agents for the treatment of moderate to severe chronic plaque psoriasis. The SLR was conducted in in November 2016 and designed to capture cost-effectiveness analyses, and cost and resource use data, for biologic therapies in the treatment of psoriasis.

Full details of the search strategy and results of the SLR are presented in Appendix G.

The SLR identified 1,397 unique articles for review at the title/abstract screening stage. After title/abstract review, 216 articles were reviewed at the full-text stage, with 12 articles ultimately meeting the inclusion criteria. Overall, the SLR identified 11 published economic evaluations, none of which assessed the cost-effectiveness of CZP. Full details of the captured economic evaluations, as well as quality assessments for each study, are presented in Appendix G. No cost-effectiveness analyses of CZP in psoriasis published since November 2016 have been found through targeted literature searching. A summary of the NICE technology appraisals in psoriasis up until July 2018 is presented in Table 64 below.

Table 64: Summary of previous NICE technology appraisals in psoriasis

Reference	Country and costing perspective	Study population	Model characteristics/type of evaluation & time horizon	Intervention & comparators	Outcomes	Sensitivity analysis	Results		
							Total costs	Total QALYs	Base case ICERs (Δ£/ΔQALY
TA103 (2006/ 7) ETN[49]	UK NHS and PSS	Moderate to severe psoriasis	Markov model, 96 weeks	ETN 25 mg int. ETN 25 mg BIW cont. ETN 50 mg BIW int. No systemic therapy	Total costs, total QALYs, ICER		12-week analysis: No systemic therapy: £72 ETN 25 mg £3,352 ETN 50 mg £4,474 96-week analysis: No systemic therapy: £578 ETN 25 mg: £8,635 ETN 50 mg: £12,175	12-week analysis: No systemic therapy: 0.011 ETN 25 mg 0.029 ETN 50 mg 0.031 96-week analysis: No systemic therapy: 0.084 ETN 25 mg: 0.236 ETN 50 mg: 0.264	12-week analysis: ETN 25 mg vs no systemic therapy: £124,732 ETN 50 mg vs 25 mg: £1,255,840 96-week analysis: ETN 25 mg vs no systemic therapy: £53,056 ETN 50 mg vs 25 mg: £127,464
TA103 (2006/ 7) EFA[49]	UK NHS and PSS	Moderate to severe psoriasis	Decision tree, 10 years	EFA Topical therapy (Cal/BD)	Total costs, total QALYs, ICER		EFA: £5,611 Topical: £123	EFA: 1.39 Topical: 0.36	EFA vs topical: £25,582
TA103 (2006/ 7) EFA York model[49]	UK NHS and PSS	Moderate to severe psoriasis	Markov model, 10 years	EFA (not available in UK); ETN 25 mg BIW int. ETN 25 mg BIW cont. ETN 50 mg BIW int. BSC	Incremental Costs, Incremental QALYs, ICERs	Scenario analyses and PSA	Relative to BSC ETN 25 mg int.: £7,743 EFA: £9,382	Relative to BSC ETN 25 mg int: 0.116 EFA: 0.112 ETN 25 mg cont: 0.116	Incremental analysis: ETN 25 mg BIW int vs BSC: £66,703

Reference	Country and costing perspective	Study population	Model characteristics/type of evaluation & time horizon	Intervention & comparators	Outcomes	Sensitivity analysis	Results		
							Total costs	Total QALYs	Base case ICERs (Δ£/ΔQALY
				Secondary analysis: MTX ciclosporin Fumaderm IFX			ETN 25mg (cont): £9,665 ETN 50 mg (int.): £14,860	ETN 50 mg int: 0.123	EFA and ETN 25 mg BIW cont: Dominated ETN 50 mg vs 25 mg BIW int: £1,035,121 Base case vs BSC: ETN 25mg int: £66,703 EFA: £84,018 ETN 25 mg cont: £83,258 ETN 50 mg int: £120,855
TA134 (2007/8) IFX[51]	UK NHS and PSS	Moderate to severe psoriasis (4th quartile DLQI at baseline)	Markov model based closely on the York model by Woolacott et al 2006, 10 years	INF ETN 25 mg BIW cont. ETN 25 mg BIW int. ETN 50 mg BIW int. EFA (no longer available in UK) BSC	Incremental Costs, Incremental QALYs, ICERs	OWSA, PSA	Relative to BSC: ETN 25 mg BIW cont: £1,531 IFX: £4,562	Relative to BSC: ETN 25 mg BIW cont: 0.089 IFX: 0.205	IFX vs BSC: £22,240 IFX vs ETN 25 mg BIW cont: £26,095
TA146 (2008) ADA[47]	UK NHS and PSS	Moderate to severe psoriasis (DLQI>10)	Markov model based closely on the York model by Woolacott et	ADA MTX CIC IFX	Incremental Costs, Incremental QALYs,		Relative to BSC: MTX: £3,844	Relative to BSC: MTX: 0.129 CIC: 0.079	Base case vs BSC: MTX: £-29,759

Reference	Country and costing perspective	Study population	Model characteristics/type of evaluation & time horizon	Intervention & comparators	Outcomes	Sensitivity analysis	Results		
							Total costs	Total QALYs	Base case ICERs (Δ£/ΔQALY
			al 2006, 10 years	ETN 25 mg BIW cont. ETN 25 mg BIW int. ETN 50 mg BIW int. EFA (no longer available in UK) BSC	ICERs		CIC: £1,987 ETN 25 mg BIW int: £4,114 ETN 50 mg BIW int: £4,699 EFA: £4,942 ADA: £4,993 ETA 25 mg BIW cont: £5,058 IFX: £7,736	ETN 25 mg BIW int: 0.11 ETN 50 mg BIW int: 0.123 EFA: 0.124 ADA: 0.164 ETN 25 mg BIW cont: 0.134 INF: 0.182	CIC: £-25,135 ETN 25 mg BIW int: £37,284 ETN 50 mg BIW int: £38,358 EFA: £39,948 ADA: £30,538 ETN 25 mg BIW cont: £37,676 IFX: £42,492
TA180 (2009) UST[54]	UK NHS and PSS	Moderate to severe psoriasis (DLQI>10)	Markov model based closely on the York model by Woolacott et al 2006, 10 years	UST 45 mg UST 90 mg ADA IFX ETN 25 mg BIW cont. ETN 25 mg BIW int. ETN 50 mg BIW int. EFA (no longer available in UK) BSC	Incremental Costs, Incremental QALYs, ICERs	OWSA, scenario analyses, subgroup analyses and PSA	Relative to BSC: EFA: £5264 ETN 25 mg BIW int: £3,989 ETN 25 mg BIW cont: £4,829 ETN 50 mg BIW cont: £5,333 ADA: $4,660 UST: £4,615 IFX: £6,327	Relative to BSC: EFA: 0.1308 ETN 25 mg BIW int: 0.1325 ETN 25 mg BIW cont: 0.1409 ETN 50 mg BIW cont: 0.1483 ADA: 0.1502 UST: 0.156	Base case vs BSC: EFA: ££40,250 ETN 25 mg BIW int: £30,111 ETN 25 mg BIW cont: £34,281 ETN 50 mg BIW cont: £35,964 ADA: £31,022 UST: £29,587

Reference	Country and costing perspective	Study population	Model characteristics/type of evaluation & time horizon	Intervention & comparators	Outcomes	Sensitivity analysis	Results		
							Total costs	Total QALYs	Base case ICERs (Δ£/ΔQALY
								IFX: 0.1616	IFX: £39,153
TA350 (2015) SEC[53]	UK NHS and PSS	Moderate to severe psoriasis (DLQI>10)	Markov model, 10 years	SEC ETN 25 mg BIW cont. ADA IFX UST 45 mg UST 90 mg BSC	Total costs, total QALYs, ICER	OWSA, scenario analyses and PSA	BSC: £73,610 ETN: £75,788 SEC: £76,361 ADA: £76,981 UST 45 mg: £79,544 UST 90 mg: £79,732 IFX: £93,539	BSC: 0.97 ETN: 1.13 SEC: 1.36 ADA: 1.22 UST 45 mg: 1.30 UST 90 mg: 1.33 IFX: 1.36	Incremental analysis: SEC vs BSC: £2,464 ETN extendedly dominated ADA, UST 45 mg, UST 90 mg, IFX dominated
TA368 (2015) APR[58]	UK NHS and PSS	Moderate to severe psoriasis (DLQI>10)	Decision tree and Markov model based closely on the York model by Woolacott et al 2006, 10 years	APR → ADA → ETN → BSC ADA → ETN → BSC	Total costs, total QALYs, ICER	OWSA, scenario analyses, subgroup analyses and PSA	APR sequence: £89,374 Comparator sequence: £92,589	APR sequence: 6.83 Comparator sequence: 6.69	APR sequence dominated comparator sequence
TA442 (2017) IXE[52]	UK NHS and PSS	Moderate to severe psoriasis (DLQI>10)	Markov model, lifetime horizon	IXE → UST90→ INF ADA → UST90→ INF ETN → UST90→ INF IFX → UST90→ ADA SEC → UST90→ INF UST45 → ADA →INF UST90 → ADA→ INF	Total costs, total QALYs, ICER	OWSA, scenario analyses, subgroup analyses and PSA	Strategy starting with: ETN: £144,635 UST45: £148,218	Strategy starting with: ETN: 1.27 UST45: 1.30 ADA: 1.32	Fully incremental analysis: UST (45 and 90), ADA, INF: extendedly dominated

Reference	Country and costing perspective	Study population	Model characteristics/type of evaluation & time horizon	Intervention & comparators	Outcomes	Sensitivity analysis	Results		
							Total costs	Total QALYs	Base case ICERs (Δ£/ΔQALY
							ADA: £148,350 UST90: £148,719 IFX: £150,350 IXE: £150,889 SEC: £177,101	UST90: 1.32 IFX: 1.33 IXE: 1.45 SEC: 1.42	SEC dominated IXE vs ETN: £33,848 Base case IXE vs comparator: ETN: £33,858 UST45: £18,278 ADA: £19,202 UST90: £16,763 IFX: £4,300 SEC: dominated
TA475 (2017) DMF[59]	UK NHS and PSS	Moderate to severe psoriasis	Markov model, 10 years	DMF → ADA → UST → BSC ADA → UST → BSC	Total costs, total QALYs, ICER	OWSA, scenario analyses, subgroup analyses and PSA	Not reported (redacted)	Not reported (redacted)	Incremental analysis: ADA → UST → BSC: Dominated
TA511 (2018) BROD[48]	UK NHS and PSS	Moderate to severe psoriasis (DLQI>10)	Markov model, 40 years	BROD→UST→SEC→BSC ADA→UST→SEC→BSC APR→UST→SEC→BSC DMF→UST→SEC→BSC ETN→UST→SEC→BSC IFX→UST→SEC→BSC IXE→UST→SEC→BSC SEC→UST→ADA→BSC	Total costs, total LYG, total QALYs, incremental costs, incremental LYG,	OWSA, scenario analyses, PSA	Strategy starting with relative to DMF: APR: £3,136 ETN: £5,690	Strategy starting with relative to DMF: APR: 0.07 ETN: 0.18 ADA: 0.46	Fully incremental analysis, strategy starting with: APR: extendedly dominated

Reference	Country and costing perspective	Study population	Model characteristics/type of evaluation & time horizon	Intervention & comparators	Outcomes	Sensitivity analysis	Results		
							Total costs	Total QALYs	Base case ICERs (Δ£/ΔQALY
				UST→ADA→SEC→BSC	incremental QALYs, ICER		ADA: £9,935 UST: £10.055 SEC: £15,423 IFX: £26,111 BRO: £9,416 IXE: £36,857	UST: 0.46 SEC: 0.47 IFX: 0.59 BROD: 0.71 IXE: 0.74	ETN: extendedly dominated ADA: dominated UST: dominated SEC: dominated IFX: dominated BROD: £13,353 IXE: £894,010
TA521 (2018) GUS[50]	UK NHS and PSS	Moderate to severe psoriasis	Cost comparison model, 5 years	GUS ADA UST	Acquisition costs, resource costs, adverse event costs	OWSA	GUS: not reported ADA: £25,785 UST: £27,928	N/A	N/A

Abbreviations: ADA: adalimumab; APR: apremilast; BIW: twice weekly; BROD: brodalumab; BSC: best supportive care; CIC: ciclosporin; DLQI: Dermatology Life Quality Index; EFA: efalizumab; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekuzumab; LYG: life years gained; MTX: methotrexate; NHS: National Health Service; OWSA: one-way sensitivity analysis; PSA: probabilistic sensitivity analysis; PSS: Personal Social Services; QALY: quality-adjusted life year; SEC: Secukinumab; UK: United Kingdom; UST: ustekinumab.

B.3.2 *Economic analysis*

Due to the lack of published analyses as described above, an adaptation of the York model was developed to determine the cost-effectiveness of CZP relative to the existing standard of care in patients with moderate-to-severe plaque psoriasis. The model structure was developed taking into consideration previous approaches (notably that taken to develop the York model),[111] the NICE Guide to the Methods of Technology Appraisal,[112] and the NICE reference case criteria.[112]

The base case analysis used PASI75 response as the endpoint for determining response to treatment at the initial treatment period, since this is the primary endpoint in the majority of psoriasis clinical trials and has been accepted by NICE in all previous appraisals in psoriasis. However, a scenario analysis is also presented in which a PASI50 response rate has been explored for determining switching to a differing therapy.

B.3.2.1 Patient population

The adaptation of the York economic model developed for this submission considered patients aged ≥18 years with moderate to severe plaque psoriasis, who are candidates for systemic biologic therapies or who have an inadequate response, contraindication or intolerance to other systemic non-biologic therapies including ciclosporin, MTX or PUVA.

For the systemic non-biologic therapy inadequate responders, the model considers the overall patient populations included within the clinical trials. An NMA for systemic non-biologic therapy inadequate responders specifically was not possible due to lack of published data. Therefore, the ITT populations of the CZP and comparator trials have been used within the NMA and these results are used in the health economic model to represent this patient population. For CZP, this consisted of the patients from CIMPASI-1, CIMPASI-2 and CIMPACT. Similar to other recent psoriasis trials,[113] including those used to support recent HTA submissions,[114-116] patients were required to have baseline PASI ≥12 to be eligible for these Phase III clinical trials. The patient population considered by this model therefore meet the minimum disease severity eligibility criteria for biologic therapy, in terms of PASI score (i.e., PASI score ≥10), according to existing NICE technology appraisals. This analysis should inform the decision for the population defined in the NICE scope as patients for whom conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated.

A separate economic analysis has been conducted to investigate the population specified in the NICE scope as patients for whom systemic non-biological treatment or phototherapy is suitable. For this analysis, a subgroup of the pooled CZP Phase III trials has been used, where patients at the start of the trial were naïve to both non-biologic and biologic systematic therapy, meeting the definition for patients eligible for systemic non-biologic therapy or phototherapy in NICE CG153.[40]

Table 65: Patient populations considered by the economic model

Analysis	Patient population
Systemic non-biologic therapy inadequate responders	Overall patient population: All patients captured in the CIMPASI-1, CIMPASI-2 and CIMPACT phase III clinical trials. This analysis should inform the decision for the population who are eligible for current biologics, defined in the NICE scope as patients for whom conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated.
Candidates for systemic non-biologic therapy	Subgroup of the pooled CZP Phase III trials, where patients at the start of the trial were naïve to both non-biologic and biologic systematic therapy.

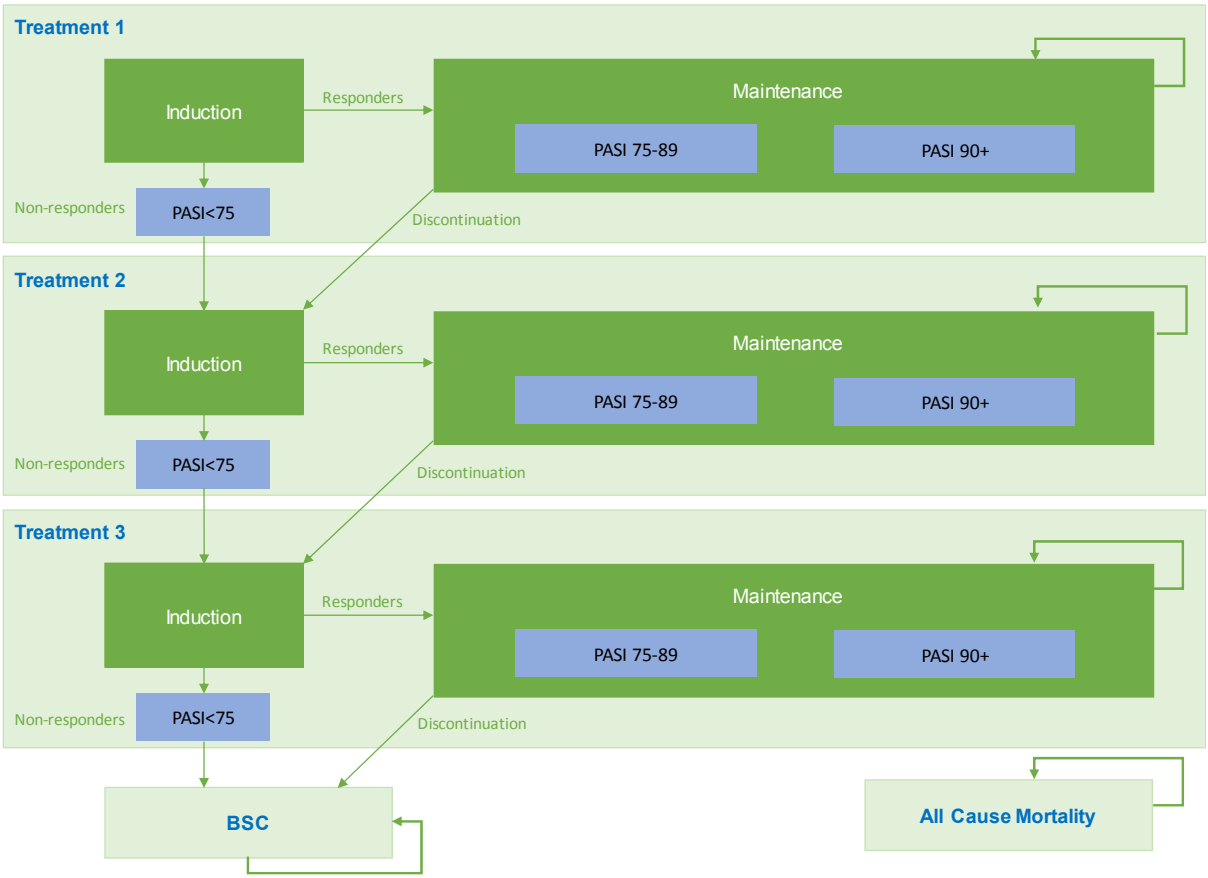
Abbreviations: CZP: certolizumab pegol; NICE: National Institute for Health and Care Excellence.

B.3.2.2 Model structure

Model schematic

The model structure employed was a state transition Markov model. The model used a two-week cycle length and considered two key phases: induction and maintenance therapy. Movement between phases was dependent on response to treatment. The model structure is shown in Figure 23:.

Figure 23: Model flow diagram



Abbreviations: BSC: best supportive care; PASI: Psoriasis Area and Severity Index.

Initial treatment phase

Patients entered the model on treatment and underwent the initial treatment period (induction). The duration of treatment during the initial treatment phase corresponded to the time until response is assessed for each treatment, based upon NICE treatment guidelines for each intervention (Table 4). This is consistent with the approach to modelling of the initial treatment period in recent technology appraisals for other biologics for moderate to severe psoriasis.[48, 52] For CZP, assessment of response was modelled to occur at 16 weeks after treatment initiation, in line with the recommendations in the SmPC.[5]

At the end of the initial treatment phase, patients were categorised according to treatment response. Patients who responded to initial treatment moved into the maintenance treatment phase and remained on the same therapy. Response to treatment was defined as achievement of PASI75 response; this was the primary outcome used in the majority of psoriasis clinical trials, and has been accepted by NICE as the marker of treatment response that is used in clinical practice.[117, 118] Non-responders (<PASI75 response) switched to a new therapy with a different mechanism of action compared to the previous therapy and re-entered the initial treatment phase.

Patients could have also experienced treatment-related adverse events during the initial treatment period. These patients discontinued their current treatment and switched to another therapy, re-entering the initial treatment period, or moved to the death health state.

Maintenance treatment phase

Patients who entered the maintenance treatment phase continued to receive the same therapy as during the initial treatment phase. Patients were modelled until discontinuation due to loss of response or death and were assumed to maintain the same PASI response from the end of the initial phase until this point. Upon discontinuation due to loss of response, patients became eligible to receive the next treatment in the treatment sequence; for these patients, the PASI score was assumed to revert to baseline PASI until the end of the initial period for the subsequent therapy. This approach is consistent with the approach to modelling of the maintenance treatment period in recent single technology appraisals for other biologics for moderate to severe psoriasis.[113, 114]

Death

Patients were at risk of all-cause mortality in both the initial and maintenance treatment phases. Mortality was based on age- and sex-dependent general mortality UK life tables.[119] No additional risk of mortality due to psoriasis has been modelled.

Features of the economic analysis

The cycle length employed in the model was 2 weeks, which was the shortest viable cycle considering both expected patient lifespan and treatment administration schedules. The model employed a lifetime time horizon, which was chosen as psoriasis is a chronic condition.[11] The model considers a UK payer (NHS) and Personal Social Services (PSS) perspective and costs and benefits are discounted at a rate of 3.5%, in accordance with NICE standards.[120] Features of the economic model are presented in Table 66.

Table 66: Features of the *de novo* economic analysis

	Previous NICE appraisals										Current submission	
Factor	**TA103 ETA**	**TA134 IFX**	**TA146 ADA**	**TA180 UST**	**TA350 SEC**	**TA419 APR**	**TA442 IXE**	**TA475 DMF**	**TA511 BROD**	**TA521 GUS**	**Chosen values**	**Justification**
Model approach	• TA103, TA134, TA146, TA180 and TA350: Decision tree and Markov model • TA419, TA442, TA475 and TA511: Markov model • TA521: Cost comparison										Markov model	The model was designed to conform with the NICE criteria.
Time horizon	• TA103, TA134, TA146, TA180, TA350, TA419, TA475: 10 years • TA442: lifetime • TA511: 40 years • TA521: 5 years										Lifetime	Psoriasis is a chronic disease. A lifetime horizon was considered appropriate and agreed in the NICE decision problem meeting. Scenario analyses were also conducted for 10- and 20-year time horizons (standard HTA sensitivity analyses) and a 1-year time horizon (to reflect the typical RCT follow-up period).
Discounting	• TA103: 6% on costs and 1.5% on outcomes • TA134, TA146, TA180, TA350, TA419, TA442, TA475, TA511: 3.5% on costs and outcomes • TA521: no discounting										3.5% on costs and outcomes	NICE reference case.[120]
Cycle length	• TA103 and TA350: 12 months • TA180: 3 months • TA419: 4 weeks • TA442: 1 month • TA475 and TA511: 2 weeks • TA511: not applicable										2 weeks	This is the shortest viable cycle length considering both expected patient lifespan and treatment administration schedules.

Treatment waning effect?	• Treatment effect assumed to be maintained with ongoing treatment. • Treatment effect assumed to be the same regardless of exposure to prior therapies.	Treatment effect assumed to be maintained with ongoing treatment with the same therapy (i.e. until treatment discontinuation). The base case analysis assumes treatment effect to be the same regardless of exposure to prior therapies.	Sensitivity analyses were conducted on the following: - Assuming varying treatment discontinuation rates in the maintenance period for different therapies - Using NMA data from patients without prior biologic exposure, since expert clinical opinion indicated that this may affect treatment efficacy.
Source of utilities	• TA103: analysis of patient-level data from 3 ETN RCTs and a regression analysis of EQ-5D and DLQI from the HODaR database • TA134, TA419, TA475: values used in TA103 • TA146: mixed model with repeated measures analysis of covariance from two ADA RCTs assessing the relationship between changes in EQ-5D, PASI response level and baseline DLQI • TA180: analysis of patient-level data from two UST RCTs and a regression analysis of EQ-5D and DLQI from the HODaR database • TA350: mixed effects regression model of 5 SEC RCTs assessing the relationship between change in EQ-5D, PASI response level and baseline DLQI • TA442: least squares regression model of three IXE RCTs assessing the relationship between change in EQ-5D-5L, PASI response level and baseline EQ-5D-5L • TA511: least squares regression model of AMAGINE-1 assessing the relationship between change in EQ-5D, PASI response level and baseline DLQI • TA521: Not applicable	Analysis of EQ-5D data from the three phase III CZP clinical trials.	NICE reference case.[120]
Source of	• TA103, TA134, TA146 and TA180: Woolacott et al. (2006) • TA350 and TA419: CG153	Fonia et al. (2010)	This was the only published UK cost study on resource

resource use	• TA442: CG153 and Fonia et al. (2010) • TA475: not specified • TA511: CG153, BAD guidelines, Fonia et al. (2010) • TA521: Not applicable		use associated with moderate to severe psoriasis identified by the SLR.
Source of unit costs	• NHS reference costs and PSSRU • TA103, TA134, TA146, TA180, TA350 and TA419: also BNF • TA442, TA475, TA511, TA521: also MIMS	NHS reference costs and PSSRU unit costs of health and social care.	NICE reference case.[120]
Adverse events	• TA103, TA134, TA146, TA180, TA419, TA475, TA521: not included • TA350: impact of AEs (NMSC, malignancies other than NMSC, severe infections) on costs included • TA442: impact of AEs (NMSC, malignancies other than NMSC, severe infections) on costs included in scenario analysis only • TA511: Impact of serious infections on costs and benefits included in base case analysis; impact of NMSC, malignancies other than NMSC and MACE on costs included in scenario analysis	TRAEs not included.	Acute hypersensitivity and infusion reactions have been identified as potential TRAEs, however, expert clinical advice indicated that these were very rare. The exclusion of TRAEs was agreed at the decision problem meeting. The cost of AEs was not modelled by all previous submissions.
Mortality	• TA103, TA134, TA146, TA180, TA419, TA521: not included • TA350, TA442 and TA475: included, not disease- or treatment-dependent • TA511: included, not treatment-dependent	Included, not disease-dependent.	Absence of robust evidence for an independent link between psoriasis and cardiovascular mortality.

Abbreviations: ADA: adalimumab; AE: adverse event; APR: apremilast; BAD: British Association of Dermatologists; BNF: British National Formulary; BROD: brodalumab; CG: Clinical Guideline; DLQI: Dermatology Life Quality Index; DMF: dimethyl fumarate; EQ-5D: EuroQoL – 5 dimensions; EQ-5D-3L: EuroQoL – 5 dimensions – 3 levels; EQ-5D-5L: EuroQoL – 5 dimensions – 5 levels; ETN: etanercept; GUS: guselkumab; HODaR: Health Outcomes Data Repository; IFX: infliximab; IXE: ixekizumab; MACE: major adverse cardiovascular events; MIMS: Monthly Index of Medical Specialities; NHS: National Health Service; NMSC: non-malignant skin cancer; PASI: Psoriasis Area and Severity Index; PSSRU: Personal Social Services Research Unit; RCT: randomised controlled trial; SEC: secukinumab; SLR: systematic literature review; TA: Technology Appraisal; TRAE: treatment-related adverse events; UST: ustekinumab.

B.3.2.3 Intervention technology and comparators

Intervention

The intervention of interest is certolizumab pegol. The main dose considered in this submission is CZP 200 mg Q2W after a loading dose of CZP 400 mg at weeks 0, 2 and 4, as this is the main dose recommended in the licence. As the licence also states CZP 400 mg Q2W can be considered in patients with insufficient response, a treatment sequence was also explored where patients who do not respond after the initial treatment period on CZP 200 mg Q2W were escalated to CZP 400 mg Q2W.

Comparators

For the overall patient population, which represents the population for whom systemic non-biologic therapy is inadequately effective, not tolerated or contraindicated, the comparators used in the model for the comparison to CZP 200 mg Q2W are the other biologic therapies licensed for psoriasis and recommended by NICE in this position, as discussed in Section B.1.1:

- Adalimumab
- Etanercept
- Ustekinumab
- Secukinumab
- Ixekizumab
- Brodalumab
- Guselkumab

In each case, the indication, treatment regimen, and endpoints assessed align with the relevant marketing authorisation and NICE guidance.

For the analysis where CZP 200 mg Q2W is escalated to CZP 400 mg Q2W, the comparator considered was the ADA escalation strategy (ADA 40 mg escalated to ADA 80 mg), which was the only similar escalation strategy. The rationale for using the ADA escalation is that this is the most realistic treatment sequence for CZP to be compared to, as ADA is also an anti-TNF with the potential for dose escalation, as per the license and also recommended in the BAD guidance.

For candidates for systemic non-biologic therapy, it was not possible to run an NMA in this population due to the lack of published data for other comparators in these patients specifically. The model uses a subgroup of the pooled CZP Phase III trials (CIMPASI-1, CIMPASI-2, CIMPACT), to compare CZP to standard of care (systemic non-biologic therapies) for these patients. The placebo arms of the pooled trials were used to represent standard of care.

Table 67: Comparators included in the cost-effectiveness analysis

Therapy	Brand	Regimen[a]	Initial therapy duration (weeks)	Total tablets/vials/syringes during initial treatment period, n	Total tablets/vials/syringes during year 1, n	Total annual tablets/vials/syringes during maintenance treatment period, n
Intervention						
CZP 200 mg	Cimzia	200 mg Q2W (LD 400 mg weeks 0, 2, 4)	16	12	29	26
Comparators for systemic non-biologic therapy inadequate responders CZP 200 mg Q2W						
ADA 40 mg	Humira	40 mg Q2W (LD 80 mg)[b]	16	10	28	26
BROD	Kyntheum	210 mg Q1W for 3 weeks, then Q2W	12	8	27	26
ETN	Enbrel (or biosimilars Benepali and Erelzi)	25 mg BIW (or 50 mg Q1W)	12	24	104	104
GUS	Tremfya	100 mg at 0 and 4, followed by Q8W	16	3	7	7
IXE	Taltz	160 mg week 0, then 80 mg Q2W until week 12, then 80 mg Q4W	12	8	16	13
SEC	Cosentyx	300 mg Q1W for 5 doses, then 300 mg every month	12	12	32	24
UST 45 mg	Stelara	45 mg weeks 0, 4, then 45 mg Q12W	16	2	5	4
UST 90 mg		90 mg weeks 0, 4, then 90 mg Q12W	16	2	5	4
Comparators for systemic non-biologic therapy inadequate responders CZP 400 mg Q2W						
ADA 80 mg[c]	Humira	80 mg Q2W	16	16	26	26

Comparators for the population who are candidates for systemic non-biologic therapy						
Standard of care	N/A	BSC from Fonia et al. 2010	N/A	N/A	Applied as a cost per cycle	Applied as a cost per cycle
Therapies used at later lines in the treatment sequence						
IFX	Remicade	5 mg/kg weeks 0, 2, 6 then Q8W	10	15	40	33
BSC	N/A	BSC from Fonia et al. 2010	N/A	N/A	Applied as a cost per cycle	Applied as a cost per cycle

[a]Regimen based on information from the BNF and EMA
[b]It has been assumed that a proportion of patients (>30kg) increase dose frequency to 40 mg every other week
[c]Please note that in the model this has been represented as one dose, therefore the number of doses each year will be half those shown in the table above
Abbreviations: ADA: adalimumab; BID: twice a week; BIW: twice a week; BNF: British National Formulary; BROD: brodalumab; BSC: best supportive care; CZP: certolizumab pegol; EMA: European Medicines Agency; ETN: etanercept; GUS: guselkumab; IFX: infliximab; IXE: ixekizumab; LD: loading dose; N/A: not applicable; Q1W: every week; Q2W: every two weeks; Q8W: every eight weeks; Q12W: every twelve weeks; SEC: secukinumab; UST: ustekinumab.

B.3.2.4 Treatment sequencing

The cost-effectiveness analysis for CZP modelled treatment sequences containing three therapies from the included biologics, before patients move to non-biologic BSC therapy. This is based upon expert clinical expert opinion which indicated that, in the UK secondary care setting, patients who require more than two lines of biologic therapy can be referred on to a specialist centre where they often receive a further line of therapy. It was also noted that it is unusual for a patient to fail to respond to three lines of biologic therapy, and that IFX is typically reserved for patients who failed to respond to other biologics.

The treatment sequences modelled for CZP 200 mg Q2W are intended to allow comparison of therapies at each line of treatment, and assessment of a potential treatment pathway that is in line with current clinical practice. The comparator sequences for the systemic non-biologic therapy inadequate responders (Table 68) have therefore been selected to reflect expert clinical opinion and the latest BAD psoriasis treatment guidelines.[4] According to BAD, within the context of biologic treatment, the recommended first-line therapies comprise ADA and SEC (regardless of whether patients also have PsA), and UST for patients without PsA. When patients fail to respond to the chosen first-line therapy, it is suggested that any of the currently licensed biologics may be tried.[42] Based on prior NICE appraisals (TA511, TA442),[48, 52] prescribing data and clinical expert opinion, patients in the model switch to UST as their second-line biologic, unless UST has been used first-line, in which case patients switch to ADA. The 90 mg dose of UST was used as the second-line biologic in the model, as was the case in TA442. The 90 mg dose is priced the same as the 45 mg UST dose, and the 45 mg dose at second-line is investigated in scenario analysis. This was agreed to be appropriate at the decision problem meeting.

Table 68: Treatment sequences modelled for systemic non-biologic therapy inadequate responders – base case analysis

Sequence	1st line	2nd line	3rd line	4th line	5th line
A	CZP 200 mg	UST 90 mg	IFX	BSC	BSC
B	ADA	UST 90 mg	IFX	BSC	BSC
C	BROD	UST 90 mg	IFX	BSC	BSC
D	ETN	UST 90 mg	IFX	BSC	BSC
E	GUS	UST 90 mg	IFX	BSC	BSC
F	IXE	UST 90 mg	IFX	BSC	BSC
G	SEC	UST 90 mg	IFX	BSC	BSC
H	UST 45 mg	ADA	IFX	BSC	BSC
I	UST 90 mg	ADA	IFX	BSC	BSC

Abbreviations: ADA: adalimumab; BROD: brodalumab; BSC: best supportive care; CZP: certolizumab pegol; ETN, etanercept; GUS: guselkumab; IFX: infliximab; IXE: ixekizumab; SEC: secukinumab; UST: ustekinumab.

An additional analysis was conducted to model the escalation of the CZP dose from 200 mg to 400 mg in patients with insufficient response. For this analysis it is assumed that this does not count as an additional line of treatment and therefore CZP is still followed by two subsequent biologics and then BSC (Table 69). Due to the issues of comparing non-equivalent treatment sequences and the spurious conclusions that can be drawn from such comparisons, the

escalation of CZP 200 mg to the 400 mg dose for patients with an insufficient response has been compared to the closest possible scenario that could occur in clinical practice, which is the escalation of ADA 40 mg Q2W to 80 mg Q2W for patients with an insufficient response to the lower dose (Table 69).[4]

Table 69: Treatment sequences modelled for systemic non-biologic therapy inadequate responders – additional analyses for dose escalation strategies (CZP 200 mg escalation to CZP 400 mg)

Sequence	1st line	2nd line	3rd line	4th line	5th line
A	CZP 200 mg	CZP 400 mg	UST 90 mg	IFX	BSC
K	ADA 40 mg	ADA 80 mg	UST 90 mg	IFX	BSC

Abbreviations: ADA: adalimumab; BSC: best supportive care; CZP: certolizumab pegol; IFX: infliximab; UST: ustekinumab.

For the candidates for systemic non-biologic therapy, the CZP treatment sequence A is compared with standard of care, with the clinical data for standard of care derived from the placebo arms of the CZP Phase III clinical trial data. Standard of care is then followed by biologics using the common biologic sequence of ADA, UST 90 mg and IFX.

Table 70: Treatment sequences modelled for candidates for systemic non-biologic therapy

Sequence	1st line	2nd line	3rd line	4th line	5th line
A	CZP 200 mg	UST 90 mg	IFX	BSC	BSC
L	SoC	ADA	UST 90 mg	IFX	BSC

Abbreviations: ADA: adalimumab; BSC: best supportive care; CZP: certolizumab pegol; IFX: infliximab; UST: ustekinumab.

The model allows only logical use of comparators in the sequence, therefore it is not possible for a given therapy to be used more than once within a single treatment sequence.

It should be noted that the availability of a number of biologic therapies for moderate-to-severe plaque psoriasis makes a variety of other treatment sequences possible. The presented treatment sequences have been selected to enable the cost-effectiveness of CZP to be compared with those sequences most likely to be used in clinical practice, as CZP is considered as a first-line treatment option. This is a similar approach to that which has been taken in recent appraisals in psoriasis, which has previously been accepted by NICE (TA511, TA442).[48, 52]

The modelling of treatment sequences, although reflecting clinical practice, can be associated with problems, where comparisons of sequences using different biologics at the different lines results in spurious results due to non-cost-effective therapies being used at second or later lines. In case this is a problem in this analysis, a scenario analysis has been carried out to compare each first-line biologic followed only by BSC (settings as per Table 71). This gives a good indication of the relative cost-effectiveness of each individual biologic, rather than comparing them within a sequence.

Table 71: Model settings for comparison of individual therapies

Sequence	1st line	2nd line	3rd line	4th line
L	CZP 200 mg	BSC	BSC	BSC

M	CZP 200 mg	CZP 400 mg	BSC	BSC
N	ADA	BSC	BSC	BSC
O	BROD	BSC	BSC	BSC
P	ETN	BSC	BSC	BSC
Q	GUS	BSC	BSC	BSC
R	IXE	BSC	BSC	BSC
S	SEC	BSC	BSC	BSC
T	UST 45 mg	BSC	BSC	BSC
U	UST 90 mg	BSC	BSC	BSC

Abbreviations: ADA: adalimumab; BSC: best supportive care; CZP: certolizumab pegol; IFX: infliximab; SEC: secukinumab; UST: ustekinumab.

Best supportive care

BSC is used as the last-line option in all treatment sequences. To model the efficacy of BSC, the PASI response is determined by both the MTX arm of the NMA (weighted at 55%) and the placebo arm of the NMA (weighted at 45%). The costs of BSC are discussed in Section B.3.5.2.

B.3.3 *Clinical parameters and variables*

For the systemic non-biologic therapy inadequate responders, clinical parameters (PASI response and overall discontinuation during the initial treatment phase) were derived from an SLR and NMA (see Appendix D). For the population who are candidates for systemic non-biologic therapy, the clinical parameters in the model were derived from the CZP and placebo arms of the pooled CZP Phase III trials for the subgroup of patients who were naïve to both biologic and non-biologic systemic therapy (for clinical data see Section B.2.6.9).

Further details regarding the clinical parameters and variables captured in the economic model can be found in the following subsections.

B.3.3.1 Starting patient characteristics

The starting patient characteristics used in the model for the systemic non-biologic inadequate responders population were based on the pooled NMA data. For the candidates for systemic non-biologic therapies patient population, starting patient characteristics were taken from the Pool E1 baseline characteristics for this subpopulation, as presented in Appendix M. Characteristics for both population are presented in Table 72 below.

Table 72: Starting patient characteristics

Model parameter	Value	Source
Systemic non-biologic inadequate responders		
Mean age, years	44.9 years	Pooled NMA data
Percentage male	69.2%	
Mean weight (kg)	87.2 kg	
Candidates for systemic non-biologic therapies		
Mean age, years	45.4 years	

Percentage male	63.4%	'All CZP' from Pool E1 candidates for systemic non-biologic subpopulation (see Appendix M)
Mean weight (kg)	91.8 kg	

Abbreviations: CZP: certolizumab pegol.

B.3.3.2 PASI response

As discussed in Section B.3.2.2, response to treatment was assessed at the at the end of the initial treatment phase, dependent on the initial intervention. Using data from the NMA (see Section B.2.9), the distribution of patients across four PASI response categories at the end of the initial treatment phase was captured for each of the therapies modelled (Table 73). ADA 80 mg Q2W was not included within the NMA and therefore the estimate for this dose was obtained by multiplying the PASI75 score for ADA 40 mg Q2W by a factor of 1.5, which was derived from the CHAMPION 1 study,[1] and all other PASI responses were adjusted proportionally.

For the candidates for systemic non-biologics population, the distribution of patients across four PASI response categories was available for both CZP doses and placebo from the subpopulation analysis from the pooled phase III CZP trials (Table 73). Unfortunately, data were not available from other comparators from the NMA, and therefore the ITT data were used as proxy.

Table 73: PASI response by therapy received, systemic non-biologic therapy inadequate responders population [derived from NMA, apart from ADA 80 mg]

	Response			
Treatment	**PASI <50**	**PASI 50–<75**	**PASI 75–<90**	**PASI 90+**
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]
ADA 80 mg*	[redacted]	[redacted]	[redacted]	[redacted]
BROD	[redacted]	[redacted]	[redacted]	[redacted]
BSC**	[redacted]	[redacted]	[redacted]	[redacted]
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]
CZP 400 mg	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]
GUS	[redacted]	[redacted]	[redacted]	[redacted]
IFX	[redacted]	[redacted]	[redacted]	[redacted]
IXE	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]
UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]
UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]

*ADA 80 mg derived from the CHAMPION study. **BSC is a mixture of placebo and MTX at a proportion of 45:55.
Abbreviations: ADA: adalimumab; BID: twice a day; BIW: twice a week; BROD: brodalumab; BSC: best supportive care; CZP: certolizumab pegol; DMF: dimethyl fumarate; ETN: etanercept; GUS: guselkumab; IFX: infliximab; IXE: ixekizumab; PASI: Psoriasis Area and Severity Index; Q1W: every week; Q2W: every two weeks; Q8W: every eight weeks; Q12W: every twelve weeks; SEC: secukinumab; UST: ustekinumab.

Table 74: PASI response by therapy received, candidates for systemic non-biologic therapy population [derived from pooled subpopulation from CZP trials]

	Response			
Treatment	**PASI <50**	**PASI 50–<75**	**PASI 75–<90**	**PASI 90+**
Standard of care*	[redacted]	[redacted]	[redacted]	[redacted]
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]
CZP 400 mg	[redacted]	[redacted]	[redacted]	[redacted]

*Standard of care was represented by the pooled placebo arms from the CZP trials in this analysis.
Abbreviations: CZP: certolizumab pegol; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks

B.3.3.3 Discontinuation

Discontinuation in the Initial Treatment Phase

The rate of treatment discontinuation during the initial treatment phase was determined for each therapy through NMA of clinical trial data (see Section B.2.9; Table 75).

Table 75: Discontinuation rate per person week during the initial and maintenance treatment phases, by therapy

Therapy	Weekly discontinuation rate: initial treatment phase	Weekly discontinuation rate: maintenance treatment phase
ADA	[redacted]	0.200
BROD	[redacted]	0.200
BSC*	[redacted]	0.200
CZP 200 mg	[redacted]	0.200
CZP 400 mg	[redacted]	0.200
ETN	[redacted]	0.200
GUS	[redacted]	0.200
IFX	[redacted]	0.200
IXE	[redacted]	0.200
SEC	[redacted]	0.200
UST 45 mg	[redacted]	0.200
UST 90 mg	[redacted]	0.200

*BSC is a mixture of placebo and MTX at a proportion of 45:55.
Abbreviations: ADA: adalimumab; APR: apremilast; BROD: brodalumab; CZP: certolizumab pegol; DMF: dimethyl fumarate; ETN: etanercept; GUS: guselkumab; IFX: infliximab; IXE: ixekizumab; MTX: methotrexate; Q1W: every week; Q2W: every two weeks; RIS: risankizumab; SEC: secukinumab; TIL: tildrakizumab; UST: ustekinumab.

Discontinuation in the maintenance phase

Long-term discontinuation was poorly reported by the captured clinical trials. Therefore, discontinuation during the maintenance treatment phase is based on real-world evidence from

the BAD Biologic Interventions Register (BADBIR).[38] According to these data, the annual rate of treatment discontinuation among psoriasis patients receiving biologic therapy (including those switching to an alternative therapy) is 20% in the 12 months following treatment initiation (Table 75).[38] This rate is assumed for all therapies during the maintenance treatment phase, and matches the discontinuation rates applied in many previous CEAs submitted to NICE (TA146, TA350, TA442, TA511).[47, 48, 52, 53]

In the recent GUS NICE appraisal in psoriasis (TA521),[50] the ERG used differential discontinuation rates in the maintenance phase for the different biologics. Data from clinical trials indicate that CZP has high durability data, which has been indicated by a UK clinical expert as being different to other anti-TNFs in psoriasis. Therefore, a class effect when it comes to long-term discontinuation cannot be assumed. Due to the lack of BADBIR data specifically on CZP, the differential discontinuation rates have not been applied in the base case, which is assumed to be a conservative assumption for CZP. Different maintenance discontinuation rates for the different biologics have been explored in scenario analyses. ADA was changed to 18%, ETN to 29% and all other biologics, including CZP, were changed to 9%.[38, 50]

B.3.3.4 Mortality

According to clinical expert opinion, there is a link between moderate to severe psoriasis and an increased risk of cardiovascular morbidity and mortality, possibly as a result of systemic inflammation. However, moderate to severe psoriasis is also associated with obesity, which in turn is itself associated with cardiovascular disease. In the absence of robust evidence establishing an independent link between psoriasis and cardiovascular mortality, no quantitative analyses have been undertaken. Mortality rates were therefore modelled using age- and sex-dependent general mortality UK life tables,[119] i.e., the CEA did not assume an additional risk of mortality due to psoriasis. This is in line with the majority of previous HTA submissions for moderate to severe psoriasis, which either did not include mortality,[115, 121-123] or included mortality but in a way that was not disease- or treatment-dependent.[114, 116, 124]

The risk of all-cause mortality has been adjusted to reflect the time spent in the initial phase to accurately capture costs and benefits (i.e. estimated as a rate per person week and applied for the relevant number of weeks).

B.3.4 *Measurement and valuation of health effects*

As per the NICE reference case, the current analysis captures health effects expressed as quality-adjusted life years (QALYs).

B.3.4.1 Health-related quality-of-life data from clinical trials

According to the NICE reference case, the preferred measure of HRQoL is EQ-5D reported directly by patients and/or carers. Furthermore, the valuation of HRQoL should reflect the preferences of a sample representative of the UK population.[112] All three phase III CZP clinical trials collected self-reported EQ-5D-3L data (Table 9); a multivariable risk equation was then developed to predict HRQoL weights (i.e. utility values) based on these data. The variables considered included age, sex and BMI (since these variables are known to predict differences in HRQoL), as well as key variables specific to this analysis:

- Baseline PASI

- PASI response (by category)
- Biologic exposed (yes versus no)
- Treatment

CZP data have been analysed as a longitudinal dataset: in the phase III trials, EQ-5D data was collected during patients visits at weeks 0, 8, 12, 16, 24, 32, and 48. Measurements from the same individual are much more likely to be correlated than measurements from different individuals, and this must be taken into consideration when analysing data with repeated measures to avoid misrepresenting uncertainty in estimates and drawing incorrect inferences.

The generalised estimating equations (GEE) approach was selected to analyse the CZP data due to the structure of the available EQ-5D datasets, which contained multiple observations per patient as described above. A GEE framework (also known as marginal or population averaged model) is an extension to general linear model which considers the correlation associated with repeated sampling from the same individual by adjusting standard errors using an imposed (pre-defined) correlation structure. The EQ-5D data were transformed prior to analysis to account for the non-normality of the EQ-5D (left skewed and kurtotic).

In order to derive final utility values, coefficients for the explanatory variables have to be back transformed using the following equation:

$$Utility\ score = 1 - EXP(Coefficient)$$

In the final regression equation, continuous variables were centred on the mean estimates for RCTs included in the NMA (BMI 28.9, age 44.9 years). A treatment variable was tested in the final regression model and a significant treatment effect was observed.

B.3.4.2 Mapping

Mapping was not required, since EQ-5D data captured from the phase III CZP clinical trials were used in the model.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify relevant utility studies; full details of the search strategy for this SLR are presented in Appendix H.

The SLR identified 45 publications meeting the eligibility criteria, corresponding to 38 unique studies. Of the studies identified in the SLR, all but one reported health utilities using the EQ-5D; the remaining study used SF-6D. Appendix H presents further details of the captured utility studies.

With the exception of one study by Pickard et al. (2016), utility values reported by the RCTs and observational studies were not stratified by health states and therefore may not be suitable for use in a CEA. In contrast, all the model-based economic evaluations stratified EQ-5D scores by health states (i.e., PASI response categories).

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

The utility values derived from the equation described in Section B.3.4.1 and employed in the base case are reported in Table 76. The analysis of the trial EQ-5D data provided a utility values for the placebo arm and for the biologics. The base case analysis uses the analysis that included a treatment effect for all biologics. A scenario analysis investigates the impact of using the regression analysis that did not include a treatment factor.

The placebo utilities have been applied to BSC in the base case and to standard of care for the population who are candidates for systemic non-biologic therapy.

Table 76: Summary of utility values for CEA

State	Utility value: mean	95% confidence interval	Reference in submission (section and page number)	Justification
No treatment effect: BSC and standard of care for candidates for systemic non-biologics				
Baseline PASI	[redacted]	NR	See Section B.3.4.1 above for methodology	Derived from EQ-5D data from the CZP Phase III trials, in accordance with the NICE reference case.
PASI <50	[redacted]	NR		
PASI 50–75	[redacted]	NR		
PASI 75–90	[redacted]	NR		
PASI 90–100	[redacted]	NR		
Treatment effect: All biologics				
Baseline PASI	[redacted]	NR	See Section B.3.4.1 above for methodology	Derived from EQ-5D data from the CZP Phase II trials, in accordance with the NICE reference case. These values have been selected to also apply to all other biologics.
PASI <50	[redacted]	NR		
PASI 50–75	[redacted]	NR		
PASI 75–90	[redacted]	NR		
PASI 90–100	[redacted]	NR		

Abbreviations: CEA: cost-effectiveness analysis; HS, health state; NR: not reported; PASI: psoriasis area and severity index; Q2W: every two weeks.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

An SLR was conducted to identify cost and healthcare resource use data for chronic plaque psoriasis patients. The SLR identified 12 publications meeting the eligibility criteria, corresponding to 12 unique studies, of which one was a healthcare resource use study. This study reported direct medical costs (medication; inpatient, ICU and HDU admissions; A&E and outpatient visits; day ward admission and phototherapy).

B.3.5.1 Intervention and comparators' costs and resource use

The base case analysis considered the following cost and healthcare resource use inputs: treatment acquisition and administration, monitoring and disease management costs. Only direct medical care costs to the NHS are captured. Costs data were sourced from NHS reference costs and the Personal Social Services Research Unit (PSSRU).

Treatment acquisition costs

Treatment acquisition costs were sourced from BNF list prices, or where available, agreed patient access scheme information. Table 77 and Table 78 present the treatment acquisition cost data captured in the base case analysis, for licensed regimens in the initial and maintenance treatment phases, respectively. The acquisition costs for CZP also include the complex PAS, where the first 12 weeks of treatment are free. The model also captures the flat pricing scheme for UST, whereby the 90 mg dose is available for the same price as the 45 mg dose. IFX dosing is based on patient body weight (Table 72); the acquisition costs for IFX have therefore been estimated using the mean baseline patient weight NMA (87.2 kg). The dose for MTX is based on 25% of patients receiving SC MTX, and 75% receiving oral MTX, following discussions with a clinical expert on the use of MTX in practice.

According to expert clinical advice, biosimilars for IFX and ETN are used in clinical practice (20% of all IFX use and 40% of all ETN use). Treatment sequences including biosimilars have been explored as a scenario analysis in the submission.

Table 77: Treatment acquisition costs during the initial treatment phase

Treatment	Drug	Regimen	Unit cost	No. of vials/ syringes/ tablets	Total costs
CZP 200 mg	Cimzia 200 mg	Per 200 mg SC injection	£357.50	12	List price: £4,290.00 PAS price: £715.00
ADA 40 mg	Humira 40 mg	Per 40 mg SC injection	£352.14	10	£3,521.40
BROD	Kyntheum 210 mg	Per 210 mg SC injection	£640.00	8	£5,120.00
ETN (originator)	Enbrel 25 mg	Per 25 mg SC injection	£89.38	24	£2,145.12
ETN (biosimilar)	Benepali 25 mg	Per 25 mg SC injection	£82.00	24	£1,968.00
ETN (biosimilar)	Erelzi 25 mg	Per 25 mg SC injection	£80.44	24	£1,930.56
GUS	Tremfya 100 mg	Per 100 mg SC injection	£2,250.00	3	£6,750.00
IFX (originator)	Remicade 100 mg	Per 100 mg infusion	£419.62	15	£6,294.30
IFX (biosimilar)	Flixabi 100 mg	Per 100 mg infusion	£377.00	15	£5,655.00
IXE	Taltz 80 mg	Per 80 mg SC injection	£1,125.00	8	£9,000.00
SEC	Cosentyx 150 mg	Per 150 mg SC injection	£609.39	12	£7,312.68
UST 45 mg	Stelara 45 mg	Per 45 mg SC injection	£2,147.00	2	£4,294.00
UST 90 mg	Stelara 90 mg	Per 90 mg SC injection	£2,147.00	2	£4,294.00

*PAS for CZP 400 mg Q2W is only applied if used as the first-line dose.
Abbreviations: ADA: adalimumab; APR: apremilast; BID: twice a day; BIW: twice a week; BROD: brodalumab; CZP: certolizumab pegol; DMF: dimethyl fumarate; ETN: etanercept; GUS: guselkumab; IFX: infliximab; IXE: ixekizumab; MTX: methotrexate; Q1W: every week; Q2W: every two weeks; Q4W: every four weeks; Q8W: every eight weeks; Q12W: every twelve weeks; SEC: secukinumab; UST: ustekinumab.

Table 78: Treatment acquisition costs during the maintenance treatment year (year 2)

Treatment	Drug	Regimen	Unit cost	No. of unit doses per year	Annual costs	Costs per two-week cycle
CZP 200 mg	Cimzia 200 mg	Per 200 mg SC injection	£357.50	26	£9,295.00	£356.28
ADA 40 mg	Humira 40 mg	Per 40 mg SC injection	£352.14	26.09	£9,187.08	£ 352.14
BROD	Kyntheum 210 mg	Per 210 mg SC injection	£640.00	26.09	£16,697.14	£ 640.00
ETN (originator)	Enbrel 25 mg	Per 25 mg SC injection	£89.38	104	£9,295.52	£ 352.30
ETN (biosimilar)	Benepali 25 mg	Per 25 mg SC injection	£82.00	104	£8,557.52	£329.14
ETN (biosimilar)	Erelzi 25 mg	Per 25 mg SC injection	£80.44	104	£8,394.72	£322.87
IFX (originator)	Remicade 100 mg	Per 100 mg infusion	£419.62	32.61	£13,684.48	£524.53
IFX (biosimilar)	Flixabi 100 mg	Per 100 mg infusion	£377.00	32.61	£12,441.00	£478.50
IXE	Taltz 80 mg	Per 80 mg SC injection	£1,125.00	13	£14,625.00	£ 560.57
SEC	Cosentyx 150 mg	Per 150 mg SC injection	£609.39	24	£14,625.00	£ 560.57
UST 45 mg	Stelara 45 mg	Per 45 mg SC injection	£2,147.00	4.33	£9,296.51	£ 356.33
UST 90 mg	Stelara 90 mg	Per 90 mg SC injection	£2,147.00	4.33	£9,296.51	£ 356.33
GUS	Tremfya 100 mg	Per 100 mg SC injection	£357.50	7	£15,750	£ 603.70

Abbreviations: ADA: adalimumab; APR: apremilast; BID: twice a day; BIW: twice a week; BROD: brodalumab; BSC: best supportive care; CZP: certolizumab pegol; DMF: dimethyl fumarate; ETN: etanercept; GUS: guselkumab; IFX: infliximab; IXE: ixekizumab; MTX: methotrexate; Q1W: every week; Q2W: every two weeks; Q8W: every eight weeks; Q12W: every twelve weeks; RIS: risankizumab; SEC: secukinumab; TIL: tildrakizumab; UST: ustekinumab.

Treatment administration costs

The applied treatment administration costs (Table 80) are consistent with previous NICE HTA submissions. The cost of training patients to self-administer subcutaneous injections required 1 x 1-hour training sessions with a nurse and was applied in the model only once at the start of subcutaneous treatment (Table 79). In contrast, intravenous administration was assumed to be captured by NHS reference cost data and was applied at each IV infusion visit (Table 79).

Table 79: Treatment administration costs

Resource Use Item	Description	Frequency	Cost Per Unit	Total Cost
Cost starting subcutaneous therapy	One hour nurse time for self-injection training[125]	1 (at start of treatment)	£36.00	£36.00
Cost per intravenous administration	NHS Reference Cost 2016-17, Dermatology: Outpatient Procedure: WF01A, "Non-admitted Face to Face Attendance, Follow-up". [126]	1 (for each IV administration)	£101.54	£101.54

Treatment monitoring costs

Treatment monitoring costs for the initial and maintenance treatment phases are captured in Table 80, including the frequency of monitoring costs. These were assumed to be similar across treatments, with IV treatment having different frequencies during the initial treatment period.

Table 80: Treatment monitoring costs per year during the initial and maintenance treatment phases

Description	Data Source	Unit Cost	Frequency	Cost	Total cycle cost
Initial treatment phase					
SC injection					
Dermatologist	Consultant Led Outpatient Attendances service code 330 in Dermatology[126]	£101.54	2	£203.08	£247.27
FBC	Currency Code: DAPS05 (Haematology)[126]	£3.06	2	£6.12	
U&E	Currency Code: DAPS04 (Clinical Biochemistry)[126]	£1.13	2	£2.26	
Chest x-ray	Portsmouth CCG[127]	£27.00	1	£27.00	
Tuberculosis tests	Currency Code: DAPS06 (Immunology)[126]	£6.55	1	£6.55	
LFT	Currency Code: DAPS04 (Clinical Biochemistry)[126]	£1.13	2	£2.26	
IV infusion					

Dermatologist	Consultant Led Outpatient Attendances service code 330 in Dermatology[126]	£101.54	3	£304.62	£354.13
FBC	Currency Code: DAPS05 (Haematology)[126]	£3.06	3	£9.18	
U&E	Currency Code: DAPS04 (Clinical Biochemistry)[126]	£1.13	3	£3.39	
Chest x-ray	Portsmouth CCG[127]	£27.00	1	£27.00	
Tuberculosis tests	Currency Code: DAPS06 (Immunology)[126]	£6.55	1	£6.55	
LFT	Currency Code: DAPS04 (Clinical Biochemistry)[126]	£1.13	3	£3.39	
Maintenance treatment phase					
SC injection or IV infusion					
Dermatologist	Consultant Led Outpatient Attendances service code 330 in Dermatology[126]	£101.54	2	£203.08	£213.72
FBC	Currency Code: DAPS05 (Haematology)[126]	£3.06	2	£6.12	
U&E	Currency Code: DAPS04 (Clinical Biochemistry)[126]	£1.13	2	£2.26	
Chest x-ray	Portsmouth CCG[127]	£27.00	0	£0.00	
Tuberculosis tests	Currency Code: DAPS06 (Immunology)[126]	£6.55	0	£0.00	
LFT	Currency Code: DAPS04 (Clinical Biochemistry)[126]	£1.13	2	£2.26	

Abbreviations: FBC: full blood count; IV: intravenous; LFT: liver function tests; N/A: not applicable; PSA: probabilistic sensitivity analysis; SC: subcutaneous; U&E: urea and electrolytes.

Best supportive care

The costs for patients on BSC (or standard of care when used as the first-line comparator for the candidates for systemic non-biologic treatments sequence) were derived from the UK study by Fonia *et al.* (2010). This study was a retrospective, observational UK cohort study of adult patients with psoriasis that had received treatment with biologics for at least six months at one centre in the UK (n=96).[128] Previous CEAs in this disease area have used this study to capture the costs for BSC. Fonia *et al.* compared the resource use and disease severity for the 12 months before and 12 months after commencement of biological therapy.[128] The model uses the secondary care costs from Fonia *et al.* for the 12 months before commencement of biologic therapy, inflated using HCHS to 2017, to calculate the secondary care costs for patients on BSC. The costs for systemic non-biologic therapies were taken from the BNF. Expert clinical opinion stated that approximately 25% of patients who receive MTX are given it subcutaneously. Therefore the cost of MTX has been derived from a weighted average of the subcutaneous and oral MTX cost using the proportion 25:75, respectively.

The proportion of patients on each systemic non-biologic treatment was taken from expert clinical opinion which indicated that fumarates are no longer used as part of BSC (Table 81). However, a scenario was performed using the proportions from Fonia *et al.* for completeness.

Table 81: Proportion of patients on each systemic non-biologic treatment in BSC

Systemic non-biologic treatment	Proportions from Fonia *et al.*, %	Proportions from expert clinical opinion (base case), %
MTX	41	55
Acitretin	24	10
Ciclosporin	47	35
Fumarates	25	0

[a]Please note that the cost per day for each treatment was taken from Fonia *et al.* (2010) and inflated using HCHS 2016/17 index.

Table 82: Costs for systemic non-biologic therapies used in BSC/standard of care

	Unit	Cost per pack (BNF)	Units per pack	Unit cost	Dose	Cost per day
Acitretin	25mg capsules	£43.00	60	£0.72	30 mg per day	£0.72
Ciclosporin	100 mg capsules	£48.89	30	£1.63	2.5 mg/kg/day (mean weight 87.2 kg)	£3.55
Methotrexate - oral	10 mg tablet	£38.00	100	£0.38	10 mg per week	£0.05
Methotrexate - SC	10 mg injection	£13.77	1	£13.77	10 mg per week	£1.97
Methotrexate weighted average (25% SC*)				£3.73	10 mg per week	£0.53

*Based on clinical expert opinion
Abbreviations: BNF, British National Formulary; SC, subcutaneous

Table 83: Costs for patients on BSC calculated from Fonia *et al.* (2010)

	Costs per annum	Costs per cycle
Systemic non-biologic therapy costs	£183.06	£7.02
Secondary care costs[a]	£3,488.60	£133.72
Total per annum	£3,671.66	£140.73

[a]Secondary care costs were inflated from Fonia *et al.* using the HCSC index to 2016/17.

B.3.5.2 Health state unit costs and resource use

Non-responder costs

Previous NICE appraisals have also included a cost for patients considered to be non-responders. This cost is applied each cycle for patients classified as non-responders in the model or have discontinued biologic treatment due to loss of response or AEs. The cost was

calculated from the total systemic non-biologic and secondary care costs from Fonia *et al.* for the 12 months before commencement of biologic therapy (i.e. the per-cycle cost used for BSC within the model [£140.738]). The cost for non-responders is applied in the initial treatment period for each treatment in the sequence, apart from if that treatment was BSC (where the costs for BSC were applied in the initial and maintenance treatment periods).

B.3.5.3 Adverse reaction unit costs and resource use

Consistent with previous UK HTA submissions, TRAEs have not been included in this analysis.

B.3.5.4 Miscellaneous unit costs and resource use

No further miscellaneous unit costs or resource use data were included in the model.

B.3.6 *Summary of base case analysis inputs and assumptions*

B.3.6.1 Summary of base case analysis inputs

A summary of the model parameters used for the base case analysis is presented in Table 84.

Table 84: Summary of variables applied in the base case for the systemic non-biologic therapy inadequate responders

Variable	Value (reference to appropriate table or figure in submission)				Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings						
Time horizon	Lifetime				N/A	Section B.3.2.2
Discount rate (costs and benefits)	3.5%				N/A	
Patient characteristics						
Age	44.89 years				N/A	Section B.3.3.1
Weight	87.20 kg				N/A	
Male, %	69.2%				N/A	
Baseline utility values						
Baseline PASI	[redacted]				+/- 20%	
Treatment effects: PASI response rates/week during the initial treatment phase						
	<PASI50	**PASI50–<PASI75**	**PASI75–<PASI90**	**PASI90**		
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	Section B.3.3.2
ADA 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
BROD	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
CZP 400 mg	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
ETN	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
GUS	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
IFX	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
IXE	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
SEC	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
Discontinuation rate during the initial treatment phase						
ADA	[redacted]				Lognormal	Section B.3.3.3
BROD	[redacted]				Lognormal	
BSC	[redacted]				Lognormal	

CZP 200 mg	[redacted]	Lognormal	
CZP 400 mg	[redacted]	Lognormal	
ETN	[redacted]	Lognormal	
GUS	[redacted]	Lognormal	
IFX	[redacted]	Lognormal	
IXE	[redacted]	Lognormal	
SEC	[redacted]	Lognormal	
UST 45 mg	[redacted]	Lognormal	
UST 90 mg	[redacted]	Lognormal	
Discontinuation rate per two-week cycle during the maintenance treatment phase			
All therapies	0.004276536	+/- 20%	Section B.3.3.3
HRQoL weights by PASI response: no treatment effect (BSC)			
Baseline PASI	[redacted]	Lognormal	Section B.3.4.4
PASI <50	[redacted]		
PASI 50–75	[redacted]		
PASI 75–90	[redacted]		
PASI 90–100	[redacted]		
HRQoL weights by PASI response: treatment effect (all biologics)			
Baseline PASI	[redacted]	Lognormal	Section B.3.4.4
PASI <50	[redacted]		
PASI 50–75	[redacted]		
PASI 75–90	[redacted]		
PASI 90–100	[redacted]		
Total treatment acquisition costs: initial treatment phase			
CZP 200 mg	£715.00 (with PAS)	N/A	Section B.3.5.1
ADA 40 mg	£3,521.40	N/A	
BROD	£5,120.00	N/A	
ETN	£2,145.12	N/A	
IFX	£6,294.30	N/A	
IXE	£9,000.00	N/A	
SEC	£7,312.68	N/A	
UST 45 mg	£4,294.00	N/A	
UST 90 mg	£4,294.00	N/A	
Treatment acquisition costs: maintenance phase cost per cycle			
CZP 200 mg	£356.28	N/A	Section B.3.5.1
ADA 40 mg	£ 352.14	N/A	

BROD	£ 640.00	N/A	
ETN	£ 356.30	N/A	
GUS	£ 603.70	N/A	
IFX	£524.53	N/A	
IXE	£ 560.57	N/A	
SEC	£ 560.59	N/A	
UST 45 mg	£ 356.33	N/A	
UST 90 mg	£ 356.33	N/A	
Treatment administration costs			
Cost starting SC therapy	£36.00	N/A	Section B.3.5.1
Cost per IV administration	£101.54	N/A	
Treatment monitoring costs per year: SC injection (initial treatment phase)			
Dermatologist	£203.08	N/A	Section B.3.5.1
FBC	£6.12	N/A	
U&E	£2.26	N/A	
Chest x-ray	£27.00	N/A	
Tuberculosis tests	£6.55	N/A	
LFT	£2.26	N/A	
Treatment monitoring costs per year: IV infusion (initial treatment phase)			
Dermatologist	£304.62	N/A	Section B.3.5.1
FBC	£9.18	N/A	
U&E	£3.39	N/A	
Chest x-ray	£27.00	N/A	
Tuberculosis tests	£6.55	N/A	
LFT	£3.39	N/A	
Treatment monitoring costs per year: maintenance treatment phase			
Dermatologist	£203.08	N/A	Section B.3.5.1
FBC	£6.12	N/A	
U&E	£2.26	N/A	
Chest x-ray	£0.00	N/A	
Tuberculosis tests	£0.00	N/A	
LFT	£2.26	N/A	
Total treatment monitoring costs			

Drug monitoring SC therapies initial period	£247.27	N/A	Section B.3.5.1
Drug monitoring IV therapies initial period	£354.13	N/A	
Drug monitoring maintenance phase	£213.72	N/A	
Best supportive care			
Cost per cycle	£140.73	N/A	Section B.3.5.1
Non-responder cost			
Cost per cycle	£140.73	N/A	Section B.3.5.2

Abbreviations: ADA: adalimumab; APR: apremilast; BID: twice a day; BIW: twice a week; BROD: brodalumab; BSC: best supportive care; CI: confidence interval; CZP: certolizumab pegol; DMF: dimethyl fumarate; ENT: etanercept; FBC: full blood count; GUS: guselkumab; HRQoL: health-related quality of life; IFX: infliximab; IXE: ixekizumab; IV: intravenous; LFT: live function test; MTX: methotrexate; N/A: not applicable; PASI: Psoriasis Area and Severity Index; Q1W: every week; Q2W: every two weeks; Q8W: every eight weeks; Q12W: every twelve weeks; SC: subcutaneous; SEC: secukinumab; U&E: urea and electrolytes; UST: ustekinumab.

Table 85: Summary of variables applied in the base case for the candidates for systemic non-biologic therapy that are different to those in the table above

Variable	Value (reference to appropriate table or figure in submission)				Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Starting patient characteristics						
Age	45.4				N/A	Section B.3.3.1
Weight	91.8 kg				N/A	
Male, %	63.4%				N/A	
Treatment effects: PASI response rates /week during the initial treatment phase						
	<PASI50	**PASI50–<PASI75**	**PASI75–<PASI90**	**PASI90**		
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	Section B.3.3.2
CZP 400 mg	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	+/- 20%	

Abbreviations: CZP: certolizumab pegol; DMF: dimethyl fumarate; ENT: etanercept; FBC: full blood count; GUS: guselkumab; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks

B.3.6.2 Assumptions (base case)

The assumptions for the base case are described in Table 86 below.

Table 86. Base case assumptions

Parameter	Assumptions	Consistent with prior TAs?	Justification
Time horizon	Lifetime	Yes[a]	Psoriasis is a chronic disease
Health states	Treatment response defined as PASI75 response	Yes	PASI75 response is the primary outcome in the majority of clinical trials, and is accepted by NICE
Treatment efficacy	Treatment effect assumed to be maintained with ongoing treatment	Yes	Clinical trial data indicates a high durability of response into the long-term with CZP. Patients not responding to treatment have been captured within the maintenance discontinuation rate
	Treatment effect assumed to be the same regardless of exposure to prior therapies	Yes	Subgroup analysis of the CZP phase III trials has shown that the efficacy benefit of CZP is similar in the biologic naïve and biologic exposed subgroups (Section B.2.7.1). The same assumption has been applied in previous appraisals in psoriasis, although this might not necessarily be true for all biologics. A sensitivity analysis has been conducted using NMA data from patients without prior biologic exposure.
Mortality	Modelled using age- and sex-dependent general mortality UK life tables (no additional risk of mortality due to psoriasis applied)	Yes	According to clinical expert opinion, there is a link between moderate to severe psoriasis and an increased risk of cardiovascular mortality. However, in the absence of robust published evidence, no quantitative analyses have been undertaken
Discontinuation	Rate of discontinuation assumed to be the same for all therapies during the maintenance treatment phase	Yes	Long-term discontinuation was poorly reported by the captured clinical trials, therefore discontinuation during the maintenance treatment phase is based on real-world evidence from BADBIR
Adverse events	TRAEs not included in this analysis	Yes	Clinical expert opinion indicated that the identified TRAEs are very rare. CZP has a similar safety profile to the other biologics.

[a]Company submission for IXE modelled a lifetime horizon
Abbreviations: BAD: British Association of Dermatology; NICE: National Institute for Health and Care Excellence; PASI: Psoriasis Area and Severity Index; TA: technology appraisal; TRAE: treatment-related adverse event.

B.3.7 *Base case results*

B.3.7.1 Base case incremental cost-effectiveness analysis results

Systemic non-biologic therapy inadequate responders

Table 87 below presents the base case fully incremental results for the treatment sequences presented in Table 68. CZP 200 mg was found to be cost-effective versus all comparators considered. CZP was dominant against UST, ADA and GUS and was cost-effective versus ETN (ICER: £11,649.66/QALY). There was a very small difference in the incremental QALYs between treatment sequences. SEC, IXE and BROD were more costly when compared to CZP 200mg, with similar efficacy (small incremental QALY) vs CZP.

Table 87: Base case fully incremental results for systemic non-biologic therapy inadequate responders – CZP with PAS

Treatment sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Fully incremental ICER (£/QALY)
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
A	CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,649.66	£11,649.66
I	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,762.95	CZP dominates
H	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,592.85	CZP dominates
B	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,390.47	CZP dominates
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£167,333.97	CZP dominates
F	SEC[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£130,588.53	£578,676.00
G	IXE[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£127,205.97	£414,497.67
C	BROD[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£148,272.21	£654,589.75

[a]ICERs represent comparator vs CZP.
Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; FOC: free of charge; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekizumab; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; SEC: secukinumab; UST: ustekinumab.

Table 88 presents the results of the CZP escalation strategy (CZP 200 mg to CZP 400 mg for those with an insufficient response to CZP 200 mg), compared to ADA (ADA 40 mg to ADA 80 mg), the only similar escalation strategy as per the label and 2017 BAD guidelines. The base case analysis indicated that compared with the ADA escalation sequence, the CZP escalation strategy is more efficacious (incremental QALY of [redacted]), but more costly (incremental costs of £[redacted]), leading to an ICER of £37,053.86.

Table 88: Base case results for systemic non-biologic therapy inadequate responders – CZP escalation strategy with PAS

Treatment sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER CZP versus comparator (£/QALY)
J	CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,053.86
K	ADA 40 mg	[redacted]	[redacted]	[redacted]				

Abbreviations: ADA: adalimumab; CZP: certolizumab pegol; FOC: free of charge; ICER: incremental cost-effectiveness ratio; IFX: infliximab; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; UST: ustekinumab

Candidates for systemic non-biologic therapy

Table 89 presents the base case results for the CZP 200 mg dose compared to the SoC treatment sequence displayed in Table 70 in the candidates for systemic non-biologic therapy population. The base care analysis indicated that CZP 200 mg was cost-effective versus standard of care sequence in this patient population, with an ICER of £3,649.53/QALY.

Table 89: Base case results for candidates for systemic non-biologic therapy – CZP with PAS

Treatment sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER CZP versus SoC (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,649.53
L	SoC	[redacted]	[redacted]	[redacted]				

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

Clinical outcomes from the model and disaggregated are presented in Appendix J.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

The incremental results from the probabilistic sensitivity analysis (1,000 simulations) are presented below for the systemic non-biologic inadequate responders and candidates for systemic non-biologics populations. Parameter uncertainty is depicted using scatter-plots, showing the cost-effectiveness planes with a willingness-to-pay threshold of £20,000/QALY.

Systemic non-biologic therapy inadequate responders

The fully incremental results from the PSA for the systemic non-biologic inadequate responder population is presented in Table 90. The PSA results confirm the conclusions of the base case deterministic results for the inadequate responders population. The CE planes versus each first-line comparator in the treatment sequences for this population (Table 68) are shown in Figure 25 to Figure 31. These planes indicate that CZP 200 mg is more likely to be cost-effective versus other comparators in this patient population, at a willingness-to-pay threshold of £20,000/QALY.

Table 90: Average probabilistic results for systemic non-biologic therapy inadequate responders – CZP with PAS

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	Fully incremental ICER (£/QALY)
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,682.25
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates
UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates
UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates
GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates
SEC[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£769,121.67
IXE[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£497,961.80
BROD[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£877,485.33

[a]ICERs represent comparator vs CZP.
Abbreviations: ADA: adalimumab; BROD: brodalumab; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekizumab; QALY: quality-adjusted life year; SEC: secukinumab; UST: ustekinumab.

Figure 24: Cost-effectiveness probabilistic results for all comparisons in the systemic non-biologic inadequate responder population

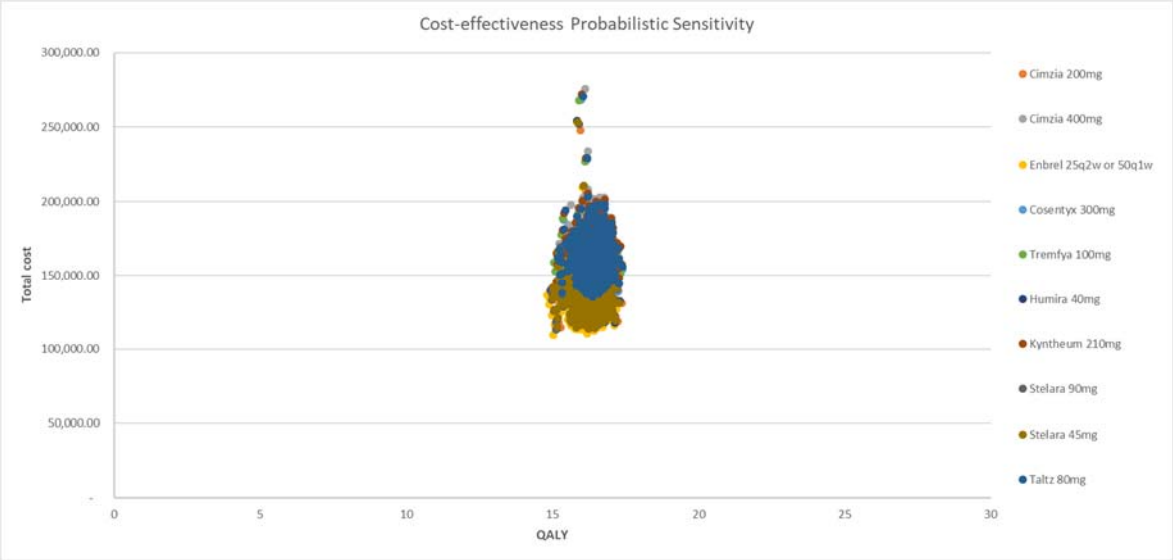
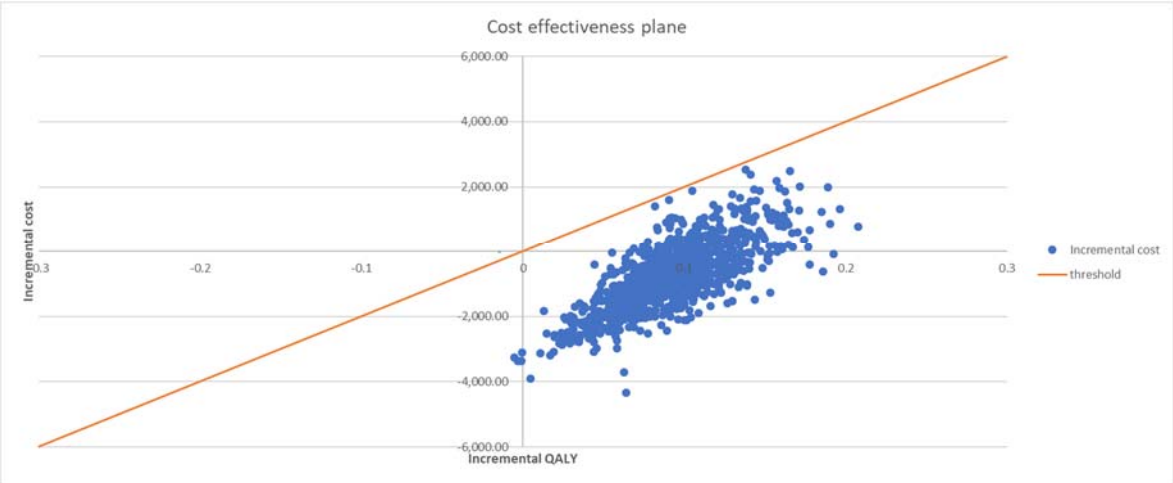


Figure 25: Cost-effectiveness plane for CZP 200 mg versus ADA 40 mg

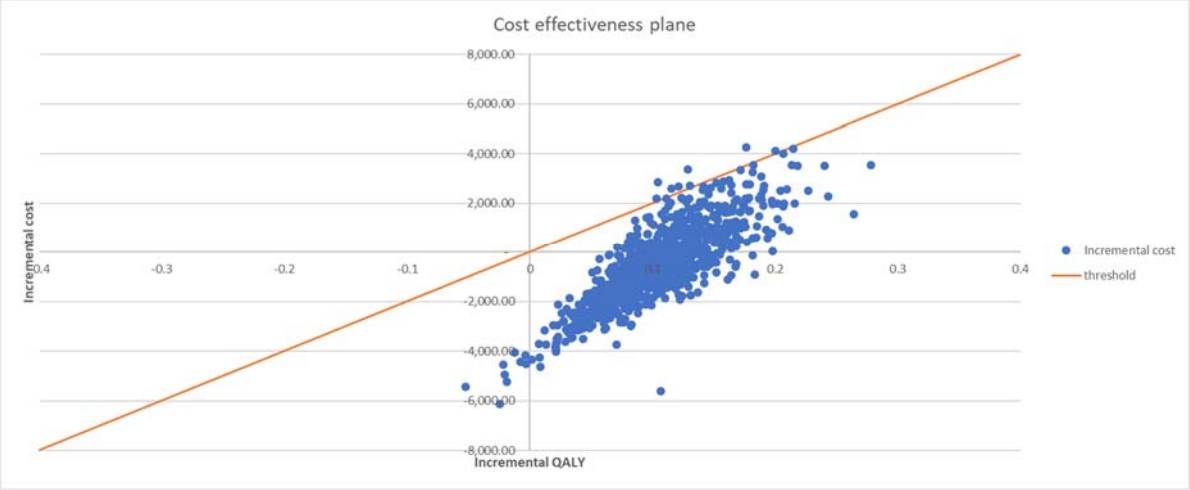
Abbreviations: ADA: adalimumab; CZP: certolizumab pegol; QALY: quality-adjusted life year.

Figure 26: Cost-effectiveness plane for CZP 200 mg versus UST 90 mg



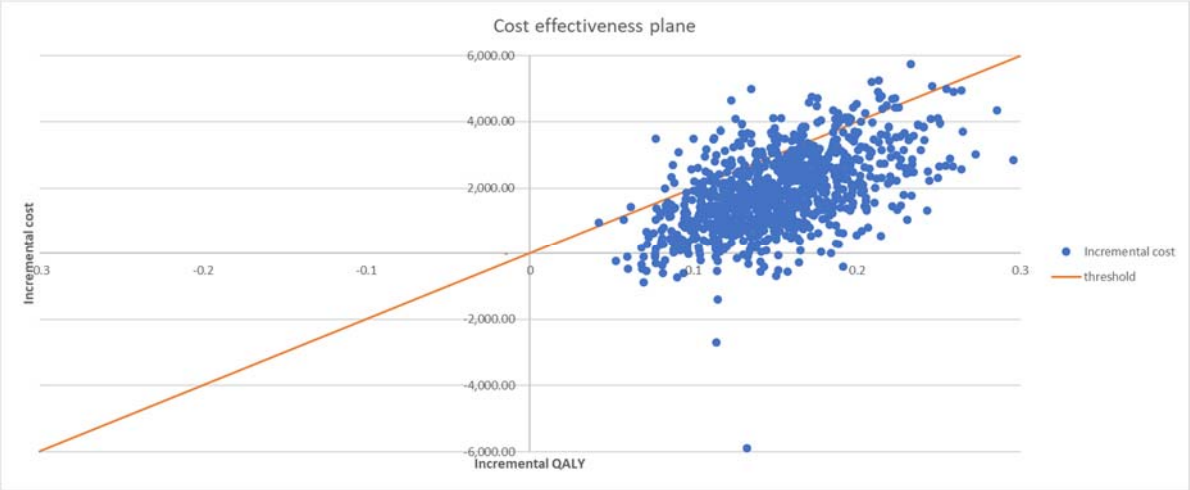
Abbreviations: CZP: certolizumab pegol; QALY: quality-adjusted life year; UST: ustekinumab.

Figure 27: Cost-effectiveness plane for CZP 200 mg versus UST 45 mg



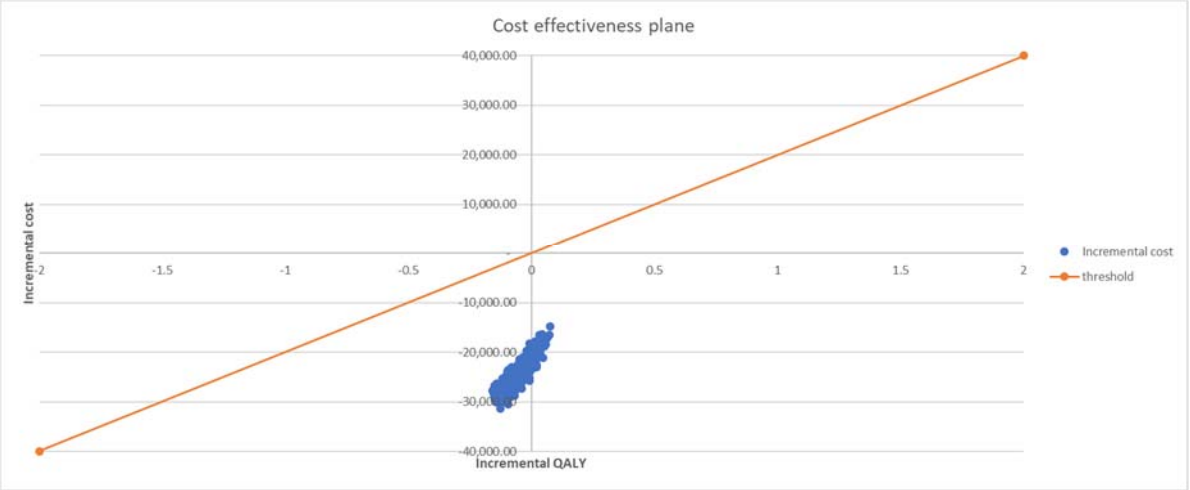
Abbreviations: CZP: certolizumab pegol; QALY: quality-adjusted life year; UST: ustekinumab.

Figure 28: Cost-effectiveness plane for CZP 200 mg versus ETN 25 mg



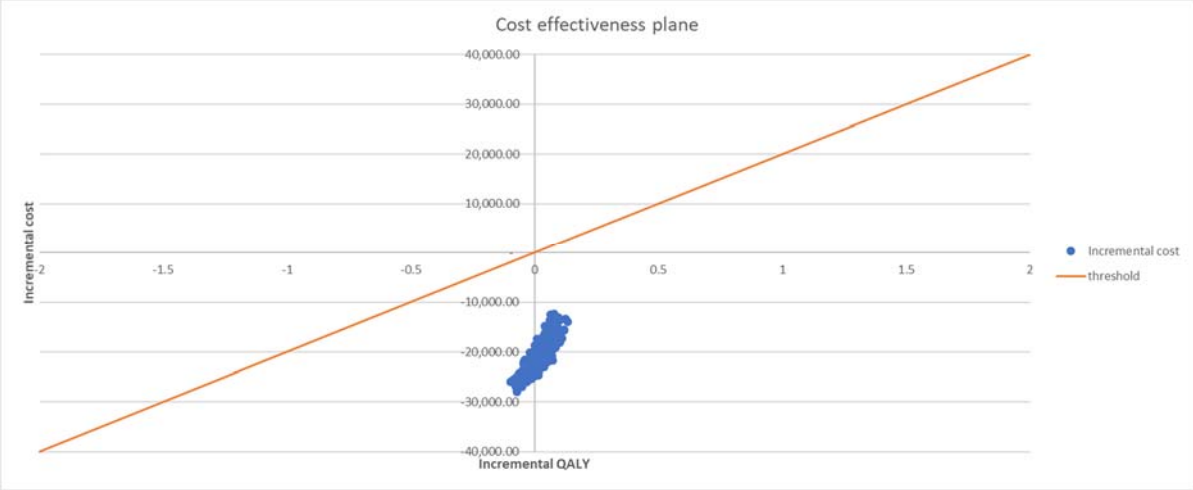
Abbreviations: CZP: certolizumab pegol; ETN: etanercept; QALY: quality-adjusted life year.

Figure 29: Cost-effectiveness plane for CZP 200 mg versus IXE



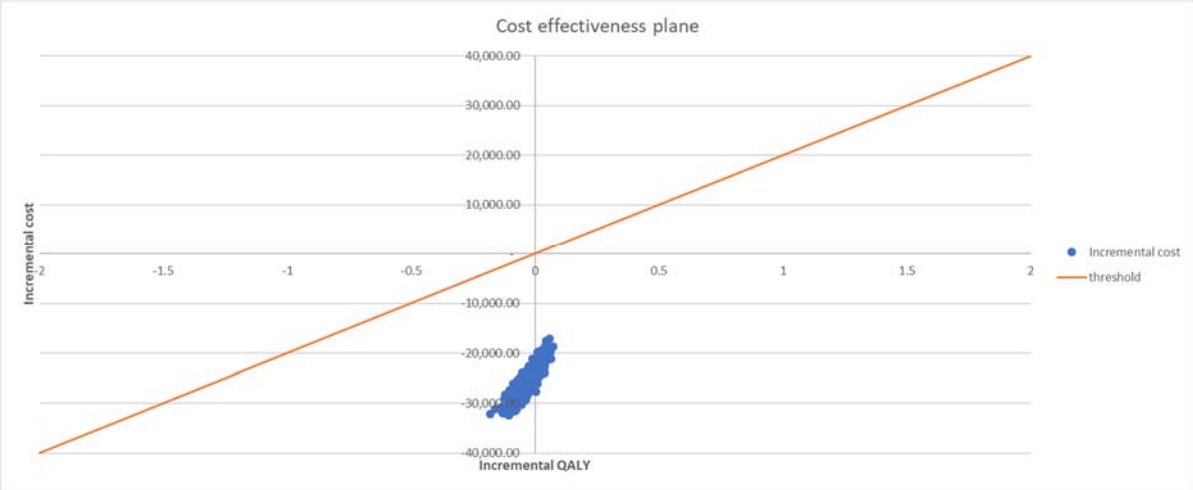
Abbreviations: CZP: certolizumab pegol; IXE: ixekizumab; QALY: quality-adjusted life year.

Figure 30: Cost-effectiveness plane for CZP 200 mg versus GUS



Abbreviations: CZP: certolizumab pegol; GUS: guselkuzmab; QALY: quality-adjusted life year.

Figure 31: Cost-effectiveness plane for CZP 200 mg versus BROD



Abbreviations: BROD: brodalumab; CZP: certolizumab pegol; QALY: quality-adjusted life year.

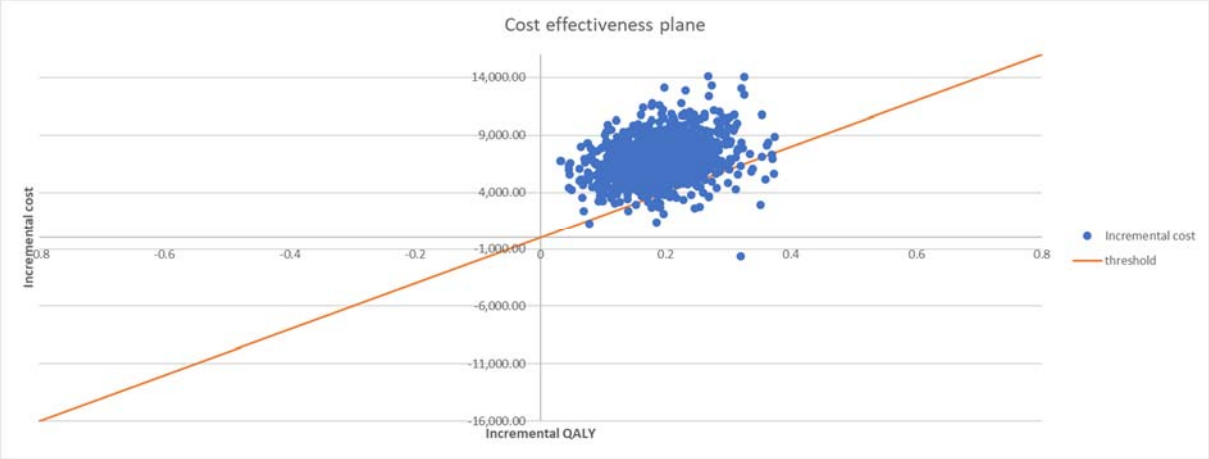
The probabilistic results for the escalation treatment sequences (CZP 200 mg followed by 400 mg and ADA 40 mg followed by ADA 80 mg) are presented in Table 91. Scatter plots of incremental costs and QALYs for CZP 200 mg versus standard of care is presented in Figure 32. The plane indicates that CZP escalation sequence is more likely to be more efficacious, but more costly versus the ADA escalation sequence, at a willingness-to-pay threshold of £20,000/QALY.

Table 91: Average probabilistic results for systemic non-biologic inadequate responders escalation sequence

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER CZP versus comparator (£/QALY)
CZP 200 mg/400 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,453.66

ADA 40 mg/80 mg	[redacted]	[redacted]	[redacted]			

Figure 32: Cost-effectiveness plane for CZP 200 mg/400 mg versus ADA 40 mg/80 mg



Abbreviations: ADA: adalimumab; CZP: certolizumab pegol; QALY: quality-adjusted life year.

Candidates for systemic non-biologic therapy

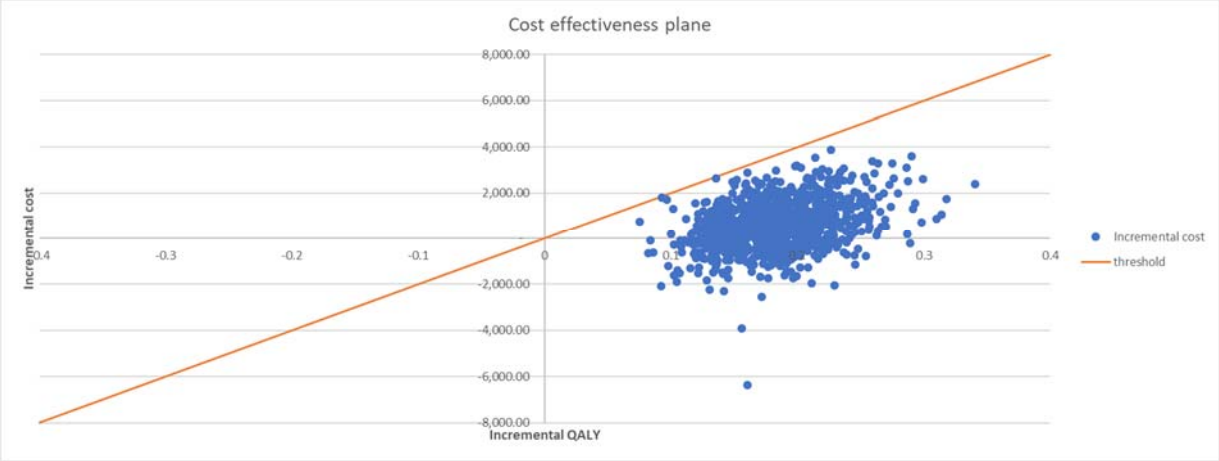
The probabilistic results for the candidates for systemic-non-biologic therapy population are presented in Table 92. Scatter plots of incremental costs and QALYs for CZP 200 mg versus standard of care is presented in Figure 33. The probabilistic results indicate that CZP 200 mg is more likely to be cost-effective compared to SoC, which is consistent with the base case ICER presented in Table 89.

Table 92: Average probabilistic results for candidates for systemic non-biologic therapy

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER CZP versus comparator (£/QALY)
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,439.83
SoC	[redacted]	[redacted]	[redacted]			

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year; SoC: standard of care.

Figure 33: Cost-effectiveness plane for CZP 200 mg versus standard of care



Abbreviations: CZP: certolizumab pegol; QALY: quality-adjusted life year.

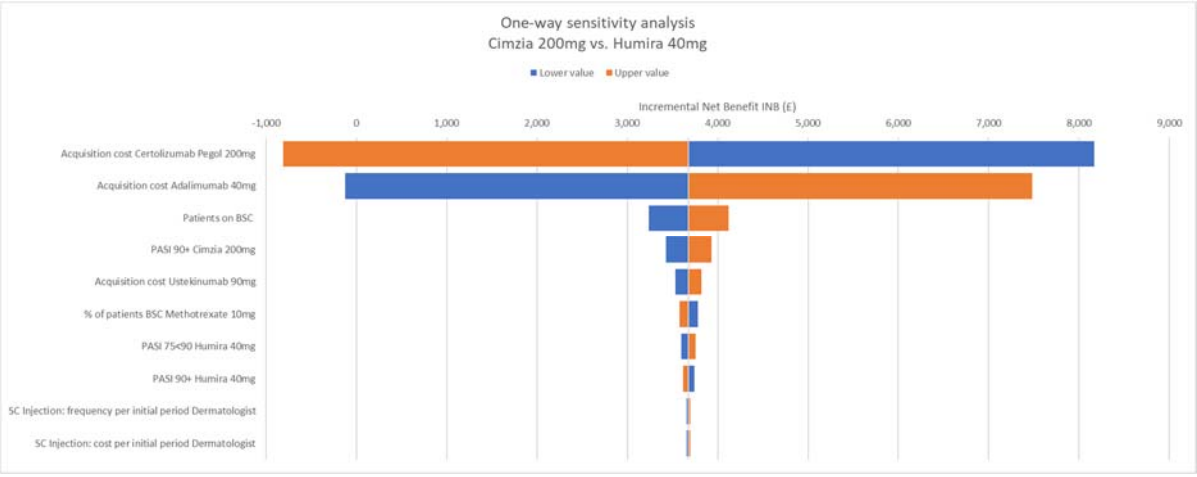
B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted by varying all parameters at lower and upper bounds of plausible values of CZP 200 mg versus all comparators in both the systemic non-biologic therapy inadequate responders and candidates for systemic non-biologics populations, as well as the escalation sequence from CZP 200 mg to CZP 400 mg for inadequate responders.

Systemic non-biologic inadequate responders

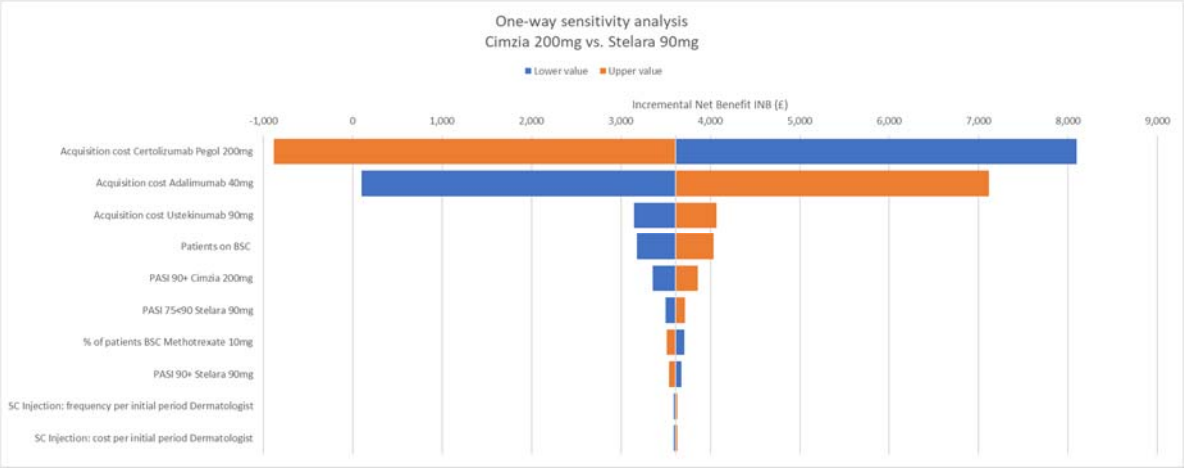
The tornado plots for CZP versus the first comparator in the treatment sequence for systemic non-biologic inadequate responders (Table 68) are presented in Figure 34 to Figure 41 below. The top two parameters that caused the most variation on the incremental net monetary benefit were the acquisition cost of CZP 200 mg and each comparator.

Figure 34: Tornado plot for systemic non-biologic therapy inadequate responders – CZP 200 mg versus ADA 40 mg



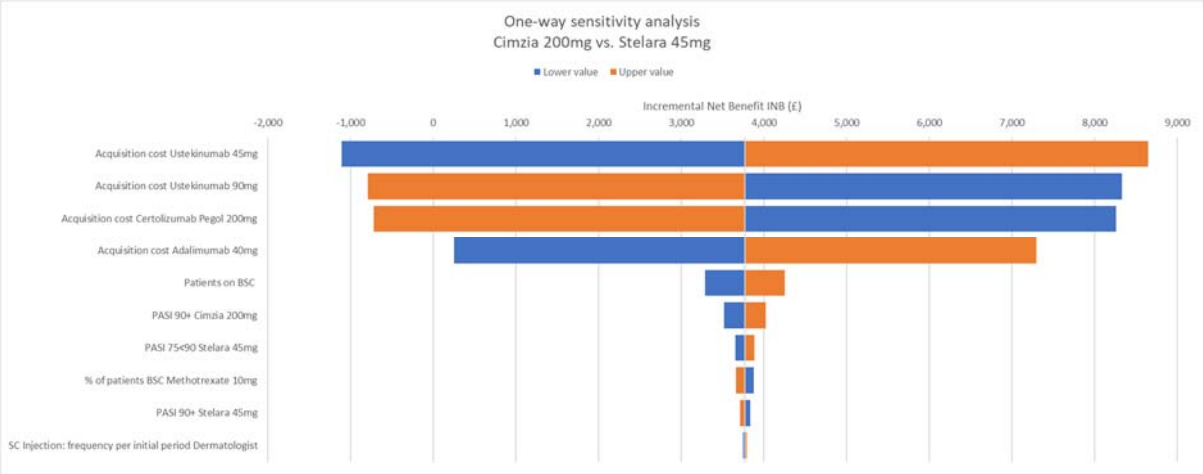
Abbreviations: ADA: adalimumab;

Figure 35: Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus UST 90 mg



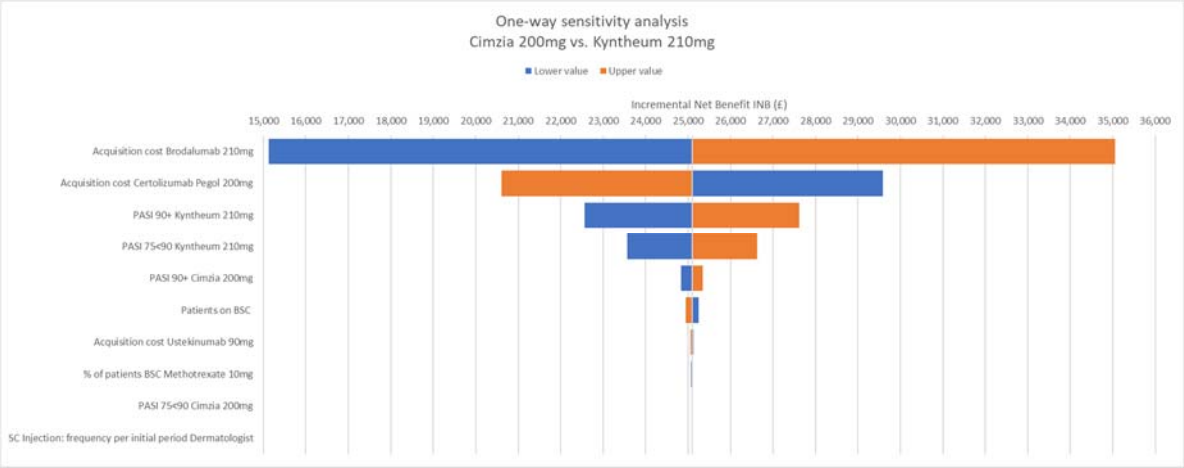
Abbreviations: BSC: best supportive care; CZP: certolizumab pegol; PASI: Psoriasis Area Severity Index; SC: subcutaneous; UST: ustekinumab.

Figure 36: Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus UST 45 mg



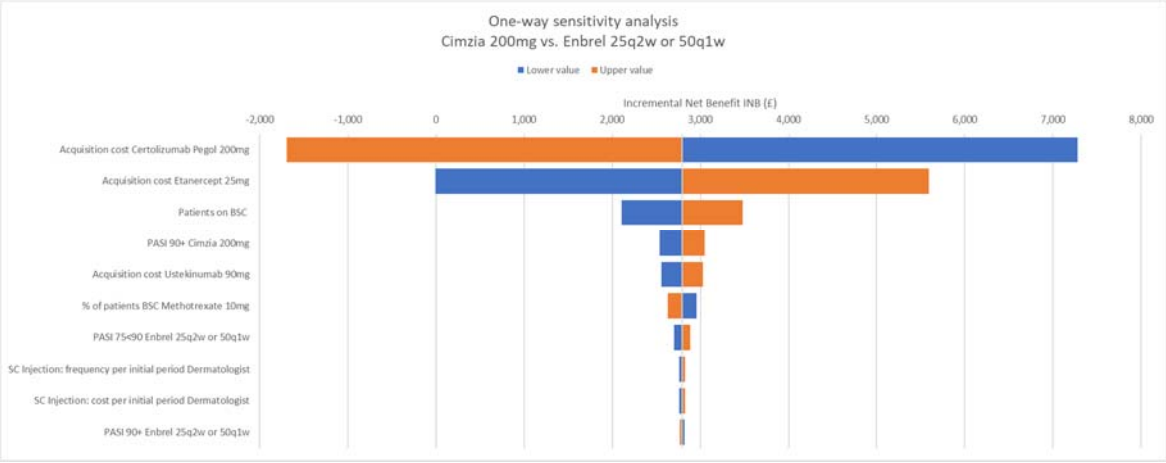
Abbreviations: BSC: best supportive care; CZP: certolizumab pegol; PASI: Psoriasis Area Severity Index; SC: subcutaneous; UST: ustekinumab.

Figure 37: Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus BROD



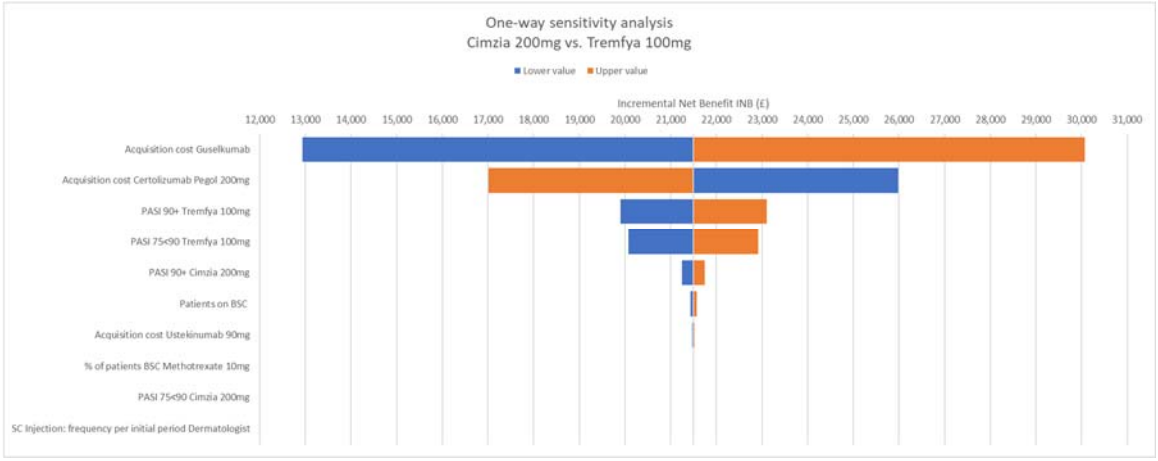
Abbreviations: BROD: brodalumab; BSC: best supportive care; CZP: certolizumab pegol; PASI: Psoriasis Area Severity Index; SC: subcutaneous.

Figure 38: Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus ETN 25 mg



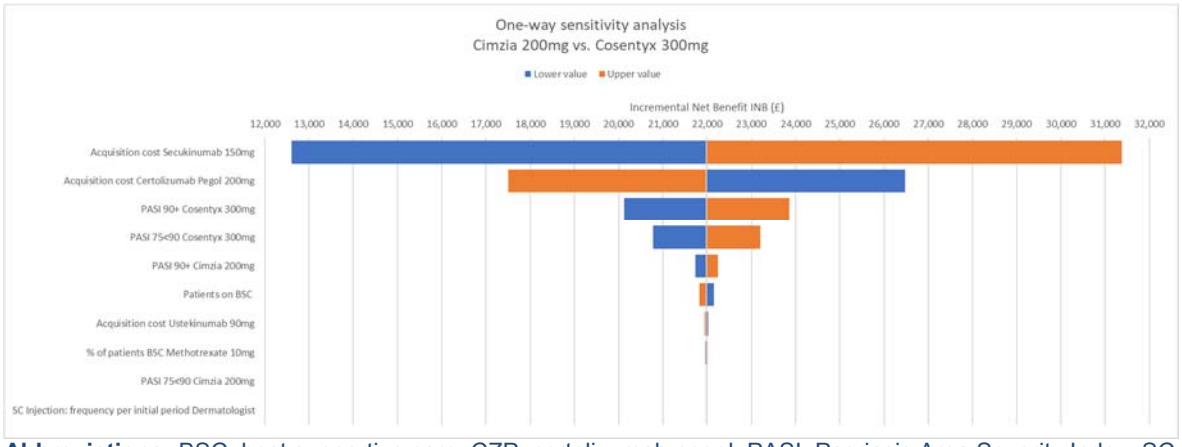
Abbreviations: BSC: best supportive care; CZP: certolizumab pegol; ETN: etanercept; PASI: Psoriasis Area Severity Index; SC: subcutaneous.

Figure 39: Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus GUS



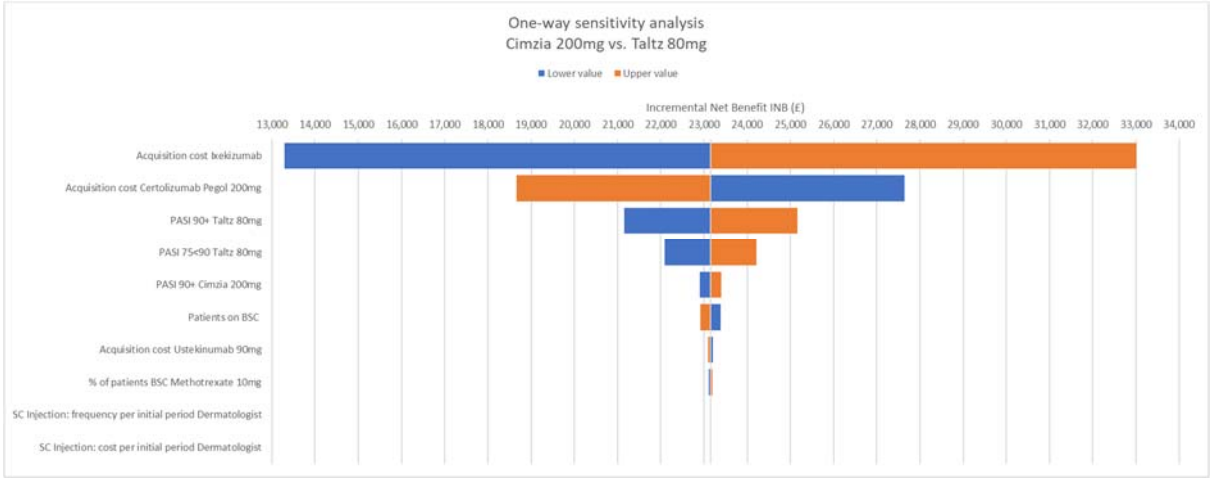
Abbreviations: BSC: best supportive care; CZP: certolizumab pegol; GUS: guselkumab; PASI: Psoriasis Area Severity Index; SC: subcutaneous.

Figure 40: Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus SEC



Abbreviations: BSC: best supportive care; CZP: certolizumab pegol; PASI: Psoriasis Area Severity Index; SC: subcutaneous; SEC: secukinumab.

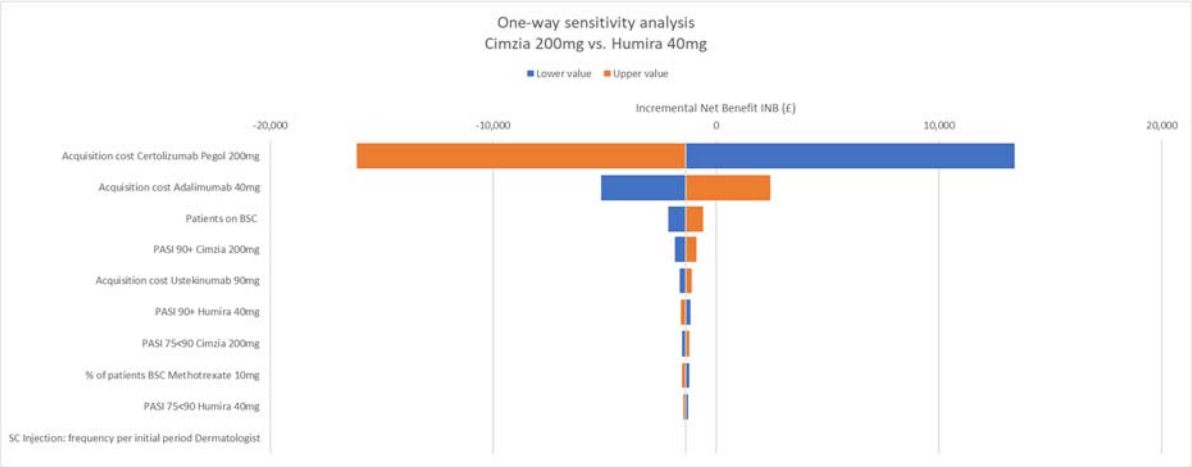
Figure 41: Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus IXE



Abbreviations: BSC: best supportive care; CZP: certolizumab pegol; IXE: ixekizumab; PASI: Psoriasis Area Severity Index; SC: subcutaneous.

The tornado plots for CZP escalation strategy vs ADA escalation strategy is presented in Figure 42. The main driver for the incremental net monetary benefit were the acquisition cost of CZP and ADA.

Figure 42: Tornado plot for systemic non-biologic inadequate responders - CZP escalation strategy with PAS vs ADA escalation strategy

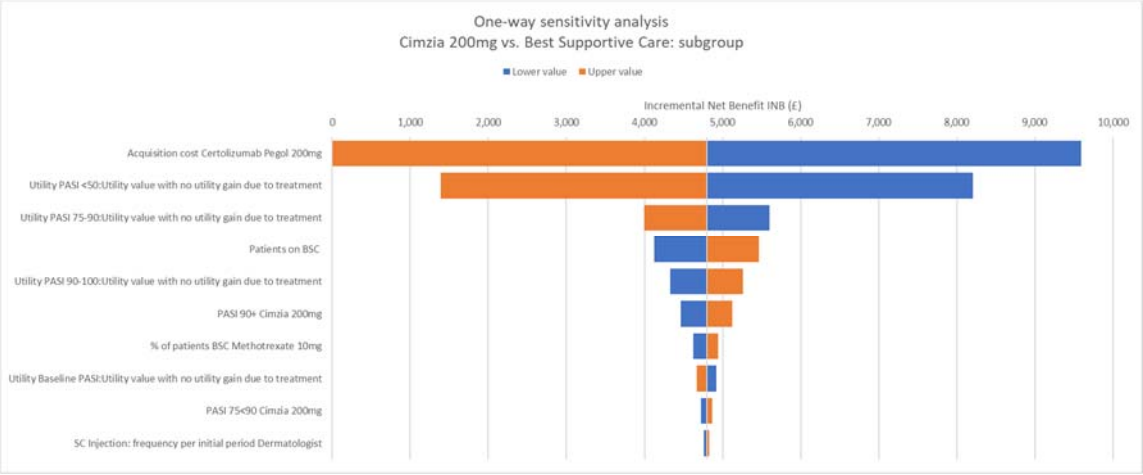


Abbreviations: ADA: adalimumab; BSC: best supportive care; CZP: certolizumab pegol; PASI: Psoriasis Area Severity Index; SC: subcutaneous.

Candidates for systemic non-biologic therapy

The tornado plot for the candidates for systemic non-biologic therapies population is presented in Figure 43. The main drivers for the incremental net monetary benefit were the acquisition cost of CZP 200 mg, PASI utilities and the non-responder cost (stated as patients on BSC in the diagram below).

Figure 43: Tornado plot for candidates for systemic non-biologic therapy – CZP 200 mg versus standard of care



Abbreviations: BSC: best supportive care; CZP: certolizumab pegol; PASI: Psoriasis Area Severity Index; SC: subcutaneous.

B.3.8.3 Scenario analysis

[redacted]

[redacted]

93 [redacted]

[redacted]

Table 93: Base case results for systemic non-biologic therapy inadequate responders – treatment sequence comparison of CZP escalation strategy with PAS [redacted]

Treatment sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER ADA versus CZP (£/QALY)
J	CZP 200 mg	[redacted]	[redacted]	[redacted]				
K	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA: adalimumab; CZP: certolizumab pegol; FOC: free of charge; ICER: incremental cost-effectiveness ratio; IFX: infliximab; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; UST: ustekinumab.

Scenario 2: Changes to the time horizon

Three different time horizons were tested in a scenario analysis with the same treatment sequences as used in the base case for the systemic non-biologic therapy inadequate responders and candidates for systemic non-biologics (see B.3.2.4). This aligns the model with time horizons used in previous appraisals, although not all previous appraisals included treatment sequences.

The results from this scenario analysis are presented in Table 94 and Table 95. When reducing the length of the time horizon, CZP is cost-effective against all treatment sequences (Table 94) in the systemic non-biologic therapy inadequate responder population. For the candidates for systemic non-biologic population, CZP is cost-effective compared to standard of care at all timepoints (Table 95).

Table 94: Scenario 2: Changes to the time horizon (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER comparator versus CZP (£/QALY)	ICER CZP versus comparator (£/QALY)
20 years									
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£8,196.33
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
I	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£619,203.98	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£449,076.14	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£742,888.10	N/A
10 years									
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
I	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£736,694.72	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£541,498.63	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£864,746.59	N/A
1 year									
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
I	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant

D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£608,190.01	N/A
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£699,147.84	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£617,554.48	N/A

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab.

Table 95: Scenario 2: Changes to the time horizon (candidates for systemic non-biologic therapy)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs SoC (£/QALY)
20 years								
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,033.57
10 years								
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
1 year								
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Scenario 3: PASI50 defines responders at end of initial period

A scenario was run whereby the PASI response criteria has been altered so that PASI50 would define responders at the end of the initial period. The results from this scenario analysis are presented in Table 96 for systemic non-biologic therapy inadequate responders. Here, CZP 200 mg remained cost-effective versus all other treatment sequences, as in the base case analyses. In the candidates for systemic non-biologic therapy (Table 96), CZP 200 mg was cost-effective versus standard of care when PASI50 was used to define responders, similarly to the conclusions from the base case analysis.

Table 96: Scenario 2: PASI50 used to define responders at end of initial period (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus CZP (£/QALY)	ICER incremental (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£1,746.77
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
I	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£893,410.66	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£689,725.69	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,150,079.30	N/A

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Table 97: Scenario 3: PASI50 used to define responders at end of initial period (candidates for systemic non-biologic therapy)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER CZP versus SoC (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,441.56

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Scenario 3: Alternative maintenance discontinuation rates

A scenario was run using different maintenance discontinuation rates, which differ between biologics. In line with Iskander *et al.* (2017) and the GUS NICE appraisal TA521, scenarios for the overall population and candidates for systemic non-biologics have been simulated with the following discontinuation rates: ADA: 18%; ETN: 29%; and, 9% for all other biologics (including CZP). [redacted] The results from this scenario analysis are presented in Table 98 for systemic non-biologic therapy inadequate responders. Under this scenario, CZP remained cost-effective versus all comparators considered. In the candidates for systemic non-biologic therapy scenario (Table 99), CZP was cost-effective when compared to standard of care, in line with the conclusions from the base case analysis.

Table 98: Scenario 4: Alternative annual maintenance discontinuation rates, different between biologics (adalimumab: 18%; etanercept: 29%; all other biologics including Cimzia: 9%) (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER comparator versus CZP (£/QALY)	ICER CZP versus comparator (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£14,766.85
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£9,295.69
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£8,779.06
I	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£8,786.14
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant

G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£629,776.82	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£449,021.59	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£810,536.92	N/A

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Table 99: Scenario 4: Alternative annual maintenance discontinuation rates, different between biologics (adalimumab: 18%; etanercept: 29%; all other biologics including Cimzia: 9%) (candidates for systemic non-biologic therapy)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER CZP versus SoC (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,820.65

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Scenario 5: Ustekinumab 45 mg dose as second line therapy

A scenario has been run with UST 45 mg dose used as a second line therapy in the treatment sequence, as opposed to UST 90 mg.

The results from this scenario analysis are presented in Table 100 for systemic non-biologic therapy inadequate responders. CZP 200 mg was cost-effective compared to all other comparators. In the candidates for systemic non-biologic therapy (Table 101) CZP remained cost effective versus standard of care.

Table 100: Scenario 5: ustekinumab 45 mg dose used as second line therapy (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER comparator versus CZP (£/QALY)	ICER CZP versus comparator (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£11,900.94

H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
I	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£598,380.51	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£433,724.76	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£719,438.28	N/A

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Table 101: Scenario 5: ustekinumab 45 mg dose used as second line therapy (candidates for systemic non-biologic therapy)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus SoC (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,727.55

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Scenario 6: Alternative utility values

A scenario has been conducted where different utilities assumptions have been used, based on the previous NICE TAs.

The results from this scenario analysis are presented in Table 102 and Table 103 for systemic non-biologic therapy inadequate responders and candidates for systemic non-biologic therapy, respectively. CZP was cost-effective compared to all comparators for systemic non-biologic therapy inadequate responders when using utility values from the secukinumab and apremilast submissions. When using the utility values from the ixekizumab submission, CZP was cost-effective versus all treatment sequences, expect versus ETN. It is important to note, that under all three assumptions, the incremental QALYs were very small between the sequences considered. In the candidates for systemic non-biologics population, CZP was cost-effective standard of care in all utility scenarios.

Table 102: Scenario 6: Treatment effect on HRQoL where utilities were varied using values from previous submissions (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER comparator versus CZP (£/QALY)	ICER CZP versus comparator (£/QALY)
Utilities from secukinumab submission									
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£17,125.10
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
I	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£575,712.71	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£439,561.78	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£666,516.02	N/A
Utilities from apremilast submission									
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£15,780.45
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
I	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£646,461.60	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£494,029.13	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£765,862.75	N/A
Utilities from ixekizumab submission									

A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£50,653.35
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
I	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,550,071.69	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,171,248.02	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,772,091.03	N/A

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Table 103: Scenario 6: Treatment effect on HRQoL where utilities are from previous submissions (candidates for systemic non-biologic therapy)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER CZP versus SoC (£/QALY)
Utilities from secukinumab submission								
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,412.92
Utilities from apremilast submission								
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,030.42
Utilities from ixekizumab submission								
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,157.98

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Scenario 7: Etanercept biosimilar

Scenarios have been run using biosimilar prices for etanercept (Benepali and Erelzi), based on the BNF. The results from this analysis are presented in Table 104 and Table 105, for Benepali and Rrelzi, respectively. Given that etanercept is not considered in the sequences for candidates for systemic non-biologic therapy, the results for this population are not included. When assuming ETN biosimilars, CZP is cost-effective versus ETN with ICERs being £19,238.16 and £20,844.80 per QALY (Table 104 and Table 105, respectively).

Table 104: Scenario 7: etanercept price set to biosimilar, Benepali (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER comparator versus CZP (£/QALY)	ICER CZP versus comparator (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£19,238.16

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Table 105: Scenario 7: etanercept price set to biosimilar, Erelzi (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER comparator versus CZP (£/QALY)	ICER CZP versus comparator (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£20,844.80

Abbreviations: ADA: adalimumab; BIW: biosimilar;BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Scenario 8: Infliximab biosimilar

A scenario was conducted where the price of IFX was changed to the price for the biosimilar (Flixabi), based on the BNF. The results for this scenario are presented in Table 106 for the systemic non-biologic inadequate responders. The results from the scenario analysis indicate that CZP was cost-effective versus all other comparators considered. For the candidates for systemic non-biologic therapies population, CZP was cost-effective versus the standard of care treatment sequence (Table 107).

Table 106: Scenario 8: infliximab price set to biosimilar, flixabi (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER comparator versus CZP (£/QALY)	ICER CZP versus comparator (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£12,853.73
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
I	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£600,317.12	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£435,400.90	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£721,488.54	N/A

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Table 107: Scenario 8: infliximab price set to biosimilar, flixabi (candidates for systemic non-biologics)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus SoC (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,923.27

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Scenario 9: Single treatment comparisons

Single treatment comparisons have been generated, comparing each comparator sequence, including CZP, to BSC. All biologic sequences assumed one single biologic line, followed by BSC. These analyses have been conducted as per the NICE decision problem meeting, however it is important to note that these sequences do not reflect the current clinical practice in England.

The results from this scenario analysis are presented in Table 108 for systemic non-biologic therapy inadequate responders. Here, CZP is cost-effective versus all other treatments with the highest ICER being £21,639.84 per QALY. In the candidates for systemic non-biologic therapy population, the ICER for CZP versus SoC was £35,247.58 (Table 109).

Table 108: Scenario 9: each treatment followed by BSC (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus CZP (£/QALY)	ICER incremental (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
D	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£21,639.84
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£5,069.00
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
I	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£543,799.04	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£393,598.69	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£656,927.26	N/A

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Table 109: Scenario 9: Each treatment followed by BSC (candidates for systemic non-biologic therapy)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER CZP versus SoC (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,247.58

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Scenario 10: Reduction in price of comparators with PAS

Scenarios have been conducted where the price of the competitor therapies with a confidential patient access scheme (PAS) was reduced. That is, a 10% reduction in the price of SEC, BROD, IXE and GUS was applied. As a change in price of these therapies will only affect costs for the systemic non-biologic inadequate responder population, and not candidates for systemic non-biologic therapies, the scenario was only run in this population. Results from this scenario analysis are shown in Table 110 and show that CZP was cost-effective versus all treatments, in line with the base case results (Table 87).

Table 110: Scenario 10: reduction in the price of SEC, BROD, IXE and GUS (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus CZP (£/QALY)	ICER incremental (£/QALY)
D	CZP 200 mg	[redacted]	[redacted]	[redacted]					
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£478,043.21	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£348,465.87	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£583,643.70	N/A

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Scenario 11: SEC as third-line option in the sequence instead of IFX

Scenarios are provided were IFX is replaced by SEC in third-line sequence, although IFX remained the third line option in the sequence where SEC is the first-line treatment. For systemic non-biologic inadequate responders (Table 111), the results indicate that the CZP sequence was cost-effective compared to all other comparators. For candidates for systemic non-biologics, IFX was replaced by SEC in the fourth-line of the standard of care sequence; results in this population indicated that CZP was cost-effective versus standard of care (Table 112).

Table 111: Scenario 11: third-line treatment changes from IFX to SEC (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus CZP (£/QALY)	ICER CZP versus

	in Sequence								comparator (£/QALY)
D	CZP 200 mg	[redacted]	[redacted]	[redacted]					
A	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£10,965.65
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
I	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£489,680.87	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£433,356.28	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£719,262.18	N/A

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Table 112: Scenario 11: IFX replaced by SEC in third-line sequence (candidates for systemic non-biologic therapy)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus SoC (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,660.90

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Scenario 12: Reduction for inpatient costs

A scenario was conducted whereby the price for inpatients for the non-responder and BSC costs was reduced by 50%, based on clinical expert feedback that the inpatient costs in Fonia *et al.* were not representative of those in clinical practice. The results for this scenario for the systemic non-biologic inadequate responder population are presented in Table 113. CZP sequence was cost-effective versus all other treatment sequences in this population. For the candidates for systemic non-biologics population, CZP was cost-effective versus standard of care.

Table 113: Scenario 12: reduction in inpatient costs (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus CZP (£/QALY)	ICER CZP versus comparator (£/QALY)
D	CZP 200 mg	[redacted]	[redacted]	[redacted]					
A	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£18,481.79
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£2,169.24
I	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£606,100.80	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£440,861.27	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£727,179.67	N/A

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Table 114: Scenario 12: reduction in inpatient costs (candidates for systemic non-biologic therapy)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER CZP versus SoC (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,218.39

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Scenario 13: Change in proportion of patients on each systemic non-biologic therapy

For the base case results, the proportion of patients on MTX, acitretin, fumarates and ciclosporin was taken from expert clinical opinion. A scenario was run where these proportions were altered to those from Fonia *et al.* (Table 81). In the systemic non-biologic inadequate responder population, the

CZP sequence was cost-effective versus all other sequences (Table 115). The results for the candidates for systemic non-biologic therapies population are presented in Table 116 and indicate that CZP was cost-effective versus standard of care.

Table 115: Scenario 13: Change in proportion of patients on each systemic non-biologic therapy (systemic non-biologic therapy inadequate responders)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus CZP (£/QALY)	ICER CZP versus comparator (£/QALY)
D	CZP 200 mg	[redacted]	[redacted]	[redacted]					
A	ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£10,905.84
H	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
I	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
E	GUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
G	SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£598,871.71	N/A
F	IXE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£433,927.43	N/A
C	BROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£720,114.68	N/A

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekinumab; LYG: life years gained; SEC: secukinumab; UST: ustekinumab; QALYs: quality-adjusted life years; UST: ustekinumab

Table 116: Scenario 13: Change in proportion of patients on each systemic non-biologic therapy (candidates for systemic non-biologic therapy)

Treatment Sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus SoC (£/QALY)
A	CZP 200 mg	[redacted]	[redacted]	[redacted]				
L	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,051.91

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

B.3.8.4 Summary of sensitivity and scenario analyses results

Systemic non-biologic inadequate responders

- The probabilistic sensitivity analysis results were consistent and supported the conclusions of the basecase analysis observed for the comparison between CZP and other biologic treatment sequences, indicating that CZP is a cost-effective treatment option.
- The one-way sensitivity analysis indicated that the main drivers for the incremental net monetary benefit were the drug acquisition costs of CZP and of the biologic comparators.
- In the majority of scenario analyses conducted, with one exception, the CZP treatment sequence remained cost-effective. When utilities from the ixekizumab NICE submission were used, CZP 200 mg was cost-effective against all treatment sequences apart from ETN.
- For the CZP escalation strategy, the probabilistic sensitivity analysis results were consistent with the basecase results observed for the comparison between CZP and ADA escalation treatment sequences. The one-way sensitivity analysis indicated that the main drivers for the incremental net monetary benefit were the acquisition cost of CZP and ADA. [redacted].

Candidates for systemic non-biologics

- The probabilistic sensitivity analysis results were consistent with the basecase results observed for the comparison between CZP and standard of care treatment sequences, indicating that CZP is a cost-effective treatment option when used earlier in the treatment pathway.
- The one-way sensitivity analysis indicated that the main drivers for the incremental net monetary benefit were the acquisition cost of CZP, PASI utilities and the non-responder cost.
- For all the scenarios in the candidates for systemic non-biologics population, CZP 200 mg dominated standard of care, which is consistent with the base case results in this population (Table 89).

B.3.9 *Subgroup analysis*

Biologic naïve subgroup

The NMA where only patients who were biologic-naïve were included was only able to compare CZP to UST 45 mg, UST 90 mg and ADA. The results are shown below in Table 117. CZP dominated UST 90 mg and ADA in this subgroup and was cost-effective versus UST 45 mg (ICER of £2,677/QALY).

Table 117: Subgroup analysis results for systemic non-biologic therapy inadequate responders who are also biologic – CZP with PAS

Treatment sequence	1st Line Treatment in Sequence	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus CZP (£/QALY)	ICER CZP versus comparator
A	CZP 200 mg	[redacted]	[redacted]	[redacted]					
I	UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£2,630.45
H	UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
B	ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant

Abbreviations: ADA: adalimumab; CZP: certolizumab pegol; FOC: free of charge; ICER: incremental cost-effectiveness ratio; IFX: infliximab; LYG: life years gained; PAS: patient access scheme; QALY: quality-adjusted life year; UST: ustekinumab.

B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

Internal validation

The structure and programming of the completed Microsoft Excel model was validated by two modelling experts not involved in this study, and a variety of stress tests were performed to ensure that the model behaved as expected. Both extreme values and equal values across treatment arms were input and results were compared against results expected. In situations where actual results diverged from expected results, debugging was performed to investigate and remedy the discrepancy.

External validation

The model was validated for its suitability for the UK by a second health economist different to the developer of the original model. The following aspects were validated: model structure (to ensure it was appropriate for the disease area and consistent with previously used structures) and model settings (to ensure the model inputs and assumptions were accurately reflecting clinical practice).

The key inputs and assumptions used in the model were validated by a clinical expert, to ensure they reflect clinical practice in England and Wales.[3] The only areas where it was believed that the model inputs may not represent clinical practice are the following:

- Disease management costs from Fonia et al. 2010. This study reports a high inpatient attendance, which is likely to have decreased since this study was run. In the absence of alternative robust resource use data, the clinical expert advised that Fonia *et al.* 2010 should be used in the base case, but that these costs should be explored within the sensitivity analysis. When these costs were reduced by 50%, CZP 200 mg was still cost-effective versus all other treatment sequences in the systemic non-biologic inadequate responders population and candidates for systemic-non biologic therapy population.
- Proportion of patients receiving the different non-biologic systemic therapies as part of BSC. The UK clinical expert believed that in current practice the proportion of patients on MTX is now higher than is reported in Fonia *et al.* 2010 and the proportion of patients on acitretin is lower. In the absence of alternative robust resource use data, the clinical expert advised that the proportions from Fonia *et al.* 2010 should be used in the base case, but that these costs should be explored within the sensitivity analysis. When the proportions were changed to Fonia *et al.*, there was some variation in the ICERs, but CZP 200 mg remained cost-effective versus all other comparators in both patient populations.

B.3.11 *Interpretation and conclusions of economic evidence*

Generalisability of the analysis

The economic evaluation is based on patient populations included in the CZP RCTs. The systemic non-biologic inadequate responders population is based on the pooled ITT data from the three CZP trials, and the candidates for systemic non-biologics is based on a pooled subpopulation of patients within these trials with no prior biologic or non-biologic treatments.

These two patient groups represent the anticipated populations that CZP will be used for in clinical practice, based on expert clinical opinion. The evaluation is relevant to all groups of patients encompassed in the decision problem.

Strengths of the economic evaluation

The model has been designed to capture a treatment pathway in line with current UK clinical practice and allow therapies to be compared at each line of treatment.

Strengths of the economic evaluation include that the efficacy of CZP within the model is based directly on data from high quality RCTs and that resource use was estimated from UK data. The efficacy profile for both the CZP arm and the standard of care comparator arm for the candidates for systemic non-biologics are derived from the same trials, which limits issues of heterogeneity and variability in this analysis.

In addition, the PASI75 endpoint used to define response is a key endpoint in psoriasis according to clinical guidelines and clinical expert opinion. The model structure allows for accurate tracking of this outcome during the assessment period.

Limitations of the economic evaluation

The treatment sequence of biologic therapies assessed are reflective of the current clinical practice, as per the clinical expert opinion and clinical guidelines, however not all possible treatment sequences have been fully explored, as this outside of the remit of the current submission.

There is limited available efficacy data for BSC (including systemic non-biologic agents) when used as fifth line in the sequence, post biologic therapy. However, economic evaluations included in previous NICE appraisals have encountered the same limitation.

Disease management costs have been based on Fonia et al. estimates, since this was the only cost resource use study identified in the systematic literature review. ERG comments in previous NICE HTA reviews have indicated that resource use estimates from Fonia et al. were likely to overestimate resource use, since the number of patients hospitalised with psoriasis has fallen in recent years due to the availability of biologics. However, it was agreed during the NICE decision problem meeting that in the absence of other available source, the Fonia et al. estimates should be used.

Conclusion

The economic analysis demonstrates that CZP with the PAS is a cost-effective treatment versus all biologic comparators considered, in the systemic non-biologic inadequate responders population. In the candidates for systemic non-biologic population, CZP with the PAS is a cost-effective treatment option versus the standard of care treatment sequence, indicating that CZP is a cost-effective treatment option when used earlier in the treatment pathway.

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Single technology appraisal

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

Dear Company,

The Evidence Review Group, Centre for Reviews and Dissemination and Centre for Health Economics (York), and the technical team at NICE have looked at the submission received on 10th August 2018 from UCB Pharma. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on 12th September 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Alan Lamb, Technical Lead (alan.lamb@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk).

Yours sincerely

Melinda Goodall
Associate Director – Appraisals
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Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Positioning and marketing authorisation

A1. **Priority question:** Please provide further justification for the choice to position certolizumab pegol as an alternative to systemic non-biological therapy, given that all biologic therapy currently approved by NICE are positioned after systemic non-biological therapy, which is narrower than their respective licensed indications.

A2. **Priority question:** In Table 2, page 17 of the company submission it states that certolizumab pegol received European marketing authorisation on 8th June 2018. Apart from details of the positive CHMP opinion there seems to be no reference to the new licensed indication in the references provided or on the EMA website. Furthermore, the EPAR and SPC provided by the company in its reference pack do not include the indication for plaque psoriasis. Please confirm that certolizumab pegol has received European marketing authorisation and provide the updated EPAR and SPC for this indication.

Trial data

A3. **Priority question:** Please provide Clinical Study Reports for the CIMPASI-1, CIMPASI-2 and CIMPACT trials.

A4. **Priority question:** Please confirm when further interim data (week 96) will be available for the CIMPASI-1, CIMPASI-2 and CIMPACT trials. Please provide this data if it is now available.

A5. **Priority question:** Please present additional results for the 'systemic non-biologic therapy inadequate responders' subgroup (Section B.2.6.10) as per the 'candidates for non-biologic systemic therapies' subgroup (Section B.2.6.9), i.e. body surface area, extra-cutaneous manifestations and quality of life results.

A6. The subgroups 'candidates for non-biologic systemic therapies' and 'systemic non-biologic therapy inadequate responders' do not make up the entire cohort of patients included in the trials (there are an additional 40 placebo patients, 106 200 mg Q2W patients and 107 400 mg Q2W patients). Is there an additional subgroup, e.g. patients for whom non-biologic therapy is contraindicated? If so, please provide further details and present results for this additional subgroup, i.e. baseline characteristics, clinical response, body surface area, extra-cutaneous manifestations and quality of life.

A7. Please confirm how many patients in each treatment arm of CIMPACT were from the UK.

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A8. Figures 9 to 13 in the appendix report the reasons that patients discontinued from the CIMPASI-1, 2 and CIMPACT studies; please provide further information on the reasons 'consent withdrawn' and 'other'.

A9. Relapse rate was an outcome specified in the decision problem. However, relapse rate data is only presented for the CIMPACT trial. Please explain why this outcome has not been presented for CIMPASI-1 and CIMPASI-2 and provide this data, if it is available.

A10. **Priority question:** Clinical effectiveness data are significantly better in the CIMPASI-2 trial compared with the other two trials. Is there a clinically plausible reason that might explain this difference in clinical effectiveness, e.g. differences in trial design or population characteristics?

A11. **Priority question:** Please provide PASI 50, 75 and 90 response rates as presented in Figure 6 of the company submission, but with an adjustment for gender and PSA. Please also include full details of this analysis along with the regression coefficients.

A12. **Priority question:** Section B2.4 presents information on the methods used for imputation of missing data, but the number of patients for whom missing data were imputed is not stated. Please present this information for the primary outcomes PASI 75 and PGA response at weeks 16 and 48 for each of the treatment groups within each of the trials.

A13. Clinical effectiveness results are presented differently for the CIMPASI trials and the CIMPACT trial. Please present PASI 75 and PASI 90 response data for all three trials in the same format as Table 20 of the company submission (i.e. PASI 75 and PASI 90 responder rate at week 48, including the number of patients included in each treatment arm and confidence intervals). Please also present the data for week 48 PGA responder rate in a similar format.

A14. The number of patients in the treatment efficacy pools E4 and E5 in Table 15 of company submission do not correspond with the patient disposition figures (Figure 10, Figure 12 and Table 19 of the appendices). Please explain the reason for the differences in numbers of patients.

A15. Under Figure 9 of the company submission it states: "Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E5)". However, in Table 15 it states that Pool E5 also includes CIMPACT. Please clarify whether Figure 9 includes data from CIMPACT.

A16. Figure 9 of the company submission states that Pool E5 CZP 400 mg Q2W includes [redacted] patients (PASI 75 responders), but in Table 15 there were only [redacted] CZP 400 mg Q2W PASI 75 responders. Please clarify the number of patients included in Pool E5.

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A17. Please present results for the CZP 200 mg/CZP 200 mg group (n=74 in CIMPASI-1 and n=76 in CIMPASI-2) for change from baseline in psoriasis percentage BSA affected at week 48 , as presented for other treatment groups in Table 23 of the company submission.

A18. Please present results for 'escape' patients from CIMPACT (n=138, receiving certolizumab pegol or placebo Table 19 of the appendices), as presented in Table 24 of company submission for change from baseline in psoriasis percentage BSA affected at week 48.

A19. Please explain why the number of patients for whom results are presented in Table 25 (change from baseline in mNAPSI score and nail psoriasis resolution (mNAPSI=0) at week 48 in pool E3- ITT population) and Table 26 (change from baseline in mNAPSI score at week 48 in CIMPACT- ITT population) in the company submission are lower than the number of patients who completed week 48 reported in Table 15 in the company submission and Figures 10, Figure 12 and Table 19 in the appendices.

A20. Please provide further information about the 'pre-determined production randomisation and/or packaging schedule' referred to in Table 9 (summary of methodologies for CIMPACT, CIMPASI-1 and CIMPASI-2) as the method of randomisation for the CIMPACT trial.

A21. Please present the number of patients for the treatment safety pools (S1 and S3).

Network Meta-Analysis

A22. The ERG have identified one RCT that was not included in the network meta-analysis (NMA): 'Caproni M, et al. (2009). Serum Levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: a randomized-controlled trial. *Journal of Clinical Immunology,* 29 (2): 210-4'. Please explain why this trial was excluded.

A23. **Priority question:** On page 108, the company submission states that "the analysis was conducted on the initial phase of treatment…with the majority of initial treatments being 16 weeks although the range across studies was 10 to 16 weeks". Please provide the time-point at which outcomes were collected for each trial included in the network meta-analysis.

A24. **Priority question:** Please provide PASI 50, PASI 75, PASI 90 and PASI 100 results separately for each treatment arm of each of the trials included in the NMA.

A25. **Priority question:** The results of the NMA imply that guselkumab has a PASI 75 response rate at 16 weeks of ~[redacted]%. The VOYAGE 1 trial, however, suggests a

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response rate of ~90%. This may suggest an error in the NMA. Can the company please check the analysis and amend as necessary.

A26. **Priority question:** Please provide all the files required to run the NMA analyses (fixed effects and random effects, with and without placebo adjustment) in WinBUGS (including data, model, and initial values for every chain).

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Section B: Clarification on cost-effectiveness data

Model structure

B1. Several recent submissions (e.g. TA442, TA511) have separated the PASI ≥ 90 state into two states: PASI 90–99 and PASI 100. Please justify why a single state was used in the company submission.

B2. **Priority question:** Please replace all proprietary drug names used in the economic model with the generic names. Denote biosimilars with the brand name in brackets.

B3. **Priority question:** Please unhide all hidden rows, columns, and sheets in the model. Please remove the macros automatically hiding rows and columns. Please make all white text visible.

Clinical effectiveness

B4. **Priority question**: Please justify why placebo data was included in the proxy best-supportive care (BSC) dataset in the comparison with BSC in the 'candidates for non-biologic systemic therapies' analysis, when placebo trial patients were not permitted to receive systemic therapies in the CIMPASI and CIMPACT trials.

B5. **Priority question:** On page 161 the company submission states: "Data from clinical trials indicate that CZP has high durability data, which has been indicated by a UK clinical expert as being different to other anti-TNFs in psoriasis". Please provide further justification for these claims, with specific reference to the cited clinical evidence, and further details of why clinical expert opinion expects certolizumab pegol will have a more durable treatment effect than other therapies.

B6. The ERG notes that despite the above (see question B5), the base-case economic analysis assumes a common discontinuation rate of 20%. Does the company therefore believe that a lower discontinuation rate may be more appropriate for certolizumab pegol? Why was this not included in the base-case analysis?

B7. **Priority question:** For treatment discontinuation during the initial treatment phase, please provide the discontinuation rate separately for each treatment arm of each of the trials included in the NMA, and please specify at which time point in the trial this data was extracted for.

B8. **Priority question:** Please provide the PASI 50,75, 90 and 100 response rates of patients who:

a) Failed to achieve PASI 75 response and moved to receive certolizumab pegol 400mg

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b) Achieve PASI 50, but failed to achieve PASI 75 response and moved to receive certolizumab pegol 400mg

B9. **Priority question:** Please provide maintenance phase data on durability of response for the groups described in question B8, including data on response rates, discontinuation rates, the proportion of patients reverting to the 200mg dose and mean duration of 400mg treatment.

Quality of life

B10. **Priority question**: Please provide details of the following:

a) Please confirm whether the UK value set (Dolan P (1997). Modelling valuations for EuroQol health states. *Med Care,* 35 (11): 1095-108) were used to estimate utility values from EQ-5D.

b) In CIMPASI-1, CIMPASI-2 and CIMPACT, the mean and standard deviation EQ-5D at baseline, in each treatment arm in each trial and for each trial overall,

c) The number of observations at each time point that EQ-5D data was collected in the trials (i.e. at weeks 0, 8, 12, 16, 24, 32, and 48)

B11. **Priority question**: Please provide further details of the regression methods used to estimate change in EQ-5D

a) Were data from all time points included in the analysis, or was the analysis restricted to data collected in the initial period of the trial?

b) How were missing values dealt with (i.e. a complete case analysis or multiple imputation of the missing data)?

c) The coefficients for each of the covariates included in the analysis, (mean, standard error, p value and 95% confidence interval).

d) Which arms of the 3 trials provided EQ-5D data for the regression analysis? Were patients in the placebo arm included?

e) Please justify why an adjustment was not made for baseline EQ-5D, as this has been used in recent submissions.

B12. Please provide further justification for why patients on best-supportive care or on non-biologic systemic therapy were assumed to have different quality of life than patients on biologic treatments, for a given PASI score. Make reference to safety profile, mode of administration and any other factors felt to be applicable. If patients

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in the placebo arms of the certolizumab pegol trials were used in the regression analysis, please provide justification as to why these utility values were considered appropriate to model patients on first-line systemic therapy, given that these patients could not receive systemic treatment in the trial.

B13. **Priority question:** Upon inspection of the model, the ERG is concerned that there may be an error in the estimation of utility values, but it is hard to detect without additional information presented by the company on the regression analyses. Please provide details on how the coefficients should be interpreted, and check the calculations in the model and confirm whether they are correct with respect to the following:

a) The coefficient PASI < 50 appears to have been applied to the calculations for baseline PASI

b) There does not appear to be a coefficient for PASI 90–100

c) The treatment effect for certolizumab pegol appears to be based on the utility coefficient for the “Treatment 400mg Q4W CZP” dose.

B14. **Priority question:** Please present the following additional analyses:

a) Results of the regression analysis using the company’s original assumptions, based on the UK value set, if these were not applied in the analyses presented in the submission

b) Results for the subgroup with baseline DLQI > 10 (using the UK value set)

c) Adjusting for baseline EQ-5D score (in the full population analysis, using the UK value set)

d) Adjusting for baseline EQ-5D score (in the DLQI > 10 analysis, using the UK value set).

Costs and resource use

B15. **Priority question:** Please confirm the per-cycle costs of best supportive care, as the values reported in the company submission do not appear to match those in the model.

B16. **Priority question:** Please can you confirm whether the company will be offering self-injection training to patients free of charge in line with competitors, and whether cost of self-injection training was applied for other biologics in the model. Please could you also clarify why ‘3 hours nurse time for subcutaneous self-injection training’ was described in the model, but only one hour of nurse time was costed for.

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B17. Please confirm the source and the rationale behind the assumptions made for the current and predicted market share of biologics over the next 5 years. Given that adalimumab biosimilars are due to enter the market in October 2018, please justify why you consider that market share for this comparator will decline over the next 5 years.

B18. **Priority question:** Please confirm the number of doses of certolizumab pegol patients received during the initial phase of treatment in the 3 trials. Were patients who did not achieve a PASI 50/75 response at week 16 given a final induction dose at week 16? In practice does the company believe that patients not achieving PASI 75 response at week 16 will be given the final dose at week 16?

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Section C: Textual clarifications and additional points

C1. The search strategies and update search strategies presented in Appendix D in Tables 1 to 9 are missing terms for the systemic non-biologic acitretin. Please could the omission of this drug from all of the search strategies be explained?

C2. Was the inclusion of RCTs of risankizumab 150mg (see Table 11 of appendices) pre-defined, or selected based on the studies that were identified by the searches?

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Single Technology Appraisal (STA)

Certolizumab pegol for treatment chronic plaque psoriasis [ID1232]

17th September 2018

UCB Response to Clarification Questions

File name	Version	Contains confidential information	Date
ID 1232 Certolizumab Pegol **Response to Clarification Questions**	**1.0**	**Yes** AIC: Highlighted in yellow and underlined CIC: Highlighted in turquoise and underlined	**17.09.2018**

UCB response to ERG Clarification Questions

UCB welcomes the opportunity to respond to the questions from the Evidence Review Group (ERG) and the NICE Technical Team, following their initial review the single technology appraisal (STA) submission for certolizumab pegol (CZP) for the treatment of moderate to severe plaque psoriasis [ID1232]. UCB encloses its responses and further clarification to these questions below.

Section A: Clarification on effectiveness data

Positioning and marketing authorisation

A1. **Priority question:** Please provide further justification for the choice to position certolizumab pegol as an alternative to systemic non-biological therapy, given that all biologic therapy currently approved by NICE are positioned after systemic non-biological therapy, which is narrower than their respective licensed indications.

UCB response:

The positioning of certolizumab pegol (CZP) as an alternative to systemic non-biological therapy is in line with the approved EU licenced indication for CZP: the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy, which includes candidates for systemic non-biological therapy. Furthermore, the choice of this position is in line with the final scope defined by NICE for the appraisal of CZP, where one of the two positions assessed was "If systemic non-biological treatment or phototherapy is suitable", for which the comparators listed in the final scope are "systemic non-biological therapies". Therefore, the choice of the CZP positioning in the UCB submission is in line with the EU indication and the final scope defined by NICE.[1]

Feedback from clinical experts in the UK has indicated that they would welcome the ability to use a biologic therapy according to their label, for a few patients who are difficult to treat and have a high unmet need. The British Association for Dermatologists (BAD) psoriasis guidelines also suggest that patients may be eligible for biologic therapy earlier in the treatment pathway (before systemic non-biologic therapy options have been exhausted), if they:

- Fulfil the disease severity criteria and have active PsA (indicating that BAD consider the presence of absence of PsA to be an important factor in treatment decisions), or
- Have psoriasis that is persistent, i.e. that relapses rapidly upon discontinuation of a therapy that cannot be continued long-term (>50% baseline disease severity within 3 months).[2]

A2. **Priority question:** In Table 2, page 17 of the company submission it states that certolizumab pegol received European marketing authorisation on 8th June 2018. Apart from details of the positive CHMP opinion there seems to be no reference to the new licensed indication in the references provided or on the EMA website. Furthermore, the EPAR and SPC provided by the company in its reference pack do not include the indication for plaque psoriasis. Please confirm that certolizumab pegol has received European marketing authorisation and provide the updated EPAR and SPC for this indication.

UCB response:
Please find attached the updated SmPC which includes the new licensed indication in psoriasis.[3]
[redacted]

Trial data

A3. **Priority question:** Please provide Clinical Study Reports for the CIMPASI-1, CIMPASI-2 and CIMPACT trials.

UCB response:

The clinical study reports (CSRs) for the CIMPASI-1, CIMPASI-2 and CIMPACT trials have been provided in the reference pack accompanying the response to these questions.[5-7]

A4. **Priority question:** Please confirm when further interim data (week 96) will be available for the CIMPASI-1, CIMPASI-2 and CIMPACT trials. Please provide this data if it is now available.

UCB response:

[redacted]

A5. **Priority question:** Please present additional results for the 'systemic non-biologic therapy inadequate responders' subgroup (Section B.2.6.10) as per the 'candidates for non-biologic systemic therapies' subgroup (Section B.2.6.9), i.e. body surface area, extra-cutaneous manifestations and quality of life results.

UCB response:

In B.2.6.10 of the original submission, the following results were provided for the 'systemic non-biologic inadequate responders' subgroup:

- Baseline characteristics
- PASI75/90 and PGA responder rates at Week 16
- PASI75/90 and PGA responder rates at Week 48

For completeness, the above results included in the original submission have also been included in this response. The additional results requested by the ERG for the 'systemic non-biologic therapy inadequate responders' subgroup are presented below.

Clinical response

Table 1: PASI75, PASI90, PASI100 and PGA 0/1 responses at Week 16 – systemic non-biologic therapy inadequate responders (Pool E1) [PASI75/90 and PGA responder rates previously presented in Table 46 of the original submission]

	Placebo (n=[redacted])	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
Responder rate at Week 16, %[a]			
PASI75	[redacted]	[redacted]	[redacted]
PASI90	[redacted]	[redacted]	[redacted]
PASI100	[redacted]	[redacted]	[redacted]
PGA 0/1 response	[redacted]	[redacted]	[redacted]

[a]Based on logistic regression model with factors for treatment, region and study using NRI (patients missing PASI or PGA response are considered to be non-responders). Responder rates are the adjusted probabilities from the logistic regression model; the model factor levels were weighted based on frequencies in the analysis population
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).
Abbreviations: CZP: certolizumab pegol; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
Source: UCB Data on File (2018)[8].

Long-term maintenance of efficacy

Table 2: PASI75, PASI90, PASI100 and PGA 0/1 responses and absolute PASI scores at Week 48 – systemic non-biologic therapy inadequate responders (Pool E3) [PASI75/90 and PGA responder rates previously presented in Table 47 of the original submission]

	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
Absolute PASI score at Week 48	[redacted]	[redacted]
Responder rate, n (%)		
PASI75	[redacted]	[redacted]
PASI90	[redacted]	[redacted]
PASI100	[redacted]	[redacted]
PGA 0/1 response, n (%)	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
Patients who meet escape criteria at Week 16 (i.e., do not achieve a PASI50) or who meet criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 are treated as non-responders at subsequent visits. For patients who achieved a PASI50 response at Week 16 but were mistakenly put into the CZP 400 mg Q2W escape arm, all visits after Week 16 are imputed with the value observed at Week 16 (i.e., Week 16 carried forward). All other missing data are imputed using NRI.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Source: UCB Data on File (2018)[8].

Body surface area

Table 3: Change from baseline at Week 16 in psoriasis percentage BSA affected – systemic non-biologic therapy inadequate responders (Pool E1)

	Placebo (n=[redacted])	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])

Baseline mean	[redacted]	[redacted]	[redacted]
Percent change from baseline to Week 16			
Change from baseline mean, % (SD)	[redacted]	[redacted]	[redacted]
P value vs placebo[a]		[redacted]	[redacted]

Based on ANCOVA model of percentage change from baseline with factors for treatment group, region, study and interaction terms for study by region and baseline BSA score as a covariate.
[a]P value for adjusted mean treatment differences.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).
Abbreviations: ANCOVA: analysis of covariance; BSA: body surface area; CZP: certolizumab pegol; LOCF: last observation carried forward; Q2W: every two weeks; SD: standard deviation.
Source: UCB data on file (2018)[9]

Table 4: Change from baseline at Week 48 in psoriasis percentage BSA affected – systemic non-biologic therapy inadequate responders (Pool E3)

	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
Baseline mean	[redacted]	[redacted]
Percent change from baseline to Week 48		
Change from baseline mean, % (SD)	[redacted]	[redacted]

For patients escaping at Week 16, Week 16 score has been used to impute all subsequent visits scores. For non-escaping patients LOCF imputation has been used to impute missing scores.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Abbreviations: BSA: body surface area; CZP: certolizumab pegol; LOCF: last observation carried forward; Q2W: every two weeks; SD: standard deviation.
Source: UCB data on file (2018)[9]

Extracutaneous manifestations

Table 5: Change from baseline in mNAPSI score and nail psoriasis resolution (mNAPSI=0) at Week 48 – systemic non-biologic therapy inadequate responders (Pool E3) [a]

	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
mNAPSI change from baseline at Week 48		
n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
Nail psoriasis resolution at Week 48		
n	[redacted]	[redacted]
Patients, n (%)	[redacted]	[redacted]

[a]One subject (CZP 200mg Q2W) had a different nail location assessed at Baseline (left hand, third finger) compared to at Week 48 (right hand thumb). For the purposes of this summary, the difference in location has been ignored.
Abbreviations: CZP: certolizumab pegol; mNAPSI: Modified Nail Psoriasis Severity Index; N/A: not applicable; NR: not reported; Q2W: every two weeks; SD: standard deviation.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Source: UCB data on file (2018)[9]

Quality of life

DLQI

Table 6: Change from baseline in DLQI score and DLQI remission rate (0/1) at Week 16 – systemic non-biologic therapy inadequate responders (Pool E1)

	Placebo (n=[redacted])	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
Change from baseline to Week 16			
n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
p value vs placebo[a]		[redacted]	[redacted]
Remission rate at Week 16[a]			
Remission rate, %	[redacted]	[redacted]	[redacted]
p value vs placebo[b]		[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; NRI: non-responder imputation; SD: standard deviation.
Based on a logistic regression model with factors for treatment, region and study, where missing data were imputed using NRI (patients missing DLQI response are considered to be non-responders). Responder rates are the adjusted probabilities from the logistic regression model; the model factor levels were weighted based on frequencies in the analysis population.
[a]p value for adjusted mean treatment differences. [b]p value for odds ratio versus placebo.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).
Source: UCB data on file (2018)[9]

Table 7: Change from baseline in DLQI score and DLQI remission rate (0/1) at Week 48 – systemic non-biologic therapy inadequate responders (Pool E3)

	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
Change from baseline at Week 48[a]		
n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
DLQI remission rate at Week 48[b]		
Remission rate, n (%)	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; LOCF: last observation carried forward; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks; SD: standard deviation.
[a]Using LOCF. [b]Patients who meet escape criteria at Week 16 (i.e., do not achieve a PASI50) or who meet criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 are treated as non-responders at subsequent visits. For patients who achieved a PASI50 response at Week 16 but were mistakenly put into the CZP 400 mg Q2W escape arm, all visits after Week 16 are imputed with the value observed at Week 16 (i.e., Week 16 carried forward). All other missing data are imputed using NRI methodology.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Source: UCB data on file (2018)[9]

SF-36

Table 8: Change from baseline in SF-36 score at Week 16 – systemic non-biologic therapy inadequate responders (Pool E2)

	Placebo (n=[redacted])	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
PCS, n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Change from baseline to Week 16			
Mean (SD)	[redacted]	[redacted]	[redacted]
P value vs placebo[a]		[redacted]	[redacted]
MCS, n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Change from baseline to Week 16			
Mean (SD)	[redacted]	[redacted]	[redacted]
P value vs placebo[a]		[redacted]	[redacted]

Based on ANCOVA model of change from baseline with treatment group, region, study and study*region as factors and baseline SF-36 Component Summary as a covariate.
[a]P value for adjusted mean treatment differences.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E2).
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; CZP: certolizumab pegol; MCS: mental component summary; PCS: physical component summary; SD: standard deviation.
Source: UCB data on file (2018)[9]

Table 9: Change from baseline in SF-36 score at Week 48 – systemic non-biologic therapy inadequate responders (Pool E3)

	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
PCS, n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Change from baseline to Week 48		
Mean (SD)	[redacted]	[redacted]
MCS, n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Change from baseline to Week 48		
Mean (SD)	[redacted]	[redacted]

For patients that escaped from their blinded randomized treatment group, their value from the time of escape is carried forward through all remaining time points up to Week 48. For all missing data, LOCF is used.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Abbreviations: CZP: certolizumab pegol; LOCF: last observation carried forward; MCS: mental component summary; PCS: physical component summary; Q2W: every two weeks; SD: standard deviation.
Source: UCB data on file (2018)[9]

Table 10: Change from baseline in HADS-A and HADS-D score at Week 16 – systemic non-biologic therapy inadequate responders (Pool E2)

	Placebo (n=[redacted])	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
HADS-A			
n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Change from baseline to Week 16			
Mean (SD)	[redacted]	[redacted]	[redacted]
P-value[a]		[redacted]	[redacted]
HADS-D			
n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Change from baseline to Week 16			
Mean (SD)	[redacted]	[redacted]	[redacted]
P-value[a]		[redacted]	[redacted]

Based on ANCOVA model of change from baseline with treatment group, region, study and study*region as factors and baseline HADS Scores as a covariate.
[a]P value for adjusted mean treatment differences.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E2).
Abbreviations: CZP: certolizumab pegol; HADS-A: hospital anxiety and depression score – anxiety; HADS-D: hospital anxiety and depression score – depression; N/A: not applicable; SD: standard deviation.
Source: UCB data on file (2018)[9]

Table 11: Change from baseline in HADS-A and HADS-D score at Week 48 – systemic non-biologic therapy inadequate responders (Pool E3)

	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
HADS-A		
n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Change from baseline to Week 48		
Mean (SD)	[redacted]	[redacted]
HADS-D		
n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Change from baseline to Week 48		
Mean (SD)	[redacted]	[redacted]

For patients that escaped from their blinded randomized treatment group, their value from the time of escape is carried forward through all remaining time points up to Week 48. For all missing data, LOCF is used.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Abbreviations: CZP: certolizumab pegol; HADS-A: hospital anxiety and depression score – anxiety; HADS-D: hospital anxiety and depression score – depression; LOCF: last observation carried forward; SD: standard deviation.
Source: UCB data on file (2018)[9]

WPAI-SHP

Table 12: Change from baseline in WPAI-SHP scores at Week 16 – systemic non-biologic therapy inadequate responders (Pool E1)

	Placebo (n=[redacted])	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
Percent work time missed due to problem			
n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]
P value vs placebo[a]		[redacted]	[redacted]
Percent impairment while working due to problem			
n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]
P value vs placebo[a]		[redacted]	[redacted]
Percent overall work impairment due to problem			
n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]
P value vs placebo[a]		[redacted]	[redacted]
Percent activity impairment due to problem			
n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]
P value vs placebo[a]		[redacted]	[redacted]

Based on ANCOVA model of change from baseline with treatment group, region, study and study*region as factors and baseline WPAI-SHP Scores as a covariate.
[a]P value for adjusted mean treatment differences.
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).
Abbreviations: ANCOVA: analysis of covariance; CZP: certolizumab pegol; N/A: not applicable; NS: not significant; Q2W: every two weeks; SD: standard deviation; WPAI-SHP: Work Productivity and Activity Impairment – Specific Health Problem.
Source: UCB data on file (2018)[9]

Table 13: Change from baseline in WPAI-SHP scores at Week 48 – systemic non-biologic therapy inadequate responders (Pool E3)

	CZP 200 mg Q2W (n=[redacted])	CZP 400 mg Q2W (n=[redacted])
Percent work time missed due to problem		
n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Percent impairment while working due to problem		
n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Percent overall work impairment due to problem		
n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]
Percent activity impairment due to problem		
n	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]

For patients that escaped from their blinded randomized treatment group, their value from the time of escape is carried forward through all remaining time points up to Week 48. For all missing data, LOCF is used.
Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E3).
Abbreviations: CZP: certolizumab pegol; N/A: not applicable; LOCF: last observation carried forward; Q2W: every two weeks; SD: standard deviation; WPAI-SHP: Work Productivity and Activity Impairment – Specific Health Problem.
Source: UCB data on file (2018)[9]

A6. The subgroups 'candidates for non-biologic systemic therapies' and 'systemic non-biologic therapy inadequate responders' do not make up the entire cohort of patients included in the trials (there are an additional [redacted] placebo patients, [redacted] 200 mg Q2W patients and [redacted] 400 mg Q2W patients). Is there an additional subgroup, e.g. patients for whom non-biologic therapy is contraindicated? If so, please provide further details and present results for this additional subgroup, i.e. baseline characteristics, clinical response, body surface area, extra-cutaneous manifestations and quality of life.

UCB response:

The 'candidates for non-biologic systemic therapies' were defined as patients who were completely treatment naïve (both non-biologic and biologic therapies). The 'systemic non-biologic therapy inadequate responders' were defined as patients who had exposure to at least one previous systemic non-biologic therapy and no previous biologic exposure. The remaining group in the population is patients who have previously been exposed to biologic therapies. This subgroup (the 'biologic-exposed' subgroup) is presented in Section B.2.7.1 of the submission,

and the patient numbers stated above match those in Table 48 of the submission (see Table 14 below for a summary of the patient numbers).

Table 14: Summary of patient numbers for the candidates for non-biologic systemic therapies, systemic non-biologic inadequate responder and biologic-exposed populations

Population	Placebo	CZP 200 mg Q2W	CZP 400 mg Q2W	Reference in original submission
Candidates for non-biologic systemic therapies	[redacted]	[redacted]	[redacted]	Section B.2.6.9
Systemic non-biologic therapy inadequate responders	[redacted]	[redacted]	[redacted]	Section B.2.6.10
Biologic-exposed	[redacted]	[redacted]	[redacted]	Section B.2.7.1
Total (Pool E1)	157	351	342	Section B.2.6.2

A7. Please confirm how many patients in each treatment arm of CIMPACT were from the UK.

UCB response:

In total [redacted] UK patients were initially randomised to the CIMPACT trial. In the ETN arm there were [redacted] patients, whilst there were [redacted] patients in the placebo arm and [redacted] patients in each of the CZP treatment arms. In the CZP 200 mg and CZP 400 mg arms, [redacted] and [redacted] patients from the UK discontinued before Week 16, respectively.[10]

A8. Figures 9 to 13 in the appendix report the reasons that patients discontinued from the CIMPASI-1, 2 and CIMPACT studies; please provide further information on the reasons 'consent withdrawn' and 'other'.

UCB response:

Patients were able to withdraw consent for any reason, therefore, no further details relating to this discontinuation category were collected. Further details regarding the specific reasons captured in the discontinuation category "other", can be found below in Table 15, Table 16 and Table 17.

Table 15: "Other" reasons for discontinuation: CIMPASI-1

Treatment arm	N	Detailed reason for discontinuation
Initial treatment period		
No patients withdrew from CIMPASI-1 during the initial treatment period for "other" reasons.		
Maintenance treatment period		
CZP 200 mg Q2W/CZP 200 mg Q2W	[redacted]	[redacted]
CZP 400 mg Q2W/CZP 400	[redacted]	[redacted]

mg Q2W		
PBO/Esc CZP 400 mg Q2W	[redacted]	• [redacted]

Abbreviations: CZP: certolizumab pegol; Esc: escape; PBO: placebo; Q2W: every two weeks.
Source: UCB. Data on File, 2017.[11]

Table 16: "Other" reasons for discontinuation: CIMPASI-2

Treatment arm	N	Detailed reason for discontinuation
Initial treatment period		
CZP 400 mg Q2W	2	• [redacted] • [redacted]
Maintenance treatment period		
CZP 200 mg Q2W/CZP 200 mg Q2W	[redacted]	• [redacted]
CZP 400mg Q2W/CZP 400mg Q2W	[redacted]	• [redacted] • [redacted]
PBO/Esc CZP 400 mg Q2W	[redacted]	• [redacted] • [redacted]
CZP 200 mg Q2W/Esc CZP 400 mg Q2W	[redacted]	• [redacted] • [redacted]

Abbreviations: CZP: certolizumab pegol; Esc: escape; IP: investigational product; PBO: placebo; Q2W: every two weeks.
Source: UCB. Data on File, 2017.[11]

Table 17: "Other" reasons for discontinuation: CIMPACT

Treatment arm	N	Detailed reason for discontinuation
Initial treatment period		
ETN	1	• [redacted]
CZP 200 mg Q2W	1	• [redacted]
CZP 400 mg Q2W	1	• [redacted]
Maintenance treatment period		
CZP 200 mg Q2W /Esc CZP 400 mg Q2W	[redacted]	• [redacted]
CZP 400 mg Q2W/Esc CZP 400 mg Q2W	[redacted]	• [redacted]
CZP 200 mg Q2W/CZP 200 mg Q2W	[redacted]	• [redacted]
CZP 200	[redacted]	• [redacted]

mg Q2W/CZP 400 mg Q4W		[redacted]
CZP 400 mg Q2W/CZP 200 mg Q2W	[redacted]	[redacted]
CZP 400 mg Q2W/PBO	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; ETN: etanercept; Q2W: every two weeks.
Source: UCB. Data on File, 2017.[11]

A9. Relapse rate was an outcome specified in the decision problem. However, relapse rate data is only presented for the CIMPACT trial. Please explain why this outcome has not been presented for CIMPASI-1 and CIMPASI-2 and provide this data, if it is available.

UCB response:

The CIMPACT trial was the only one of these three trials for which time to relapse was a pre-specified outcome. Relapse rate was not a pre-defined endpoint for CIMPASI-1 or CIMPASI-2.[5-7]

A10. **Priority question:** Clinical effectiveness data are significantly better in the CIMPASI-2 trial compared with the other two trials. Is there a clinically plausible reason that might explain this difference in clinical effectiveness, e.g. differences in trial design or population characteristics?

UCB response:

The responder rates in each treatment group in CIMPASI-2 were higher than the respective treatment groups observed in CIMPASI-1 and CIMPACT.[12] There were several demographic and baseline clinical characteristic differences between CIMPASI-2 and the other two trials for CZP in psoriasis (CIMPASI-1 and CIMPACT), including prior anti-TNF therapy use. However, there is no clear evidence available to indicate that these differences had any effect on the clinical outcomes observed across all three studies. Furthermore, the sample sizes across all three trials (CIMPASI-1, CIMPASI-2 and CIMPACT) are smaller than other Phase III trials in psoriasis. This makes it difficult to determine whether observed study variations are a consequence of uncertainty arising from patient numbers, as opposed to a reflection of true differences in efficacy between trials.[13] However, the data from these three trials are still generalisable to the overall psoriasis patient population, including psoriasis patients in the UK, given that the demographics observed in each treatment arm were typical of Phase III psoriasis trials.[13, 14] It should also be noted that the efficacy was similar to that observed in Phase II studies for CZP in psoriasis and the results mirror what is seen in clinical practice.[13, 15]

A11. **Priority question:** Please provide PASI 50, 75 and 90 response rates as presented in Figure 6 of the company submission, but with an adjustment for gender and PSA. Please also include full details of this analysis along with the regression coefficients.

UCB response:

A re-analysis of the PASI response rates including two additional factors in the logistics regression could not be completed due to the complexity of the methodology used, however subgroup analysis are provided in the additional information included in this response.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

A12. **Priority question:** Section B2.4 presents information on the methods used for imputation of missing data, but the number of patients for whom missing data were imputed is not stated. Please present this information for the primary outcomes PASI 75 and PGA response at weeks 16 and 48 for each of the treatment groups within each of the trials.

UCB response:

CIMPASI-1

The overall n numbers for each treatment group, alongside the number of observed cases for each treatment group for PASI 75 and PGA 0/1 at Week 16 and Week 48 are presented in Table 18 below.

Table 18: Overall patient numbers (imputed data and observed cases) for PASI75 and PGA 0/1 at Week 16 and Week 48 in CIMPASI-1 for randomised treatment groups[a]

	Placebo	CZP 200 mg Q2W	CZP 400 mg Q2W
PASI75			
Week 16			
Number of patients randomised to each treatment arm	51	95	88
Observed cases	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]
Week 48			
Number of patients randomised to each treatment arm	[redacted]	95	88
Observed cases	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]
PGA 0/1			
Week 16			
Number of patients randomised to each treatment arm	51	95	88
Observed cases	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]
Week 48			
Number of patients randomised to each treatment arm	[redacted]	95	88
Observed cases	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]

[a]The number of patients at Week 48 in the placebo arms is not reported, as the numbers above are for the randomised treatment groups, rather than the maintenance treatment groups. Results for the CZP 200 mg and 400 mg arms are presented until Week 48 in the original submission only.
Abbreviations:

Source: Data on File. CIMPASI-1 data tables.[16]

CIMPASI-2

The overall n numbers for each treatment group, alongside the number of observed cases for each treatment group for PASI 75 and PGA 0/1 at Week 16 and Week 48 are presented in Table 19.

Table 19: Overall patient numbers and observed cases for PASI75 and PGA 0/1 at Week 16 and Week 48 in CIMPASI-2

	Placebo	CZP 200 mg Q2W	CZP 400 mg Q2W
PASI75			
Week 16			
Number of patients randomised to each treatment arm	49	91	87
Observed cases	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]
Week 48			
Number of patients randomised to each treatment arm	[redacted]	91	87
Observed cases	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]
PGA 0/1			
Week 16			
Number of patients randomised to each treatment arm	49	91	87
Observed cases	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]
Week 48			
Number of patients randomised to each treatment arm	[redacted]	91	87
Observed cases	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]

[a]The number of patients at Week 48 in the placebo arms is not reported, as the numbers above are for the randomised treatment groups, rather than the maintenance treatment groups. Results for the CZP 200 mg and 400 mg arms are presented until Week 48 in the original submission only.
Abbreviations:
Source: CIMPASI-2 data tables[17]

CIMPACT

The overall n numbers for each treatment group, alongside the number of observed cases for each treatment group for PASI 75 and PGA 0/1 at Week 16 are presented in Table 20. For Week 48, results are presented by blinded maintenance treatment group (Table 21).

Table 20: Overall patient numbers and observed cases for PASI75 and PGA 0/1 at Week 16 in CIMPACT

	Placebo	CZP 200 mg Q2W	CZP 400 mg Q2W
PASI75			
Week 16			
n	57	165	167
Observed cases	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]
PGA 0/1			
Week 16			
n	57	165	167
Observed cases	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]

Abbreviations:
Source: CIMPACT data tables[18]

Table 21: Overall patient numbers and observed cases for PASI75 and PGA 0/1 at Week 48 in CIMPACT by blinded maintenance treatment group

Treatment group	n	Observed cases	Difference
PASI75			
CZP 200 mg Q2W/placebo	22	[redacted]	[redacted]
CZP 200 mg Q2W/ CZP 200 mg Q2W	44	[redacted]	[redacted]
CZP 200 mg Q2W/CZP 400 mg Q4W	44	[redacted]	[redacted]
CZP 400 mg Q2W/placebo	25	[redacted]	[redacted]
CZP 400 mg Q2W/ CZP 200 mg Q2W	50	[redacted]	[redacted]
CZP 400 mg Q2W/ CZP 400 mg Q2W	49	[redacted]	[redacted]
PGA 0/1			
CZP 200 mg Q2W/placebo	22	[redacted]	[redacted]
CZP 200 mg Q2W/ CZP 200 mg Q2W	44	[redacted]	[redacted]
CZP 200 mg Q2W/CZP 400 mg Q4W	44	[redacted]	[redacted]

CZP 400 mg Q2W/placebo	25	[redacted]	[redacted]
CZP 400 mg Q2W/ CZP 200 mg Q2W	50	[redacted]	[redacted]
CZP 400 mg Q2W/ CZP 400 mg Q2W	49	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; ETN: etanercept; PASI: Psoriasis Area Severity Index; PGA: Physician Global Assessment; Q2W: every 2 weeks.
Source: CIMPACT data tables[18]

A13. Clinical effectiveness results are presented differently for the CIMPASI trials and the CIMPACT trial. Please present PASI 75 and PASI 90 response data for all three trials in the same format as Table 20 of the company submission (i.e. PASI 75 and PASI 90 responder rate at week 48, including the number of patients included in each treatment arm and confidence intervals). Please also present the data for week 48 PGA responder rate in a similar format.

UCB response:

The reason for the difference in format is due to the difference in trial design between CIMPACT and CIMPASI-1 and CIMPASI-2, as in CIMPACT there was a re-randomisation stage at Week 16. In the original submission, Table 73 in the appendices presents the PASI75 and PASI90 results for CIMPASI-1 and CIMPASI-2, whilst Table 75 presents the PGA responder rate for each trial. As requested, please find below the results for CIMPASI-1 and CIMPASI-2 presented in the same format as Table 20 of the original submission, in Table 22 and Table 23 below.

Table 22: PASI70, PASI90 and PGA 0/1 responder rates at Week 48 by treatment group in CIMPASI-1 – ITT population RS set

Treatment group	Responder rate, % (95% CI)
PASI75	
CZP 200 mg Q2W (n=95)	67.2 (57.09. 77.39)
CZP 400 mg Q2W (n=88)	87.1 (79.81, 94.45)
PASI90	
CZP 200 mg Q2W (n=95)	42.8 [redacted]
CZP 400 mg Q2W (n=88)	60.2 [redacted]
PGA 0/1	
CZP 200 mg Q2W (n=95)	52.7 (41.99, 63.32)
CZP 400 mg Q2W (n=88)	69.5 (59.24, 79.77)

PASI75 and PASI90: Subjects who met the escape criterion (i.e. did not achieve PASI50) at Week 16 were treated as nonresponders at all subsequent timepoints. Subjects who met the criterion for mandatory withdrawal due to not achieving a PASI50 response at Week 32 or later were treated as nonresponders at subsequent missing timepoints. If a subject achieved a PASI50 response at Week 16 but was mistakenly put in the escape arm by the IVRS/IWRS, their Week 16 value was carried forward to Week 48. Similarly, if a subject achieved a PASI50 response at Weeks 32 or 40 but was mistakenly withdrawn by the IVRS/IWRS, their values at the visit at which they were withdrawn were carried forward to Week 48.
Multiple imputation using MCMC methodology was used for all other missing data. A logistic regression was used with factors for treatment, region, and prior biologic exposure (yes/no) on the multiply-imputed datasets.
Abbreviations: CI: confidence interval; CZP: certolizumab pegol; NRI: non-responder imputation; PASI: Psoriasis Area Severity Index; PGA: Physician Global Assessment; Q2W: every two weeks.
Source: Data on file - CIMPASI-1 CSR[5]

Table 23: PASI70, PASI90 and PGA 0/1 responder rates at Week 48 by treatment group in CIMPASI-2 – ITT population RS set

Treatment group	Responder rate, % (95% CI)
PASI75	
CZP 200 mg Q2W (n=91)	78.7 [redacted]
CZP 400 mg Q2W (n=87)	81.3 [redacted]
PASI90	
CZP 200 mg Q2W (n=91)	58.7 [redacted]
CZP 400 mg Q2W (n=87)	62.3 [redacted]
PGA 0/1	
CZP 200 mg Q2W (n=91)	72.6 [redacted]
CZP 400 mg Q2W (n=87)	66.6 [redacted]

Subjects who met the escape criterion (i.e. did not achieve PASI50) at Week 16 were treated as nonresponders at all subsequent time points. Additionally, subjects who met the criterion for mandatory withdrawal due to not achieving a PASI50 response at Week 32 or later were treated as nonresponders for subsequent missing time points. If a subject achieved a PASI50 response at Week 16 but was mistakenly put in the escape arm by the IVRS/IWRS, their Week 16 value was carried forward to Week 48. PGA 0/1: Subjects that meet the criterion for mandatory withdrawal due to not achieving a PASI50 response at Week 32 or later are treated as non-responders at subsequent missing time points.
Multiple imputation using MCMC methodology was used for all other missing data. A logistic regression model was used with factors for treatment, region, and prior biologic exposure (yes/no) on the multiply-imputed data sets.
Abbreviations: CI: confidence interval; CZP: certolizumab pegol; NRI: non-responder imputation; PASI: Psoriasis Area Severity Index; PGA: Physician Global Assessment; Q2W: every two weeks.
Source: Data on file - CIMPASI-2 CSR[6]

A14. The number of patients in the treatment efficacy pools E4 and E5 in Table 15 of company submission do not correspond with the patient disposition figures (Figure 10, Figure 12 and Table 19 of the appendices). Please explain the reason for the differences in numbers of patients.

UCB response:

The reason for the difference in number of patient in the treatment efficacy pools E4 and E5 in Table 15 of the original submission and the patient disposition figures (Figure 12 and Table 19 of the appendices) is due to the patients who escaped treatment within each pool. All subjects who escaped received at least one rescue open label dose of investigational product. Pool E4 consists of all rescued subjects who did not reach a PASI50 response, thereby including all subjects who escaped in CIMPASI-1 and CIMPASI-2 as well as only a subgroup of CIMPACT subjects who were not PASI50 responders, whereas the CIMPACT disposition table includes all PASI75 non-responders (more subjects than in Pool E4). In Pool E5, the number patients should be the same in CIMPACT as the response definition is the same (PASI75 responders), whereas for CIMPASI-1 and CIMPASI-2, Pool E5 consists of a subset of PASI responders, only selecting those subjects who were PASI75 responders.

A15. Under Figure 9 of the company submission it states: “Pooled data is from CIMPASI-1 and CIMPASI-2 (Pool E5)”. However, in Table 15 it states that Pool E5 also includes CIMPACT. Please clarify whether Figure 9 includes data from CIMPACT.

UCB response:

Thank you for your note. Indeed, the footnote figure is not complete, as the figure includes data from CIMPACT. The text in the footnote of Figure 9 should state "Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E5)".

A16. Figure 9 of the company submission states that Pool E5 CZP 400 mg Q2W includes [redacted] patients (PASI 75 responders), but in Table 15 there were only [redacted] CZP 400 mg Q2W PASI 75 responders. Please clarify the number of patients included in Pool E5.

UCB response:

The overall number of patients in the Pool E5 treatment arms are: CZP 200 mg Q2W/CZP 200 mg Q2W, n=[redacted]; and CZP 400 mg Q2W/CZP 400 mg Q2W arm n=[redacted] (Table 24 below). These are the n numbers presented in the legend of Figure 9 in the original submission and correspond to the number of patients who achieved a PASI75 response at Week 16 and continued on the treatment to which they were randomised at the start of the initial treatment period.
The additional responder rates provided in Table 15 of the original submission, and Table 24 below are correspond to the number of patients who were PGA 0/1, PASI75, PASI90 and PASI100 responders at Week 16. The n=[redacted] reported in Table 15 was an error.

Table 24: Treatment efficacy Pool E5

Pool	Studies included	Treatment groups included	Treatment periods included
E5	CIMPASI-1 CIMPASI-2 CIMPACT	CZP 200 mg Q2W/CZP 200 mg Q2W ([redacted]) • PGA responders (n=[redacted]) • PASI75 responders (n=[redacted]) • PASI90 responders (n=[redacted]) • PASI100 responders (n=[redacted]) CZP 400 mg Q2W/ CZP 400 mg Q2W ([redacted]) • PGA responders (n=[redacted]) • PASI75 responders (n=[redacted]) • PASI90 responders (n=[redacted]) • PASI100 responders (n=[redacted])	Maintenance treatment period (Weeks 16–48)

Abbreviations: CZP: certolizumab pegol; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q2W: every two weeks.
Source: UCB Data on File (2017–2018).[19]

A17. Please present results for the CZP 200 mg/CZP 200 mg group (n=74 in CIMPASI-1 and n=76 in CIMPASI-2) for change from baseline in psoriasis percentage BSA affected at week 48 , as presented for other treatment groups in Table 23 of the company submission.

UCB response:

As requested, results for the CZP 200 mg/CZP 200 mg group in CIMPASI-1 and CIMPASI-2 have been presented to match Table 23 of the original submission, and are presented below.

Table 25: Change from baseline in psoriasis percentage BSA affected at Week 48 in CIMPASI-1 and CIMPASI-2 by blinded maintenance treatment group – ITT population

	CZP 200 mg Q2W/ CZP 200 mg Q2W
CIMPASI-1	
n	74
Week 48 n	[redacted]
Baseline mean	[redacted]
Change from baseline to Week 48	
Change from baseline mean (SD)	[redacted]
CIMPASI-2	
n	76
Week 48 n	[redacted]
Baseline mean	[redacted]
Change from baseline to Week 48	
Change from baseline mean (SD)	[redacted]

Abbreviations: BSA: body surface area; CZP: certolizumab pegol; Esc: escape; ETN: etanercept; Q2W: every two weeks; SD: standard deviation.
Source: CIMPASI-1 Data Tables[20]; CIMPASI-2 Data Tables[21].

A18. Please present results for 'escape' patients from CIMPACT (n=138, receiving certolizumab pegol or placebo Table 19 of the appendices), as presented in Table 24 of company submission for change from baseline in psoriasis percentage BSA affected at week 48.

UCB response:

As requested, results for the 'escape' patients from CIMPACT are now presented to match Table 24 of the original submission, and are presented below.

Table 26: Change from baseline in psoriasis percentage BSA affected at Week 48 in CIMPACT by maintenance treatment group – ITT population

	Placebo/Esc CZP 400 mg Q2W (n=53)	CZP 200 mg Q2W/ Esc CZP 400 mg Q2W (n=49)	CZP 400 mg Q2W/ Esc CZP 400 mg Q2W (n=36)
Psoriasis BSA, n	[redacted]	[redacted]	[redacted]
Baseline mean	[redacted]	[redacted]	[redacted]
Change from baseline to Week 48			
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: BSA: body surface area; CZP: certolizumab pegol; ETN: etanercept; Q2W: every two weeks; SD: standard deviation.
Source: CIMPACT Data Tables[22].

A19. Please explain why the number of patients for whom results are presented in Table 25 (change from baseline in mNAPSI score and nail psoriasis resolution (mNAPSI=0)

at week 48 in pool E3- ITT population) and Table 26 (change from baseline in mNAPSI score at week 48 in CIMPACT- ITT population) in the company submission are lower than the number of patients who completed week 48 reported in Table 15 in the company submission and Figures 10, Figure 12 and Table 19 in the appendices.

UCB response:

Change from baseline in mNAPSI and nail psoriasis resolution are provided only for patients who had nail disease at baseline, which was not all patients included in the trials. The number of patients who completed Week 48 reported in Table 15 of the original submission and Figures 10, 12 and Table 19 in the appendices include all patients who completed Week 48, not just those with nail psoriasis.

In reviewing this question, we took the opportunity to provide the numbers of Pool E3 patients for which mNAPSI change from baseline data are available at Week 48, which was missing from Table 25 of the original submission. Table 25 of the original submission reports the number of patients for which mNAPSI data were available at baseline (listed as "n" in the NICE submission, and "Baseline n" below), but does not report the number of patients for which data are available at Week 48 (referred to as "Week 48 n" below). An updated version of Table 25, to which the "Week 48 n" have been added for the change from baseline, can be found below. The "Week 48 n" values below match the Week 48 n numbers for nail psoriasis resolution at Week 48 in Table 25 of the original submission.

Table 27: Change from baseline in mNAPSI score and nail psoriasis resolution (mNAPSI=0) at Week 48 in Pool E3 – ITT population

	Placebo [redacted]	CZP 200 mg Q2W [redacted]	CZP 400 mg Q2W [redacted]
mNAPSI change from baseline at Week 48			
Baseline n	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]
Week 48 n	[redacted]	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]
Nail psoriasis resolution at Week 48			
n	[redacted]	[redacted]	[redacted]
Patients, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; mNAPSI: Modified Nail Psoriasis Severity Index; N/A: not applicable; NR: not reported; Q2W: every two weeks; SD: standard deviation.
Patients who remained on the treatment to which they were randomised at baseline.
Source: UCB Cimzia Plaque Psoriasis Integrated Summary of Efficacy[23].

A20. Please provide further information about the 'pre-determined production randomisation and/or packaging schedule' referred to in Table 9 (summary of methodologies for CIMPACT, CIMPASI-1 and CIMPASI-2) as the method of randomisation for the CIMPACT trial.

UCB response:

[redacted]

A21. Please present the number of patients for the treatment safety pools (S1 and S3).

UCB response:

The number of patients for the treatment safety pools are available in Table 55 and Table 59 in the original submission, which presented the AEs for each pool, and are provided in the table below, which is based upon Table 16 in the original submission, which summarises the treatment groups included in each pool.

Table 28: Treatment safety pools

Pool	Studies included	Treatment groups included	Treatment periods included	Original submission tables
S1	CIMPASI-1 CIMPASI-2 CIMPACT	Patients exposed to: CZP 400 mg Q2W (n=342) CZP 200 mg Q2W (n=350) Placebo (n=157) All CZP (n=692)	Initial treatment period (Weeks 0–16)	Table 55, Table 56, Table 57, Table 58
S3[a]	CIMPASI-1 CIMPASI-2 CIMPACT	Patients exposed to: CZP 200 mg Q2W ([redacted]) CZP 400 mg Q2W (n=[redacted]) All Phase 3 CZP (n=[redacted])	Initial, maintenance and OLE treatment periods (Weeks 0–144)	Table 59, Table 60, Table 61, Table 62

[a]This pool also included patients from studies C87040 (NCT00245765) and C87044 (NCT00329303). However, data presented in this submission only includes patients from CIMPASI-1, CIMPASI-2 and CIMPACT.
Abbreviations: CZP: certolizumab pegol; Q2W: every two weeks; Q4W: every four weeks.
Source: Certolizumab pegol 2.7.4 Summary of Clinical Safety[24]

Network Meta-Analysis

A22. The ERG have identified one RCT that was not included in the network meta-analysis (NMA): 'Caproni M, et al. (2009). Serum Levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: a randomized-controlled trial. *Journal of Clinical Immunology,* 29 (2): 210-4'. Please explain why this trial was excluded.

UCB response:

This trial was excluded because the primary outcome of this study was not PASI response, but rather the levels of IL-17 and IL-22 in patients. This study has also been excluded from a previous NICE submission.[25] However, PASI responses are reported at Week 12 for PASI 50 and PASI 75. The different etanercept dosages have a number of studies linking them to other treatments within the network, therefore it is anticipated that this additional study is unlikely to cause any material difference in the estimated values.

A23. **Priority question:** On page 108, the company submission states that "the analysis was conducted on the initial phase of treatment…with the majority of initial treatments being 16 weeks although the range across studies was 10 to 16 weeks". Please provide the time-point at which outcomes were collected for each trial included in the network meta-analysis.

UCB response:

Please find the time-point at which outcomes were collected for each trial included in the network meta-analysis (NMA) has been included in Appendix A.

A24. **Priority question:** Please provide PASI 50, PASI 75, PASI 90 and PASI 100 results separately for each treatment arm of each of the trials included in the NMA.

UCB response:

The PASI results for each treatment arm of each of the trials included in the NMA is provided in Appendix B.

A25. **Priority question:** The results of the NMA imply that guselkumab has a PASI 75 response rate at 16 weeks of [redacted]%. The VOYAGE 1 trial, however, suggests a response rate of ~90%. This may suggest an error in the NMA. Can the company please check the analysis and amend as necessary.

UCB response:

Following the review of the NMA results, we believe that the methodology used is correct, and the data considered into the NMA align with the published results from the GUS studies considered in the NMA. However, we believe there may be several possible reasons why the results of the NMA imply a different response rate for GUS compared to the clinical trial data for GUS:

- The NMA presented in the original submission includes the trial X-PLORE (Gordon 2015), which was not included in the GUS NICE submission NMA. This trial compared GUS, ADA and placebo and was also included in the NMA provided in the IXE NICE manufacturer submission, although did not include the GUS arms. Furthermore, the submitted NMA included a larger network of evidence compared to NMAs from recent TAs.

- A multinomial model was used in the base case of the NMA, which is based on strong assumptions and is a different approach compared to binomial models.

- At time of the conduct of the submitted NMA, PASI50 data for GUS were not publically available. Therefore, the PASI50 data for this comparator was imputed within the multinomial NMA.

We have further explored the above points, to understand the difference in the GUS results from the submitted NMA vs published clinical trials. A comparison of probability of response results was conducted between the NMA presented in the UCB original submission, and the results in the IXE NICE submission,[25] to assess the methodology of the UCB NMA, including whether the Gordon et al 2015 study could influence the conclusions. It should be noted that although both NMAs used a multinomial approach, the models used might differ (eg in terms of adjustments); furthermore, the network was larger in the UCB submission vs IXE TA. Despite these limitations, as shown in Table 29 below, the results between the two NMAs are comparable regarding ADA estimates. Furthermore, in both NMAs, conclusions indicated that [redacted]

Table 29: Comparison of NMA results from UCB original submission and the IXE NICE submission

	UCB original submission (placebo-adjusted random effects)	IXE NICE submission (random effects)
ADA		
PASI50	[redacted]	0.778 (0.689, 0.855)
PASI75	[redacted]	0.575(0.464, 0.682)
PASI90	[redacted]	0.317 (0.223, 0.422)
SEC		
PASI50	[redacted]	0.932 (89.5, 96.1)
PASI75	[redacted]	0.818 (0.749, 0.881)
PASI90	[redacted]	0.596 (0.500, 0.693)

As it was not possible to identify the reason why the NMA estimates for GUS differed compared to the publications or to re-run the full NMA due to time constraints, a scenario analysis was conducted to assess the impact of the GUS NMA estimates on the submitted cost-effectiveness analysis. For this scenario, the PASI NMA estimates for IXE were used as a proxy for GUS. This is a conservative approach, in line with the conclusion from the recent GUS appraisal. Results from this scenario are presented below, and indicates that CZP is still the most cost-effective treatment option in this patient population, conclusions which are in line with the submitted basecase.

Table 30: Base case fully incremental results for systemic non-biologic therapy inadequate responders – CZP with PAS

1st Line Treatment in Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Fully incremental ICER (£/QALY)
ETN	[redacted]	[redacted]	-			
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£11,470.53	£11,470.53
UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	£51,528.43	Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	£45,655.86	Dominated
UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	£43,529.12	Dominated
SEC	[redacted]	[redacted]	[redacted]	[redacted]	£128,929.95	Extendedly dominated
IXE	[redacted]	[redacted]	[redacted]	[redacted]	£125,644.48	£91,804.96
BROD	[redacted]	[redacted]	[redacted]	[redacted]	£146,412.55	Dominated
GUS	[redacted]	[redacted]	[redacted]	[redacted]	£130,179.42	£130,179.42

A26. **Priority question:** Please provide all the files required to run the NMA analyses (fixed effects and random effects, with and without placebo adjustment) in WinBUGS (including data, model, and initial values for every chain).

UCB response:

The files required to run the NMA analyses in WinBUGS have been provided in Appendix C.

Section B: Clarification on cost-effectiveness data

Model structure

B1. Several recent submissions (e.g. TA442, TA511) have separated the PASI ≥ 90 state into two states: PASI 90–99 and PASI 100. Please justify why a single state was used in the company submission.

UCB response:

The cost-effectiveness model in UCB submission was built on the previous York model used in the disease area, as well as the model used in the appraisal of secukinumab in psoriasis.[26] At the time of model development, the models identified through the economic systematic literature review (SLR) of cost-effectiveness analyses included 4 health states, and these models did not separate the PASI≥90 state into two further states (the SLR was ran until November 2016). Therefore, the model structure used in this submission conforms with model structures used up until this date. However, the difference in health state utilities between PASI 90–99 and PASI 100 are minimal in previous submissions,[25, 27] thus it is not anticipated that the exclusion of this health state will have a considerable impact on the cost-effectiveness results.

B2. **Priority question:** Please replace all proprietary drug names used in the economic model with the generic names. Denote biosimilars with the brand name in brackets.

UCB response:

Please find alongside the response to these questions a version of the model in which all proprietary drug names used in the model are replaced with the generic names. Rather than biosimilars being included as separate comparators within the model, the costs were updated in the 'DrugCosts' tab of the cost-effectiveness model for each biosimilar treatment. This was the most efficient way of running the results when including the biosimilar treatments for ETN and IFX.

B3. **Priority question:** Please unhide all hidden rows, columns, and sheets in the model. Please remove the macros automatically hiding rows and columns. Please make all white text visible.

UCB response:

Please find alongside the response to these questions a version of the model in which all rows, columns and sheets have been unhidden within the model, and the macro which automatically performs the hiding removed. All text is now visible throughout the model.

Clinical effectiveness

B4. **Priority question**: Please justify why placebo data was included in the proxy best-supportive care (BSC) dataset in the comparison with BSC in the 'candidates for non-biologic systemic therapies' analysis, when placebo trial patients were not permitted to receive systemic therapies in the CIMPASI and CIMPACT trials.

UCB response:

Due to the lack of published data for other comparators in patients who are candidates for systemic non-biologic therapy, it was not possible to run an NMA in this population. In the absence of the NMA, the model uses a subgroup of the pooled CZP Phase III trials (CIMPASI-1, CIMPASI-2, CIMPACT), to compare CZP to standard of care (systemic non-biologic therapies) for these patients. The placebo arms of the pooled trials were used to represent standard of care. A scenario analysis has been conducted to address the ERG question, where the PASI response estimates for MTX from the NMA in the 'biologic-naïve' population subgroup were used as a proxy for PASI response for standard of care. This population ('biologic naïve' subgroup) was chosen as the baseline characteristics were most comparable to the 'candidates for systemic non-biologic therapies' subgroup. However, this is an unrealistic scenario, as it is anticipated that 55% of patients would receive MTX whist on BSC, and the remainder on acitretin and ciclosporin. As MTX is the cheapest systemic non-biologic inadequate responder, and in the NMA had the highest PASI response rates compared to acitretin and ciclosporin, the results here are extremely conservative. The results for this scenario analysis are presented below.

Table 31: Base case results for candidates for systemic non-biologic therapy using biologic-naïve MTX data as a proxy for standard of care– CZP with PAS

1st Line Treatment in Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER CZP versus SoC (£/QALY)
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£18,145.34
SoC	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; MTX: methotrexate; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

B5. **Priority question:** On page 161 the company submission states: "Data from clinical trials indicate that CZP has high durability data, which has been indicated by a UK clinical expert as being different to other anti-TNFs in psoriasis". Please provide further justification for these claims, with specific reference to the cited clinical evidence, and further details of why clinical expert opinion expects certolizumab pegol will have a more durable treatment effect than other therapies.

UCB response:

Data from the CZP clinical studies indicated that [redacted]% of CZP 400 mg Q2W responders at Week 16 and [redacted]% of CZP 200 mg Q2W responders at Week 16, respectively, retained their PASI75 response at Week 48 (Figure 9a, UCB original submission).

Long-term responder rates for those achieving a PASI75 response are readily available in the published literature for other biologic therapies, permitting a naïve indirect comparison of durability data. Although naïve comparisons that do not take into account potential differences in trial populations and study design should be interpreted with caution, the absolute data indicate that CZP has a high level of durability relative to a number of other biologics, including other anti-TNFs and therapies with other mechanisms of action.

Table 32: Long-term responder rates across different biologic treatments

Biologic	Timepoint	Proportion maintaining response among early responders	Source
CZP 200 mg Q2W	48 weeks	[redacted]	UCB data on file
CZP 400 mg Q2W	48 weeks	[redacted]	
BROD 210 mg Q2W	52 weeks	80% (AMAGINE-2) 80% (AMAGINE-3)	AMAGINE-2, AMAGINE-3[29]
SEC 150 mg	52 weeks	62.1%	Bartos 2016[28]
SEC 300 mg	52 weeks	78.2%	
UST 45 mg	76 weeks	81.8%	
UST 90 mg	76 weeks	86.6%	
ADA 40 mg	52 weeks	95.2%	

B6. The ERG notes that despite the above (see question B5), the base-case economic analysis assumes a common discontinuation rate of 20%. Does the company therefore believe that a lower discontinuation rate may be more appropriate for certolizumab pegol? Why was this not included in the base-case analysis?

UCB response:

UCB does believe that a lower discontinuation rate may be more appropriate for CZP compared to other anti-TNFs, to reflect the high durability of response observed in the clinical trials for CZP (see Section B.2.6.2 of the original submission). However, given the absence of controlled studies that allow for a comparison of long-term efficacy, we acknowledge that robust comparative data of long-term efficacy is not available to support this assertion. For this reason, it was considered appropriate to have a conservative approach in the base case analysis and include a lower discontinuation rate for CZP as a scenario analysis only (Scenario 4 in the original submission). Under this scenario, CZP remained cost-effective versus all comparators considered in the inadequate responders population (Table 98 in original submission). In the candidates for systemic non-biologic therapy scenario (Table 99 in original submission), CZP was cost-effective when compared to standard of care, in line with the conclusions from the base case analysis.

B7. **Priority question:** For treatment discontinuation during the initial treatment phase, please provide the discontinuation rate separately for each treatment arm of each of the trials included in the NMA, and please specify at which time point in the trial this data was extracted for.

UCB response:

The discontinuation rates for each treatment arm for each of the trials included in the NMA, including the timepoint at which the data were extracted from, is presented in Appendix D.

B8. **Priority question:** Please provide the PASI 50,75, 90 and 100 response rates of patients who:

a) Failed to achieve PASI 75 response and moved to receive certolizumab pegol 400mg

UCB response:

The requested data is provided below. Among patients that do not achieve a PASI75 response at Week 16 following CZP 200 mg Q2W, [redacted]) achieve a PASI 75 response after 32 weeks of escalation therapy with CZP 400mg Q2W (ie by wk48). [redacted]. Furthermore, among patients that achieve PASI 75 by wk48 after escalating to CZP 400mg, [redacted] had already reached a PASI90 response by Week 48.

Table 33: Week 48 PASI responder rates of patients who failed to achieve PASI75 response at Week 16 and escaped to CZP 400 mg in CIMPACT

Responder rate, % (95% CI)	Placebo/Esc CZP 400 mg Q2W (n=[redacted])	ETN/Esc CZP 400 mg Q2W (n=[redacted])	CZP 200 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])	CZP 400 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])
PASI50	[redacted]	[redacted]	[redacted]	[redacted]
PASI75	[redacted]	[redacted]	[redacted]	[redacted]
PASI90	[redacted]	[redacted]	[redacted]	[redacted]
PASI100	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CZP: certolizumab pegol; Esc: escape; ETN: etanercept; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks.
Source: UCB. Data on File, 2018.[8]

Table 34: Week 32 PASI responder rates of patients who failed to achieve PASI75 response at Week 16 and escaped to CZP 400 mg in CIMPACT

Responder rate, % (95% CI)	Placebo/Esc CZP 400 mg Q2W (n=[redacted])	ETN/Esc CZP 400 mg Q2W (n=[redacted])	CZP 200 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])	CZP 400 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])
PASI50	[redacted]	[redacted]	[redacted]	[redacted]
PASI75	[redacted]	[redacted]	[redacted]	[redacted]
PASI90	[redacted]	[redacted]	[redacted]	[redacted]
PASI100	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CZP: certolizumab pegol; Esc: escape; ETN: etanercept; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks.
Source: UCB. Data on File, 2018.[8]

b) Achieve PASI 50, but failed to achieve PASI 75 response and moved to receive certolizumab pegol 400mg

UCB response:

The requested data is provided below. Among patients that achieve a PASI50 but not a PASI 75 response at Week 16 following CZP 200 mg Q2W, [redacted] achieved a PASI 75 response after 32 weeks of escalation therapy with CZP 400 mg Q2W (i.e. by wk48). Furthermore, among patients that achieve PASI 75 by wk48 after escalating to CZP 400 mg, [redacted] had already reached a PASI90 response by Week 48.

Table 35: Week 48 PASI responder rates of patients who achieved PASI50, but failed to achieve PASI75 response at Week 16 and escaped to CZP 400 mg in CIMPACT

Responder rate, % (95% CI)	Placebo/Esc CZP 400 mg Q2W (n=[redacted])	ETN/Esc CZP 400 mg Q2W (n=[redacted])	CZP 200 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])	CZP 400 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])
PASI50	[redacted]	[redacted]	[redacted]	[redacted]
PASI75	[redacted]	[redacted]	[redacted]	[redacted]
PASI90	[redacted]	[redacted]	[redacted]	[redacted]
PASI100	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CZP: certolizumab pegol; Esc: escape; ETN: etanercept; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks.
Source: UCB. Data on File, 2018.[8]

Table 36: Week 32 PASI responder rates of patients who achieved PASI50, but failed to achieve PASI75 response at Week 16 and escaped to CZP 400 mg in CIMPACT

Responder rate, % (95% CI)	Placebo/Esc CZP 400 mg Q2W (n=[redacted])	ETN/Esc CZP 400 mg Q2W (n=[redacted])	CZP 200 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])	CZP 400 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])
PASI50	[redacted]	[redacted]	[redacted]	[redacted]
PASI75	[redacted]	[redacted]	[redacted]	[redacted]
PASI90	[redacted]	[redacted]	[redacted]	[redacted]
PASI100	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CZP: certolizumab pegol; Esc: escape; ETN: etanercept; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks.
Source: UCB. Data on File, 2018.[8]

B9. **Priority question:** Please provide maintenance phase data on durability of response for the groups described in question B8, including data on response rates, discontinuation rates, the proportion of patients reverting to the 200mg dose and mean duration of 400mg treatment.

UCB response:

As per the clarification meeting with the ERG the below data is provided for the CIMPACT study only.

Patients who failed to achieve PASI75 response at Week 16 and escaped to CZP 400 mg in CIMPACT

Response rates

Please find the response rates at Week 48 for this population in response to Question B8 (Table 33) above.

Discontinuation rates

Discontinuation rates for patients who were PASI75 non-responders at Week 16 and escaped to CZP 400 mg Q2W in CIMPACT are presented in Table 37 below.

Table 37: Discontinuation rates for patients who failed to achieve PASI75 response at Week 16 and escaped to CZP 400 mg in CIMPACT (Week 48 data)

	Placebo/Esc CZP 400 mg Q2W (n=[redacted])	ETN/Esc CZP 400 mg Q2W (n=[redacted])	CZP 200 mg Q2W/Esc CZP 400 mg Q2W (n=[redacted])	CZP 400 mg Q2W /Esc CZP 400 mg Q2W (n=[redacted])
Discontinuation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Consent withdrawn	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Other: mandatory withdrawal due to not achieving PASI50 response	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; CZP: certolizumab pegol; Esc; escape; ETN: etanercept; PASI: Psoriasis Area Severity Index; Q2W: every 2 weeks.
Source: Data on File – CIMPACT data tables[18]

Proportion of patients reverting to CZP 200 mg Q2W dose

The proportion of patients reverting to the CZP 200 mg dose is not available from the maintenance period, as dose de-escalation was not allowed up to week 48, as per the trial protocols.

Mean duration of CZP 400 mg Q2W treatment

The mean duration of CZP 400 mg Q2W treatment is not available from the maintenance period of the study, as patients who did not achieve a PASI75 response escaped from blinded treatment to receive CZP 400 mg Q2W. Escape arm patients not achieving a PASI50 response at Week 32 or a subsequent timepoint were withdrawn from the study. Furthermore, patients initially

randomised to CZP 400 mg Q2W were re-randomised (2:2:1) to CZP 200 mg Q2W or CZP 400 mg Q2W or placebo. Patients who relapsed (<PASI50 response) during the maintenance treatment period were removed from the double-blind placebo-controlled maintenance treatment period and entered into the open-label extension (OLE), receiving CZP 400 mg Q2W. Patients entering the OLE from the escape arm of the initial treatment period continued to receive CZP 400 mg Q2W. All other patients entering the OLE (i.e. those completing the Week 48 visit of the maintenance treatment period without relapse) received CZP 200 mg Q2W.

Patients who achieved PASI50, but failed to achieve PASI75 response at Week 16 and escaped to CZP 400 mg in CIMPACT

Response rates

Please find the response rates at Week 48 for this population in response to Question B8 (Table 35) above.

Discontinuation rates

Table 38: Discontinuation rates for patients who achieved PASI50, but failed to achieve PASI75 response at Week 16 and escaped to CZP 400 mg in CIMPACT by escape maintenance group (Week 48)

	Placebo/ESC CZP 400 mg Q2W (N=[redacted])	ETN/ESC CZP 400 mg Q2W (N=[redacted])	Placebo/ESC CZP 400 mg Q2W (N=[redacted])	Placebo/ESC CZP 400 mg Q2W (N=[redacted])
Discontinuation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]		[redacted]	[redacted]
Consent withdrawn	[redacted]	[redacted]	[redacted]	[redacted]
Other: mandatory withdrawal due to not achieving PASI50 response	[redacted]	[redacted]	[redacted]	[redacted]

Quality of life

B10. **Priority question**: Please provide details of the following:

a) Please confirm whether the UK value set (Dolan P (1997). Modelling valuations for EuroQol health states. *Med Care,* 35 (11): 1095-108) were used to estimate utility values from EQ-5D.

UCB response:

UCB can confirm that the UK value set was used to estimate the utility values from EQ-5D used within the original submission.

b) In CIMPASI-1, CIMPASI-2 and CIMPACT, the mean and standard deviation EQ-5D at baseline, in each treatment arm in each trial and for each trial overall,

UCB response:

The mean and standard deviation EQ-5D utility scores are baseline for CIMPASI-1, CIMPASI-2 and CIMPACT are presented below. Unfortunately due to time constraints it was not possible to provide the mean utility scores at baseline for each treatment arm within each trial.

Table 39: Mean EQ-5D utility score at baseline in CIMPASI-1

	CIMPASI-1 (n=[redacted])	CIMPASI-2 (n=[redacted])	CIMPACT (n=[redacted])
Mean EQ-5D utility score at baseline (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: CZP: certolizumab pegol; EQ-5D: EuroQoL – 5 dimensions; SD: standard deviation.
Source: UCB. Data on File, 2018[8]

c) The number of observations at each time point that EQ-5D data was collected in the trials (i.e. at weeks 0, 8, 12, 16, 24, 32, and 48)

UCB response:

The number of observations at each time point that EQ-5D data was collected in CIMPASI-1, CIMPASI-2 and CIMPACT are presented in Table 40 below.

Table 40: The number of observations at each time point that EQ-5D data was collected in CIMPASI-1, CIMPASI-2 and CIMPACT

Number of observations	CIMPASI-1 (n=[redacted])	CIMPASI-2 (n=[redacted])	CIMPACT (n=[redacted])
Week 0	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D: EuroQoL – 5 dimensions.
Source: UCB. Data on File, 2018[8]

B11. **Priority question**: Please provide further details of the regression methods used to estimate change in EQ-5D

a) Were data from all time points included in the analysis, or was the analysis restricted to data collected in the initial period of the trial?

UCB response:

Data from all timepoints from weeks 0–48 where EQ-5D data was collected were included in the analysis (see response to question B10 for details of the timepoints of data collection).

b) How were missing values dealt with (i.e. a complete case analysis or multiple imputation of the missing data)?

UCB response:

The analysis was based on observed EQ-5D data, with no imputation for missing data.

c) The coefficients for each of the covariates included in the analysis, (mean, standard error, p value and 95% confidence interval).

UCB response:

The coefficients for each of the covariates included in the analysis are presented in Table 41 below.

Table 41: Coefficients used in the EQ-5D regression analysis

Parameter	Mean	Std. Err.	95% LCI	95% UCI	Pr > ChiSq
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI <50*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50<75*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75<90*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (centred 44 yrs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (centred 28kg/m2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Biologic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 200mg Q2W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 400mg Q2W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 400mg Q4W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI Score*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The regression equation used to generate utility values by PASI response category health state was as follows:

EQ-5D = intercept + PASI_4level + (Age-44.90) + (BMI-28.87) + Sex + Prior_Biologic + TRT + Baseline_PASI

d) Which arms of the 3 trials provided EQ-5D data for the regression analysis? Were patients in the placebo arm included?

UCB response:

The regression analysis included all patients from all the treatment arms at all timepoints across CIMPASI-1, CIMPASI-2 and CIMPACT.

e) Please justify why an adjustment was not made for baseline EQ-5D, as this has been used in recent submissions.

UCB response:

Recent submissions such as that for ixekizumab and brodalumab both utilised regression models where change from baseline in EQ-5D utility represented the dependent variable.[25, 27] In contrast,

the regression model employed in the UCB analysis generated absolute utility values by health state. The utility values used in the UCB model therefore reflected the utility of patients in a given PASI responder state in the studies informing the analysis, rather than an estimate of the extent to which the utility of patients in this PASI responder group had changed from baseline.

B12. Please provide further justification for why patients on best-supportive care or on non-biologic systemic therapy were assumed to have different quality of life than patients on biologic treatments, for a given PASI score. Make reference to safety profile, mode of administration and any other factors felt to be applicable. If patients in the placebo arms of the certolizumab pegol trials were used in the regression analysis, please provide justification as to why these utility values were considered appropriate to model patients on first-line systemic therapy, given that these patients could not receive systemic treatment in the trial.

UCB response:

The rationale behind why patients on BSC or non-biologic systemic therapy were assumed to have different quality-of-life than patients on biologic treatments for a given PASI score is based on the mode of administration of systemic non-biologic therapies compared to biologics. Topical treatments, phototherapies, and systemic agents may be inconvenient and time-consuming to apply, particularly where patients have an extensive surface area requiring coverage (in the case of topical treatments).[30] This is in comparison to biologic therapies, which are often self-administered using a range of easy-to-use devices, and administered at less regular intervals. In the regression analyses performed to derive utility values for PASI health states, when testing a treatment variable in the regression a significant treatment effect on utility was observed. Therefore, biologics were modelled to have a different utility value to BSC for a given PASI health state. This was explored in scenario analysis: in scenario 6 in the cost-effectiveness analysis in the original submission, the utility values were assumed to be the same for all treatments, including BSC. In this scenario, the conclusions were similar to those in the base case, indicating that the impact of applying different utility values for BSC and standard of care on the cost-effectiveness results is limited and does not change the base case conclusions.

B13. **Priority question:** Upon inspection of the model, the ERG is concerned that there may be an error in the estimation of utility values, but it is hard to detect without additional information presented by the company on the regression analyses. Please provide details on how the coefficients should be interpreted, and check the calculations in the model and confirm whether they are correct with respect to the following:

a) The coefficient PASI < 50 appears to have been applied to the calculations for baseline PASI

UCB response:

The coefficient PASI<50 has been applied to the calculations of baseline PASI, as these utility values are assumed to be the same. This is because the approach used did not generate a utility for baseline PASI. The baseline PASI does not refer to the PASI score at baseline, but rather another confounding variable which may affect the utility value for each PASI health state. Whilst confirming this we have noticed that there was a difference in the coefficients included for baseline PASI and PASI<50, as the PASI<50 utility value did not include the coefficient for

baseline PASI score. This was also the case for the PASI50–75, PASI75–90 and PASI90–100 utility values. This has been corrected in the version of the model provided alongside this response. The revised utility values (also taking into account the change in treatment effect coefficient used in the calculations [see response to Question B13 c below] from CZP 400 mg Q4W to CZP 200 mg Q2W) are presented below.

Table 42: Summary of revised utility values used in the CEA

State	Utility value: mean
No treatment effect: BSC and standard of care for candidates for systemic non-biologics	
Baseline PASI	[redacted]
PASI <50	[redacted]
PASI 50–75	[redacted]
PASI 75–90	[redacted]
PASI 90–100	[redacted]
Treatment effect: All biologics	
Baseline PASI	[redacted]
PASI <50	[redacted]
PASI 50–75	[redacted]
PASI 75–90	[redacted]
PASI 90–100	[redacted]

b) There does not appear to be a coefficient for PASI 90–100

UCB response:

Within the regression equation, the category of PASI 90–100 was used as the reference category. Therefore, there is no co-efficient associated with PASI 90-100 and the coefficients for the other PASI categories are relative to the PASI 90-100 reference.

c) The treatment effect for certolizumab pegol appears to be based on the utility coefficient for the "Treatment 400mg Q4W CZP" dose.

UCB response:

In considering this question we have identified an error within the model. The treatment effect for CZP (and therefore all biologics within our model) should be based on the utility coefficient for the "Treatment 200 mg Q2W CZP" dose. This was the intended approach, given that the utility values for CZP 200 mg Q2W are lower than for the CZP 400 mg dose. This has been corrected in the model provided alongside this response (revised utility values are presented in Table 42 above.

As this represented an error in the original model, we have re-run all base case cost-effectiveness results from Sections B.3.7 in the original submission, as well as the probabilistic sensitivity analysis results and have provided the updated basecase results below. The

conclusions of the updated base case analysis are consistent with those from the original basecase. CZP is cost-effective versus all other biologic comparator considered for systemic non-biologic inadequate responders. When compared against the ADA escalation strategy, CZP was more efficacious (incremental QALY of [redacted]), but more costly (incremental costs of [redacted]), leading to an ICER of £36,637.86. In the candidates for systemic non-biologic population, CZP is a cost-effective treatment option versus the standard of care treatment sequence (ICER for CZP 200 mg versus standard of care: £3,601.54/QALY).

Base case results

Systemic non-biologic inadequate responders

Table 43: Base case fully incremental results for systemic non-biologic therapy inadequate responders – CZP with PAS

1st Line Treatment in Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Fully incremental ICER (£/QALY)
ETN	[redacted]	[redacted]	[redacted]	[redacted]		
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£11,470.53	£11,470.53
UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	£51,528.43	Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	£45,655.86	Dominated
UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	£43,529.12	Dominated
GUS	[redacted]	[redacted]	[redacted]	[redacted]	£164,663.89	Dominated
SEC	[redacted]	[redacted]	[redacted]	[redacted]	£128,929.95	Extendedly dominated
IXE	[redacted]	[redacted]	[redacted]	[redacted]	£125,644.48	£432,904.41
BROD	[redacted]	[redacted]	[redacted]	[redacted]	£146,412.55	Dominated

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; FOC: free of charge; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekizumab; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; SEC: secukinumab; UST: ustekinumab.

Table 44: Base case results for systemic non-biologic therapy inadequate responders – CZP escalation strategy with PAS

1st Line Treatment in Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER CZP versus comparator (£/QALY)
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£36,637.86
ADA	[redacted]	[redacted]			

Abbreviations: ADA: adalimumab; CZP: certolizumab pegol; FOC: free of charge; ICER: incremental cost-effectiveness ratio; IFX: infliximab; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; UST: ustekinumab

Candidates for systemic non-biologic therapy

Table 45: Base case results for candidates for systemic non-biologic therapy – CZP with PAS

1st Line Treatment in Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER CZP versus SoC (£/QALY)
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£3,601.54
SoC	[redacted]	[redacted]			

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

Probabilistic sensitivity analysis results

Systemic non-biologic inadequate responders

Table 46: Average probabilistic results for systemic non-biologic therapy inadequate responders – CZP with PAS

1st Line Treatment in Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Fully incremental ICER (£/QALY)
ETN	[redacted]	[redacted]				
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£11,921.70	£11,921.70
UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	£50,942.04	Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	£45,836.89	Dominated
UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	£43,168.82	Dominated
GUS	[redacted]	[redacted]	[redacted]	[redacted]	£165,911.86	Dominated
SEC	[redacted]	[redacted]	[redacted]	[redacted]	£130,913.98	Extendedly dominated
IXE	[redacted]	[redacted]	[redacted]	[redacted]	£127,369.76	£438,623.87
BROD	[redacted]	[redacted]	[redacted]	[redacted]	£148,135.09	Dominated

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; FOC: free of charge; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekizumab; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; SEC: secukinumab; UST: ustekinumab.

Table 47: Average probabilistic results for systemic non-biologic inadequate responders escalation sequence

Treatment	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER CZP versus comparator (£/QALY)
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£36,775.09
ADA	[redacted]	[redacted]			

Abbreviations: ADA: adalimumab; CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life yea.

Candidates for systemic non-biologic therapy

Table 48: Average probabilistic results for candidates for systemic non-biologic therapy

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER CZP versus comparator (£/QALY)
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,103.90
SoC	[redacted]	[redacted]	[redacted]			

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year; SoC: standard of care.

B14. **Priority question:** Please present the following additional analyses:

a) Results of the regression analysis using the company's original assumptions, based on the UK value set, if these were not applied in the analyses presented in the submission

UCB response:

As discussed in Question B10a, the UK value set were applied in the analyses presented in the submission, and as such the results of the regression analysis have not been presented again here. The results of the regression analysis can be found in Section B.3.4.4 of the original submission.

b) Results for the subgroup with baseline DLQI > 10 (using the UK value set)

UCB response:

Please find below the coefficients and utility values for the subgroup with baseline DLQI>10.

Table 49: Coefficients used in the EQ-5D regression analysis for subgroup DLQI >10

Parameter	Mean	Std. Err.	95% LCI	95% UCI	Pr > ChiSq
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI <50*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50<75*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75<90*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (centred 44 yrs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (centred 28kg/m2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Biologic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 200mg Q2W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 400mg Q2W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 400mg Q4W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI Score*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 50: Summary of utility values for DLQI>10

State	Utility value: mean
No treatment effect: BSC and standard of care for candidates for systemic non-biologics	
Baseline PASI	[redacted]
PASI <50	[redacted]
PASI 50–75	[redacted]
PASI 75–90	[redacted]
PASI 90–100	[redacted]
Treatment effect: All biologics	
Baseline PASI	[redacted]
PASI <50	[redacted]
PASI 50–75	[redacted]
PASI 75–90	[redacted]
PASI 90–100	[redacted]

c) Adjusting for baseline EQ-5D score (in the full population analysis, using the UK value set)

UCB response:

Please find below the coefficients and utility values for the full population analysis, adjusted for baseline EQ-5D score.

Table 51: Coefficients used in the EQ-5D regression analysis adjusted for baseline EQ-5D

Parameter	Mean	Std. Err.	95% LCI	95% UCI	Pr > ChiSq
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI <50*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50<75*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75<90*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (centred 44 yrs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (centred 28kg/m2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Biologic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 200mg Q2W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 400mg Q2W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 400mg Q4W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI Score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 52: Summary of utility values adjusted for baseline EQ-5D

State	Utility value: mean
Baseline PASI	[redacted]
PASI <50	[redacted]
PASI 50–75	[redacted]
PASI 75–90	[redacted]
PASI 90–100	[redacted]

d) Adjusting for baseline EQ-5D score (in the DLQI > 10 analysis, using the UK value set).

UCB response:

Please find below the coefficients and utility values for the DLQI >10 subgroup, adjusted for baseline EQ-5D score.

Table 53: Coefficients used in the EQ-5D regression analysis adjusted for baseline EQ-5D

Parameter	Mean	Std. Err.	95% LCI	95% UCI	Pr > ChiSq
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI <50*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50<75*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75<90*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (centred 44 yrs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (centred 28kg/m2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Biologic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 200mg Q2W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 400mg Q2W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment 400mg Q4W CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI Score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 54: Summary of utility values adjusted for baseline EQ-5D

State	Utility value: mean
Baseline PASI	[redacted]
PASI <50	[redacted]
PASI 50–75	[redacted]
PASI 75–90	[redacted]
PASI 90–100	[redacted]

Costs and resource use

B15. **Priority question:** Please confirm the per-cycle costs of best supportive care, as the values reported in the company submission do not appear to match those in the model.

UCB response:

The BSC costs listed on the 'Drugcosts' sheet are not actually being used within the cost calculations for BSC. The values that are being used within the calculations in the model for BSC are inputted in the PSOCosts sheet, in cells F42:J45, and the values in cells K45 and L45 match those in Table 83 of the original submission.

B16. **Priority question:** Please can you confirm whether the company will be offering self-injection training to patients free of charge in line with competitors, and whether cost of self-injection training was applied for other biologics in the model. Please could you also clarify why '3 hours nurse time for subcutaneous self-injection training' was described in the model, but only one hour of nurse time was costed for.

UCB response:

All new patients are offered up to [redacted] nurse visits (each lasting approximately [redacted]) as part of the homecare scheme, to train the patient to self-inject. If the hospital does not opt for homecare, then the hospital nurse will be required to train the patient to self-inject.

With regards to the nurse time applied in the model, the reference to 3 hours of nurse time is an error in the labelling of this input within the model. Originally the model used 3 hours of nurse training for each subcutaneous treatment (applied for all biologics given subcutaneously within the model), based on a recent appraisal.[25] However, following clinical expert feedback this was revised down to 1 hour, as it was considered that 3 hours was too long. The cost actually applied in the model is 1 hour, consistent with that noted in the original submission.

B17. Please confirm the source and the rationale behind the assumptions made for the current and predicted market share of biologics over the next 5 years. Given that adalimumab biosimilars are due to enter the market in October 2018, please justify why you consider that market share for this comparator will decline over the next 5 years.

UCB response:

It is difficult to predict the future uptake of biosimilars within the market in the UK. The assumption that the market share of ADA declines in the current market is based on the introduction of new treatment types within the market (notably the IL-inhibitors), which are anticipated to increase in use over the next five years. Therefore, for the predicted market share, the decline in ADA reflects an anticipated increased use of IL-inhibitors, as well as uptake of CZP.

B18. **Priority question:** Please confirm the number of doses of certolizumab pegol patients received during the initial phase of treatment in the 3 trials. Were patients who did not achieve a PASI 50/75 response at week 16 given a final induction dose

at week 16? In practice does the company believe that patients not achieving PASI 75 response at week 16 will be given the final dose at week 16?

UCB response:

The number of doses of CZP received by patients during the initial phase of treatment in CIMPASI-1, CIMPASI-2 and CIMPACT are listed below:

- CIMPASI-1 and CIMPASI-2: Study treatments (including placebo) were administered by dedicated, trained site personnel at Baseline, and at Weeks 2, 4, 6, 8, 10, 12, and 14.
- CIMPACT: All CZP and placebo treatments were administered by dedicated unblinded site personnel at Weeks 0, 2, 4, 6, 8, 10, 12, and 14. The Initial Treatment Period concluded with completion of the safety and efficacy assessments performed at Week 16.

Within the cost-effectiveness analysis it is assumed that patients receive one dose of CZP at Week 16 of the initial treatment period. This was modelled based on consideration of the pack size of CZP: CZP 200 mg contains 2 units in one pack (totalling 400 mg). When considering the posology of CZP over the initial treatment period, this results in pack use as described in Table 55.

Table 55: CZP administration over the initial treatment period

Week	Required dose	Practical CZP pack usage
0 (baseline)	400 mg	First 2 x 200 mg pack opened: used in entirety
2	400 mg	Second 2 x 200 mg pack opened: used in entirety
4	400 mg	Third 2 x 200 mg pack opened: used in entirety
6	200 mg	Fourth 2 x 200 mg pack opened: 200 mg used
8	200 mg	Fourth 2 x 200 mg pack: remaining 200 mg used
10	200 mg	Fifth 2 x 200 mg pack opened: 200 mg used
12	200 mg	Fifth 2 x 200 mg pack: remaining 200 mg used
14	200 mg	Sixth 2 x 200 mg pack opened: 200 mg used
16	N/A: assessment of response status at week 16 but no final induction dose	Although no final induction dose is administered, the sixth pack has already been opened at Week 14

Therefore, although no final induction dose of CZP is administered at Week 16, the sixth pack of CZP has already been opened and the cost incurred is therefore that of 6 packs. For this reason, 6 packs of CZP were costed for the initial treatment period in the model. In the appraisal for brodalumab, the ERG costed 8 doses rather than 7 during the initial treatment period because unit packs of two doses cannot be split.[27] The approach taken for CZP in this submission is therefore consistent with this. This will also provide a conservative approach in the cost-effectiveness analysis, which is slightly overestimating the actual administration of CZP.

Section C: Textual clarifications and additional points

C1. The search strategies and update search strategies presented in Appendix D in Tables 1 to 9 are missing terms for the systemic non-biologic acitretin. Please could the omission of this drug from all of the search strategies be explained?

UCB response:

The SLR conducted to inform the NMA did not include acitretin as a comparator in the inclusion criteria. The exclusion of acitretin was supported by the latest EADV guidelines on the systemic treatment of psoriasis vulgaris, that indicated "we cannot make a recommendation for or against the use of acitretin as a monotherapy". Furthermore, UK clinical expert opinion indicated that acitretin is not a treatment option commonly used in the clinical practice in this patient population (candidates to systemic non-biologics). Given the limited amount of studies identified in the SLR as being of interest for the other comparators and, at the same time containing data on acitretin, it is reasonable to assume that the effect of acitretin on the NMA results is very limited.

C2. Was the inclusion of RCTs of risankizumab 150mg (see Table 11 of appendices) pre-defined, or selected based on the studies that were identified by the searches?

UCB response:

The inclusion of RCTs of risankizumab 150 mg was pre-defined in the search strategy for the clinical SLR (included in search terms as bi 655066 in Table 2 of the appendices). This was to use the placebo or comparator arms from these trials within the NMA.

References

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Appendix A – Timepoints at which outcomes are collected in the NMA

Table 56: Timepoint at which outcomes were collected for each trial included in the NMA

Author	Study Name	Treatment Name	Timepoint
Asahina	Asahina	Adalimumab 40 mg	Week 16
		PBO	Week 16
Bachelez	Bachelez	Etanercept 50 mg	Week 12
		PBO	Week 12
Barker	RESTORE 1	Infliximab 5 mg/kg	Week 16
		MTX	Week 16
Blauvelt	FEATURE	Secukinumab 300 mg	Week 12
		PBO	Week 12
		Secukinumab 150 mg	Week 12
Blauvelt	VOYAGE 1	Adalimumab 40 mg	Week 16
		Guselkumab 100 mg	Week 16
		PBO	Week 16
Cai	Cai	Adalimumab 40 mg	Week 12
		PBO	Week 12
Chaudhari	Chaudhari	Infliximab 5 mg/kg	Week 10
		PBO	Week 10
CIMPACT	CIMPACT	CZP 200 mg Q2W	Week 16
		CZP 400 mg Q2W	Week 16
		Etanercept 50 mg	Week 12
		PBO	Week 16
CIMPASI 1	CIMPASI 1	CZP 200 mg Q2W	Week 16
		CZP 400 mg Q2W	Week 16
		PBO	Week 16
CIMPASI 2	CIMPASI 2	CZP 200 mg Q2W	Week 16
		CZP 400 mg Q2W	Week 16
		PBO	Week 16
de Vries	PIECE	Etanercept 50 mg	Week 12
		Infliximab 5 mg/kg	Week 12
Gisondi	Gisondi	Etanercept 25 mg	Week 12
		Acitretin	Week 12
Goldminz	Goldminz	Adalimumab 40 mg	Week 16
		MTX	Week 16
Gordon	X-PLORE	Guselkumab 100 mg	Week 16
		Adalimumab 40 mg	Week 16
		PBO	Week 16
Gordon	M05- 258	Adalimumab 40 mg	Week 12
		PBO	Week 12
Gottlieb	SPIRIT	Infliximab 5 mg/kg	Week 10
		PBO	Week 10

Gottlieb-A	Gottlieb-A	Etanercept 25 mg	Week 12
		PBO	Week 12
Gottlieb-B	Gottlieb-B	Etanercept 50 mg	Week 12
		PBO	Week 12
Griffiths	ACCEPT	Ustekinumab 45 mg	Week 12
		Ustekinumab 90 mg	Week 12
		Etanercept 50 mg	Week 12
Griffiths	UNCOVER 3	Etanercept 50 mg	Week 12
		Ixekizumab 80 mg	Week 12
		PBO	Week 12
Griffiths	UNCOVER 2	Etanercept 50 mg	Week 12
		Ixekizumab 80 mg	Week 12
		PBO	Week 12
Griffiths	UNCOVER 1	Ixekizumab 80 mg	Week 12
		PBO	Week 12
Igarashi	Igarashi	Ustekinumab 45 mg	Week 12
		Ustekinumab 90 mg	Week 12
		PBO	Week 12
IMMvent	IMMvent	Risankizumab 150 mg	Week 16
		Adalimumab 40 mg	Week 16
Kimball	PHOENIX 1	Ustekinumab 45 mg	Week 12
		Ustekinumab 90 mg	Week 12
		PBO	Week 12
Krueger	Krueger	Ustekinumab 45 mg	Week 12
		Ustekinumab 90 mg	Week 12
		PBO	Week 12
Langley	FIXTURE	Secukinumab 300 mg	Week 12
		Etanercept 50 mg	Week 12
		PBO	Week 12
		Secukinumab 150 mg	Week 12
Langley	ERASURE	Secukinumab 300 mg	Week 12
		PBO	Week 12
		Secukinumab 150 mg	Week 12
Lebwohl	AMAGINE 2	Brodalumab 210 mg	Week 12
		Ustekinumab 45 mg or 90 mg	Week 12
		PBO	Week 12
Lebwohl	AMAGINE 3	Brodalumab 210 mg	Week 12
		Ustekinumab 45 mg or 90 mg	Week 12
		PBO	Week 12
Leonardi	Leonardi	Etanercept 25 mg	Week 12
		Etanercept 50 mg	Week 12
		PBO	Week 12
Meffert	Meffert	Cyclosporin 2.5 mg	Week 10

		PBO	Week 10
Menter	REVEAL	Adalimumab 40 mg	Week 16
		PBO	Week 16
Menter	EXPRESS II	Infliximab 5 mg/kg	Week 10
		PBO	Week 10
Mrowietz	BRIDGE	Dimethyl fumarate	Week 16
		PBO	Week 16
Nakagawa	Nakagawa	Brodalumab 210 mg	Week 12
		PBO	Week 12
Ohtsuki	Ohtsuki	Apremilast 30 mg	Week 16
		PBO	Week 16
Papp	ESTEEM 1	Apremilast 30 mg	Week 16
		PBO	Week 16
Papp	CORE	PBO	Week 16
		Apremilast 30 mg	Week 16
Papp	PHOENIX 2	Ustekinumab 45 mg	Week 12
		Ustekinumab 90 mg	Week 12
		PBO	Week 12
Papp	AMAGINE 1	Brodalumab 210 mg	Week 12
		PBO	Week 12
Papp-B	Papp-B	Etanercept 25 mg	Week 12
		Etanercept 50 mg	Week 12
		PBO	Week 12
Papp-C	Papp-C	Brodalumab 210 mg	Week 12
		PBO	Week 12
Papp-D	Papp-D	Tildrakizumab 100 mg	Week 16
		PBO	Week 16
		Tildrakizumab 200 mg	Week 16
Paul	ESTEEM 2	Apremilast 30 mg	Week 16
		PBO	Week 16
Paul	JUNCTURE	Secukinumab 300 mg	Week 12
		PBO	Week 12
		Secukinumab 150 mg	Week 12
Reich	VOYAGE 2	Adalimumab 40 mg	Week 16
		Guselkumab 100 mg	Week 16
		PBO	Week 16
Reich	LIBERATE	Apremilast 30 mg	Week 16
		Etanercept 50 mg	Week 16
		PBO	Week 16
Reich	reSURFACE 1	Tildrakizumab 200 mg	Week 12
		Tildrakizumab 100 mg	Week 12
		PBO	Week 12
Reich	EXPRESS	Infliximab 5 mg/kg	Week 10

		PBO	Week 10
Reich	reSURFACE 2	Tildrakizumab 100 mg	Week 12
		PBO	Week 12
		Etanercept 50 mg	Week 12
		Tildrakizumab 200 mg	Week 12
Reich	IXORA-S	Ustekinumab 45 mg or 90 mg	Week 12
		Ixekizumab 80 mg	Week 12
Reich	Reich	CZP 200 mg Q2W	Week 12
		CZP 400 mg Q2W	Week 12
		PBO	Week 12
Saurat	CHAMPION	MTX	Week 16
		Adalimumab 40 mg	Week 16
		PBO	Week 16
Strober	Strober	Etanercept 50 mg	Week 12
		PBO	Week 12
Thaci	CLEAR	Secukinumab 300 mg	Week 16
		Ustekinumab 45 mg	Week 16
Torii	Torii	Infliximab 5 mg/kg	Week 10
		PBO	Week 10
Tsai	PEARL	Ustekinumab 45 mg	Week 12
		PBO	Week 12
Tyring	Tyring	Etanercept 50 mg	Week 12
		PBO	Week 12
ultIMMa-1	ultIMMa-1	Risankizumab 150 mg	Week 16
		Ustekinumab 45 mg or 90 mg	Week 16
		PBO	Week 16
ultIMMa-2	ultIMMa-2	Risankizumab 150 mg	Week 16
		Ustekinumab 45 mg or 90 mg	Week 16
		PBO	Week 16
Van de Kerkhof	Van de Kerkhof	Etanercept 50 mg	Week 12
		PBO	Week 12
Warren	METOP	MTX	Week 16
		PBO	Week 16
Yang	Yang	Infliximab 5 mg/kg	Week 10
		PBO	Week 10
Zhu	LOTUS	Ustekinumab 45 mg	Week 12
		PBO	Week 12

Abbreviations: CZP: certolizumab pegol; MTX: methotrexate; PBO: placebo; Q2W: every two weeks.

Appendix B – NMA results by treatment arm

The NMA results for each treatment arm have been provided in the Excel file alongside this response.

Appendix C – WinBUGS code for NMA

[redacted]

[redacted]

Appendix D – NMA discontinuation rates

The discontinuation rates for each treatment arm for each of the trials included in the NMA, including the timepoint at which the data were extracted from can be found below.

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
ERASURE	PBO	248	NA	NA	NA	NA	16	248	12	12	NA	NA	52	52
	Secukinumab 150 mg	245	-	-	-	NA	15	245		12	44	245	52	
	Secukinumab 300 mg	245	-	-	-	NA	7	245		12	30	245	52	
FIXTURE	PBO	326	NA	NA	NA	NA	25	326	12	12	NA	NA	52	52
	Secukinumab 150 mg	327	-	-	-	NA	12	327		12	51	327	52	
	Secukinumab 300 mg	327	-	-	-	NA	15	327		12	37	327	52	
	Etanercept	326	-	-	-	NA	21	326		12	63	326	52	
CLEAR	Secukinumab 300 mg	337	-	-	-	NA	8	337	16	16	25	337	52	52
	Ustekinumab	339	-	-	-	NA	17	339		16	41	339	52	
ADALIMUMAB M04-688	PBO	46	6	NA	24	24	NA	NA	NA	NA	NA	NA	NA	NA
	Adalimumab 40	38	4	NR		24	NR	NR	NR	NR	NR	NR	NR	NR
	Adalimumab 40 mg loading dose	43	8	NA		24	NA	NA	NA	NA	NA	NA	NA	NA
	Adalimumab 80 mg	42	4	NR		24	NR	NR	NR	NR	NR	NR	NR	NR
SPIRIT	PBO	51	37	51	30	30	NA	NA	NA	NA	NA	NA	NA	NA
	Infliximab 3 mg	99	30	99		30	NR	NR	NR	NR	NR	NR	NR	NR
	Infliximab 5 mg	99	18	99		30	NA	NA	NA	NA	NA	NA	NA	NA
Gottlieb 2003	PBO	55	-	-	-	NA	15	55	12	12	43	55	24	24
	Etanercept	57	-	-	-	NA	4	57		12	9	57	24	

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
FEATURE	PBO	59	NA	NA	NA	NA	3	59	12	12	NA	NA	NA	NA
	Secukinumab 150 mg	59	-	-	-	NA	1	59		12	11	59	52	52
	Secukinumab 300 mg	59	-	-	-	NA	3	59		12	7	59	52	
Leonardi 2003	PBO	166	NA	NA	NA	24	NA	NA	NA	NA	NA	NA	NA	NA
	Etanercept 25 mg once weekly	160	26	160		24	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept 25 mg twice weekly	162	22	162		24	NA	NA	NA	NA	NA	NA	NA	NA
	Etanercept 50 mg twice weekly	164	13	164	24	24	NA	NA	NA	NA	NA	NA	NA	NA
PHOENIX 1	PBO	255	NA	NA	NA	NA	12	255	12	12	NA	NA	40	40
	Ustekinumab 45 mg	255	-	-	-	NA	1	255		12	55	255	40	
	Ustekinumab 90 mg	256	-	-	-	NA	10	256		12	42	256	40	
REVEAL	PBO	398	NA	NA	NA	NA	43	398	16	16	NA	NA	16-33	NA
	Adalimumab	814	NA	NA	NA	NA	31	814		16	30	580		NA
SCULPTURE	Secukinumab 150 mg	482	NA	NA	NA	NA	18	482	12	12	17	203	12-52	NA
	Secukinumab 300 mg	484	NA	NA	NA	NA	20	484		12	18	217	12-52	NA
Papp 2005	PBO	193	-	-	-	NA	15	193	12	12	25	193	24	24
	Etanercept 25 mg	196	-	-	-	NA	5	196		12	11	196	24	
	Etanercept 50 mg	194	-	-	-	NA	4	194		12	9	194	24	
PHOENIX 2	PBO	410	NA	NA	NA	NA	18	410	12	12	NA	NA	28	28
	Ustekinumab 45 mg	409	-	-	-	NA	6	409		12	43	409	28	

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
	Ustekinumab 90 mg	411	-	-	-	NA	9	411		12	41	411	28	
ESTEEM 1	PBO	282	-	-	-	NA	33	282	16	16	Not evaluable	Not evaluable	Not evaluable	32
	Apremilast	562	-	-	-	NA	59	562		16	138	562	32	
ESTEEM 2	PBO	137	-	-	-	NA	25	137	16	16	Not evaluable	Not evaluable	Not evaluable	32
	Apremilast	274	-	-	-	NA	35	274		16	80	274	32	
EXPRESS	PBO	77	-	-	-	-	9	77	24	24	NA	NA	24-50	24-50
	Infliximab	301	-	-	-	-	32	301		24	30	266		24-50
CHAMPION	PBO	53	5	53	16	16	NA	NA	NA	NA	NA	NA	NA	NA
	MTX	110	6	110		16	NA	NA	NA	NA	NA	NA	NA	NA
	Adalimumab	108	4	108		16	NA	NA	NA	NA	NA	NA	NA	NA
UNCOVER-2	PBO	168	-	-	-	-	10	168	12	12	NA	NA	12-60	12-60
	Etanercept	358	-	-	-	-	25	358		12	NA	NA	12-60	12-60
	Ixekizumab Q4W	347	-	-	-	-	19	347		12	11	85	12-60	12-60
	Ixekizumab Q2W	351	-	-	-	-	9	351		12	NA	NA	12-60	12-60
UNCOVER-3	PBO	193	-	-	-	-	10	193	12	12	NA	NA	60	60
	Etanercept	382	-	-	-	-	13	382		12	74	386	60	60
	Ixekizumab Q4W	386	-	-	-	-	26	386		12	NR	NR	60	60
	Ixekizumab Q2W	385	-	-	-	-	22	385		12	NA	NA	60	60
UNCOVER-1	PBO	431	-	-	-	-	24	43	12	12	NA	NA	NA	NA

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
								1						
	Ixekizumab Q4W	432	-	-	-	-	24	432		12	NA	NA	NA	NA
	Ixekizumab Q2W	433	-	-	-	-	18	433		12	NA	NA	NA	NA
ACCEPT	Etanercept	347	NA	NA	NA	NA	11	347	12	12	NA	NA	12-64	12-64
	Ustekinumab 45 mg	209	NA	NA	NA	NA	8	209		12	2	174		12-64
	Ustekinumab 90 mg	347	NA	NA	NA	NA	5	347		12	7	270		12-64
JUNCTURE	PBO	61	-	-	-	-	2	61	12	12	NA	NA	52	52
	Secukinumab 150 mg	61	-	-	-	-	3	61		12	10	61		52
	Secukinumab 300 mg	60	-	-	-	-	0	60		12	2	30		52
van der Kerkhof	PBO	46	NA	NA	NA	NA	10	46	12	12	NA	NA	NA	NA
	Etanercept 50 mg	96	NA	NA	NA	NA	6	96		12	NA	NA	NA	NA
Asahina	Tofacitinib 5mg	43	-	-	-	-	0	43	16	16	NA	NA	NA	NA
	Tofacitinib 10mg	44	-	-	-	-	5	44		16	NA	NA	NA	NA
Cai 2016	PBO	87	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Adalimumab 40 mg	338	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gordon 2015	PBO	42	-	-	-	-	3	42	16	16	NA	NA	40	40
	Guselkumab 5 mg	41	-	-	-	-	3	41		16	12	41	40	
	Guselkumab 15 mg	41	-	-	-	-	0	41		16	4	41	40	
	Guselkumab 50 mg	42	-	-	-	-	3	42		16	5	42	40	
	Guselkumab 100 mg	42	-	-	-	-	2	42		16	3	42	40	
	Guselkumab 200 mg	42	-	-	-	-	4	42		16	7	41	40	
	Adalimumab 80 mg	43	-	-	-	-	4	43		16	11	43	40	
Gottlieb 2012	Etanercept+PBO	239	-	-	-	NR	14	239	12	12	33	239	24	24
	Etanercept+methorexate	239	-	-	-	NR	15	239		12	28	239	24	
Igarashi 2012	PBO	32	NA	NA	NA	NA	4	32	12	12	NA	NA	72	72

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
	Ustekinumab 45 mg	64	-	-	-	NA	0	64		12	6	64	72	
	Ustekinumab 90 mg	62	-	-	-	NA	4	62		12	8	62	72	
AMAGINE-2	PBO	309	NA	NA	NA	NA	9	309	12	12	NA	NA	NA	NA
	Ustekinumab	300	NA	NA	NA	NA	9	300		12	NA	NA	NA	NA
	Brodalumab 140 mg	610	NA	NA	NA	NA	22	610		12	NA	NA	NA	NA
	Brodalumab 210 mg	612	NA	NA	NA	NA	15	612		12	NA	NA	NA	NA
AMAGINE-3	PBO	315	NA	NA	NA	NA	14	315	12	12	NA	NA	NA	NA
	Ustekinumab	313	NA	NA	NA	NA	10	313		12	NA	NA	NA	NA
	Brodalumab 140 mg	629	NA	NA	NA	NA	25	629		12	NA	NA	NA	NA
	Brodalumab 210 mg	624	NA	NA	NA	NA	16	624		12	NA	NA	NA	NA
Lee 2016	Acitretin 10 mg	18	7	19	24	24	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept 25 mg + acitretin	19	4	20		24	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept 50 mg	21	4	21		24	NR	NR	NR	NR	NR	NR	NR	NR
Leonardi 2012	PBO	27	4	27	12	12	NR	NR	NR	NR	NR	NR	NR	NR
	Ixekizumab 10 mg	28	6	28		12	NR	NR	NR	NR	NR	NR	NR	NR
	Ixekizumab 25 mg	30	1	30		12	NR	NR	NR	NR	NR	NR	NR	NR
	Ixekizumab 75 mg	29	1	29		12	NR	NR	NR	NR	NR	NR	NR	NR
	Ixekizumab 150 mg	28	1	28		12	NR	NR	NR	NR	NR	NR	NR	NR
Papp 2015	PBO	46	-	-	-	-	6	46	16	16	NA	NA	NA	NA
	Tildrakizumab 5mg	42	-	-	-	-	2	42		16	3	13	16-72	16,72
	Tildrakizumab 25mg	92	-	-	-	-	5	92		16	NA	NA	NA	NA
	Tildrakizumab 100 mg	89	-	-	-	-	1	89		16	NA	NA	NA	NA
	Tildrakizumab 200 mg	86	-	-	-	-	2	86		16	NA	NA	NA	NA
Papp 2013	PBO	22	11	22	36	36	NR	NR	NR	NR	NR	NR	NR	NR

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
	Secukinumab 1 x 25	29	15	29		36	NR	NR	NR	NR	NR	NR	NR	NR
	Secukinumab 3 x 25	26	10	26		36	NR	NR	NR	NR	NR	NR	NR	NR
	Secukinumab 3 x 75	21	4	21		36	NR	NR	NR	NR	NR	NR	NR	NR
	Secukinumab 3 x 150	27	7	27		36	NR	NR	NR	NR	NR	NR	NR	NR
Papp 2012	PBO	38	3	38	16	16	NA	NA	NA	NA	NA	NA	NA	NA
	Brodalumab 70 mg	39	1	39		16	NR	NR	NR	NR	NR	NR	NR	NR
	Brodalumab 140 mg	39	1	39		16	NA	NA	NA	NA	NA	NA	NA	NA
	Brodalumab 210 mg	40	3	40		16	NA	NA	NA	NA	NA	NA	NA	NA
	Brodalumab 280 mg	42	2	42		16	NR	NR	NR	NR	NR	NR	NR	NR
AMAGINE-1	PBO	220	NA	NA	NA	NA	12	220	12	12	NA	NA	NA	NA
	Brodalumab 140 mg	219	NA	NA	NA	NA	11	219		12	NA	NA	NA	NA
	Brodalumab 210 mg	222	NA	NA	NA	NA	10	222		12	NA	NA	NA	NA
LIBERATE	PBO	84	NA	NA	NA	NA	9	84	16	16	NA	NA	NA	NA
	Apremilast	83	NA	NA	NA	NA	6	83		16	18	74	16-52	16-52
	Etanercept	83	NA	NA	NA	NA	2	83		16	NA	NA	NA	NA
Rich 2013	PBO	67	NR	NR	NR	NR	9	67	12	12	NR	NR	NR	NR
	Secukinumab single	66	NR	NR	NR	NR	5	66		12	NR	NR	NR	NR
	Secukinumab monthly	138	NR	NR	NR	NR	4	138		12	NR	NR	NR	NR
	Secukinumab early	133	NR	NR	NR	NR	6	133		12	NR	NR	NR	NR
Bissonnette 2015	Tofacitinib 5 mg	331	-	-	-	-	34	331	24	24	NR	NR	NR	NR
	Tofacitinib 10 mg	335	-	-	-	-	38	335		24	NR	NR	NR	NR
RESTORE1	MTX	215	88	215	26	26	NA	NA	NA	NA	NA	NA	NA	NA
	Infliximab	653	112	653		26	NA	NA	NA	NA	NA	NA	NA	NA
Chaudhari 2001	PBO	11	1	11	10	10	NA	NA	NA	NA	NA	NA	NA	NA

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
	Infliximab 5 mg	11	1	11		10	NA	NA	NA	NA	NA	NA	NA	NA
	Infliximab 10 mg	11	1	11		10	NR	NR	NR	NR	NR	NR	NR	NR
Gisondi 2008	Acitretin 0.4 mg/kg	20	4	20	24	24	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept	22	0	22		24	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept + acitretin	18	0	18		24	NR	NR	NR	NR	NR	NR	NR	NR
Caproni 2009	Acitretin	30	0	30	12	12	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept	30	0	30		12	NR	NR	NR	NR	NR	NR	NR	NR
PIECE	Infliximab	25	-	-	-	NA	2	25	24	24	2	11	24-48	24-48
	Etanercept	23	-	-	-	NA	5	23		24	1	11		24-48
Goldminz 2015	MTX	15	0	15	16	16	NA	NA	NA	NA	NA	NA	NA	NA
	Adalimumab	15	0	15		16	NA	NA	NA	NA	NA	NA	NA	NA
OPT Compare	PBO	107	12	107	12	12	NA	NA	NA	NA	NA	NA	NA	NA
	Tofacitinib 5 mg	329	23	329		12	NA	NA	NA	NA	NA	NA	NA	NA
	Tofacitinib 10 mg	330	24	330		12	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept 50 mg	335	22	335		12	NA	NA	NA	NA	NA	NA	NA	NA
M02-528 and M02-529	PBO	52	-	-	-	NA	2	52	12	12	NA	NA	60	60
	Adalimumab 40 mg eow	45	-	-	-	NA	2	45		12	10	45	60	
	Adalimumab 40 mg/wk	50	-	-	-	NR	3	50		12	17	50	60	
A3921047	PBO	50	20	50	16	16	NA	NA	NA	NA	NA	NA	NA	NA
	Tofacitinib 2 mg	49	11	49		16	NR	NR	NR	NR	NR	NR	NR	NR
	Tofacitinib 5 mg	49	11	49		16	NA	NA	NA	NA	NA	NA	NA	NA
	Toafacitinib 15 mg	49	6	49		16	NR	NR	NR	NR	NR	NR	NR	NR
OPT Pivotal 1	PBO	177	45	177	16	16	NA	NA	NA	NA	NA	NA	NA	NA
	Tofacitinib 5 mg	363	50	363		16	NA	NA	NA	NA	NA	NA	NA	NA

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
	Tofacitinib 10 mg	360	40	360		16	NR	NR	NR	NR	NR	NR	NR	NR
OPT Pivotal 2	PBO	196	44	196	16	16	NA	NA	NA	NA	NA	NA	NA	NA
	Tofacitinib 5 mg	382	51	382		16	NA	NA	NA	NA	NA	NA	NA	NA
	Tofacitinib 10 mg	381	40	381		16	NR	NR	NR	NR	NR	NR	NR	NR
Bagel 2012	PBO	62	13	62	24	24	NA	NA	NA	NA	NA	NA	NA	NA
	Etanercept 50 mg	62	10	59		24	NA	NA	NA	NA	NA	NA	NA	NA
M10-114	PBO	68	5	68	12	12	NA	NA	NA	NA	NA	NA	NA	NA
	Etanercept	141	7	141		12	NA	NA	NA	NA	NA	NA	NA	NA
	Briakinumab	138	10	138		12	NR	NR	NR	NR	NR	NR	NR	NR
M10-315	PBO	72	6	72	12	12	NA	NA	NA	NA	NA	NA	NA	NA
	Etanercept	139	12	139		12	NA	NA	NA	NA	NA	NA	NA	NA
	Briakinumab	139	8	139		12	NR	NR	NR	NR	NR	NR	NR	NR
EXPRESS II	PBO	208	-	-	-	-	24	208	14	14	NA	NA	14-50	14-50
	Infliximab 3 mg	313	-	-	-	-	21	313		14	36	148		14-50
	Infliximab 5 mg	314	-	-	-	-	17	314		14	31	150		14-50
Lebwohl 2013	Etanercept	297	-	-	-	-	NR	NR	12	12	NR	NR	24	24
	Etanercept + clobetasol propionate	295	-	-	-	-	NR	NR		12	NR	NR		24
Maari 2014	PBO	10	0	10	12	12	NA	NA	NA	NA	NA	NA	NA	NA
	Adalimumab	10	0	10		12	NA	NA	NA	NA	NA	NA	NA	NA
NAIL	Etanercept 50 mg BIW/QW	36	7	38	26	26	NA	NA	NA	NA	NA	NA	NA	NA
	Etanercept 50 mg	33	5	34		26	NA	NA	NA	NA	NA	NA	NA	NA

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
	QW/QW													
PSOR-005	PBO	88	NA	NA	NA	NA	16	88	16	16	NA	NA	24	24
	Apremilast 10 mg	89	-	-	-	NR	10	89		16	12	77	24	
	Apremilast 20 mg	87	-	-	-	NR	21	87		16	7	66	24	
	Apremilast 30 mg	88	-	-	-	NA	18	88		16	2	67	24	
Nakagawa 2016	PBO	38	4	38	12	12	NA	NA	NA	NA	NA	NA	NA	NA
	Brodalumab 70 mg	39	2	39		12	NR	NR	NR	NR	NR	NR	NR	NR
	Brodalumab 140 mg	37	0	37		12	NA	NA	NA	NA	NA	NA	NA	NA
	Brodalumab 210 mg	37	0	37		12	NA	NA	NA	NA	NA	NA	NA	NA
Papp 2013	PBO	87	-	-	-	NR	19	87	12	12	NR	NR	NR	NR
	Apremilast 20 mg QD	87	-	-	-	NR	17	87		12	NR	NR	NR	NR
	Apremilast 20 mg BID	85	-	-	-	NR	11	86		12	NR	NR	NR	NR
TRANSIT	Ustekinumab with immediate MTX withdrawal	244	NR	NR	NR	NR	4	244	12	12	NR	NR	NR	NR
	Ustekinumab with gradual methrotexate withdrawal	245	NR	NR	NR	NR	4	245		12	NR	NR	NR	NR
Reich 2012	PBO	59	-	-	-	NA	19	59	12	12	32	59	36	36
	Certolizumab 200 mg	59	-	-	-	NA	5	59		12	14	59	36	
	Certolizumab 400 mg	58	-	-	-	NA	4	58		12	8	58	36	
Tyring 2006	PBO	307	-	-	-	-	15	307	12	12	NA	NA	12-96	NA
	Etanercept	311	-	-	-	-	6	311		12	71	304		12-96
PEARL	PBO	60	NA	NA	NA	NA	5	60	12	12	NA	NA	36	NA
	Ustekinumab	61	NA	NA	NA	NA	4	61		12	5	61		36
BELIEVE	Adalimumab + vehicle	364	26	364	16	16	NR	NR	NR	NR	NR	NR	NR	NR
	Adalimumab + calcipotriol	366	28	366		16	NR	NR	NR	NR	NR	NR	NR	NR
Sofen 2014	PBO	4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Guselkumab 10 mg	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
	Guselkumab 30 mg	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Guselkumab 100 mg	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Guselkumab 300 mg	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PRISTINE	Etanercept 50 mg once weekly	137	10	137	24	24	-	-	-	-	-	-	-	-
	Etanercept 50 mg twice weekly	136	12	136		24	-	-	-	-	-	-	-	-
EGALITY	Etanercept	267	NA	NA	NA	NA	12	267	12	12	14	151	12-52	12-52
	GP2015	264	NA	NA	NA	NA	8	264		12	7	150	12-30	12-30
van Bezooijen 2016	Etanercept monotherapy	15	NR	NR	NR	NR	5	15	24	24	NR	NR	NR	NR
	Etanercept and fumarates	18	NR	NR	NR	NR	0	18		24	NR	NR	NR	NR
Yang 2012	PBO	45	NA	NA	NA	NA	1	45	10	10	NA	NA	NA	NA
	Infliximab	84	NA	NA	NA	NA	1	84		10	10	84	26	26
Krueger 2015	PBO	1	0	1	24	24	NR	NR	NR	NR	NR	NR	NR	NR
	BI 655066 0.01 mg i.v.	3	0	3		24	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	1	0	1		24	NR	NR	NR	NR	NR	NR	NR	NR
	BI 655066 0.05 mg i.v.	3	0	3		24	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	1	0	1		24	NR	NR	NR	NR	NR	NR	NR	NR
	BI 655066 0.25 mg i.v.	3	0	3		24	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	1	0	1		24	NR	NR	NR	NR	NR	NR	NR	NR
	BI 655066 1 mg i.v.	3	0	3		24	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	1	0	1		24	NR	NR	NR	NR	NR	NR	NR	NR
	BI 655066 3 mg i.v.	3	0	3		24	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	1	0	1		24	NR	NR	NR	NR	NR	NR	NR	NR
	BI 655066 5 mg i.v.	3	1	3		24	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	1	0	1		24	NR	NR	NR	NR	NR	NR	NR	NR
	BI 655066 0.25 mg s.c.	7	0	7		24	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	1	0	1		24	NR	NR	NR	NR	NR	NR	NR	NR

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
	BI 655066 1 mg s.c.	6	0	6		24	NR	NR	NR	NR	NR	NR	NR	NR
Lynde 2012	Etanercept	38	3	38	12-24	12-24	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept + nbUVB	37	10	37		12-24	NR	NR	NR	NR	NR	NR	NR	NR
SCORE	PBO	62	43	62	6-32	6-32	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept	58	20	58		6-32	NR	NR	NR	NR	NR	NR	NR	NR
Park 2013	Etanercept	15	5	15	12	12	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept + NB-UVB	15		15		12	NR	NR	NR	NR	NR	NR	NR	NR
REFINE	Etanercept	144	12	144	12	12	NR	NR	NR	NR	NR	NR	NR	NR
	Etanercept + topical agent	143	8	143		12	NR	NR	NR	NR	NR	NR	NR	NR
STATURE	Secukinumab 300 mg	21	1	21	8	8	NR	NR	NR	NR	NR	NR	NR	NR
	Secukinumab 10 mg/kg	22	2	22		8	NR	NR	NR	NR	NR	NR	NR	NR
Bissonnette 2013	Control	10	0	10	16	16	NA	NA	NA	NA	NA	NA	NA	NA
	Adalimumab	20	1	20		16	NA	NA	NA	NA	NA	NA	NA	NA
Krueger 2007	PBO	64	NR	NR	NR	NR	13	64	16	16	NR	NR	NR	NR
	Ustekinumab 45 mg	64	NR	NR	NR	NR	7	64		16	NR	NR	NR	NR
	Ustekinumab 90 mg	64	NR	NR	NR	NR	3	64		16	NR	NR	NR	NR
	Ustekinumab 45 mg x 4	64	NR	NR	NR	NR	3	64		16	NR	NR	NR	NR
	Ustekinumab 90 mg x 4	64	NR	NR	NR	NR	4	64		16	NR	NR	NR	NR
PRESTA	Etanercept 50 mg twice weekly	379	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Etanercept 50 mg once weekly	373	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Torii 2010	PBO	19	NA	NA	NA	NA	4	19	14	14	NA	NA	NA	NA
	Infliximab	35	NA	NA	NA	NA	3	35		14	NA	NA	NA	NA
LOTUS	PBO	162	NA	NA	NA	NA	2	161	12	12	NA	NA	NA	NA
	Ustekinumab	160	NA	NA	NA	NA	3	16		12	NA	NA	NA	NA

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
								0						
CIMPASI 1	PBO	51	NA	NA	NA	NA	5	51	16	16	NA	NA	NA	NA
	CZP 200 mg	95	NA	NA	NA	NA	3	95		16	3	74	16-48	16-48
	CZP 400 mg	88	NA	NA	NA	NA	1	88		16	7	77		16-48
CIMPASI 2	PBO	49	NA	NA	NA	NA	4	49	16	16	NA	NA	NA	NA
	CZP 200 mg	91	NA	NA	NA	NA	7	91		16	12	76	16-48	16-48
	CZP 400 mg	87	NA	NA	NA	NA	4	87		16	8	69		16-48
CIMPACT	PBO	57	NA	NA	NA	NA	2	57	16	16	0	2	16-48	16-48
	Etanercept	170	NA	NA	NA	NA	11	170		16	NA	NA		NA
	CZP 200 mg	165	NA	NA	NA	NA	6	165		16	4	44		16-48
	CZP 400 mg	167	NA	NA	NA	NA	5	167		NA	0	49		16-48
M02-538	PBO	68	23	68	12	12	NR	NR	NR	NR	NR	NR	NR	16-48
	Adalimumab	68	17	68		12	NR	NR	NR	NR	NR	NR	NR	NR
Hueber 2010	PBO	18	0	18	12	12	NR	NR	NR	NR	NR	NR	NR	NR
	Secukinumab	18	0	18		12	NR	NR	NR	NR	NR	NR	NR	NR
Krueger 2012	PBO	8	3	40	20	20	NR	NR	NR	NR	NR	NR	NR	NR
	Ixekizumab 5 mg	8				20	NR	NR	NR	NR	NR	NR	NR	NR
	Ixekizumab 15 mg	8				20	NR	NR	NR	NR	NR	NR	NR	NR
	Ixekizumab 50 mg	8				20	NR	NR	NR	NR	NR	NR	NR	NR
	Ixekizumab 150 mg	8				20	NR	NR	NR	NR	NR	NR	NR	NR
VOYAGE 1	PBO	174	-	-	-	-	7	174	16	16	N/A	N/A	48	48
	Guselkumab	329	-	-	-	-	7	329		16	28	329		48
	Adalimumab	334	-	-	-	-	10	334		16	52	334		48
Elewski 2017	PBO	108	14	108	26	26	-	-	-	-	-	-	-	-
	Adalimumab	109	15	109		26	-	-	-	-	-	-	-	-

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
Jin 2017	PBO	6	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Tofacitinib 5 mg	5	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Tofacitinib 10 mg	7	NR	NR	NR	NR	-	-	-	-	-	-	-	-
NAVIGATE	Guselkumab	135	9	135	28	28	-	-	-	-	-	-	-	-
	Ustekinumab	133	20	133		28	-	-	-	-	-	-	-	-
Ohtsuki 2017	PBO	84	-	-	-	-	12	84	16	16	N/A	N/A	68	68
	Apremilast 20 mg	85	-	-	-	-	16	85		16	28	85		68
	Apremilast 30 mg	85	-	-	-	-	9	85		16	18	85		68
Papp 2017	Ustekinumab	40	-	-	-	-	1	40	12	12	19	39	24-48	24-48
	Risankizumab 18 mg	43	-	-	-	-	4	43		12	29	39		24-48
	Risankizumab 90 mg	41	-	-	-	-	2	41		12	4	39		24-48
	Risankizumab 180 mg	42	-	-	-	-	2	42		12	7	40		24-48
Papp 2017-ABP 501	Adalimumab	175	-	-	-	-	19	175	16	16	8	79	16-52	16-52
	ABP 501	175	-	-	-	-	23	175		16	19	152		16-52
VOYAGE 2	PBO	248	-	-	-	-	15	248	16	16	N/A	N/A	28	28
	Guselkumab	496	-	-	-	-	18	496			26	496		28
	Adalimumab	248	-	-	-	-	11	248			20	248		28
reSURFACE 1	PBO	155	-	-	-	-	9	155	12	12	N/A	N/A	N/A	N/A
	Tildrakizumab 100 mg	309	-	-	-	-	9	309		12	31	299	12-28	12-28
	Tildrakizumab 200 mg	308	-	-	-	-	10	308		12	29	308	28	28
reSurFACE 2	PBO	156	-	-	-	-	14	156	12	12	N/A	N/A	N/A	N/A
	Etanercept	313	-	-	-	-	24	313		12	36	313	28	28

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
	Tildrakizumab 100 mg	307	-	-	-	-	12	307		12	5	294	12-28	12-28
	Tildrakizumab 200 mg	314	-	-	-	-	14	314		12	20	314	28	28
IXORA-S	Ustekinumab	166	-	-	-	-	2	166	12	12	8	166	24	24
	Ixekizumab	136	-	-	-	-	4	136		12	5	136		24
Krueger 2016	PBO	3	0	3	12	12	-	-	-	-	-	-	-	-
	Tofacitinib	9	1	9		12	-	-	-	-	-	-	-	-
Akcali 2014	Cyclosporine	21	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Acitretin	25	NR	NR	NR	NR	-	-	-	-	-	-	-	-
Akhyani 2010	MTX	18	3	18	24	24	-	-	-	-	-	-	-	-
	MMF	20	3	20		24	-	-	-	-	-	-	-	-
Al-Hamamy 2014	MTX	37	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	MTX + NBUVB	38	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	NBUVB	38	NR	NR	NR	NR	-	-	-	-	-	-	-	-
Ali 2009	MTX	20	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Leflunomide	20	NR	NR	NR	NR	-	-	-	-	-	-	-	-
Beissert 2009	Cyclosporine	26	-	-	-	-	7	27	12	12	2	26	12-24	12-24
	MMF	26	-	-	-	-	6	27		12	7	27		12-24
Dogra 2012	MTX 10 mg	30	5	30	12	12	-	-	-	-	-	-	-	-
	MTX 25 mg	30	4	30		12	-	-	-	-	-	-	-	-
Elder 1995	Cyclosporine (Neoral)	18	2	18	12	12	-	-	-	-	-	-	-	-
	Cyclosporine (Sandimmune)	19	3	19		12	-	-	-	-	-	-	-	-
Fallah Arani 2011	MTX	27	-	-	-	-	11	30	16	16	0	19	16-20	16-20
	Fumarates	27	-	-	-	-	10	30		16	4	22		16-20
Finzi 1993	Cyclosporine	36	-	-	-	-	2	36	12	12	5	NR	12-36	12-36

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
	Etretinate	40	-	-	-	-	7	40		12	4	NR		12-36
Heydendael 2003	Cyclosporine	42	-	-	-	-	1	42	16	16	6	42	17-52	17-52
	MTX	43	-	-	-	-	12	43		16	10	43		17-52
Ho 2009	PBO	20	3	20	24	24	-	-	-	-	-	-	-	-
	MTX	20	1	20		24	-	-	-	-	-	-	-	-
	Traditional Chinese Medicine	21	7	21		24	-	-	-	-	-	-	-	-
Koo 1998	Cyclosporine (Neoral)	152	27	152	24	24	-	-	-	-	-	-	-	-
	Cyclosporine (Sandimmune)	157	32	157		24	-	-	-	-	-	-	-	-
Mahajan 2010	MTX	20	1	20	NR	NR	-	-	-	-	-	-	-	-
	NBUVB	20	2	20		NR	-	-	-	-	-	-	-	-
Sandhu 2003	MTX	15	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Cyclosporine	15	NR	NR	NR	NR	-	-	-	-	-	-	-	-
Reitamo 2001	Sirolimus 0.5	16	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Sirolimus 1.5	20	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Sirolimus 3.0	20	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Sirolimus 0.5 + cyclosporine 1.25	21	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Sirolimus 1.5 + cyclosporine 1.25	20	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Sirolimus 3.0 + cyclosporine 1.25	19	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Cyclosporine 1.25	19	NR	NR	NR	NR	-	-	-	-	-	-	-	-
	Cyclosporine 5.0	15	NR	NR	NR	NR	-	-	-	-	-	-	-	-
Meffert 1997	PBO	39	-	-	-	-	NR	NR	NR	NR	NR	NR	NR	NR
	Cyclosporine 1.25	40	-	-	-	-	NR	NR	NR	NR	NR	NR	NR	NR
	Cyclosporine 2.5	41	-	-	-	-	NR	NR	NR	NR	NR	NR	NR	NR
Reich 2011	Briakinumab	154	48	154	52	52	-	-	-	-	-	-	-	-

Study name	Intervention arm	Treatment Number	Overall				Short				Long-term			
			r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks	r	N	Analysis time - Wks	Analysis time - Wks
	MTX	163	118	163		52	-	-	-	-	-	-	-	-
BRIDGE	PBO	137	-	-	-	-	39	137	16	16	NR	66	16-52	16-52
	LAS41008	279	-	-	-	-	103	279		16	NR	150		16-52
	Fumaderm	283	-	-	-	-	107	283		16	NR	153		16-52
Mahrle 1995	Cyclosporine	140	7	NR	10	10	-	-	-	-	-	-	-	-
	Etretinate	70	5	NR		10	-	-	-	-	-	-	-	-
Laburte 1994	Cyclosporine 2.5 mg	119	-	-	-	-	NR	NR	NR	NR	88	251	88	88
	Cyclosporine 5 mg	132	-	-	-	-	NR	NR	NR	NR				88
Engst 1994	Cyclosporine 1.25 mg	10	3	10	52	52	NR	NR	NR	NR	NR	NR	NR	NR
	Cyclosporine 2.5 mg	12	5	12		52	NR	NR	NR	NR	NR	NR	NR	NR
METOP	PBO	29	-	-	-	-	7	29	16	16	N/A	N/A	52	N/A
	MTX	91	-	-	-	-	14	91		16	35	91		52
Zhang 2017	PBO	88	-	-	-	-	11	88	16	16	N/A	N/A	52	52
	Tofacitinib 5 mg	88	-	-	-	-	4	88		16	9	88		52
	Tofacitinib 10 mg	90	-	-	-	-	7	90		16	9	90		52

NICE National Institute for Health and Care Excellence

Patient organisation submission

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis Association
3. Job title or position	Chief Executive
4a. Brief description of the organisation (including who funds it). How many members does it have?	Patient Support Organisation and Charity. The Psoriasis Association currently has around 2300 members who help to fund the organisation via an annual fee. Other sources of income include fundraising (individuals, legacies and trusts), investments and unrestricted educational grants from the Pharmaceutical Industry for projects (there is a policy that no more than 15% of the total income of the Psoriasis Association can come from the Pharmaceutical Industry). In addition to traditional members, the Psoriasis Association regularly communicates with, or offers a platform enabling people whose lives are affected by the condition to communicate with one another via online forums on their own websites (6,000 registered users), and Social Media (12,000 people). The main Psoriasis Association website averages 45, 000 visits per month.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the	This submission has been informed by informal, anecdotal information that we hear from patients and carers themselves, through the following channels provided by the Psoriasis Association:-

experiences of patients and carers to include in your submission?	the Psoriasis Association website (566,961 visitors in 2017) telephone helpline (850 enquiries in 2017) online forums (8,490 registered users in 2017) social media channels (including Facebook Group, Twitter and Instagram, 15,000 people in 2017)
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Psoriasis is a lifelong condition with varying degrees of severity. The patients for whom this treatment is intended, those with moderate to severe disease, will have a degree of psoriasis that will not only be visible to others, but also be itchy, painful and produce excess scales. The scales are unsightly, and can cause problems with employment and work colleagues in many industries. Owing to the highly visible nature of psoriasis, and its unsightliness, patients can often adopt negative coping mechanisms such as avoiding social situations (in the hope of avoiding negative reactions from members of the general public). This can mean that the condition itself is isolating and lonely. This can in turn lead to adopting unhealthy lifestyle choices, such as alcohol and drug use, lack of exercise and smoking. Patients with moderate to severe psoriasis have usually been through a long journey of treatment trial and error and expense. When psoriasis is first diagnosed, patients will usually be prescribed topical treatments (creams and ointments). Our latest membership survey found that people were spending on average two hours every day treating their (mild) psoriasis. This involves regularly moisturising the skin (essential in order to keep the skin comfortable, to help with itch and to reduce flakes from falling – having

	to share a desk at work can be very difficult for people with psoriasis), and applying creams and ointments with more active ingredients. The majority of respondents in our membership survey reported psoriasis impacting on their choice of clothing, from regularly "covering up" in the summer months in long sleeves and long trousers, to the colour of clothing on the top half of the body (men report frequently having light suits for work to help conceal the shedding of scales, whilst women consciously sought certain fabrics so as not to have clothing ruined by treatments). It is often unsustainable to treat psoriasis with topical treatments alone, and patients will need more help to cope with a flare, or to maintain the condition at a manageable level. The traditional next stage has been Ultraviolet Light Therapy, but for some patients this form of treatment is not considered owing to the time commitment required (attending the Dermatology Department three times per week for 10 weeks). Traditional systemic treatments for psoriasis would then be considered if the psoriasis was deemed to be moderate to severe in nature. It is vitally important however to measure, record and treat not only the physical symptoms of psoriasis, but the psychological impact the condition can have. Being a lifelong condition, the psychological impact may not initially be realised, which is why it is important for this assessment to be made over the course of the disease. Psoriasis in high impact areas such as the hands, feet, face or genitals is not only a problem for people owing to the visibility of the condition. Deep cracks to the fingertips (not to mention nail psoriasis) can be disabling for those whose trade requires use of the hands and fingers (e.g. musicians, artists, mechanics, not to forget general office-based administration roles). Psoriasis on the feet can make walking difficult, even wearing shoes. Psoriasis on the face can be especially distressing, and we know people avoid

	intimate relationships so as not to have to expose genital psoriasis. For those in steady relationships, sexual relationships can be difficult owing to the pain experienced by genital psoriasis. People report deliberately not having children in case they too develop psoriasis. For those with moderate – severe psoriasis who do want children, their choice of treatment is limited owing to the teratogenicity of traditional systemic medications. Psoriasis therefore can affect every stage of life to varying degrees – from bullying in school, through to difficulty writing in exams, choice of career, having children, holidays and long-term relationships. Access to treatments that are appropriate, suitable and reliable is vital.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There has long been a frustration amongst those with clinically moderate psoriasis that their psoriasis is not "bad enough" to warrant systemic, or newer biological therapies, yet it is too severe to manage with topical treatments alone. This patient population are stuck in limbo. Sadly there is a postcode lottery in terms of care available on the NHS, for some, usually those who have been in the system for a while, it is good. For many there is little access to secondary care (where drugs for moderate to severe psoriasis are prescribed) as lists are closed or extremely lengthy or GPs are unwilling / unable to refer. A recent caller to the Psoriasis Association with schizophrenia in addition to moderate – severe psoriasis, said that living with schizophrenia was made easier than living with psoriasis as he could access specialist services more readily. He questioned why it had taken 12 years for him to be referred to see a Dermatologist.
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	It is a highly targeted treatment for psoriasis, moving away from the blanket immune suppression of traditional systemic treatments for psoriasis. Being an every-other-week injection, it does not impact too greatly on a patient's life. Certolizumab pegol is the only biologic treatment licensed for use in women during pregnancy and breastfeeding, making it a much-needed option for women of childbearing age with moderate to severe psoriasis.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The fact that it is an injection will always concern a cohort of patients.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those for whom other treatments have failed – recent biologic treatment advances in psoriasis have taken the form of interleukin inhibitors. Although there are a number of anti-TNF agents available, there will be a cohort of patients who have lost long-term efficacy on the available anti-TNFs but for whom the newer interleukin inhibitors are not suitable. This group in particular would benefit from a new anti-TNF agent. Certolizumab pegol is the only biologic treatment licensed for use in women during pregnancy and breastfeeding, making it a much-needed option for women of childbearing age with moderate to severe psoriasis.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The PASI is not a suitable assessment for psoriasis on high impact sites (such as the hands, feet, face and genitals). It is also not as robust a measure in black skin. Women of childbearing age deserve to have effective treatments available to them in order to manage their chronic condition without compromising their family plans.
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Psoriasis is a lifelong condition in which individuals respond differently to different treatments. For this reason a range of treatment options for all degrees of severity is required.
- There is currently unmet need in the treatment of people with moderate psoriasis (for whom topical treatments nor biologics are suitable).

- High impact sites such as the face, hands, feet and genitals should not be overlooked when defining treatment criteria (these sites will not produce a high PASI score).
- Itch should be considered as a treatment outcome.
- This technology addresses an unmet need in people for whom anti-TNFs are most suitable but long-term efficacy has been lost with current options, as well as women of childbearing age.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Certolizumabpegol for treating chronic plaque psoriasis [ID1232]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
3. Job title or position	Chief Executive
4a. Brief description of the organisation (including who funds it). How many members does it have?	PAPAA is a national charity, which provides information and support to people affected by psoriasis and psoriatic arthritis. The current incarnation followed the merger of two separate organisations, with the oldest dating back to 1992. Although the charity has no formal membership, it has a supporter register of >13,000 people which includes both patients and healthcare professionals. In a changing 21st century, activity and support has evolved with more taking place online, with most interaction via that medium. The main charity website had >800,000 page views during the past year. Regular use of feedback forms and online surveys help to direct the charity's work and how it represents its constituent group. Funding is via donations, subscriptions and from the sale of promotional items. Financial support is not accepted from the pharmaceutical industry, either as direct payment or in-kind, this includes third-party work via PR or research agencies. The organisation values its independence and feels this provides an agenda which is patient-centred and not driven by marketing or promotional activities that may be behind such support, however arms-length or segmented.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include inyour	Data for this submission has been gathered via our online surveys and direct feedback. We compile ongoing views and opinions of those who interact with us to provide a broad consensus that we think reflects the general psoriasis population that is likely to be those who would potentially qualify for certolizumab pegol.

submission?	
Living with the condition	
6. What is it like to live with the condition?What do carers experience when caring for someone with the condition?	The condition affects people differently, many people live with psoriasis and manage it without any issues, but there is a significant number of people who find it difficult to deal with, which does not always relate to severity. Mild disease can have a profound affect, which often causes huge emotonal and psychological issues for the person with psoriasis, their family and carers. Different groups have different needs dependent on age and time of life. The following are typical of such issues and reflective of all the comments received: “I didn’t want to go to school because of being bullied.” “I was bullied for being 'different'.” “Serious flaking and pain from flakes made concentrating difficult. Constant itching and 'shedding' is very embarrassing. “ “I was very self conscience and teased about it, embarrassed added to lack of confidence, not in education anymore.” “I have visible psoriasis on my hands and face and I am embarrassed during coursework or doing presentations.” “Constantly having to take time out to apply creams, sore skin being quite distracting and people laughing at it.” “Can't get jobs working with food.”

	"I worked in a bank & customers commented on the psoriasis. I eventually had a uniform shirt with long sleeves specially made." "A trail of skin around my work station can make me feel paranoid. Treatments can be demanding 3 visits a week during work hours [for phototherapy]." "Stopped me from becoming a nurse and has proved a problem in nursing care jobs I've had." "Psoriasis sometimes flares up in unwanted areas. Very hard to explain that to someone during intimacy." "I'm self conscious of how I look, no confidence, no self esteem frightened of what others think." "I avoid activities that require me to expose my affected skin." "Generally not affected anymore, as I've learnt to accept who I am, but definitely used to struggle." "I suffer self loathing at times." "Has affected my choice of career I wanted to do which has affected the quality of life I can strive for" "Hard to plan around random flare ups that can leave you exhausted and in pain or embarrassed." "Due to depression and health scared to be away from medical team that know me. Many hospital admissions." "All the things I wanted from life I'm unable to do. I'm 26 and my life is on hold because of a stupid illness." "I would like a relationship but don't want to expose myself to rejection as a reaction to my skin" "I have decided not to have children as I don't think I'd cope with caring for a child"

	"It's restricting the type of work I can do so its jeopardising the type of life I want " "I don't know what the future holds as I cannot make any plans such as booking a holiday in advance in case I get a flare up" "It has made me depressed and affects me throughout the whole year." "I want more children and certain meds I can't take while being pregnant. I have none. Just living day to day. Depression is my life."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	For most the treatments do work and provide relief, but for some the therapies either don't work, cause adverse events or are too inconvenient to even contemplate.
8. Is there an unmet need for patients with this condition?	Although over recent years the psoriasis population has seen a wealth of new therapies becoming available, there is often a point where these stop being effective and an individual has exhausted the range of therapies, therefore there is still a need to find some form of alternative treatment.
Advantages ofthe technology	
9. What do patients or carers think are the advantages of the technology?	There appears to be little difference between this agent and other anti-TNFs. Although, nail psoriasis, which can be a huge issue for people with psoriasis, appears to be recorded as improved in trial. This may be an anomaly of reporting, as early trials of other anti-TNFs, may not have measured this as an outcome, although it would useful to patients if this could be identified as an advantage for selection of an agent, which has better response in specific disease domains, as would efficacy for psoriatic arthritis.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We have no information related to the drug being appraised, so would assume that any disadvantages would be similar to other same class agents. Therefore as with other agents, access due to high cost may delay people moving onto these targeted treatments, or being delayed by having to try other less effective therapies first.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those with psoriatic arthritis could benefit, if it is proven to be effective in that element of the disease too.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and	We don't believe there are any equality issues that need to be considered as set out in law. Although, there are those who have needle phobias and there could be individuals who have arthritic hands which might make self-injection difficult, but provision already exists to help these individuals.

the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Psoriasis is a life-long lonely disease with unpredictable flares and remission
- Psoriasis causes huge emotonal and psychological issues for the person with psoriasis, their family and carers.
- Not everyone responds, so further choice is needed
- Nail psoriasis is an important disease domain with an unmet need
- Psoriatic arthritis needs to be considered as potentially benefiting, when skin psoriasis is treated.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	British Association of Dermatologists

3. Job title or position	
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a charity whose charitable objectives are the practice, teaching, training and research of Dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of Dermatology services across all service settings. It is funded by the activities of its Members
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	• Control of psoriasis with the aim of a 'clear' or 'nearly clear' by Physician's Global Assessment rating • Reducing the impact of the disease on quality of life

disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Current guidelines (specifically the published 2017 BAD guidelines on biologic therapies for psoriasis, and prior NICE STAs have defined a minimum clinically significant improvement as: • ≥ 50% reduction in baseline disease severity, e.g. a PASI50 response, or percentage BSA where PASI is not applicable, and Clinically relevant improvement in physical, psychological or social functioning (e.g. ≥ a 4-point improvement in DLQI score or resolution of low mood)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes: 1. In real-world practice, not all people with psoriasis who fulfil NICE criteria for biologic therapy respond to existing biologic therapies; secondary failure is also common (Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Br J Dermatol. 2017 May;176(5):1297-1307. doi: 10.1111/bjd.15027. Epub 2017 Mar 20. PubMed PMID:27589476; Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015 Nov;135(11):2632-2640. doi: 10.1038/jid.2015.208. Epub 2015 Jun 8. PubMed PMID:26053050; Differential Drug Survival of Second-Line Biologic Therapies in Patients with Psoriasis, J Invest Dermatol. 2018 Apr;138(4):775-784. doi: 10.1016/j.jid.2017.09.044. Epub 2017 Dec 6. **N.B.** Additional reference: Biologics may be less effective in the real world, cf. to trial data due to use of biologic therapies. Comparison of Drug Discontinuation, Effectiveness, and Safety Between Clinical Trial Eligible and Ineligible Patients in BADBIR JAMA Dermatol. 2018 May 1;154(5):581-588. doi: 10.1001/jamadermatol.2018.0183. 2. Use of biologic therapy in the UK is currently limited to those with severe disease as defined by a PASI 10.

	This excludes use of highly effective biologic therapy including certolizumab pegol (within the licensed indication – i.e. moderate or severe) where the disease is associated with a severe impact on their QoL, physical, social or psychological function. Specifically (i) people with 'moderate' disease and (ii) those with severe disease but of limited extent – i.e. high-need areas such as the face, hands, feet, flexural/genital sites. People in these two groups will not have a PASI score of 10 but nevertheless will suffer major impact from their disease. Options for these patients are profoundly limited if methotrexate is not effective or cannot be tolerated. Newer small molecule drugs (e.g. dimethyl fumarate and apremilast) are not approved by NICE for patients with a PASI <10 either.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	With NICE-approved biologic therapies and biosimilars; apremilast; dimethyl fumarate; standard systemic therapies (see NICE CG153).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes: ➔ BAD guideline for biologic therapy for psoriasis http://onlinelibrary.wiley.com/doi/10.1111/bjd.15665/full ➔ NICE CG153 www.nice.org.uk/guidance/cg153 Please note the following comments regarding the final scope below ➔ There should be mention of psoriatic arthritis as an important, common co-morbidity and that when present, of the standard systemic therapies used in psoriasis, only methotrexate is helpful for both joints and skin. As previously communicated for more recent biologic STAs for psoriasis, the final scope mentions that "most treatments reduce the severity of psoriasis flares rather than prevent episodes" – there is no evidence that any of the treatments are disease-modifying. This would better describe the point being made here (rather than "most treatments reduce the severity….") as many of the new biologic treatments do clear or nearly clear the disease and maintain it in this state.
• Is the pathway of care well defined? Does it	Yes – please see NICE CG153. Data from BADBIR national pharmacovigilance registry suggest that most people with psoriasis fulfil stipulated

vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	criteria, e.g. PASI mean (SD) = 16.4 (8.3) – please see Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. Br J Dermatol. 2015 Aug;173(2):510-8. doi: 10.1111/bjd.13908. Epub 2015 Jul 6. PubMed PMID:25989336. **N.B.** Clinical re-audit report based on CG153 standards www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-audits/psoriasis/psoriasis-2017 (July 2018)
• What impact would the technology have on the current pathway of care?	An additional TNF inhibitor available for use in people with severe psoriasis will be a helpful intervention in the psoriasis treatment pathway in the following scenarios: Use in in women of child bearing potential planning conception or who are pregnant: Certolizumab pegol is not thought to cross the placenta as it lacks the Fc domain. Psoriasis is common in young women of child bearing age and in those with severe disease our only option at present is ciclosporin; this cannot be used long-term. This patient group necessarily progresses on to biologic therapy, with the risks (largely unknown – see systematic review) and benefits (avoiding severe unstable psoriasis and possibly therefore adverse effects on fetal health although the benefits of controlling of skin inflammation in terms of fetal health is less well documented than in IBD, for example) weighed up on a case-by-case basis. Further, in women who are pregnant on biologic therapy we actively aim to discontinue drug after 16 weeks as mAb are actively transported to the developing fetus – this can result in disease relapse. Finally, all mothers exposed to biologics during pregnancy must ensure the baby's immunisation schedule is deferred for at least 6 months post-delivery. For all these reasons having access to a drug that does not cross over to the placenta presents a major advantage in this patient group. Patients developing anti-TNF failure due to ADA formation (common with adalimumab and infliximab): These ADA are drug-specific and therefore a second (i.e. different) anti-TNF may result in positive response. In addition, whilst it is difficult to compare risk (and impact) of certolizumab pegol, ADA with IgG anti-TNF mAb (because certolizumab has a different format (Fab) which impacts drug tolerance ADA assays in a different way). On the basis of pharmacokinetic data (drug levels), certolizumab ADA levels appear to be less of a problem compared to adalimumab (Sanquin, personal communication).

	Patients with a poor (primary) response to another TNF inhibitor: Despite the number of 'new' biologic therapies available for psoriasis, anti-TNFs remain the most effective class for people with both psoriasis and psoriatic arthritis (perhaps up to a third of the population of people with psoriasis). Failure to respond to one anti-TNF does not preclude a good response to another and thus the availability of certolizumab pegol will be useful especially for people with pa More agents within the same 'market' may provide motivation to drive down the price.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, biologic therapy is a well-established intervention in psoriasis.
• How does healthcare resource use differ between the technology and current care?	There would not be any expected differences in health resource use compared to existing NICE-approved biologic agents.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist clinics.
• What investment is needed to introduce the technology? (For example, for facilities,	No additional investment would be required.

equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	N/A
• Do you expect the technology to increase health-related quality of life more than current care?	Potentially yes, by providing an additional treatment option for this major, chronic debilitating disease, especially in women of child bearing potential who are planning conception and often do not want to 'risk' biologic therapy and therefore suffer with their disease (see above).
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	See above; particularly useful for women, and in those with psoriatic arthritis
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Biologic therapy has been available on the NHS for people with moderate-to-severe psoriasis who meet the eligibility criteria.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The published 2017 BAD guidelines recommended biologic therapy for the following people with psoriasis: Offer biologic therapy to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated (see NICE guidelines CG153) and the psoriasis has a large impact on physical, psychological or social functioning (e.g. Dermatology Life Quality Index [DLQI] or Children's DLQI > 10 or clinically relevant depressive or anxiety symptoms) and one or more of the following disease severity criteria apply: • the psoriasis is extensive [defined as body surface area (BSA) > 10% or Psoriasis Area and Severity Index (PASI) ≥ 10] • the psoriasis is severe at localized sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high-impact and difficult-to-treat sites such as

	the face, scalp, palms, soles, flexures and genitals). These criteria do extend to additional (small) subsets of people with psoriasis currently not covered by the NICE criteria for biologic therapy and were introduced due the limitations of the PASI disease severity tool (i.e. it is strongly dependent on body surface area affected, and for some people with localised disease at high-need sites the PASI will not reach 10) and the specific burden (and limited options) for people with disease in both compartments (skin and joint). Generally, therapy is stopped when: • the minimal response criteria are not met, either initially or further down the line (i.e. secondary failure) • adverse effects arise, e.g. development of neurological symptoms suggestive of demyelinating disease, or new/worsening pre-existing heart failure • the risks outweigh the benefits in a) pregnant females or females planning conception and b) people undergoing elective surgery • live vaccines need to be administered No additional testing from what is already recommended for biologics.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year	Yes: The calculation of the QALY does not encompass time off work or other limitations that psoriasis imposes (e.g. social isolation, avoidance of relationships, stigma, depression, anxiety). Furthermore, the DLQI is often mapped to EQ5D but whilst important, the DLQI doesn't capture anxiety and depression (which are common in psoriasis); we also know that the mapping algorithms are not necessarily accurate (Generating EQ-5D-3L Utility Scores from the Dermatology Life Quality Index: A Mapping Studying Patients with Psoriasis, Value in Health, article in press DOI:

(QALY) calculation?	https://doi.org/10.1016/j.jval.2017.10.024).
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Lack of placental transfer of certolizumab pegol during pregnancy, Ann Rheum Dis. 2018, 77, 228-33. See notes above
• Is the technology a 'step-change' in the management of the condition?	Yes, it is a PEGylated anti-TNF and the only biologic that does not cross the placenta
• Does the use of the technology address any particular unmet need of the patient population?	Yes, women of child-bearing potential who are planning conception or are pregnant
17. How do any side effects or adverse effects of the technology affect the management of the condition	Certolizumab pegol seems to have a comparable safety profile with other biologic therapies, although there is currently little data about its safety in a real-world population.

and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	**The following outcomes were reported in the trials:** PASI90, PASI75, PASI50, PGA 0/1, DLQI, serious AEs. All these outcomes are important and relevant. Other outcomes that may not have been reported but are highly relevant include: • **Psoriasis improvement on the face, scalp, nails:** Plus, other high-need sites, i.e. hands and feet, flexural/genital psoriasis. • **Response rate:** Over what time period? It would be important to include longer treatment outcomes eg: 2-5 years. • **Relapse rate:** over what time period? It would be important to include longer treatment outcomes, • **Adverse effects of treatment:** infection; separate out adverse effects in the very short term, e.g. during loading doses.

	• **Health-related quality of life (including dermatology quality of life index [DLQI]):** Include other measures of impact, i.e. depression, anxiety; and impact on psoriatic arthritis.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	See notes above.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There is very limited information about use of the technology outside clinical trials. It would be extremely important for all people with psoriasis who meet the eligibility criteria to be enrolled in BADBIR when prescribed this agent to ensure capture of high quality pharmacovigilance data and to allow relevant comparisons with other biologic agents (N.B. > 16,000 patients now registered – please see www.badbir.org.uk; advanced negotiations are currently taking place for UCB to enter BADBIR)
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology	No; however, ciclosporin cannot be used for > 1 year and is therefore not a relevant comparator for this STA.

appraisal guidance [TAXXX]?	
21. How do data on real-world experience compare with the trial data?	Not yet available for this technology.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The PASI may underestimate disease severity in people with darker skin (type IV-VI) as redness may be less evidence (a key component of the PASI). DLQI will underestimate the impact in people who are not sexually active, or older (retired) or socially isolated; it does not capture anxiety and depression.
22b. Consider whether these issues are different from issues with current care and why.	These are generic issues.
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Important alternative technology
- The lack of placental transfer, important in pregnant patients with severe psoriasis in whom ciclosporin has not been efficacious
- Existing therapies, while effective for many, do not work for *all* those requiring treatment
- NICE criteria for biologic therapy – if applied here – limit access for people who would benefit (not just applicable to this technology)

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Certolizumab for treating moderate to severe plaque psoriasis [ID1232]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**University of Oxford**

3. Job title or position	**Senior Clinical Research Fellow and Honorary Consultant Rheumatologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**British Society for Rheumatology**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	The aim of treatment in psoriasis is to control skin inflammation to improve symptoms such as pain and itch as well as improving quality of life for patients. Around 20% of patients with psoriasis also have psoriatic arthritis, an inflammatory arthritis so many patients are co-managed by dermatology and rheumatology.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The British Association of Dermatologists and most published studies advise that a clinically significant response is a PASI75 which is a 75% decrease in the psoriasis area and severity index (PASI). This represents a significant decrease in the area, erythema, induration and scaling of psoriasis all over the body.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – although many more therapies have become available over the last decade, a significant proportion of patients do not respond to the therapies available at present and newer therapies are required. Certolizumab is another TNF blocking therapy but is slightly different in its structure from the other TNF inhibitors and may help where other drugs have failed. It is also thought to not cross the placenta so may have an additional role in pregnancy, for which it is licensed.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Psoriasis is currently treated using topical therapies (for very mild disease only), light therapy, standard oral therapies (such as methotrexate or cyclosporin) and biological therapies (TNF inhibitors, IL12/23 inhibitor and IL17A inhibitors).
• Are any clinical guidelines used in the treatment of the	Dermatologists predominantly follow the British Association of Dermatology guidelines. This supports the use of either ustekinumab, adalimumab or secukinumab as first line biologics once standard therapies have been failed. Physicians obviously have to abide by the NICE TAs for the use of biologics in England. NICE

condition, and if so, which?	and the BAD guidelines recommend switching to alternative biologics if these are not effective and brodalumab could be used.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is quite well defined. Those with moderate to severe psoriasis would be required to fail two standard therapies (either phototherapy or oral disease modifying agents such as methotrexate/cyclosporin) prior to access to biologics. They are also required to have certain severity markers such as PASI score and DLQI scores.
• What impact would the technology have on the current pathway of care?	This technology would offer a slightly different molecule targeting the important cytokine TNFalpha pathway. The access to biologics would likely remain the same but this would be another option for therapy alongside previously approved biologics. It is also thought to not cross the placenta so may have an additional role in pregnancy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Resource use would be similar. Certolizumab is given as a subcutaneous injection as are most of the approved biologic therapies so patients usually have one training session on how to give the injection and then self-administer at home. Pre-therapy infection screening and ongoing safety monitoring with blood tests is the same as existing biologic therapies for psoriasis.
• In what clinical setting should the technology be	Secondary care dermatology, supervised by a consultant dermatologist

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nothing. This would fit into existing clinical care models.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – this drug provides a new option for patients that may not have responded to existing therapy. It is also thought to not cross the placenta so may have an additional role in pregnancy.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	No, the improvement in QoL is generally significant across all of the biologic therapies at a group or population level. However some individuals respond to one biologic when they do not respond to another. Certolizumab offers a slightly different TNF inhibiting molecule and may therefore allow an increase in HR-QoL for individuals who would not have responded to some other therapies. It may allow continuation of use in pregnancy which can currently be a difficult decision.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, other than pregnant women or women who might become pregnant in the course of treatment
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Same as existing biologics. Similar pre-treatment screening (for TB and hepatitis) and similar ongoing safety monitoring (regular routine blood tests and annual skin checks)

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I presume that access to certolizumab would be similar to other biologics requiring moderate to severe psoriasis to be eligible for treatment (based on PASI and DLQI, failed standard therapy) and then treatment would only be continued if a PASI response is achieved.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	No

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	Yes – it has a slightly different structure so could provide efficacy where other therapies have failed. It is also thought to not cross the placenta so may have an additional role in pregnancy.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Generally speaking certolizumab and the biologic therapies are well tolerated by patients. Risks and side effects are similar to existing therapies such as the other TNF inhibitors. The most commonly seen side effects are infections which are a known risk and usually treated easily with antibiotics. Certolizumab has been used for many years now in PsANo
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – similar entry criteria to those stipulated by NICE for similar biologic therapy TAs

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Quality of life and proportions of patients achieving clearance or high response to therapy.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator	No

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	
21. How do data on real-world experience compare with the trial data?	Little available to date
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

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Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Anthony Bewley**
2. Name of organisation	**Barts Health NHS Trust**

3. Job title or position	**Consultant Dermatologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ Yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of the treatment is to clear cutaneous psoriasis as much as possible, and for as long as possible.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	PASI 75 or PASI 50 & a 5 point drop in the DLQI
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is still an unmet need. Despite successful initial response to treatment, there is still an unmet need for treatments that maintain a high response over a longer period. In real world practice patients respond differently to different treatments, therefore it is important to have different options available. Individual patient needs may necessitate a personalized treatment approach and consequently tailoring the drug to meet these needs is required. A subset of patients treated with biologics fail to respond to treatment and some patients who initially respond will lose response over time. As a result, in clinical practice some patients might require dose escalation of biologics as a measure to improve efficacy.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	The vast majority of patients are managed in primary care with appropriate education, emollients and topical anti-inflammatory ointments / creams. Patients who do not respond will be referred to secondary or tertiary care for consideration of phototherapy, systemic therapy, small molecule therapy or biologics. therapy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. Primary Care Dermatology Society and British Association of Dermatologists.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	See above for current pathway. Choice is an important factor in treatment for psoriasis, and the availability of different treatment options is key in order to alleviate symptoms in a broad range of patients, especially when patients move onto biologics. It is up to clinicians and patients to determine which biologic may be best suited to a particular patient, based on their needs.
• What impact would the technology have on the current pathway of care?	Certolizumab is highly effective drug as shown by clinical trials in plaque psoriasis and has been appraised by NICE already in the UK for psoriatic arthritis. Clinical trials demonstrated maintenance of response to certolizumab. The clinical trials also demonstrated an increased efficacy for the higher dose of certolizumab pegol, allowing the possibility of dose escalation. Certolizumab pegol is a TNF inhibitor with a different structure than other biologics, that provides different clinical benefits. It is reported to be safer in pregnancy and breast feeding women patients.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – will be used the same as current biologics.
• How does healthcare resource use differ between the technology and current care?	unknown
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary and tertiary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There should be no need for additional training, and most departments are used to introducing newer biologics. I would recommend that Certolizumab is included in the BADBIR registry.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes

• Do you expect the technology to increase length of life more than current care?	unknown
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, as being a treatment option with additional benefits for this chronic life-long disease, and the medication is reported to be safer in pregnant and breast feeding female patients.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The population in which certolizumab is appraised is appropriate, i.e. moderate to severe plaque psoriasis.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Certolizumab will be used in dermatology practice similarly to current biologics and should not have additional impact on patients or healthcare professionals.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Certolizumab will be used in line with the 2017 BAD guidelines as an alternative to other biologic therapies for plaque psoriasis. No additional testing will be required.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	It is possible that there may be improvement in anxiety, depression, work related productivity, joint disease, nail disease that are not captured in the QALY

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, as mentioned above. Certolizumab is different from other TNF inhibitors. Certolizumab pegol lacks an Fc region, thus it does not bind FcRn and is consequently not expected to undergo FcRn mediated transfer across the placenta. There is also the possibility of dose escalation if necessary.
• Is the technology a 'step-change' in the management of the condition?	While TNF inhibitors are established standard of care in psoriasis, there is variation between drugs and patient responses. As mentioned previously certolizumab may provide better outcomes compared to other TNF inhibitors and additional choice for patients and physicians.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. Clinical trials have demonstrated a high maintenance of response to certolizumab in patients with plaque psoriasis. Also, a subset of patients treated with biologics fail to respond to treatment and some patients who initially respond will lose response over time. As a result, in clinical practice some patients might require dose escalation of biologics as a measure to improve efficacy. The clinical trials have also demonstrated an increased efficacy for the higher dose of certolizumab, thus supporting the possibility of dose escalation for these patients. In addition, active transport of Immunoglobulin G (IgG) across the placenta is mediated by the neonatal Fc receptor (FcRn). Certolizumab lacks an Fc region, thus it does not bind FcRn and is consequently not expected to undergo FcRn mediated transfer across the placenta. Physiologically, only minimal amounts of certolizumab are likely to cross into breast milk and be absorbed by the infant, due to its large molecule

	size. The certolizumab CRIB and CRADLE studies demonstrated minimal transfer of active drug from mother to infant across the placenta and into breastmilk
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Certolizumab has similar safety profiles to TNF inhibitors
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	Not applicable
• What, in your view, are the most important	Response rate PASI (initial clearance / sustained over time) and psoriasis symptoms (e.g. nails). Health-related quality of life (DLQI) also other measures as depression, anxiety.

outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not applicable
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Evidence with certolizumab in psoriatic arthritis (RAPID-PsA) (NICE TA445)
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No

22. How do data on real-world experience compare with the trial data?	Not yet available
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not applicable
23b. Consider whether these issues are different from issues with current care and why.	Not applicable
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Certolizumab is different to other TNF inhibitors and these differences may convey different benefits
- It is a highly effective drug in clinical trials in patients with moderate to severe plaque psoriasis
- It offers the possibility of a dose escalation.
- As certolizumab lacks Fc portion, it is not actively transported across the placenta from mother to foetus. It may therefore offer advantages in women of childbearing age
- Established safety profile, similar to the TNF inhibitor class

Thank you for your time.

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References

1. Mariette X, Förger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis 2017.
2. Clowse M, Förger F, Hwang C, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study Ann Rheum Dis 2017;76:1890–1896.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Hector Chinoy**
2. Name of organisation	**The University of Manchester / Salford Royal NHS Foundation Trust**

3. Job title or position	**Senior Lecturer / Honorary Consultant Rheumatologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of Certolizumab Pegol (CZP) is to treat and improve psoriasis.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response would be at least a 50% reduction in the size of psoriatic plaques by 3 months
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is an unmet need in psoriasis of having access to an alternative subcutaneous anti-TNF agent which has a potential for lower immunogenicity and ongoing high efficacy on both the skin and joints.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	The condition is treated with topical treatments, then oral immunosuppressants. If these fail to work, then there is the option of biologic therapy. There is usually only one anti-TNF drug used in psoriasis, adalimumab and then the option of other mechanisms, including IL17 or IL23 inhibition.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are regional guidelines used to treat psoriasis in the North West. http://gmmmg.nhs.uk/docs/guidance/HCD-pathway-for-psoriasis.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined regionally, but can vary between regions.
• What impact would the technology have on the current pathway of care?	It would introduce the option for an effective 2nd subcutaneous anti-TNF drug, especially in circumstances where the patient may have developed resistance to the first drug (formation of neutralising antibodies).
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	CZP has high efficacy and maintenance of response in both psoriasis and psoriatic arthritis. CZP is already prescribed in UK clinical practice for PsA, demonstrating high efficacy on both skin and joints.

• How does healthcare resource use differ between the technology and current care?	CZP is unique in having a pegylated structure, and is therefore different to other TNFs Data to show a similar effect on efficacy between previous biologic exposed patients and biologic naïve patients The value of having the option of dosing up to 400mg for those with insufficient response Safe during pregnancy
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	CZP should be used in secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Education for prescribers about CZP if they are not already familiar with the drug
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Please refer to "How does healthcare resource use differ between the technology and current care?" above.
• Do you expect the technology to increase	No

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. With continuity of TNF-inhibition and the option to dose increase at no further cost.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with both psoriatic arthritis and psoriasis, as well as patients who are already biologic non-responders. Also, patients already prescribed CZP 200mg fortnighty for psoriatic arthritis who have ongoing active psoriasis would benefit from increasing to the 400mg dose. Pregnant patients – evidence of safety during pregnancy
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	No additional clincal requirements will be necessary

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	None other than already exist
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in	Yes. Please refer to “How does healthcare resource use differ between the technology and current care?” above.

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Opportunity to dose adjust. Unique molecular structure. Added option of TNF inhibition in psoriasis. Efficacious in both skin and joint disease. Works in both biologic naïve and non-responder populations. Safe during pregnancy.
• Does the use of the technology address any particular unmet need of the patient population?	As previous answer
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Skin scores by PASI
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	N/A
22. How do data on real-world experience compare with the trial data?	N/A
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in	

the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- CZP unique molecule which is different to other available anti-TNF drugs
- CZP has high efficacy and maintenance of response
- CZP is already in UK clinical practice for PsA demonstrating high efficacy for both skin and joints
- A similar effect on both biologic-naïve and exposed patients
- The value of having the option of dosing up to 400mg for those with insufficient response

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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Evidence Review Group's Report
Certolizumab pegol for treating moderate to severe plaque psoriasis

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Declared competing interests of the authors

None.

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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

Sahar Sharif and Ros Wade wrote the clinical effectiveness sections of the report. Matthew Walton, Lindsay Claxton and Robert Hodgson wrote the cost-effectiveness sections and conducted the economic analyses. Melissa Harden wrote the sections on the search strategies. Alison Eastwood provided advice, commented on drafts of the report and took overall responsibility for the clinical and cost-effectiveness sections.

Note on the text

All commercial-in-confidence (CIC) data and all academic-in-confidence (AIC) data have been redacted.

Copyright statement

Table of Contents

Table of Contents

Table of Tables

Table of Figures

List of abbreviations

ADA	Adalimumab
APR	Apremilast
BAD	British Association of Dermatologists
BID	Twice daily
BIW	Twice a week
BROD	Brodalumab
BSA	Body surface area
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CG	Clinical Guideline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CS	Company's submission
CSR	Clinical study report
CZP	Certolizumab pegol
DIC	Deviance Information Criterion
DLQI	Dermatology Life Quality Index
DMARDs	Disease-modifying anti-rheumatic drugs
DMF	Dimethyl fumarate
EAS	Efficacy analysis set
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol-5D questionnaire
ERG	Evidence Review Group
ETN	Etanercept
FAS	Full analysis set
Fc	Fragment-crystallizable
FcRn	Fc receptor
FDA	Food and Drug Administration
GUS	Guselkumab
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related quality of life
HTA	Health Technology Assessment

ICER	Incremental cost-effectiveness ratio
INB	Incremental net benefit
IgG	Immunoglobulin G
IL	Interleukin
IFX	Infliximab
IXE	Ixekizumab
mg	milligram
MTX	Methotrexate
NAPSI	Nail Psoriasis Severity Index
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
NRI	Non-responder imputation
NT	Not tested
PAS	Patient access scheme
PASI	Psoriasis Area and Severity Index
PASI 50	50% or greater improvement in PASI score
PASI 75	75% or greater improvement in PASI score
PASI 90	90% or greater improvement in PASI score
PASI 100	100% improvement in PASI score (total skin clearance)
PEG	Polyethylene glycol
PGA	Physician's global assessment
PML	Progressive multifocal leukoencephalopathy
PSA	Probabilistic sensitivity analysis
PSI	Psoriasis Symptom Inventory
PSSI	Psoriasis Scalp Severity Index
PSS	Personal social services
PUVA	Psoralen and long-wave ultraviolet radiation
QALY	Quality-adjusted life year
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
RCT	Randomised controlled trial

SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SIB	Suicidal ideation and behaviour
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SPC	Summary of product characteristics
STA	Single Technology Appraisal
TA	Technology Appraisal
TNF	Tumour necrosis factor
UST	Ustekinumab

1 Summary

1.1 Critique of the decision problem in the company's submission

Certolizumab pegol (Cimzia®, CZP) is a fragment-crystallizable-(Fc)-free, PEGylated, anti-tumour necrosis factor (TNF). The CS states that as CZP lacks an Fc region, it does not bind FcRn, and is thus not expected to undergo Fc receptor mediated transfer across the placenta. It received European marketing authorisation for use in the treatment of moderate to severe plaque psoriasis on 8th June 2018.[1] The recommended posology is 200mg subcutaneous injection, comprising a loading dose of 400mg at weeks 0, 2 and 4 followed by a maintenance dose of 200mg every 2 weeks. A maintenance dose of 400mg every 2 weeks can be considered in patients with insufficient response. Doses of 200mg and 400mg are licensed for certolizumab pegol.[2]

The population specified in the NICE scope and in the license is adults with moderate to severe plaque psoriasis who are candidates for systemic therapy. The population addressed in the company submission (CS) further specifies the following subgroups: patients who are candidates for non-biologic systemic therapy, patients for whom standard systemic non-biological treatment or phototherapy is inadequately effective, not tolerated or contraindicated and biologic-exposed patients. Other biological therapies appraised by NICE for moderate to severe plaque psoriasis have been licensed for use in patients who are candidates for systemic therapy, but have been positioned for use only in patients for whom non-biologic systemic therapy is inadequately effective, not tolerated or contraindicated.[3-6] Therefore, the ERG considers that patients for whom standard systemic treatment or phototherapy is inadequately ineffective, not tolerated or contraindicated to be the most relevant population for this indication. Furthermore, clinical advice to the evidence review group (ERG) confirmed that generally biologic therapies are used after non-biological systemic therapy in the treatment pathway.

No definition of moderate to severe psoriasis is specified in the NICE scope but the NICE pathway recommends biologics for patients with PASI≥10 and DLQI≥10. Inclusion criteria for the trials was PASI≥12, BSA ≥10% and PGA score ≥3, with no inclusion criteria relating to DLQI score. However, the mean baseline DLQI scores for the different treatment groups across the trials ranged from 12.8 to 15.3. Therefore, the population in the trials is likely to be similar to the majority of patients eligible for biologic treatment in practice. However, all three trials excluded patients who had a history of primary failure to any biologic (primary failure defined as no response within the first 12 weeks of treatment with the biologic) or had received previous treatment with >2 biologics. Therefore, the trial populations may exclude a proportion of the eligible population who are harder to treat and therefore, less likely to achieve a response.

The comparators included in the CS are restricted to systemic non-biologic therapies, anti-TNF therapies (adalimumab, etanercept), interleukin (IL) -17 inhibitors (brodalumab, ixekizumab, secukinumab), IL-23 inhibitor (guselkumab), IL-12/IL-23 inhibitor (ustekinumab) and best supportive care. The NICE scope also included phototherapy, dimethyl fumarate (DMF), apremilast and infliximab as comparators. However, phototherapy is no longer used routinely in people with psoriasis due to the higher risk of skin cancer.[7] DMF and apremilast are only considered for use in patients unsuitable or unwilling to receive biologic treatment and infliximab is only recommended for patients with very severe psoriasis. Therefore, the ERG agrees that the restricted list of comparators is acceptable. Biosimilar versions of the other anti-TNF biologics etanercept and infliximab are currently available in the UK and biosimilar versions of adalimumab will be available within the next few months.[8]

The outcomes assessed in the submission match those specified in the NICE scope. Although specific results relating to psoriasis symptoms on the face and scalp and treatment effect on mortality are not presented, which the company state is due to data limitations. The co-primary endpoints in CIMPASI-1 and CIMPASI-2 were psoriasis area and severity index (PASI) 75 and physician's global assessment (PGA) clear or almost clear; the primary endpoint in CIMPACT was PASI 75.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted a systematic literature review (SLR) to identify evidence on the clinical effectiveness and safety of certolizumab and relevant comparators for the treatment of adult patients with moderate to severe plaque psoriasis.

Three multicentre randomised controlled trials (RCTs) are described in the submission: CIMPASI-1 (NCT02326298), CIMPASI-2 (NCT02326272)[9] and CIMPACT (NCT02346240).[10] All three studies included two different doses of certolizumab: 200 mg and 400 mg every 2 weeks (Q2W). The CIMPASI-1 and CIMPASI-2 trials were identical in design. All three trials appear to have been well conducted. The primary efficacy outcomes in CIMPASI-1 and CIMPASI-2 were the proportion of patients achieving a PASI 75 response and the proportion of patients achieving a PGA response at week 16. The primary efficacy outcome for CIMPACT was the proportion of patients achieving a PASI 75 response at week 12.

The CIMPASI-1, CIMPASI-2 and CIMPACT trials consist of an initial treatment period which lasts 16 weeks, followed by a maintenance period until week 48 after which there is an open-label

treatment phase, which is ongoing. In CIMPASI-1 and CIMPASI-2, patients were randomised in a 2:2:1 ratio to receive CZP 200 mg Q2W, CZP 400 mg Q2W or placebo. In CIMPACT, patients were randomised in a 3:3:3:1 ratio to receive CZP 200 mg Q2W, CZP 400 mg Q2W, ETN 50 mg twice a week (BIW) or placebo.

The certolizumab trials demonstrated that certolizumab (200 mg Q2W and 400 mg Q2W) significantly reduced the severity of psoriasis and its impact on health-related quality of life, compared with placebo. A statistically significant difference was found between certolizumab (200 mg and 400 mg) and placebo for all of the outcomes reported at 16 weeks, including PASI 75 response (66.5-82.6% versus 3.8-11.6%), PASI 90 response (35.8-55.4% versus 0.3-4.5%), PGA score of 0 or 1 (47-71.6% versus 2-4.2%) and mean change in psoriasis percentage BSA affected (-16.3 to -20.5 versus -0.1 to -4.2). In the pooled results for all three trials, statistically significant improvements were observed for mean change from baseline in DLQI score at 16 weeks in both the CZP 200 mg group (-9.1) and the CZP 400 mg group (-10.4) compared to the placebo group (-2.4). In comparison with etanercept (CIMPACT trial), only patients treated with CZP 400 mg had a statistically significantly higher PASI 75 response (66.7%) compared to patients treated with etanercept (53.3%) at week 12. The PGA responder rate at week 12 was comparable for etanercept (39.2%) versus CZP 200 mg (39.8%), with CZP 400 mg (50.3%) showing a higher PGA response rate.

From week 16 of the three trials, patients with an inadequate response to certolizumab, placebo or etanercept escaped from blinded treatment to receive CZP 400 mg. Of those patients randomised to CZP 200 mg for the maintenance phase, 9.5-30.8% received escape therapy. Of those patients randomised to CZP 400 mg, 9.4-22.5% received escape therapy. Whereas, out of the patients randomised to placebo in the maintenance phase, 75.5-96.3% received escape therapy.

In CIMPASI-1 and CIMPASI-2, psoriasis severity at week 48 was assessed using pooled results. The PASI 75 response rate was slightly higher at week 48 (83.6%) than at week 16 (82.0%) in the CZP 400 mg group. However, the PASI 75 response rate decreased at week 48 (70.7%) compared to week 16 (76.7%) in the CZP 200 mg group. At week 48, the PGA clear/almost clear responder rate was maintained in the CZP 200 mg group (61.0%) and the CZP 400 mg group (68.9%). In both studies, decreases from baseline in psoriasis percentage BSA affected were greater at week 48 compared with week 16. The mean change in baseline DLQI was maintained through to week 48 in both CZP treatment groups. In CIMPACT, PASI response was maintained through to week 48. The patients who were randomised to CZP 400 mg throughout the whole study had the highest PASI 75 (98.0%) and PASI 90 (87.8%) response rates compared to all other patients at week 48. The mean change in baseline BSA affected at week 48 was very similar across the CZP treatment groups, ranging from

[redacted] to [redacted]. Mean decreases from baseline in DLQI score for patients receiving certolizumab at week 48 were similar across treatment groups, ranging from [redacted] to -14.2. Whereas, patients who were initially treated with certolizumab and then re-randomised to placebo had smaller changes in DLQI score (range: -2.6 to [redacted]).

In the subgroup of systemic non-biologic inadequate responder patients, the PASI response rates, PGA responses and DLQI change from baseline score for all three certolizumab trials pooled were similar to the pooled results for the ITT population at week 16. Subgroup results for the biologic exposed group were also generally similar to the ITT pooled population at week 16. However, PASI 75, PASI 90 and PGA response rates were considerably lower at week 48 than at week 16 in the subgroup of biologic-exposed patients, compared with the biologic naïve patients, suggesting that certolizumab is poor at improving or maintaining response over time in biologic exposed patients. However, these results should be interpreted with caution, in view of the small numbers of patients in the subgroups.

Across the three certolizumab trials withdrawal rates in patients treated with certolizumab were low, with 93% in CIMPASI-1, 86% in CIMPASI-2 and 90% in CIMPACT completing the study to 48. The ERG notes this is comparable with the drug survival rates published for other biologics.

During the 16-week initial treatment phase, the proportion of patients with an adverse event was higher in the CZP 400 mg group than the CZP 200 mg group. However, the rates are similar between the CZP 400 mg group and the placebo group (63.5% vs 61.8%). This suggests that the safety profiles of both doses of certolizumab are acceptable. The rate of adverse events increased from week 16 to week 144, suggesting that the risk of adverse events with certolizumab increases with longer exposure. In all three trials, the most common adverse events in the initial 16-week phase were infections and infestations (33.5%). In the initial 16-week phase, the rate of serious adverse events across all three trials was [redacted] This increased to [redacted]% in the maintenance and open-label phase at 144 weeks. The proportion of patients with any, serious or severe adverse events was slightly higher in the CZP 400 mg group than the CZP 200 mg group in all patients exposed to certolizumab, up to week 144. The number of deaths due to adverse events was low in the maintenance phase, 0.3% in each treatment group.

The CS mentions one phase II study [11] that compares certolizumab with placebo, which was identified by the SLR. It is described as a 'supportive study, not presented in the submission', but is included in the network meta-analysis.

Network meta-analysis

A NMA was undertaken in order to compare certolizumab with the other therapies available at the same point in the treatment pathway. The base-case NMA included data from 65 RCTs, which included licensed doses of the therapies specified in the scope.

[redacted]

Similar results were seen for PASI 90 response rates.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The evidence for the clinical effectiveness of certolizumab is based on three relatively good quality RCTs. The systematic review also identified one relevant phase II study [11], which was not included in the submission. The study had a smaller sample size (n=176) than the larger phase III RCTs and patients were initially treated for only 12 weeks rather than 16 weeks, as in the longer phase III RCTs, which would make comparisons difficult. Therefore, the ERG considers that focusing on the larger phase III RCTs was acceptable. In CIMPASI-1 and CIMPASI-2, certolizumab and placebo were administered by unblinded personnel and in CIMPACT, patients receiving etanercept were unblinded, increasing the risk of bias. However, the ERG consider that the results are likely to be reliable.

Overall, the baseline characteristics of the intention to treat (ITT) population do not show any concerning imbalances across the treatment groups. However, the ERG notes that the percentage of males is lower in the CIMPASI-2 trial (55.9%), compared to the CIMPASI-1 (69.2%) and CIMPACT trials (68.2%). Clinical advice to the ERG is that males tend to have a poorer treatment response than females. The CIMPASI-2 trial also had a higher proportion of patients with psoriatic arthritis (25.1%) than the CIMPASI-1 trial (12.4%) and the CIMPACT trial (16.1%). The ERG notes that the proportion of patients achieving PASI 75, PASI 90 and PASI 100 in both the CZP 200 mg and CZP 400 mg groups was greater in CIMPASI-2 than CIMPASI-1 and CIMPACT. The baseline imbalances between the trials may explain the higher response rate in CIMPASI-2, however it is unclear what is driving the difference between the study results. Therefore, the ERG is uncertain whether it is appropriate to pool results of all three trials, considering the heterogeneity between the trial results.

In the three certolizumab trials, the proportion of patients who had not received any previous systemic therapy (including non-biologic) ranged from [redacted]% to [redacted]%. The ERG considers that the population most relevant to this submission is patients who have previously received systemic non-biologic therapy, as they resemble the patients most likely to be treated with certolizumab in clinical practice. Subgroup analysis results are presented for non-biologic naïve patients, non-biologic inadequate responders and biologic exposed patients, which are assessed from the pooled study results. The health economic model uses data from the non-biologic inadequate responder subgroup and the non-biologic naïve subgroup. However, these results may not be reliable due to the small numbers of patients and the potentially inappropriate pooling of CIMPASI-2 with CIMPASI-1 and CIMPACT.

Network meta-analysis

The NMA appears to have included all relevant trials of certolizumab and the comparator therapies. Studies were assessed for quality using appropriate criteria and the results of the quality assessment suggest that generally, the risk of bias for most studies was low. Several trials (7/65) were not double-blinded or had open-label phases which increased the risk of performance bias. Adequate details of the included studies are presented in the submission.

The CS assessed heterogeneity for the 65 studies included in the NMA. Inevitably the trials included in the NMA vary by design and patient characteristics. There were some notable differences in patient characteristics across trials. There was a substantial difference in the proportion of patients with psoriatic arthritis between the studies included (0% to 37%). There was also considerable variation in the time since diagnosis, ranging from 11 years to 24 years and mean baseline PASI score ranged from 15 to 33. The time-point at which the primary outcome was collected varied amongst the trials. The initial treatment period in the majority of trials (54%) was 12 weeks. However, the main endpoint (PASI 75 response) in CIMPASI-1, CIMPASI-2 and CIMPACT was collected at week 16. In addition, when comparing the certolizumab trials with other trials in the NMA, CIMPASI-1 and CIMPASI-2 had a higher proportion of biologic naïve patients, where reported. CIMPASI-2 also had a lower proportion of male patients than many of the other studies included in the NMA. All of these differences increase the risk of between study heterogeneity, which reduces the reliability of the NMA results.

Between-study standard deviation and total residual deviance were reviewed for subgroups and sensitivity models to determine whether inclusion of an effect modifier reduced heterogeneity or improved model fit. However, these were not detailed in the CS. Therefore, the ERG is uncertain whether the sensitivity adjustments made are appropriate.

The NMA results presented were PASI response rates (PASI 50, PASI 75 and PASI 90), which are appropriate outcomes for patients with moderate to severe psoriasis. However, NMAs undertaken for the development of the British Association of Dermatologists' (BAD) guidelines for biologic therapy for psoriasis, published in April 2017, also assessed PGA clear/almost clear, mean change in DLQI score and tolerability.[12]

The main analysis was conducted using a placebo-adjusted multinomial ordered probit model, where PASI response was treated like a categorical variable. However, the model makes a stronger proportional odds assumption than a standard binomial analysis. The CS states that cross validation of the results from the binomial models with those predicted from the multinomial model indicated that the treatment effects of each therapy do not appear to be consistent for PASI 50, PASI 75 and PASI 90. Therefore, the results from the multinomial model may not be fully reliable. However, the ERG considers that the multinomial logit model is the most appropriate, given the multiple PASI outcomes addressed.

The ERG identified several problems with the WinBUGS code used for the NMA. The CS reports that the approach used for the multinomial NMA has been adapted from the NICE Decision Support Unit (DSU) technical support document example in psoriasis (Example 6).[13] However, there is little similarity between the code used by the company and the example code in the DSU document. The code provided does not appear to be able to produce the results reported in the CS. There is no information about which trials were used for the baseline response. It is also uncertain from the code provided whether only placebo-controlled studies were used to assess baseline risk. Furthermore, the WinBUGS code is not consistent with the methods that are reported on page 50-54 of the Appendix, as it does not include code for a random effects or fixed effects model, for which results are presented. Due to these issues, the ERG was unable to re-run the NMA.

The results of the NMA, in terms of ranking order of effectiveness, were consistent with those of NMAs undertaken in other recent STAs of treatments for moderate to severe plaque psoriasis in adults and the NMA undertaken for the development of the BAD guidelines.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's search did not identify any published cost-effectiveness study of certolizumab. As such, the ERG considers the *de novo* cost-effectiveness analysis reported in the company submission to be the most relevant source of evidence.

The cost-effectiveness of certolizumab was evaluated using a Markov state-transition model developed in Microsoft Excel, with health states based on PASI response assessed after an initial

treatment period. The use of a Markov model was justified based on the need to evaluate treatment sequences over an appropriate time horizon, considering separate treatment induction and maintenance phases for each treatment option.

The analysis considered the cost-effectiveness of certolizumab in two patient populations: *(i)* those who are candidates for systemic non-biologic therapies, and *(ii)* those who have an inadequate response, are contraindicated, or intolerant to systemic non-biologic therapies.

In the analysis of systemic non-biologic inadequate responders, the model included a total of nine treatment sequences which include three lines of active therapy, followed by best supportive care. Certolizumab was included in a first line position alongside other comparators recommended by NICE for psoriasis patients following failure on systemic non-biologic therapies. A scenario was also explored in which patients who did not achieve a PASI 75 response on the certolizumab 200mg dose were escalated to certolizumab 400mg Q2W.

In the analysis on candidates for systemic non-biologic therapies, certolizumab was positioned as a direct comparator against the standard of care, comprising methotrexate, ciclosporin, and acitretin, followed by three lines of biologic therapy.

Certolizumab and each biologic comparator treatment were assumed to be followed by a second- and a third-line biologic therapy. Second- and third-line biologic therapies were selected by the company based on clinical guidelines and advice, alongside consideration of the mechanism of action to the preceding line. Across the majority of sequences, ustekinumab and infliximab were included as the second and third-line treatments, respectively.

Each line of treatment in a sequence starts with an induction period lasting between 10 and 16 weeks. At the end of the induction period, individuals are assigned to one of four PASI response categories based on the NMA results. Individuals who achieve a response of PASI≥75 are assumed to continue with the same treatment and enter the maintenance phase of the model. Individuals who achieve PASI≤50 are assumed to discontinue their treatment and then switch to the next treatment in the sequence.

During the maintenance period, individuals were assumed to continue to receive the same treatment and maintain the same PASI response until the treatment is discontinued due to loss of response and/or adverse events. In line with previous economic studies identified by the company, it was assumed that individuals discontinue treatment at the same constant annual rate for all treatments.

Individuals who do not respond to the final line of active treatment (or who initially respond but then subsequently discontinue treatment) move to the BSC state with individuals assumed to be treated with non-biologic supportive therapies.

The measure of treatment effectiveness used in the model was the proportion of individuals achieving a specific threshold of PASI response relative to baseline. In the analysis of systemic non-biologic inadequate responders, the PASI responses during the induction period were based on the company's NMA, and on the observed response rates in the three certolizumab RCTs in the analysis of candidates for systemic therapy. In the company base-case analysis, it was assumed that prior biologic treatment did not modify treatment response and that the effectiveness of a drug was independent of its position in a sequence.

Outcomes of the model were expressed using quality-adjusted life years (QALYs). The utility values used in the model were derived from EuroQol-5D questionnaire (EQ-5D) -3L data (UK tariffs applied) collected in the CIMPASI-1, CIMPASI-2 and CIMPACT trials of certolizumab. The utility values in the model were based on the proportion of individuals in the different PASI response categories (<50, 50-75, 75-90, ≥90) and the change in utility from baseline associated with each PASI response category.

The resource use and costs included in the model comprised drug acquisition, administration, monitoring and BSC. Unit costs were sourced from relevant UK sources including NHS reference costs, British National Formulary (BNF) and Personal Social Services Research Unit (PSSRU), and resource use was based on published literature and clinical expert opinion.

In the analysis of candidates for biologic therapy, fully incremental cost-effectiveness ratios (ICERs) and pairwise ICERs for each comparator sequence compared with a baseline sequence (with the lowest total costs and QALYs) were reported. The CS reported results incorporating the patient access scheme (PAS) for certolizumab. Secukinumab, apremilast, brodalumab, ixekizumab, and guselkumab have an associated confidential PAS discount. In the fully incremental ICER comparison, there were three non-dominated sequences. Of the non-dominated sequences, the least effective and lowest cost was the sequence starting with etanercept. The deterministic ICER of the certolizumab sequence was reported to be £11,471 per QALY compared to the etanercept sequence. The ixekizumab sequence was the most effective and most costly of the non-dominated sequences. The ICER of the ixekizumab sequence versus the certolizumab sequence was £432,904 per QALY. In the pairwise comparisons versus etanercept, the ICER ranged from £11,471 (versus the certolizumab sequence) to £164,664 (versus the guselkumab sequence). None of the sequences were cost-effective versus best supportive care, with a pairwise ICER of £70,086 for certolizumab.

In the dose escalation analysis, dose-escalated certolizumab was compared with dose-escalated adalimumab. The ICER of dose-escalated certolizumab compared with dose-escalated adalimumab was estimated as £36,638 per QALY gained. In the analysis of candidates for systemic non-biologic therapy, the ICER of certolizumab as first-line therapy compared with a sequence starting with standard care followed by adalimumab was estimated as £3,650 per QALY gained.

The company also presented ICER results from their probabilistic analysis. The ICERs were similar to the deterministic estimates. In the analysis of systemic non-biologic inadequate responders, the company reported that, at a threshold of £20,000 per QALY gained, the certolizumab sequence had the highest probability of being cost-effective (89%), followed by the etanercept sequence (11%). At a £30,000 threshold, the certolizumab sequence was reported to have a 99% probability of being the most cost-effective.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG's critique identified seven main issues:

(i) The ERG identified a significant number of calculation errors in the executable model. These related to the calculation of the costs of administration and training, the number of applications of administration costs, treatment monitoring costs across all treatment phases, and the calculation of year 1 per cycle certolizumab costs. A further error in the calculation of incremental QALYs was also identified and corrected by the ERG.

(ii) Scenarios presented by the company considering the cost-effectiveness of a certolizumab dose escalation strategy did not consider an appropriate set of comparators, with the company comparing certolizumab to an adalimumab based dose escalation strategy. The ERG considers the most appropriate counterfactual to certolizumab with dose escalation to be certolizumab without dose escalation. Clinical advice to the ERG also suggests that while only adalimumab and etanercept are licensed for dose escalation, the 90mg ustekinumab dose is available at no extra charge and thus is generally the only drug for which dose escalation is used in practice, and typically only in those weighing >90kg.

(iii) In line with the NICE scope for certolizumab, the company presents scenarios in which certolizumab is positioned as an alternative to systemic non-biological therapies. The ERG do not consider the company to have presented sufficient evidence to support this positioning of certolizumab. This sequence is unprecedented in previous guidance issued by NICE and relies on accurate and representative treatment sequencing, which is very difficult to do in the context of the available clinical data and structure of the economic model.

(iv) The sequences evaluated by the company were restrictive in terms of the number of sequences evaluated and the position of certolizumab within these, which focused on

certolizumab as first-line biologic therapy. The ERG raised concerns about the clinical plausibility of this, given the entrenchment of similar efficacious alternatives including adalimumab, which will also potentially be significantly cheaper due to the imminent arrival of adalimumab biosimilars. The ERG is also concerned that the modelling of selective sequences could provide misleading estimates of cost-effectiveness, particularly if there are treatments included in a sequence which are not cost-effective themselves.

(v) Due to the cost-ineffectiveness of all comparators versus best supportive care in the company's base-case and the lifetime duration of the model, it is beneficial for patients to discontinue treatment with biologics as soon as possible, as the QALYs gained on BSC are cheaper than on biologics. This perversely inflates the apparent cost-effectiveness of drugs with a lower response rate, and means increasing the discontinuation rate of a drug increases its cost-effectiveness.

(vi) The ERG considered that the utility regression model used in the company base-case should have been run only for patients with a DLQI score >10 because this represents the population eligible for treatment with certolizumab. The ERG also questions the appropriateness of assuming differential utilities for patients treated with biologic and non-biologic therapies. While the ERG considers this potentially plausible the evidence used to support this assumption is based on a population who received no active therapy. This assumption is also inconsistent with previous appraisals.

(vii) The ERG noted that there is uncertainty regarding the appropriateness of assuming a constant annual discontinuation rate for all treatments.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The clinical effectiveness evidence is derived from three relatively good quality RCTs, one of which compared certolizumab with an active comparator, in addition to placebo. A NMA was undertaken in order to compare certolizumab with the other therapies available at the same point in the treatment pathway.

The ERG considered the company's economic model to meet the requirements of the NICE reference case and largely consistent with previous NICE appraisals in this indication. The ERG acknowledges the additional data provided by the company in response to the points for clarification.

1.6.2 Weaknesses and areas of uncertainty

One of the main areas of uncertainty is the positioning of certolizumab in the treatment pathway. The ERG considers that the population most relevant to this submission is patients who have previously

received systemic non-biologic therapy, as they resemble the patients most likely to be treated with certolizumab in clinical practice. However, the population addressed in the company submission also includes patients who are non-biologic naive.

Another area of uncertainty is the higher PASI 75, PASI 90 and PASI 100 response rates seen in CIMPASI-2 compared to the CIMPASI-1 and CIMPACT trials. The baseline imbalances between the trials may partially explain the higher response rate in CIMPASI-2, however it is unclear what is driving the difference between the study results. Therefore, the ERG is uncertain whether it is appropriate to pool results of all three trials, considering the heterogeneity between the trial results.

Regarding the cost-effectiveness evidence, the ERG considered that the lack of appropriate clinical evidence on the sequential use of biological therapies, limitations of the model structure, the appropriateness of BSC as a post-biologics treatment and its influence on the behaviour of the model, and a restrictive number (and length) of sequences compared in the model to be the most important uncertainties. The ERG proposed an alternative approach to inform the cost-effectiveness of alternative sequences using a net-benefit framework and associated net-monetary benefits (NMB) rankings of each individual treatment compared to certolizumab to inform the cost-effectiveness of certolizumab relative to other active comparators.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

In the ERG's exploratory scenarios, the ERG took an alternative modelling approach to the company whereby each comparator is the only biologic in its sequence, and is compared to every other biologic, allowing a direct comparison of the costs and benefits associated with each option. Incremental net monetary benefit (NMB = λ x $\Delta E - \Delta C$) is presented for each comparator versus certolizumab at a £20,000 and £30,000 per QALY threshold. This provides a basis for establishing whether certolizumab is a cost-effective treatment option versus other currently available biologics, and allows the ranking of cost-effectiveness without estimating fully incremental ICERs.

While the ERG believes the inputs and assumptions employed in its alternative base-case are more plausible than those used in the company's base-case, structural limitations in the model meant not all issues could be fully addressed.

The ERG's exploratory analyses addressed the following key uncertainties:

1. Sequencing and head-to-head comparisons
2. Assumptions regarding cost and HRQoL from TA511
3. Time horizons
4. Alternative HRQoL data sources

5. Biosimilar costs and uptake
6. Certolizumab trial data sources
7. Dose escalation scenario
8. Alternative positioning of biologics in the treatment pathway

Across the ERG's scenario analyses and alternative base cases, certolizumab was consistently ranked in the top three biologics by net-monetary benefit at a £20,000 and £30,000 cost-effectiveness threshold. Certolizumab had the highest NMB of all biologics in 10 of the 16 scenarios explored at a cost-effectiveness threshold of £30,000. In those scenarios which applied a discount to the current list price of adalimumab in anticipation of the launch of biosimilars, adalimumab was ranked first in terms of NMB.

An alternative ERG base-case was proposed which combined changes from three separate scenarios, comprising a head-to-head comparison of single biologics within a net monetary benefit framework, HRQoL values were derived from a more relevant sub-population of the certolizumab trials, and biosimilar costs were applied for etanercept and infliximab. The ERG considered these to provide more appropriate or plausible assumptions than the company base-case. The ERG also generated several scenarios on the alternative base-case, firstly including different levels of price reduction for adalimumab, and secondly applying assumptions in line with those adopted in TA511.

In the ERG's alternative base-case analysis, certolizumab ranks second behind etanercept at a cost-effectiveness threshold of £20,000 and £30,000. However, with the introduction of a 20% discount on the current list price of adalimumab (which may be conservative), certolizumab drops to third behind both adalimumab and etanercept in net-monetary benefit.

However, the ERG consider the results to sufficiently demonstrate that certolizumab is a cost-effective treatment option amongst currently used biologics at this point in the treatment pathway. Using the ERG's preferred assumptions for the two other treatment strategies proposed by the company, i.e. dose escalation and treating candidates for non-biologic systemic therapies, certolizumab was not found to be a cost-effective treatment option.

These results exclude the confidential PAS schemes for several comparators (brodalumab, guselkumab, ixekizumab, secukinumab). The impact of including these confidential PAS schemes is presented in a separate confidential appendix.

2 Background

2.1 Critique of company's description of underlying health problem

The CS includes an appropriate and relevant summary of the underlying health problem.

Psoriasis is a chronic inflammatory skin condition. The CS states that psoriasis is reported to affect around 1.75% of the population of England and Wales,[14] equating to approximately 1.02 million people.[15] Chronic plaque psoriasis is the most common form of psoriasis, accounting for 90% of all cases.[14, 16] Around 20% of patients have moderate to severe disease (approximately 184,000 patients in England and Wales).[17] Symptoms can include pain, itching and bleeding arising from the presence of skin lesions.[16] These symptoms can have an impact on a patient's daily activities, sleep and physical functioning.[18] Patients may experience an additional burden of disease as a result of nail and joint disease, as well as a broad spectrum of comorbidities.[16] Patients face a higher risk of developing mental health problems such as anxiety, depression and suicidal ideation,[16] and appear to be more likely to face difficulty in gaining employment.[19]

2.2 Critique of company's overview of current service provision

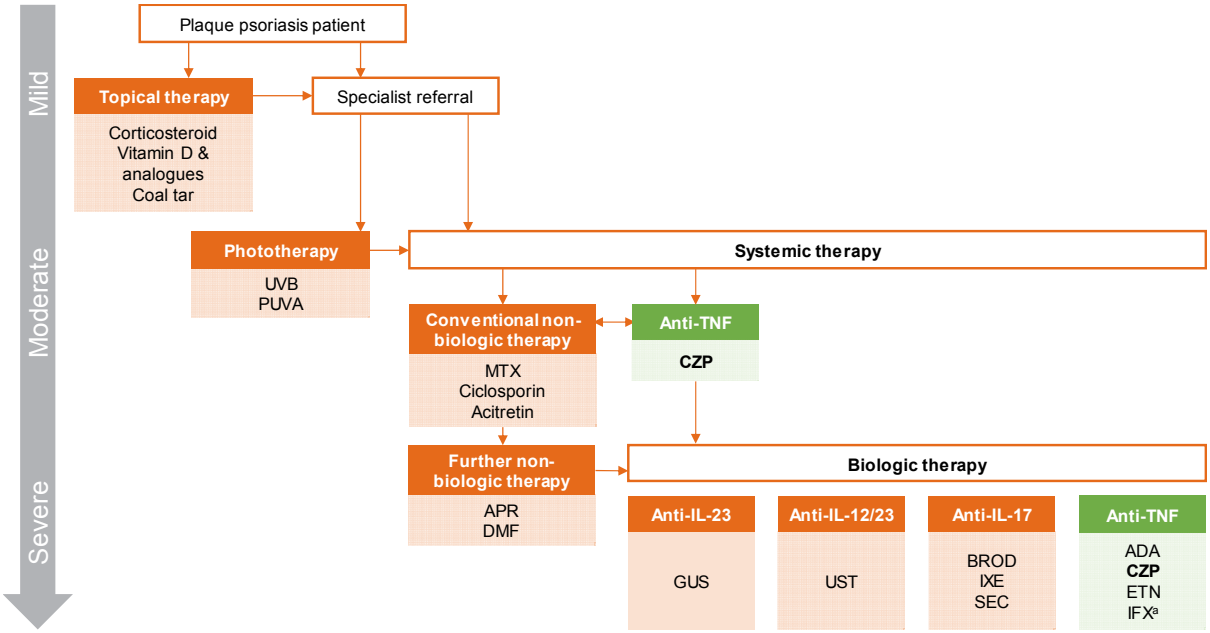
Overall, the CS provides an appropriate and relevant summary of the current service provision for patients with moderate to severe plaque psoriasis.

Current NICE clinical guidelines (CG153) recommend topical therapy as first-line treatment for moderate to severe plaque psoriasis; systemic non-biologic therapies, such as ciclosporin, methotrexate and acitretin, or phototherapy constitute second-line treatment.[14] For adults with severe disease (PASI score ≥10 and DLQI score >10) who have not responded to, or have an intolerance or contraindication to standard systemic therapies, NICE recommends systemic biologic therapies, apremilast or dimethyl fumarate;[14] guidance on their use is based on recommendations from the NICE technology appraisal process. Patients have the option to switch biologic treatment if they do not respond adequately to a first biological drug (primary failure), or they initially respond adequately but subsequently lose this response (secondary failure), or the first biological drug cannot be tolerated or becomes contraindicated.[14]

There are several existing biologic therapies available for adults with severe psoriasis: adalimumab, etanercept, infliximab (for patients with very severe disease), ixekizumab, secukinumab, ustekinumab, brodalumab and guselkumab. Biosimilar versions of the other anti-tumour necrosis factor (TNF) biologics etanercept and infliximab are currently available in the UK and biosimilar versions of adalimumab will be available within the next few months.[8] The CS states that in clinical practice apremilast and dimethyl fumarate would only be considered for use in patients unsuitable for biologic treatment or unwilling to receive biologic treatment.

As shown in Figure 1, the CS positions certolizumab pegol (Cimzia®, hereafter referred to as certolizumab) alongside conventional non-biologic systemic therapies, as well as alongside other biologic systemic therapies, in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy. This is in line with its marketing authorisation (received 8 June 2018).[1] However, other biologic therapies appraised by NICE have been licensed for use earlier in the pathway, but have been positioned for use only in patients for whom non-biologic systemic therapy is inadequately effective, not tolerated or contraindicated.

Figure 1: Treatment pathway for patients with plaque psoriasis (from CS, Figure 1, page 31)



Abbreviations: ADA: adalimumab; APR: apremilast; BROD: brodalumab; CZP: certolizumab pegol; DLQI: Dermatology Life Quality Index; DMF: dimethyl fumarate; ETN: etanercept; GUS: guselkumab; IFX: infliximab; IL: interleukin; IXE: ixekizumab; MTX: methotrexate; PASI: Psoriasis Area and Severity Index; PDE4: phosphodiesterase 4; PUVA: psoralen and ultraviolet A; SEC: secukinumab; TNF: tumour necrosis factor alpha; UST: ustekinumab. CZP: Proposed positioning within current NICE pathway.

The CS states that certolizumab is the only fragment-crystallizable-(Fc)-free, polyethylene glycol (PEG)ylated anti-TNF. Active transport of Immunoglobulin G (IgG) across the placenta is mediated by the neonatal Fc receptor (FcRn), therefore, as certolizumab lacks an Fc region, it does not bind FcRn and is consequently not expected to undergo FcRn mediated transfer across the placenta. A recent analysis of prospective data on maternal certolizumab exposure and pregnancy outcomes (from the UCB Pharma safety database up to 6 March 2017; outcomes were known for 528/1137 prospectively reported pregnancies with maternal exposure to certolizumab) concluded that analysis of pregnancy outcomes does not indicate a teratogenic effect of certolizumab, compared to the general population, nor an increased risk of foetal death.[20] However, this paper only reported a limited range of outcomes and did not assess whether immunity was suppressed in the newborns (which has implications for the use of live vaccines). British Association of Dermatologists guidelines for

biologic therapy for psoriasis recommend advising mothers who have received biologic therapy for psoriasis beyond 16 weeks' gestation that their infants should not receive any live vaccinations until they have reached 6 months of age.[21]

3 Critique of company's definition of decision problem

3.1 Population

The population specified in the NICE scope is adults with moderate to severe plaque psoriasis. The population addressed in the company submission (CS) further specifies the following subgroups: patients who are candidates for non-biologic systemic therapy, patients for whom standard systemic non-biological treatment or phototherapy is inadequately effective, not tolerated or contraindicated and biologic-exposed patients. Biological therapies such as certolizumab are often licensed for use in patients who are candidates for systemic therapy, however, clinical advice to the evidence review group (ERG) confirmed that generally biologic therapies are used after non-biological systemic therapy in the treatment pathway. This is mainly due to non-biologic therapies being less costly; therefore, these patients can be treated successfully at a much lower cost than when treated with biologic therapies. The NICE guidelines recommend systemic biologic therapies, apremilast or dimethyl fumarate for adults with severe disease (PASI score ≥10 and DLQI score >10) who have not responded to, or have an intolerance or contraindication to standard non-biologic systemic therapies.[14] Furthermore, other biologic therapies appraised by NICE have been licensed for use earlier in the pathway, but have been positioned for use only in patients for whom non-biologic systemic therapy is inadequately effective, not tolerated or contraindicated.[3-6] Therefore, the ERG considers only patients for whom standard systemic treatment or phototherapy is inadequately ineffective, not tolerated or contraindicated as the most relevant population for this indication.

No definition of moderate to severe psoriasis is specified in the NICE scope, but patients with severe psoriasis considered for other biological therapies, apremilast and DMF should have a PASI score ≥ 10 and DLQI > 10.[14] The inclusion criteria for the clinical trials presented in the submission specified a baseline PASI score ≥ 12, body surface area (BSA) affected ≥ 10% and a physician's global assessment (PGA) score ≥ 3, with no inclusion criteria stated regarding DLQI score. However, the mean baseline DLQI scores for the different treatment groups across the trials ranged from 12.8 to 15.3. Subgroup analyses for patients with a DLQI score of <10 versus ≥10 are presented in Table 53, page 105 of the CS. Therefore, in terms of disease severity, the ERG considers the population in the clinical evidence presented sufficiently reflects the eligible NHS population. However, all three trials excluded patients who had a history of primary failure (defined as no response within the first 12 weeks of treatment with the biologic) to any biologic or had received previous treatment with >2

biologics. Therefore, the trial populations may exclude a proportion of the eligible population who are harder to treat and therefore less likely to achieve a response.

3.2 Intervention

The intervention presented in the CS is certolizumab pegol (Cimzia®, CZP), which matches the NICE scope. The recommended posology is 200mg subcutaneous injection, comprising a loading dose of 400mg at weeks 0, 2 and 4 followed by a maintenance dose of 200mg every 2 weeks.[2] The clinical trials presented in the CS also include treatment arms with a maintenance dose of 400mg every 2 weeks, following a loading dose of 400mg at weeks 0, 2 and 4. Both doses of 200mg and 400mg are licensed for certolizumab pegol.

Certolizumab received European marketing authorisation for use in the treatment of moderate to severe plaque psoriasis on 8th June 2018.[1] In response to the ERG's points for clarification, the company stated that [redacted]. The company provided the decision letter from the EMA with the granted marketing authorisation.

3.3 Comparators

The comparators listed in the NICE scope are systemic non-biologic therapies and phototherapy if systemic non-biological treatment is suitable, anti-TNF therapies (adalimumab, etanercept, infliximab), interleukin (IL) -17 inhibitors (brodalumab, ixekizumab, secukinumab), IL-23 inhibitor (guselkumab), IL-12/IL-23 inhibitor (ustekinumab), apremilast, DMF and best supportive care if systemic non-biological treatment is inadequately effective, not tolerated or contraindicated.

The comparators considered in the CS did not include phototherapy as the company stated that phototherapy is not expected to be used in clinical practice at the same position as systemic non-biological or biological therapies. The British Association of Dermatologists (BAD) state that phototherapy is no longer used routinely in people with psoriasis due to the higher risk of skin cancer [7]. Therefore, the ERG considers that the company's rationale for excluding phototherapy is acceptable.

The CS also excluded infliximab as a comparator with the rationale that it is not considered to be a first-line biologic as it is recommended for patients with very severe psoriasis (PASI≥20, DLQI>18), which is a more restricted patient population than considered in the submission. However, infliximab has been included in the network meta-analysis and as a third-line biologic in the treatment sequences in the cost-effectiveness analyses.

DMF and apremilast were also not considered as comparators in the CS with the rationale that in practice these treatments would only be considered for use in patients unsuitable for or unwilling to

receive biologic treatment. Clinical advice to the ERG agrees that DMF and apremilast would not displace biological therapies and therefore their exclusion appears acceptable.

3.4 Outcomes

The outcomes specified in the NICE decision problem were:

- Severity of psoriasis
- Psoriasis symptoms on the face, scalp, nails and joints
- Mortality
- Response rate
- Duration of response
- Relapse rate
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

The outcomes reported in the CS included severity of psoriasis, psoriasis symptoms on the nails, relapse rate, adverse events, HRQoL and work productivity and social activities. Outcomes listed in the NICE scope but not addressed in the CS were psoriasis symptoms on the face and scalp and treatment effect on mortality, which the company state is due to data limitations. The CS states that psoriasis symptoms in the joints was an outcome listed in the decision problem and included in the submission, however it is not reported. In addition, relapse rate was only reported for the CIMPACT trial. The primary endpoints in all three clinical trials include psoriasis area and severity index (PASI) 75 and physician's global assessment (PGA) clear or almost clear.

3.5 Other relevant factors

The CS includes analysis of the subgroups specified in the NICE scope (previous use of systemic non-biological therapy, previous use of biological therapy and severity of psoriasis).

The CS stated that there are no equality issues arising in relation to certolizumab pegol.

The CS gives details of a patient access scheme (PAS) agreed with the Patient Access Scheme Liaison Unit/Department of Health.

4 Clinical Effectiveness

4.1 Critique of the methods of review(s)

The CS describes a SLR of the clinical effectiveness and safety of CZP as well as licenced non-biological and biological therapies for the treatment of adult patients with moderate to severe plaque psoriasis. Details of the SLR methods are presented in Appendix D of the CS.

4.1.1 Searches

The CS describes the literature searches used to identify RCTs of the efficacy and safety of certolizumab pegol and licensed non-biologic and biologic therapies for the treatment of moderate to severe plaque psoriasis. The full search strategies were reported in Appendix D. The results of the searches were used to inform both the clinical effectiveness SLR and the network meta-analysis.

The following databases were searched on 29th November 2016 and again on 11th December 2017: MEDLINE (including Epub Ahead of Print, MEDLINE in process and other non-indexed citations, MEDLINE Daily and MEDLINE (R)), Embase and the Cochrane Central Register of Controlled Trials (CENTRAL).

In addition, the following conference proceedings were hand searched: World Congress of Dermatology (WCD) 23rd WCD 2015, European Association of Dermatology & Venereology 2015 and 2016 annual meetings and the European Society for Dermatological Research 2016 annual meeting. ClinicalTrials.gov was searched on 11th December 2017 to identify ongoing studies. Reference checking of relevant reviews was also carried out to identify studies.

The searches of MEDLINE and EMBASE were limited to English language studies and incorporated a study design search filter to limit retrieval to randomised controlled trials.

The searches overall were appropriate, however some issues with the strategies were identified which may have impacted on retrieval of relevant studies.

Most of the search strategies were reported in detail in Appendix D. In Section D.1.1. Table 1 lists PubMed as a database that was searched, however no search strategy for PubMed was reported. Under grey literature searches no details were reported for the search of Google and search strings were not provided for the search of ClinicalTrials.gov, making it difficult to assess if the searches of these particular resources were adequate.

The searches of MEDLINE, EMBASE and CENTRAL contained all of the drugs listed under interventions in the inclusion criteria in Table 11 (Section D.1.2), with the exception of the drug acitretin which was missing from all search strategies. Acitretin was also listed as a comparator for the

network meta-analysis in Table 54 (page 107) of the main submission. As it was not included in the search strategy it is possible that studies for acitretin would not have been identified by the searches presented. An additional drug tofacitinib appears in the search strategies but it is not clear why this drug was included as it was not listed in the inclusion criteria in Table 11. Brand names for some of the drugs are missing from the search strategy, (e.g. Kyntheum, the brand name for brodalumab is missing). The drug name risankizumab was also missing from the strategy, with only the drug code bi 655066 for risankizumab included in the strategies. These omissions may have led to studies being missed by the searches.

Medical subject headings (MeSH) are available in the CENTRAL database and it is usual to incorporate relevant MeSH into systematic review search strategies. However no MeSH for the drugs were included in the search strategies presented for CENTRAL, therefore it is not clear if all relevant studies would have been identified from CENTRAL. There are also some mistakes with the line combinations in the CENTRAL strategy presented in Table 6; at line 5, line 28 and line 48. However, the number of records retrieved for these lines appears correct, so it seems that these could be typing errors at the write-up stage of the searches.

Finally, the PRISMA diagram (Section D.1.2. Figure 1) reports results from the first set of searches carried out on 29th November 2016. The results from the searches on 11th December 2017 have not been incorporated into the PRISMA diagram.

4.1.2 Inclusion criteria

Full eligibility criteria for the SLR of licensed non-biologic and biologic therapies are presented in Table 11 of the CS Appendices. RCTs that assessed the biologic therapies (certolizumab, brodalumab, secukinumab, etanercept, infliximab, adalimumab, ustekinumab, guselkumab, tildrakizumab, riselkinumab and ixekizumab) or the non-biologics (apremilast, methotrexate, cyclosporine, dimethyl fumarate and acitretin) in adult patients with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy were included in the review. Comparators in included studies could be placebo or any non-biologic or biologic therapy licensed in the EU or US up to 2018. Studies had to report PASI 50, PASI 75 or PASI 90 responder rate to be included.

The CS does not specify the methods used for screening title and abstracts or full texts. Therefore, it is unclear whether appropriate methods were used to reduce the potential for bias and error at this stage. A PRISMA flow diagram (Figure 1) and a list of studies excluded from the systematic review with the reason for exclusion (Table 13) are included in the CS appendix. The CS included three phase III RCTs of certolizumab (CIMPASI-1, CIMPASI-2 and CIMPACT).[9, 10] However, the CS did not present the phase II RCT by Reich et al.[22], which is included in the network meta-analysis (NMA), as

stated in Table 6 (page 35 of the CS), despite the study meeting eligibility criteria for the review. However, since this was a smaller study in which patients were initially treated for 12 weeks (rather than 16 weeks, as in the larger phase III trials), it appears acceptable for the CS to focus on the larger, longer-term trials.

4.1.3 Critique of data extraction

The CS does not specify the methods of data extraction from the studies included in the SLR. Furthermore, no information is given on how many reviewers undertook data extraction, so it is not clear if appropriate methods were used to reduce the risk of bias and error. The ERG considers there to be sufficient data from the three phase III certolizumab trials: CIMPASI-1, CIMPASI-2[9] and CIMPACT[10] presented in the submission. Minimal baseline characteristics for the phase II certolizumab RCT by Reich et al. were presented in Table 14 of the appendices and very brief results were presented in appendix M.10 [11], no further details of this study were presented.

4.1.4 Quality assessment

Quality assessment of the trials was done using the concise critical appraisal checklist provided by NICE in the STA user guide.[23] The checklist covered randomisation, concealment of treatment allocation, similarity of baseline characteristics, blinding, imbalances in drop-outs, completeness of outcome reporting and intention-to-treat analysis. Results of quality assessment of the CIMPASI-1, CIMPASI-2 and CIMPACT trials are presented in Table 17 of the CS, and further details are presented in Table 20 in Appendix D, this is discussed further in Section 4.2.2 of this report. Results of the quality assessment of the trials included in the NMA are presented in Table 17 of Appendix D of the CS.

The three certolizumab trials were considered to be of relatively good quality with low risk of bias. There was sufficient information provided on all domains. However, there was no information given on how many reviewers undertook quality assessment.

4.1.5 Evidence synthesis

Results of the three certolizumab trials are presented separately and as pooled analyses. The company pooled the efficacy data from CIMPASI-1, CIMPASI-2 and CIMPACT in five different treatment efficacy groups, which are listed below and are outlined in Table 15 of the CS.

- Pool E1 consists of all patients randomised in all three certolizumab trials at week 16.
- Pool E2 includes only patients randomised to CIMPASI-1 and CIMPASI-2 at week 16.
- Pool E3 consists of patients randomised to CIMPASI-1 and CIMPASI-2 at week 48.

- Pool E4 includes all patients who were PASI 50 non-responders and escaped in all three certolizumab trials between week 16 and 48.

- Pool E5 consists of all patients who were PASI 75 responders in all three certolizumab trials between week 16 and 48.

Safety data were pooled for the three trials at week 16 (Pool S1) and for the initial, maintenance and open label extension treatment periods at week 144 (Pool S3). A network meta-analysis (NMA) was conducted to estimate the relative efficacy of certolizumab against all relevant comparators, which is described in Section 4.3 of this report.

4.1.6 Ongoing studies

The CIMPASI-1, CIMPASI-2 and CIMPACT trials are all currently ongoing. The full set of analyses for each trial will be available for week 144, [redacted]. In addition, the CS reports another study of certolizumab for the treatment of moderate to severe plaque psoriasis. This is a multi-centre, double blind, RCT in 149 Japanese patients. The estimated study completion date is January 2019.[24]

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Trials included in the systematic review

Three phase III RCTs of certolizumab pegol are presented in the submission: CIMPASI-1, CIMPASI-2 and CIMPACT.[9, 10] All three studies included two different doses of certolizumab: 200 mg and 400 mg every 2 weeks (Q2W). The Summary of Product Characteristics (SmPC) states that after the initial starting dose of 400 mg Q2W, the maintenance dose for adults with plaque psoriasis is 200 mg Q2W. A dose of 400 mg Q2W can be considered in patients with insufficient response.[2]

The CS mentions one phase II study[11] that was identified by the SLR. It is described as a 'supportive study, not presented in the submission', but is included in the network meta-analysis. Brief results are presented in Appendix M.10 of the CS.

4.2.1.1 Trial design

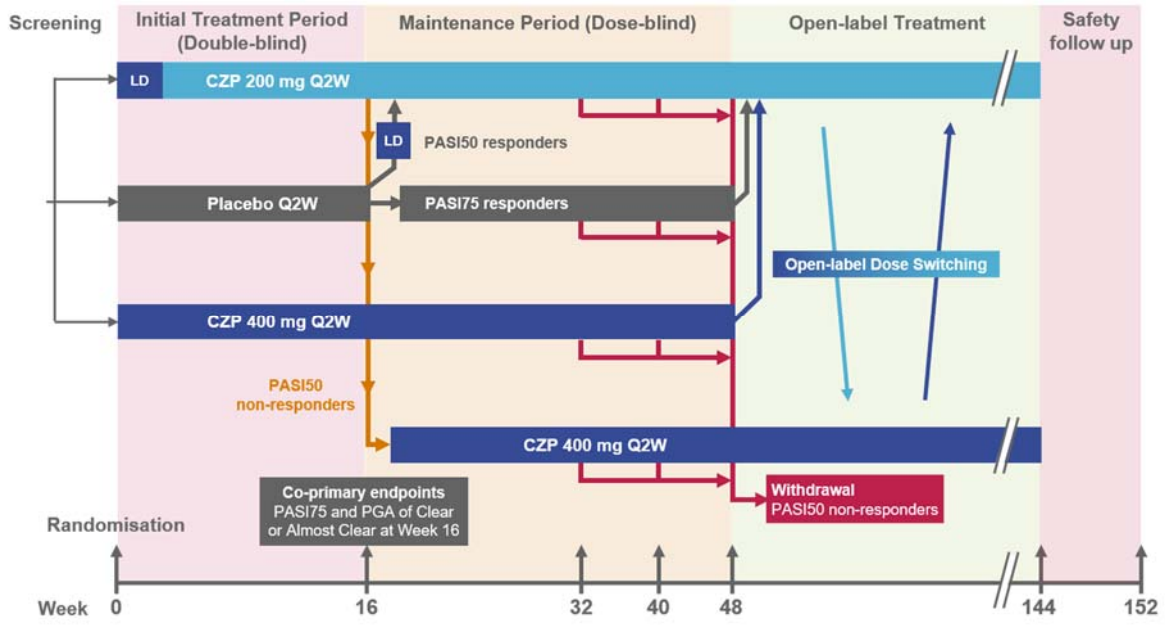
CIMPASI-1 and CIMPASI-2

CIMPASI-1 and CIMPASI-2 are two ongoing phase III, randomised, placebo-controlled clinical trials of certolizumab pegol for the treatment of chronic plaque psoriasis in adults[9]. They were conducted at 53 sites across Canada, Europe and the USA. The trials consist of an initial treatment period which lasts 16 weeks, followed by a maintenance period until week 48 after which there is an open-label treatment phase. The study design is shown in Figure 2.

Patients were randomised in a 2:2:1 ratio to receive CZP 200 mg Q2W, CZP 400 mg Q2W or placebo. At week 16 patients who responded (PASI 50 response if receiving CZP 200 mg or CZP 400 mg and PASI 75 response if receiving placebo) continued to receive the therapy to which they were randomised at baseline. Patients randomised to placebo who achieved a PASI 50 response but not a PASI 75 response at week 16 crossed over to the CZP 200 mg Q2W arm (receiving 3 loading doses of CZP 400 mg followed by CZP 200 mg Q2W). Non-responders at week 16 (patients who did not achieve a PASI 50 response) escaped from blinded treatment and received open-label CZP 400 mg Q2W. Patients who did not achieve a PASI 50 response at week 32 or later were withdrawn from the study.

Open-label treatment started at week 48. Responders (patients who achieved PASI 50 and escape patients who achieved PASI 75) received CZP 200 mg Q2W. Patients who did not achieve PASI 50 response at weeks 60, 72, 84, 96, 108, 120 or 132 were switched to receive CZP 400 mg Q2W for a minimum of 12 weeks, at the investigator's discretion. This also applied to PASI 50 responders who did not achieve PASI 75. Patients who achieved a PASI 75 response after 12 weeks could be switched back to CZP 200 mg Q2W. Whereas, PASI 50 non-responders were withdrawn.

Figure 2 Study design of CIMPASI-1 and CIMPASI-2 RCTs (from CS, Figure 2, page 41, source: CIMPASI clinical study report and CIMPASI-2 clinical study report)



CZP: certolizumab pegol; LD: loading dose; PASI: Psoriasis Area and Severity Index; PGA: physicians global assessment; Q2W: every 2 weeks

CIMPACT

CIMPACT was conducted at 70 sites across Europe, UK and the USA. Patients were randomised in a 3:3:3:1 ratio to receive CZP 200 mg Q2W, CZP 400 mg Q2W, ETN 50 mg twice a week (BIW) or placebo. The study design is shown in Figure 3.

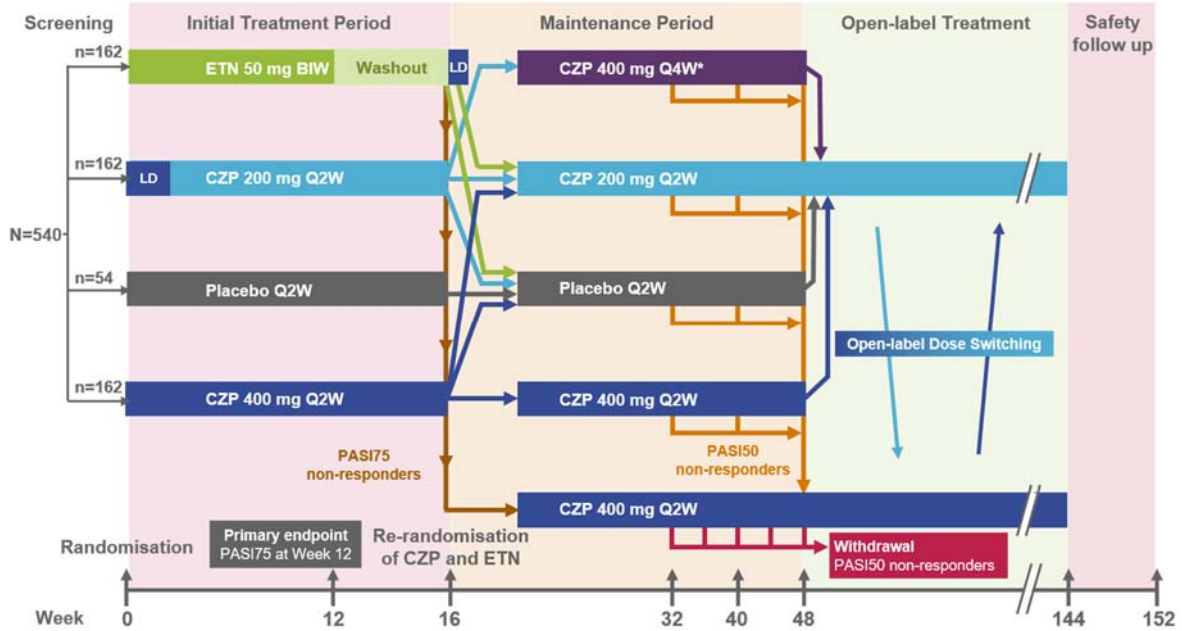
At week 16 patients who did not achieve a PASI 75 response escaped from blinded treatment to receive CZP 400 mg Q2W. Escape arm patients who did not achieve a PASI 50 response at week 32 (or a subsequent timepoint) were withdrawn from the study.

For patients who did achieve a PASI 75 response at week 16:

- Patients initially randomised to placebo continued to receive placebo
- Patients initially randomised to etanercept (ETN) were re-randomised (2:1) to either CZP (loading dose of 400 mg at weeks 16, 18 and 20 followed by 200 mg Q2W) or placebo
- Patients initially randomised to CZP 200 mg Q2W were re-randomised (2:2:1) to receive either CZP 200 mg Q2W or CZP 400 mg Q4W or placebo. Patients initially randomised to CZP 400 mg Q2W were re-randomised (2:2:1) to receive either CZP 200 mg Q2W or CZP 400 mg Q2W or placebo

All patients entering the open-label extension after week 48 with a PASI 50 response received CZP 200 mg Q2W. Patients who relapsed (PASI 50 non-responders) before week 48 entered the open-label extension, receiving CZP 400 mg Q2W. Patients receiving CZP 400 mg Q2W who did not achieve a PASI 50 response at week 32 (or a subsequent timepoint) were withdrawn from the study.

Figure 3 Study design of CIMPACT (from CS, Figure 3, page 43)



CZP: certolizumab pegol; LD: loading dose; ETN: etanercept; PASI: psoriasis area and severity index; PGA: physicians global assessment; Q2W: every 2 weeks.

Open-label phase

Patients from all three trials were eligible for an open-label extension phase at week 48 which is planned to last for a further 2 years (until week 144). However, this data is not presented in the submission, only data up to week 48 is presented. In the points for clarification, the company stated that

[redacted]

4.2.1.2 Trial endpoints

Efficacy assessments were conducted throughout the studies, with key assessments at week 16 and 48. In CIMPASI-1 and CIMPASI-2 the co-primary endpoints were the proportion of patients achieving PASI 75 at week 16 and achieving a PGA clear or almost clear response. Whereas, in CIMPACT the primary endpoint was the proportion of patients achieving a PASI 75 response at week 12. However, the CS presented CIMPACT outcomes at week 16 to be comparable to the CIMPASI-1 and CIMPASI-2 trials. Both PASI response and PGA were measured by blinded outcome assessors. The ERG considers these endpoints and outcome measures to be appropriate.

4.2.1.3 Trial populations

The eligible population for all three trials was adults who were candidates for systemic psoriasis therapy with chronic plaque psoriasis for at least 6 months. The CS presented three separate subgroups alongside the intention to treat (ITT) population. In response to the ERG's points for clarification, the company stated these as being: 'candidates for non-biologic systemic therapies' defined as patients who were completely treatment naïve (both non-biologic and biologic therapies), 'systemic non-biologic therapy inadequate responders' defined as patients who had exposure to at least one previous systemic non-biologic therapy and no previous biologic exposure and 'biologic exposed' who were patients previously exposed to biologic therapies. The ERG considers the biologic exposed and the systemic non-biologic therapy inadequate responders to be the most relevant populations, as they resemble the patients most likely to be treated with certolizumab in clinical practice. Whilst certolizumab is licenced for patients who are candidates for non-biologic systemic therapies, clinical advice to the ERG was that it would be less likely to be used in patients before standard systemic non-biologic therapies, such as methotrexate, primarily due to the difference in cost between the two treatments.

Patients were required to have a baseline PASI score ≥ 12, involvement of ≥ 10% of the body surface area and a PGA score ≥ 3. As discussed in Section 3.1 of this report, this is not entirely consistent with the threshold specified in the NICE pathway for patients to be considered for biologic therapies, apremilast and DMF: PASI score ≥10 and DLQI score >10. The mean DLQI scores for the CIMPASI-1, CIMPASI-2 and CIMPACT trials ranged from 12.8 - 15.3. Across the three certolizumab trials, [redacted] patients had a DLQI score <10, which is below the threshold specified by NICE. Subgroup analyses for patients with a DLQI score of <10 versus ≥10 are presented in Table 53, page 105 of the CS. The ERG considers the population in the trials to be sufficiently representative of the NHS population eligible for biologic therapy.

Exclusion criteria included medical conditions that could prevent patients from completing the study or interfere with the interpretation of results, for example history of chronic or recurrent infections or congestive heart failure. Patients who were breastfeeding, pregnant or planned to become pregnant during the study or within 3 months of the final dose were also excluded. Full inclusion and exclusion criteria are listed in Table 100, Appendix N of the CS.

The CIMPASI-1, CIMPASI-2 and CIMPACT trials excluded patients who had a history of primary failure (defined as no response within the first 12 weeks of treatment with the biologic) to any biologic or had previous treatment with >2 biologics. This may exclude a proportion of the eligible population who are harder to treat and therefore, less likely to achieve a response. Therefore, the results of the included trials may not be generalisable to these more difficult to treat patients in practice. This is reflective of clinical trials recruiting fitter, healthier patients, which may not be fully representative of the NHS population. Furthermore, due to the clinical trials being conducted in different countries the population may not be wholly representative of patients in the UK. In response to the ERG's points for clarification the company stated that in the CIMPACT trial [redacted] patients were from the UK.

Baseline characteristics of the three certolizumab trials are shown in Table 1 below (Table 10, page 50 of the CS). Overall, the baseline characteristics of the intention to treat (ITT) population do not show any concerning imbalances across the treatment groups. In both CIMPASI-1 and CIMPASI-2 less patients in the placebo group had psoriatic arthritis (PsA) compared with the CZP 400 mg group. In CIMPASI-1, 7.8% had PsA in the placebo group, whereas 17.0% had PsA in the CZP 400 mg group. In CIMPASI-2, 18.4% of patients had PsA in the placebo group, whereas 29.9% had PsA in the CZP 400 mg group. In the CIMPASI-2 trial there was a slightly higher proportion of male patients in the CZP 200 mg arm (63.7%) compared to the CZP 400 mg arm (49.4%) and the placebo arm (53.1%). In addition, BMI categories by quintiles indicated that patients in the CZP 200 mg Q2W group were slightly heavier compared with the CZP 400 mg Q2W and placebo groups. The placebo group in

CIMPASI-2 appeared to include patients with slightly less severe disease based on mean and median PASI scores, mean and median DLQI scores, and duration of disease (Table 1). In CIMPACT, BMI categories by quintiles indicated that patients in the placebo group were slightly heavier compared with the CZP and ETN groups. Furthermore, the placebo group had slightly less disease activity compared with the other treatment groups based on median PASI score, mean BSA affected by psoriasis, and prior exposure to biologics (Table 1). However, these differences need to be interpreted with caution as the sample size of the placebo group was smaller than the certolizumab groups.

The baseline characteristics of the subgroup of systemic non-biologic therapy inadequate responders are reported in Table 94, Appendix M8 of the CS. The characteristics are similar to the overall ITT population. There were more female patients in the placebo group (46.4%) compared to the CZP 200 mg group (35.0%) and the CZP 400 mg group (40.0%). The baseline characteristics of the biologic exposed patients are also comparable to the ITT population. However, biologic exposed patients had a higher duration of disease and a larger proportion of patients had concomitant psoriatic arthritis compared with biologic naïve patients. More patients in the placebo arm of the biologic exposed subgroup had received previous anti-TNF therapy (60.0%) than in the CZP 200 mg arm (46.2%) and the CZP 400 mg arm (40.2%). These baseline characteristics were reported in Table 95, Appendix M of the CS. The baseline characteristics of candidates for non-biologic systemic therapies are reported in Table 85, Appendix M of the CS.

The ERG notes that the percentage of males is lower in the CIMPASI-2 trial (55.9%) compared to the CIMPASI-1 (69.2%) and CIMPACT trials (68.2%). Clinical advice to the ERG is that males tend to have a poorer treatment response than females. This may explain the higher response rates seen in the CIMPASI-2 trial, compared to the CIMPASI-1 and CIMPACT trials. Furthermore, the CIMPASI-2 trial also had a higher proportion of patients with psoriatic arthritis (25.1%) than the CIMPASI-1 trial (12.4%) and the CIMPACT trial (16.1%).

In the three certolizumab trials, the range of patients had not received any previous systemic therapy (including non-biologic) was [redacted]% to [redacted]% and [redacted]% to [redacted]% had not received previous phototherapy. The ERG considers that the population most relevant to this submission is patients who have previously received systemic non-biologic therapy and also possibly previous systemic biologic therapy. Therefore, the results of the ITT population of the trials may not be entirely generalizable to the eligible NHS population. However, subgroup analysis results are presented for patients who had received previous systemic non-biologic therapy and patients who had received previous biologic therapy.

Table 1 Demographics and baseline characteristics of the CIMPASI-1, CIMPASI-2 and CIMPACT trials (from CS, Table 10, page 50)

	CIMPASI-1			CIMPASI-2			CIMPACT			
Characteristic	**Placebo (n=51)**	**CZP 200 mg (n=95)**	**CZP 400 mg (n=88)**	**Placebo (n=49)**	**CZP 200 mg (n=91)**	**CZP 400 mg (n=87)**	**Placebo (n=57)**	**ETN (n=170)**	**CZP 200 mg (n=165)**	**CZP 400 mg (n=167)**
Age, years										
Mean (SD)	47.9 (12.8)	44.5 (13.1)	43.6 (12.1)	43.3 (14.5)	46.7 (13.3)	46.4 (13.5)	46.5 (12.5)	44.6 (14.1)	46.7 (13.5)	45.4 (12.4)
Gender, n (%)										
Male	35 (68.6)	67 (70.5)	60 (68.2)	26 (53.1)	58 (63.7)	43 (49.4)	34 (59.6)	127 (74.7)	113 (68.5)	107 (64.1)
Female	16 (31.4)	28 (29.5)	28 (31.8)	23 (46.9)	33 (36.3)	44 (50.6)	23 (40.4)	43 (25.3)	52 (31.5)	60 (35.9)
Racial group, n (%)										
White	45 (88.2)	87 (91.6)	79 (89.8)	44 (89.8)	86 (94.5)	81 (93.1)	57 (100)	163 (95.9)	158 (95.8)	162 (97.0)
Black	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographical region, n (%)										
North America	26 (51.0)	49 (51.6)	45 (51.1)	35 (71.4)	61 (67.0)	61 (70.1)	10 (17.5)	29 (17.1)	26 (15.8)	27 (16.2)
Europe	25 (49.0)	46 (48.6)	43 (48.9)	14 (28.6)	30 (33.0)	26 (29.9)	[redacted]	[redacted]	[redacted]	[redacted]
Central/East Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36 (63.2)	111 (65.3)	107 (64.8)	109 (65.3)
Western Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11 (19.3)	30 (17.6)	32 (19.4)	31 (18.6)
Weight, kg										
Mean (SD)	95.2 (19.5)	92.6 (21.0)	92.2 (21.7)	87.1 (26.4)	97.8 (25.6)	91.8 (27.7)	93.7 (29.7)	88.6 (20.7)	89.7 (20.6)	86.3 (20.0)
BMI, kg/m^2										
Mean (SD)	32.2 (6.8)	31.1 (7.3)	30.7 (6.7)	30.2 (8.0)	32.8 (8.3)	31.7 (8.9)	31.2 (8.5)	29.5 (6.3)	29.8 (6.1)	28.9 (5.9)
Baseline clinical characteristics										
PASI score										
Mean (SD)	19.8 (7.5)	20.1 (8.2)	19.6 (7.9)	17.3 (5.3)	18.4 (5.9)	19.5 (6.7)	19.1 (7.1)	21.0 (8.2)	21.4 (8.8)	20.8 (7.7)

	CIMPASI-1			CIMPASI-2			CIMPACT			
Characteristic	**Placebo (n=51)**	**CZP 200 mg (n=95)**	**CZP 400 mg (n=88)**	**Placebo (n=49)**	**CZP 200 mg (n=91)**	**CZP 400 mg (n=87)**	**Placebo (n=57)**	**ETN (n=170)**	**CZP 200 mg (n=165)**	**CZP 400 mg (n=167)**
PGA score, n (%)										
3	35 (68.6)	62 (65.3)	65 (73.9)	37 (75.5)	66 (72.5)	61 (70.1)	40 (70.2)	115 (67.6)	114 (69.1)	113 (67.7)
4	16 (31.4)	33 (34.7)	23 (26.1)	12 (24.5)	25 (27.5)	26 (29.9)	17 (29.8)	55 (32.4)	51 (30.9)	54 (32.3)
BSA affected by psoriasis										
Mean (SD)	26.1 (16.1)	25.4 (16.9)	24.1 (16.6)	20.0 (9.5)	21.4 (12.2)	23.1 (11.6)	24.3 (13.8)	27.5 (15.5)	28.1 (16.7)	27.6 (15.3)
DLQI total score										
Mean (SD)	13.9 (8.3)	13.3 (7.4)	13.1 (6.5)	12.9 (7.3)	15.2 (7.2)	14.2 (7.2)	13.2 (7.6)	14.1 (7.4)	12.8 (7.0)	15.3 (7.3)
Duration of disease, years										
Mean (SD)	18.5 (12.9)	16.6 (12.3)	18.4 (12.9)	15.4 (12.2)	18.8 (13.5)	18.6 (12.4)	18.9 (12.9)	17.4 (12.0)	19.5 (13.2)	17.8 (11.5)
Previous biologic therapy, n (%)										
Never used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 therapy	13 (25.5)	22 (23.2)	22 (25.0)	11 (22.4)	22 (24.2)	21 (24.1)	[redacted]	[redacted]	[redacted]	[redacted]
2 therapies	2 (3.9)	8 (8.4)	7 (8.0)	3 (6.1)	10 (11.0)	8 (9.2)	[redacted]	[redacted]	[redacted]	[redacted]
Any previous systemic treatment for psoriasis, n (%)[b]										
Yes	36 (70.6)	66 (69.5)	61 (69.3)	36 (73.5)	65 (71.4)	63 (72.4)	[redacted]	[redacted]	[redacted]	[redacted]
No	15 (29.4)	29 (30.5)	27 (30.7)	13 (26.5)	26 (28.6)	24 (27.6)	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant PsA, n (%)[d]										
Yes	4 (7.8)	10 (10.5)	15 (17.0)	9 (18.4)	22 (24.2)	26 (29.9)	12 (21.1)	27 (15.9)	27 (16.4)	24 (14.4)
No	47 (92.2)	85 (89.5)	73 (83.0)	40 (81.6)	69 (75.8)	61 (70.1)	45 (78.9)	143 (84.1)	138 (83.6)	143 (85.6)

4.2.2 Summary of the quality of the included trials

The CS included a summary of the quality assessment of the certolizumab trials in accordance with the NICE-recommended checklist for RCTs (Table 17, Page 60 of the CS), with a more detailed rationale for decisions in Table 20 in Appendix D. All three trials were RCTs with placebo and/or active controls. Randomisation appears to be appropriate, patients in all three trials were randomised by a centralised interactive voice response system (IVRS). Re-randomisation at 16 weeks was also executed by the central voice response system. The concealment of treatment allocation for all three trials also appears adequate, as an IVRS was used for randomisation.

Participants and outcome assessors were blinded until the end of the maintenance phase in the CIMPASI-1 and CIMPASI-2 trials. However, certolizumab and placebo were administered by unblinded personnel. This may have increased the risk of bias; however, care providers were not otherwise involved in the study. All outcome assessors were blinded in the CIMPACT trial until the end of the maintenance phase. In the certolizumab and placebo arms, patients were also blinded until the end of the maintenance phase. However, patients in the CIMPACT trial receiving etanercept were unblinded as etanercept could only be produced in a commercial presentation. Placebo and etanercept were also provided by unblinded personnel. This introduces a potential risk of performance bias as patients and administrators of etanercept may have been able to distinguish treatment allocation between etanercept and the other treatment arms.

There were a few imbalances between treatment groups in the trials, which are described above in Section 4.2.1.3. The numbers of discontinuations were similar across treatment groups for the CIMPASI-2 trial, however there were some differences in the CIMPASI-1 and CIMPACT trials. Slightly more patients in the placebo group (9.8%) discontinued prior to week 16 compared to the CZP 200 mg group (3.2%) and the CZP 400 mg group (1.1%) in CIMPASI-1. In CIMPACT, the proportion of patients who completed the initial treatment period was similar across the CZP 200 mg (96.4%), CZP 400 mg (97.0%), and placebo (96.5%) groups but slightly lower in the ETN group (93.5%); this difference was mainly due to a higher percentage of patients discontinuing due to an adverse event in the ETN group (2.4%) compared with the other groups (≤0.6%). Among the escape maintenance treatment groups, a higher percentage of patients discontinued prior to Week 48 in the CZP 200 mg/Esc CZP 400 mg group (26.5%) compared with the other escape groups (range: 13.2% to 16.7%).

The outcomes listed in the protocol match the ones reported in the trial clinical study reports (CSR); however, the CS only reported outcomes which were relevant for modelling cost-effectiveness. The risk of selective outcome reporting is low. Intention-to-treat analysis, with non-responder imputation (NRI) or Markov Chain Monte Carlo (MCMC) for missing data, was used for most analyses. In

response to a request for clarification, the company provided data on the number of missing values for key endpoints. These were similar across the three certolizumab trials, however the number of missing values imputed was higher in the CZP 200 mg arm than the CZP 400 mg arm for the CIMPASI-1 trial. The proportion of missing values imputed was small for the PASI response and PGA outcomes at week 16 (ranging from [redacted]% to [redacted]%). Whereas, these were higher at week 48, ranging from [redacted]%-[redacted]%. Overall, the ERG considers the three certolizumab trials are of relatively good quality with a low risk of bias except for potential performance bias in the etanercept arm in the CIMPACT trial.

4.2.3 Summary of the results of the included trials

4.2.3.1 Efficacy results

The key efficacy endpoints in the three certolizumab trials are PASI 75 and PASI 90 response rate at week 16 and PGA clear or almost clear response rate at week 16. These are summarised in Table 2.

.

Table 2 Key efficacy outcomes for the CIMPASI-1, CIMPASI-2 and CIMPACT trials at week 16 (adapted from the CS, Figures 5, 6 and 11)

	CIMPASI-1			CIMPASI-2			CIMPACT		
Outcome	**Placebo (N = 51)**	**CZP 200 mg (N = 95)**	**CZP 400 mg (N = 88)**	**Placebo (N = 49)**	**CZP 200 mg (N = 91)**	**CZP 400 mg (N = 87)**	**Placebo (N = 57)**	**CZP 200 mg (N=165)**	**CZP 400 mg (N=167)**
PASI 75, %	6.5	66.5	75.8	11.6	81.4	82.6	3.8	68.2	74.7
p value vs placebo	—	<0.0001	< 0.0001	—	<0.0001	< 0.0001	—	<0.0001	<0.0001
PASI 90, %	0.4	35.8	43.6	4.5	52.6	55.4	0.3	39.8	49.1
p value vs placebo	—	<0.0001	< 0.0001	—	<0.0001	< 0.0001	—	<0.0001	<0.0001
PASI 100, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p value vs placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA score of 0 or 1, %	4.2	47.0	57.9	2.0	66.8	71.6	3.4	48.3	58.4
p value vs placebo	—	<0.0001	< 0.0001	—	<0.0001	< 0.0001	—	<0.0001	<0.0001

CIMPASI-1 and CIMPASI-2

Psoriasis severity at week 16

In the ITT population, both the 200 mg and 400 mg doses of certolizumab pegol show statistically significant greater efficacy than placebo in all of the key endpoints at week 16 (Table 2). The 400 mg dose of CZP had numerically higher PASI 75 and PASI 90 response rates than the 200 mg dose in CIMPASI-1, however, the difference between the two doses was not statistically significant. The response rate was similar between the two doses of certolizumab pegol in CIMPASI-2. In CIMPASI-1, the CZP 200mg dose had a slightly higher PASI 100 response rate compared to the CZP 400 mg group. Whereas, in CIMPASI-2 the CZP 400 mg group had a higher PASI 100 response rate at week 16 compared with the CZP 200 mg group (Table 2). In CIMPASI-1, the mean absolute PASI scores had decreased in the CZP 200 mg and CZP 400 mg groups by 14.9 and 15.7 points, respectively. Similarly, in CIMPASI-2, the mean absolute PASI scores had decreased by 14.6 and 16.1 points, respectively (Table 72, page 180 of CS Appendix M). The ERG notes that the proportion of patients achieving PASI 75, PASI 90 and PASI 100 in both the CZP 200 mg and CZP 400 mg groups was greater in CIMPASI-2 than CIMPASI-1 and CIMPACT. The ERG carried out a t-test to assess the difference between the study results, which was statistically significant, demonstrating that there is a substantial difference between CIMPASI-2 and the other two studies. Both CIMPASI trials had identical study designs; however, there are a few notable differences in baseline characteristics, which are discussed in Section 4.2.1.3. The proportion of males was lower in the CIMPASI-2 trial than CIMPASI-1 and CIMPACT (Table 1). Clinical advice to the ERG is that males tend to have a poorer treatment response than females. The CIMPASI-2 trial also had a higher proportion of patients with psoriatic arthritis (25.1%) than the CIMPASI-1 trial (12.4%) or the CIMPACT trial (16.2%). These imbalances may have contributed to the difference in response rates. In response to the ERG's points for clarification, the company stated that there is no clear evidence available to indicate that these differences had any effect on the clinical outcomes observed across the three trials. Therefore, the ERG is unclear about what is driving the difference between the study results. Psoriasis severity results at 48 weeks were only presented as a pooled analysis, these are discussed in the pooled results section on page 51.

Significantly more patients achieved a PGA response (clear or almost clear) at week 16 with both CZP 200 mg and CZP 400 mg than with placebo ($p<0.0001$ in both trials). There was no statistically significant difference in PGA response between the CZP 200 mg group and the CZP 400 mg group. However, the CZP 400 mg group had numerically higher responder rates. Similarly to PASI response, the CIMPASI-2 study had higher PGA response rates than CIMPASI-1 (Table 2). In both studies, larger mean decreases in psoriasis percentage BSA affected from baseline to week 16 were observed

in the CZP 200 mg and 400 mg groups (range: -16.3 to -18.0) compared with placebo (range: -1.6 to -4.2). The decreases from baseline were generally similar between the CZP 200 mg and CZP 400 mg groups.

The CS only presented results for mean change in psoriasis percentage BSA affected for patients who remained on their CZP 400 mg treatment through to week 48. In both studies, decreases from baseline in psoriasis percentage BSA affected were greater at week 48 compared with week 16. The change from baseline mean BSA affected was [redacted] in CIMPASI-1 (n=69) and [redacted] in CIMPASI-2 (n=61) at week 48. In the points for clarification, the ERG requested these results for the patients who remained on 200 mg of CZP. The mean change from baseline in BSA affected was also greater at week 48 than at week 16 for these patients ([redacted] in CIMPASI-1 (n=70) and [redacted] in CIMPASI-2 (n=64)).

Escape therapy at week 16

From week 16, patients in the CZP 200 mg and CZP 400 mg groups who did not achieve a PASI 50 response to certolizumab escaped to open-label CZP 400 mg Q2W. Patients in the placebo group who did not achieve a PASI 50 response escaped to CZP 400 mg Q2W. Patients in the placebo group who achieved a PASI 50 response but not a PASI 75 response moved to CZP 200 mg Q2W. Of those patients who received CZP 200 mg in the initial treatment period, [redacted]% in CIMPASI-1 and [redacted]% in CIMPASI-2 received escape therapy in the maintenance treatment period. Of those patients who received CZP 400 mg Q2W in the initial treatment period, [redacted]% in CIMPASI-1 and [redacted]% in CIMPASI-2 received escape therapy in the maintenance treatment phase. Whereas, out of the patients who received placebo in the initial treatment period, [redacted]% in CIMPASI-1 and [redacted]% in CIMPASI-2 received escape therapy during the maintenance treatment phase.

Health related quality of life

DLQI results at week 16 were only presented for the pooled data in the main submission (Table 6 below), with each individual trial presented in the appendices. Week 48 data were presented for the separate trials. In CIMPASI-1 and CIMPASI-2 the mean change in baseline DLQI was maintained through to week 48 in both CZP treatment groups (Table 30 in the CS, page 85). There is a greater mean change from baseline in DLQI score in the CIMPASI-2 trial (-10.7 with CZP 200 mg and -10.9 with CZP 400 mg) compared to the CIMPASI-1 trial (-8.8 with CZP 200 mg and -9.8 with CZP 400 mg) at week 48. In CIMPASI-1 and CIMPASI-2, greater improvements from baseline in SF-36 were reported for patients in both CZP treatment groups compared to placebo at week 16. The CS also reported the hospital anxiety and depression score (HADS-A and HADS-D) for CIMPASI-1 and

CIMPASI-2 (Table 34, page 90 in the CS); both the HADS-A and HADS-D generally showed greater reductions from baseline for patients treated with CZP compared to placebo, which were mostly maintained through to week 48. The CS also reported the workplace productivity and daily activities (WPAI-SHP) for all three certolizumab studies (Table 36, page 93 in the CS).

CIMPACT

Psoriasis severity at week 16

Table 3 shows key outcomes for the CIMPACT trial at week 16 and week 48. The PASI 75 response rate at week 16 was 68.2% in the CZP 200 mg group and 74.7% in the CZP 400 mg group compared with 3.8% in the placebo group. PASI 75, PASI 90 and PGA response were significantly higher in both the CZP 200 mg and CZP 400 mg groups than the placebo group at week 16 ($p<0.001$). The PASI 100 results for CZP 200 mg and CZP 400 mg compared to placebo were associated with p-values of [redacted] and [redacted], respectively. The 200 mg CZP and 400 mg CZP groups also had greater mean changes from baseline in psoriasis percentage BSA affected (-18.2 and -20.5, respectively) at week 16 compared to placebo (-0.1).

The CIMPACT trial included a group of patients treated with etanercept. PASI response rate results for these patients were presented at week 12, not at week 16. Only patients treated with CZP 400 mg had a statistically significantly higher PASI 75 response (66.7%) compared to patients treated with etanercept (53.3%) at week 12. PASI 90 responder rates were numerically higher but not statistically significantly different in the CZP 200 mg and CZP 400 mg groups compared to the etanercept group (31.2%, 34.0% and 27.1%, respectively). The PGA responder rate at week 12 was comparable for ETN (39.2%) versus CZP 200 mg (39.8%), with CZP 400 mg (50.3%) showing a higher PGA response rate. No statistical comparisons were presented in the CS.

Escape therapy at week 16

From week 16, patients in the placebo, etanercept, CZP 200 mg and CZP 400 mg groups who did not achieve a PASI 75 response to certolizumab escaped to open-label CZP 400 mg Q2W. Of the patients who received CZP 200 mg Q2W in the initial treatment period, 30.8% escaped in the maintenance treatment phase to CZP 400 mg Q2W and of the patients who received CZP 400 mg Q2W in the initial treatment period, 22.5% received escape therapy in the maintenance treatment phase. A much larger percentage of patients randomised to ETN (53.5%) and placebo in the initial treatment period then received escape therapy in the maintenance treatment period (96.4%). The CS presented the results for escape patients in a pooled analysis, which is discussed later in this section of the report. However, the ERG requested the change from baseline in psoriasis percentage BSA affected for escape patients in CIMPACT in the points for clarification as these had been presented for CIMPASI-

1 and CIMPASI-2 in the CS. The mean change from baseline in BSA affected for the three escape treatment groups was larger at week 48 than for patients at week 16 but was smaller than for patients who responded and were re-randomised to CZP. The mean change from baseline to week 48 was -20.7, -22.1 and -22.7 in the placebo escape group, CZP 200 mg escape group and the CZP 400 mg escape group, respectively.

Psoriasis severity at week 48

The CS also presents results on maintenance of PASI response at week 48 split into re-randomisation groups (Table 3). All response outcomes in Table 3 were higher at week 48 than at week 16 for patients on certolizumab. However, the patients receiving certolizumab at week 48 were only those who had a PASI 75 response at week 16 and were re-randomised to either placebo, CZP 200 mg or CZP 400 mg for the maintenance phase. The patients who were randomised to CZP 400 mg throughout the whole study had the highest PASI 75 (98.0%) and PASI 90 (87.8%) response rates compared to all other patients at week 48. Patients randomised to CZP 200 mg at baseline and re-randomised to CZP 200 mg had lower PASI 75 and PASI 90 response rates than patients who were randomised to CZP 200 mg at baseline and re-randomised to CZP 400 mg at week 16. The PGA responder rates also followed a similar trend and were highest in the patients who stayed on CZP 400 mg throughout the study (87.8%). The CS reported mean change in baseline BSA affected at week 48 (Table 24 on page 79), which was very similar across the CZP treatment groups, ranging from [redacted] to [redacted]. The CS also reported the modified nail psoriasis severity index for the CIMPACT trial at week 48 in Table 26 on page 82. The mean decrease from baseline in mNAPSI was generally greater in those groups that remained on CZP for 48 weeks compared to those groups re-randomised to placebo at week 16.

Relapse rate data was assessed in the CIMPACT trial as time to not achieving a PASI 50 response for those who achieved PASI 75 at week 16. Time to relapse among patients achieving a PASI 75 response at week 16 was longer for those receiving CZP than placebo during the maintenance phase ([redacted]) (Figure 15 in the CS, page 80). A similar proportion of patients relapsed between weeks 16 and 48 in the CZP 200 mg /400 mg Q2W group (11.4%) and the CZP 400 mg /200 mg Q2W group (10.0%). A higher proportion of patients relapsed in the CZP 200 mg/400 mg Q4W group (4.5%) than the CZP 400 mg/400 mg Q2W group (2.0%).

Health-related quality of life

In the CIMPACT trial, mean decreases from baseline in DLQI score were generally maintained through week 48 in patients receiving certolizumab. These were similar across treatment groups, ranging from [redacted] to -14.2. Whereas, patients who were initially treated with certolizumab and then

re-randomised to placebo had smaller changes in DLQI score (range: -2.6 to [redacted]). The mean change from baseline in fatigue assessment scale (FASca) for the CIMPACT trial was reported in Table 27 on page 83.

Table 3 Clinical responses at week 16 and week 48 in the CIMPACT trial (adapted from Figures 5, 6, 8 and 11 and Tables 20, 22 and 24 of the CS)

	Week 16			Week 48 [a]					
Endpoint	**Placebo (N = 57)**	**CZP 200 mg (N=165)**	**CZP 400 mg (N=167)**	**CZP 200 mg/ Placebo (N=22)**	**CZP 200 mg/CZP 200 mg (N = 44)**	**CZP 200 mg/ CZP 400 mg* (N = 44)**	**CZP 400 mg/ Placebo (N=25)**	**CZP 400 mg/CZP 200 mg (N=50)**	**CZP 400 mg/ CZP 400 mg (N=49)**
PASI 75 response, (%)	3.8	68.2[†]	74.7[†]	45.5	79.5	88.6	36.0	80.0	98.0
PASI 90 response, (%)	0.3	39.8[†]	49.1[†]	18.2	61.4	68.2	12.0	60.0	87.8
PGA 0 (clear/almost clear), (%)	3.4	48.3[†]	58.4[†]	13.6	61.4	70.5	12.0	64.0	87.8
BSA, mean change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients who received CZP 200 mg or 400 mg until week 16, had a PASI 75 response at week 16 and were re-randomised to placebo, CZP 200 mg or CZP 400 mg.
[†] Adjusted *p* value (vs placebo) < 0.0001
*Frequency for this treatment group is Q4W
PASI, Psoriasis Area and Severity Index; Q2W; PGA, physician global assessment; BSA: body surface area affected

Table 4 Clinical responses at week 16 and week 48 in the CIMPASI-1 trial (adapted from Figures 5, 6 and 11 and Table 22 of the CS and Table 70, 73 and 75 of the CS Appendix)

	Week 16			Week 48	
	Placebo (N = 51)	**CZP 200 mg (N=95)**	**CZP 400 mg (N=88)**	**CZP 200 mg (N=95)**	**CZP 400 mg (N = 88)**
PASI 75 response, (%)	6.5	66.5[†]	75.8[†]	67.2	87.1
PASI 90 response, (%)	0.4	35.8[†]	43.6[†]	42.8	60.2
PASI 100 response, (%)	0.2	13.7[*]	12.7[b]	21.8	23.6
PGA 0 (clear/almost clear), (%)	4.2	47.0[†]	57.9[†]	52.7	69.5

[a] Patients who received CZP 200 mg or 400 mg until week 16, had a PASI 50 response at week 16 and continued receiving the treatment to which they had been randomised in the initial treatment period.

[†] Adjusted *p* value (vs placebo) < 0.0001

[*] *p* value =0.0043

[b] *p* value = 0.0070

PASI, Psoriasis Area and Severity Index; Q2W; PGA, physician global assessment; BSA: body surface area affected

Table 5 Clinical responses at week 16 and week 48 in the CIMPASI-2 trial (adapted from Figures 5, 6 and 11 and Table 22 of the CS and Table 70, 73 and 75 of the CS Appendix)

	Week 16			Week 48	
	Placebo (N = 49)	**CZP 200 mg (N=91)**	**CZP 400 mg (N=87)**	**CZP 200 mg (N=91)**	**CZP 400 mg (N = 87)**
PASI 75 response, (%)	11.6	81.4[†]	82.6[†]	78.7	81.3
PASI 90 response, (%)	4.5	52.6[†]	55.4[†]	59.6	62.0
PASI 100 response, (%)	1.8	15.4[*]	18.8[b]	31.4	38.3
PGA 0 (clear/almost clear), (%)	2.0	66.8[†]	71.6[†]	72.6	66.6

[a] Patients who received CZP 200 mg or 400 mg until week 16, had a PASI 50 response at week 16 and continued receiving the treatment to which they had been randomised in the initial treatment period.

[†] Adjusted *p* value (vs placebo) < 0.0001

**p* value =0.0251

[b]*p* value = 0.0131

PASI, Psoriasis Area and Severity Index; Q2W; PGA, physician global assessment; BSA: body surface area affected

Pooled results

Efficacy data from CIMPASI-1, CIMPASI-2 and CIMPACT studies was pooled to further explore effect estimates of treatment with CZP. Pool E1 includes efficacy data from 850 patients in all three studies in the initial treatment period up to week 16. Table 6 shows key efficacy outcomes for the pooled data. The proportions of patients achieving PASI 75, PASI 90 and PGA clear/almost clear responses were higher in the CZP 200 mg and CZP 400 mg groups compared to the placebo group ($p<0.0001$). The CZP 400 mg group has numerically higher response rates to CZP 200 mg for PASI 75, PASI 90 and PGA. The mean change from baseline in DLQI score was higher in the CZP 200 mg and CZP 400 mg groups than the placebo group, but was comparable between the two certolizumab groups (Table 6). The CIMPASI-2 results are substantially higher than the other two trials. Therefore, the ERG is uncertain whether it is appropriate to pool results of all three trials, considering the heterogeneity between the results.

The ERG requested PASI 50, PASI 75 and PASI 90 response rates for Pool E1 but with an adjustment for gender and psoriatic arthritis. The company stated that a re-analysis of the PASI response rates including two additional factors in the logistic regression could not be completed due to the complexity of the methodology used. There were baseline differences in gender and proportion of patients with psoriatic arthritis between the CIMPASI-2 trial and the CIMPASI-1 and CIMPACT trials, therefore an adjustment for these factors would have been helpful to further understand what is causing the higher response rates in CIMPASI-2. Without these analyses, it is unclear what effect these baseline differences have on the pooled PASI results.

Psoriasis severity at week 48

Figure 4 shows maintenance of PASI response rates to week 48 in CIMPASI-1 and CIMPASI-2. The PASI 75 response rate in both studies pooled was slightly higher at week 48 (83.6%) than in week 16 (82.0%) in the CZP 400 mg group. However, the PASI 75 response rate decreased at week 48 (70.7%) compared to week 16 (76.7%) in the CZP 200 mg group. By week 48, PASI 90 responder rates were 50.0% in the CZP 200 mg group and 61.6% in the CZP 400 mg group.

Therefore, the majority of patients who achieved a PASI 75 response at week 16 and continued blinded treatment with either CZP 200 mg or CZP 400 mg continued to be PASI 75 responders. However, this maintenance cohort only includes patients who were PASI 50 responders (CZP 200/CZP 400); 186 patients in the CZP 200 mg arm and 175 patients in the CZP 400 mg arm. There were 10 patients randomised to placebo who achieved a PASI 50 response but not a PASI 75 response

at week 16 and were crossed over to receive CZP 200 mg. However, the CS does not present any results for these patients.

At week 48, the PGA clear/almost clear responder rate was maintained in the pooled results for CIMPASI-1 and CIMPASI-2 for the CZP 200 mg group (61.0%) and the CZP 400 mg group (68.9%). These were both higher than the PGA responder rates at week 16. The PGA responder rates were numerically higher in the CZP 400 mg group compared with the CZP 200 mg group throughout the maintenance period.

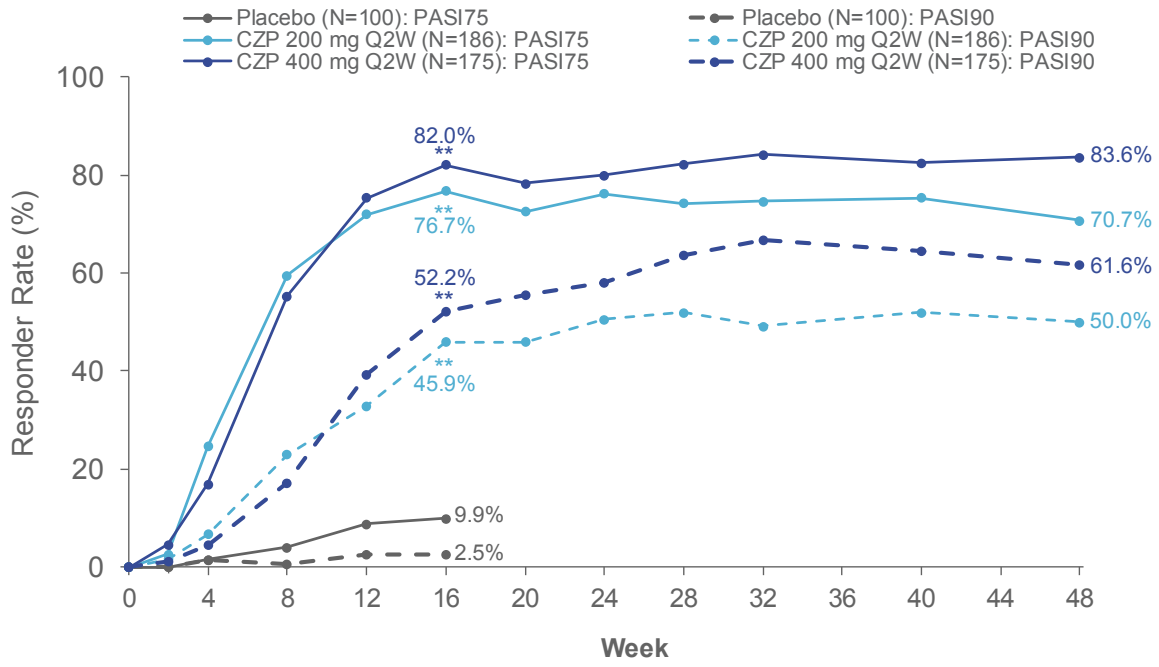
The CS reported the modified nail psoriasis severity index (mNAPSI) for CIMPASI-1 and CIMPASI-2 pooled together in Table 25, page 82 of the CS. The mean decrease from baseline in mNAPSI score was similar in the CZP 200 mg and CZP 400 mg groups (-4.5 and -4.3, respectively) at week 48. The CS reports that the majority of patients with psoriatic nail disease at baseline achieved an absence of nail disease (mNAPSI score of 0) at week 48 (67.6% in the CZP 200 mg group and 64.6% in the CZP 400 mg group). In response to the ERG's points for clarification, the company stated that change from baseline in mNAPSI is only provided for patients who had nail disease at baseline. The company provided the number of patients for which mNAPSI change from baseline data are available at week 48. In the CZP 200 mg arm, 14% of patients who had nail disease at baseline were missing data and in the CZP 400 mg arm, 14% of patients who had nail disease at baseline were missing data at week 48.

Table 6 Key efficacy outcomes for pooled data (CIMPASI-1, CIMPASI-2 and CIMPACT) at week 16 (adapted from Figures 5, 6 and 11 and Tables 19 and 29 of CS)

	E1 pool		
Outcome	**Placebo (N = 157)**	**CZP 200 mg (N = 351)**	**CZP 400 mg (N = 342)**
PASI 75, %	7.5	74.5	80.1
p value vs placebo	—	<0.0001	< 0.0001
PASI 90, %	1.6	44.5	52.2
p value vs placebo	—	<0.0001	< 0.0001
PASI 100, %	[redacted]	[redacted]	[redacted]
p values vs placebo			
PGA clear/almost clear, %	2.8	54.6	63.7
p value vs placebo	—	<0.0001	< 0.0001
DLQI score*	-2.4	-9.1	-10.4
p value vs placebo		<0.0001	<0.0001

*mean change from baseline

Figure 4 Maintenance of PASI 75 and PASI 90 responder rates to week 48 in pooled CIMPASI-1 and CIMPASI-2 (Figure 7 of CS)



**** p<0.0001 vs placebo**

The CS presented another pooled data set, E5, which includes [redacted] patients in CIMPASI-1, CIMPASI-2 and CIMPACT randomised to CZP 200 mg or CZP 400 mg, who responded to treatment and stayed on the same dose of certolizumab until week 48. In Pool E5, out of the CZP 200 mg treated patients who achieved a PASI 75 response at week 16, [redacted] maintained their level of PASI 75 response at week 48; [redacted] of these patients achieved PASI 90 response at week 48. In Pool E5, out of the CZP 400 mg treated patients who achieved PASI 75 response at week 16, [redacted] maintained their PASI 75 response at week 48 and [redacted] achieved a PASI 90 response.

Pool E4 presented in the CS includes 203 patients in CIMPASI-1, CIMPASI-2 and CIMPACT who were PASI 50 non-responders at week 16 and received CZP 400 mg escape therapy. The greatest improvement in non-responders was seen for patients initially treated with placebo at week 16 who escaped to CZP 400 mg (74.1%) compared to patients randomised to CZP 400 mg who escaped to CZP 400 mg (65.7%) and patients who were randomised to CZP 200 mg and escaped to CZP 400 mg (51.9%) (Figure 10, page 72 of the CS). Similarly, for PGA response, patients who were initially treated with placebo and escaped to CZP 400 mg had the greatest improvement (63.8%). Whereas, CZP 200 mg treated patients who escaped to CZP 400 mg saw a smaller but notable improvement (38.5%) in PGA response rate (Figure 14, page 76 of the CS).

Health-related quality of life

In Pool E1, statistically significant improvements were observed for mean change from baseline in DLQI score in both the CZP 200 mg group (-9.1) and the CZP 400 mg group (-10.4) compared to the placebo group (-2.4) at week 16 (Table 6).

Subgroup analyses

The trials included a range of pre-specified subgroup analyses, listed in Table 9 of the CS.

Subgroup analyses were performed for the pooled CIMPASI-1, CIMPASI-2 and CIMPACT data on PASI 75 and PGA response rates at week 16 (Pool E1) and for the pooled CIMPASI-1 and CIMPASI-2 data at week 48 (Pool E3). Subgroup analyses were also presented separately for the CIMPACT trial on PASI 75 response rates at week 12. The subgroups: candidates for non-biologic systemic therapies, non-biologic therapy inadequate responders, biologic naïve/exposed and severity of psoriasis by DLQI are presented in the CS. Whereas, all the other subgroup analyses are presented in Appendix E. In response to the ERG's points for clarification, the company state that no treatment by subgroup interaction terms of $p<0.1$ were observed for these subgroups. The company state these results should be interpreted with caution due to the small sample sizes for many of the categories, as well as the potential interactions between variables that could confound the results.

Non-biologic therapy inadequate responders (biologic naïve)

One of the populations in the NICE scope and presented by the company is patients for whom conventional systemic non-biological treatment or phototherapy is inadequately effective, not tolerated or contraindicated. In the CS this population are patients who have had previous non-biologic treatments but are naïve to biologic therapy. The ERG considers this population to be the most relevant to where certolizumab is likely to be positioned in clinical practice.

The PASI response rates and PGA clear/almost clear responses and DLQI change from baseline score are presented in Table 7 for the systemic non-biologic inadequate responder patients for all three certolizumab trials pooled. The week 16 results are similar to the pooled results for the ITT population (Pool E1) and are comparable to the CIMPASI-1 and CIMPACT trial individual response rates. All response rates are higher for the CZP groups than placebo and they are higher in the CZP 400 mg group than the CZP 200 mg group. The PASI 75 response rate stays the same in the CZP 200 mg group from week 16 to week 48 ([redacted]%). However, the PASI 75 response rate decreases slightly from week 16 to week 48 in the CZP 400 mg group ([redacted]%).

The mean change in DLQI score at week 16 was substantially higher in the CZP groups compared to the placebo group. The mean changes in the CZP groups slightly increased at week 48 (-10.1 in the

CZP 200 mg group and -10.3 in the CZP 400 mg group). The ERG requested results for body surface area affected, extra-cutaneous manifestations and quality of life in systemic non-biologic inadequate responders in the points for clarification. These were generally similar to the overall ITT population.

Candidates for non-biologic systemic therapy (non-biologic and biologic naïve)

Table 7 also presents the key efficacy outcomes at week 16 for patients who are 'candidates of non-biologic therapy' (both biologic and non-biologic naïve). Candidates of non-biologic therapy had similar PASI 75 response rates to the pooled ITT population (Pool E1), although the PASI 90 response rates were lower. The mean change in DLQI was similar between candidates for non-biologic therapy and the full ITT population. Further efficacy outcomes for this subgroup are presented in Section B.2.6.9 of the CS.

Biologic exposed patients

Subgroup analyses for the biologic naïve and biologic exposed subgroups are presented in Section B.2.7.1 of the CS. The results for these subgroups are generally similar to the ITT pooled population (Pool E1). Patients in the CZP 200 mg group who were biologic naïve had lower PASI 75 and PASI 90 response rates than biologic exposed patients. Whereas, patients in the CZP 400 mg group who were biologic naïve had higher PASI 75 response rates than biologic exposed patients. The PASI 90 response rates were comparable between these subgroups. At week 48 biologic naïve patients had higher PASI 75, PASI 90 and PGA 0/1 response rates than biologic exposed patients in the CZP 400 mg Q2W arm. The response rates were comparable across both subgroups in the CZP 200 mg Q2W arm. However, these results should be interpreted with caution, in view of the small numbers of patients in the subgroups.

Severity of psoriasis by DLQI

Subgroup analyses for patients with a DLQI score of <10 versus ≥10 are presented in Table 53, page 105 of the CS. Patients with more severe disease (DLQI ≥10) who were treated with CZP 400 mg have higher PASI 75, PASI 90 and PGA 0/1 response rates than patients with less severe disease (DLQI<10) treated with CZP 400 mg. Whereas, patients with less severe disease (DLQI <10) who were treated with CZP 200 mg have higher response rates than patients with more severe disease (DLQI≥10) treated with CZP 200 mg. Since a DLQI score of <10 does not meet the NICE pathway for treatment with biologic therapies, results for these patients may not be reflective of NHS patients at this point in the treatment pathway. However, if certolizumab is positioned alongside systemic non-biological therapy, then results for patients with a DLQI score <10 are also applicable.

Table 7 Key efficacy outcomes at week 16 in Pool E1 (CIMPASI-1, CIMPASI-2 and CIMPACT pooled) for three subgroups of patients (adapted from Table 41, 44, 46, 48 and 51 of CS and Table 6 in the points for clarification)

Non-biologic therapy inadequate responders (Biologic naïve)				Candidates for non-biologic systemic therapy (Non-biologic and biologic naïve)			Biologic-exposed		
	Placebo (n=[redacted])	CZP 200 mg (n=[redacted])	CZP 400 mg (n=[redacted])	Placebo (n=[redacted])	CZP 200 mg (n=[redacted])	CZP 400 mg (n=[redacted])	Placebo (n=[redacted])	CZP 200 mg (n=[redacted])	CZP 400 mg (n=[redacted])
PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA 0/1 response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI score [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[b]mean change from baseline

CZP: certolizumab pegol; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; DLQI: dermatology quality life index

Withdrawals

In both CIMPASI-1 and CIMPACT, the proportion of randomised patients across all treatment arms that completed the 16-week initial treatment phase was 96%. In CIMPASI-2, 93% completed the 16-week treatment period. The 48-week maintenance phase was completed by 94% of patients in CIMPASI-1 and 9% in CIMPACT. Whereas, it was lowest in CIMPASI-2, in which 86% of patients completed the 48-week maintenance phase of the study. The ERG notes this is comparable with the drug survival rates published for other biologics.

The CS provided patient disposition figures with reasons for discontinuation in Appendix D.2 of the CS. For all randomised patients in the three trials, the main reason for patients discontinuing was consent withdrawal, followed by adverse events and mandatory withdrawal due to not achieving PASI 50 response. The ERG requested further information on the reasons 'consent withdrawn' and 'other'. The company could not provide any further details regarding the 'consent withdrawn' reason but more information was given for the discontinuation category 'other' in response to the ERG's points for clarification. The reasons for discontinuation classed as 'other' included [redacted], [redacted], [redacted] and [redacted].

4.2.3.2 Safety

The safety analyses were conducted using the safety analysis set, which consists of all patients in the randomised set who had received at least one dose of study medication. Safety data from the CIMPASI-1, CIMPASI-2 and CIMPACT trials was pooled into two treatment pools. Pool S1 includes all patients in all three trials who were exposed to at least one dose of certolizumab or placebo up to week 16 ([redacted]). The S3 pool includes [redacted] patients in all three trials who were exposed to at least one dose of certolizumab throughout the initial, maintenance and open-label extension phase (week 0 to week 144). Safety data was not presented separately for each certolizumab trial in the CS. The median exposure for all patients who were exposed to certolizumab up to week 144 (Pool S3) was [redacted] days, presented in Table 59 of the CS. In the CZP 400 mg and CZP 200 mg groups the median exposure was [redacted] days and [redacted] days, respectively. In the etanercept group in the CIMPACT trial the median duration of exposure was [redacted] days up to week 16. Only [redacted] patients had received certolizumab for at least 24 months.

Table 8 shows the rates of adverse events across the treatment arms in all three trials. During the 16-week initial treatment period, the proportion of patients with an adverse event was higher in the CZP 400 mg group than the CZP 200 mg group. However, the rates are similar between the CZP 400 mg group and the placebo group (63.5% vs 61.8%). Similarly, the rate of serious and severe adverse events are similar between the CZP 400 mg group and the placebo group and are lowest in the CZP

200 mg group. This suggests that the safety profiles of both doses of certolizumab are acceptable. The proportion of patients with any, serious or severe adverse events was slightly higher in the CZP 400 mg group than the CZP 200 mg group in Pool S3, up to week 144. The number of deaths due to adverse events was low up to Week 144, 0.3% in each treatment group.

Table 8 Summary of adverse events in the certolizumab trials (adapted from CS, Table 55, page 116 and Table 60, page 122)

Induction phase, pool S1 (to week 16) **Adverse event, n (%)**	**Placebo** n=157	**CZP 200 mg** n=350	**CZP 400 mg** n=342	**ETN** n=168	**ALL CZP** n=692
Any	97 (61.8)	197 (56.3)	217 (63.5)	78 (46.4)	[redacted]
Serious	7 (4.5)	5 (1.4)	16 (4.7)	1 (0.6)	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leading to discontinuation of study	0	4 (1.1)	4 (1.2)	4 (2.4)	[redacted]
Deaths (TEAEs leading to death)	0	0	0	0	0
Induction, maintenance and open-label extension phase, pool S3 (to week 144) **Adverse event, n (%)**	**Placebo** n=0	**CZP 200 mg** [redacted]	**CZP 400 mg** [redacted]	**ETN** [redacted]	**All CZP** [redacted]
Any	-	[redacted]	[redacted]	[redacted]	[redacted]
Serious	-	[redacted]	[redacted]	[redacted]	[redacted]
Severe	-	[redacted]	[redacted]	[redacted]	[redacted]
Leading to discontinuation of study	-	[redacted]	[redacted]	[redacted]	[redacted]
Deaths (TEAEs leading to death)	-	[redacted]	[redacted]	[redacted]	[redacted]

Common adverse events

The most common adverse events in the initial 16-week phase were infections and infestations (33.5%), gastrointestinal disorders (8.8%), musculoskeletal and connective tissue disorders (7.4%), nervous system disorders (7.2%), general disorders and administrative site conditions (7.4%) and skin and subcutaneous tissue disorders (11.1%). All of these were more frequent in the CZP 400 mg group than the CZP 200 mg group or placebo group, except for skin and subcutaneous tissue disorders, which were more frequent in the placebo group (14.0%) than the CZP 400 mg group (12.6%) and musculoskeletal and connective tissue disorders, which were also more common in the placebo group (10.8%) than the 400mg CZP group (7.9%).

Serious adverse events

In the initial 16-week phase, the rate of serious adverse events across all three trials was [redacted]

[redacted]The most common serious adverse events across the three studies were injury, poisoning and procedural complications, psychiatric disorders and musculoskeletal and connective tissue disorders. Up to Week 144, the rate of patients reporting serious adverse events was higher in the CZP 400 mg group ([redacted]%) and the CZP 200 mg group ([redacted]%) (Table 61, page 124 of the CS). The most common serious adverse event in this phase of the studies was infections and infestations ([redacted] in the CZP 400 mg group and [redacted] in the CZP 200 mg group). The incidence of severe TEAEs was numerically higher in the etanercept arm compared with both the CZP 200 mg and CZP 400 mg treatment groups (CIMPACT trial).

4.2.4 Supporting data from other trials

Brief results (PASI 75 responder rate and discontinuations due to adverse events) of a phase II study were presented in Appendix M.10[11]. This study was a randomised, double-blind, placebo-controlled study in which patients were allocated to placebo, CZP 200 mg Q2W or CZP 400 mg Q2W for 12 weeks, followed by a 12 week follow-up period without treatment. Week 12 PASI 75 responder rate data from this study were included in the network meta-analysis, which feeds into the cost-effectiveness analyses presented as part of this submission. The results were generally consistent with the three phase III certolizumab RCTs.

4.2.5 Conclusions from critique of trials of the technology of interest

The CIMPASI-1, CIMPASI-2 and CIMPACT trials are of relatively good quality with a low risk of bias except for potential performance bias in the etanercept arm in the CIMPACT trial. The three trials included non-biologic naïve patients, non-biologic non-responders and biologic exposed patients in the ITT population. The ERG considers the biologic exposed and the systemic non-biologic therapy inadequate responders to be the most relevant populations, as they resemble the patients most likely to be treated with certolizumab in clinical practice.

Trial inclusion criteria appear to have been appropriate. However, patients were required to have a baseline PASI score ≥12 and there was no criteria for DLQI score. This is not entirely consistent with the threshold specified in the NICE pathway for patients to be considered for biologic therapies; PASI score ≥10 and DLQI score >10. Across the three certolizumab trials, [redacted]patients had a DLQI score <10, which is below the threshold specified by NICE. In addition, the CIMPASI-1, CIMPASI-2 and CIMPACT trials excluded patients who had a history of primary failure (defined as no response within the first 12 weeks of treatment with the biologic) to any biologic or had previous treatment with >2 biologics. This may exclude a proportion of the eligible population who are harder to treat

and therefore, less likely to achieve a response. Therefore, the results of the certolizumab trials may not be entirely generalisable to the proposed eligible population.

Overall, the baseline characteristics of the intention to treat (ITT) population do not show any concerning imbalances across the treatment groups. The baseline characteristics of the subgroup of systemic non-biologic therapy inadequate responders are similar to the overall ITT population. However, there were more female patients in the placebo group ([redacted]%) compared to the CZP 200 mg group ([redacted]%) and the CZP 400 mg group ([redacted]%). The ERG notes that the percentage of males is lower in the CIMPASI-2 trial (55.9%), compared to the CIMPASI-1 (69.2%) and CIMPACT trials (68.2%). Clinical advice to the ERG is that males tend to have a poorer treatment response than females. This may explain the higher response rates seen in the CIMPASI-2 trial, compared to the CIMPASI-1 and CIMPACT trials. Furthermore, the CIMPASI-2 trial also had a higher proportion of patients with psoriatic arthritis (25.1%) than the CIMPASI-1 trial (12.4%) and the CIMPACT trial (16.1%). In the three certolizumab trials, 26.3% to 31.6% of patients had not received any previous systemic therapy (including non-biologic). The ERG considers that the population most relevant to this submission is patients who have previously received systemic non-biologic therapy. However, subgroup analysis results are presented for patients who had received previous systemic non-biologic therapy and patients who had received previous biologic therapy.

In all three trials, both the 200 mg and 400 mg doses of certolizumab pegol show statistically significant greater efficacy than placebo in all the key endpoints at week 16 (Table 2). The CZP 400mg group has numerically higher response rates to CZP 200 mg in all PASI response rates. Efficacy data from CIMPASI-1, CIMPASI-2 and CIMPACT studies was pooled. The proportions of patients achieving PASI 75, PASI 90 and PGA clear/almost clear responses were higher in the CZP 200 mg and CZP 400 mg groups compared to the placebo group ($p<0.0001$). The PASI 75 response rate in the CIMPASI-1 and CIMPASI-2 studies pooled was slightly higher at week 48 (83.6%) than in week 16 (82.0%) in the CZP 400 mg group. However, the PASI 75 response rate decreased at week 48 (70.7%) compared to week 16 (76.7%) in the CZP 200 mg group. In CIMPACT, PASI response was maintained through to week 48. The patients who were randomised to CZP 400 mg throughout the whole study had the highest PASI 75 (98.0%) and PASI 90 (87.8%) response rates compared to all other patients at week 48. In all three studies, decreases from baseline in psoriasis percentage BSA affected were greater at week 48 compared with week 16. In CIMPACT, only patients treated with CZP 400 mg had a statistically significantly higher PASI 75 response (66.7%) compared to patients treated with etanercept (53.3%) at week 12. Statistically significant improvements were observed for mean change from baseline in DLQI score in both the CZP 200 mg group (-9.1) and the CZP 400 mg group (-10.4) compared to the placebo group (-2.4) for all three trials pooled at week 16. Mean

decreases from baseline in DLQI score were generally maintained through week 48 in patients receiving certolizumab in all three trials separately.

The ERG notes that the proportion of patients achieving PASI 75, PASI 90 and PASI 100 in both the CZP 200 mg and CZP 400 mg groups was greater in CIMPASI-2 than CIMPASI-1 and CIMPACT. However, the ERG is unclear about what is driving the difference between the study results. Therefore, the ERG is uncertain whether it is appropriate to pool results of all three trials, considering the heterogeneity between the results.

The PASI response rates, PGA clear/almost clear responses and DLQI change from baseline score for the systemic non-biologic inadequate responder patients for all three certolizumab trials pooled are similar to the pooled results for the ITT population at week 16. Subgroup results for the biologic exposed subgroup were also generally similar to the ITT pooled population at week 16. However, these results should be interpreted with caution, in view of the small numbers of patients in the subgroups.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

A network meta-analysis (NMA) is presented which compares the efficacy of certolizumab with the licensed therapies acitretin, adalimumab, apremilast, brodalumab, cyclosporine, dimethyl fumarate, etanercept, guselkumab, ixekizumab, infliximab, methotrexate, secukinumab, tildrakizumab and ustekinumab. Risankizumab, although not a comparator, was included as part of the NMA as it features in trials with licensed treatments and helps form links within the network meta-analysis. In response to the ERG's points for clarification, the company stated that the inclusion of risankizumab was pre-defined in the search strategy for the clinical systematic literature review. The base-case NMA includes all EMA/FDA licensed doses of the therapies specified in the scope.

A systematic literature review was undertaken to conducted to identify all potentially relevant RCTs for inclusion in the NMA. The CS describes the search strategy used to identify relevant RCTs of certolizumab and potential comparator therapies used for the treatment of moderate to severe plaque psoriasis in Appendix D.1.1 (page 9 to page 30). Systematic searches were carried out in MEDLINE, Embase and CENTRAL-indexed databases for RCTs that were published to December 11th 2017. These searches also encompassed annual proceedings for scientific meetings held through (2015 and 2016). The reporting of the searches was clear with sufficient detail to allow the database searches to be reproduced.

The inclusion criteria used to select the studies for inclusion in the NMA appear appropriate (Table 54, page 107 of the CS). The title and abstracts of records identified through the database searches

were assessed against the eligibility criteria. The CS did not specify if screening of title and abstracts or of full texts was performed in duplicate. Hence, the risk of reviewer error and bias is unclear. A table listing all the trials excluded from the SLR at the full text review stage is presented in Appendix D.1.2 on page 38 (Table 13). A PRISMA flow diagram (Figure 1) is presented in Appendix D.1.2. The CS did not specify the methods of data extraction. The outcomes specified in the inclusion criteria were PASI 50, 75 and 90 response rates. Studies were assessed for quality using appropriate criteria; the results of the quality assessment (Table 17 of Appendix D.1.7) suggests that generally, the risk of bias for most studies was low. Several trials (7/65) were not double-blinded or had open-label phases which increased the risk of performance bias.

The ERG did not undertake independent searches to check that all relevant studies were included in the NMA, due to time constraints. However, a comparison of studies included in this STA with the earlier STAs of brodalumab, secukinumab and ixekizumab was undertaken. No relevant trials appear to have been excluded from the NMA.

The network diagram for all studies identified in the SLR and included in the NMA is presented in Figure 18, page 110 of the CS. The base case NMA included data from 65 studies consisting of 27,640 patients with moderate to severe plaque psoriasis who were eligible for systemic therapy. The majority (57/65) of the trials compared to placebo, with a small number (8/65) of studies comparing to active comparators. All studies reported data at the end of the initial phase of the treatment, which varied amongst trials. The CS states that the majority of initial treatments were 16 weeks. However, in response to the ERG's points for clarification the company provided a table specifying the time points at which outcomes were collected in each trial, which confirms that the majority of initial treatments (54%) were 12 weeks, whereas 34% and 12% of the studies had initial treatment periods of 16 weeks and 10 weeks, respectively.

The CS presents the key baseline characteristics of the studies included in the NMA in Table 14, page 41 of Appendix D.1.4. The baseline characteristics, previous use of systemic therapy and previous use of phototherapy were not provided. There were some notable differences in patient characteristics across trials, which are discussed on page 109 of the CS. There was a substantial difference in the proportion of patients with psoriatic arthritis between the studies included (0% to 37%). There was also considerable variation in the time since diagnosis, ranging from 11 years to 24 years and mean baseline PASI score ranged from 15 to 33. The studies included were either Phase II, III or IV with publication dates of between 2001 and 2017. The CS did not report how many trials were phase II. There were also a number of studies that had a high risk of performance bias due to being open-label, resulting in a difference in the reliability of the results.

When comparing the certolizumab trials with other trials in the NMA, CIMPASI-1 and CIMPASI-2 had a higher proportion of biologic naïve patients, where reported. This may be due to the inclusion of patients who were eligible for systemic non-biologic therapy in the certolizumab trials. CIMPASI-2 also had a lower proportion of male patients than many of the other studies included in the NMA. All of these differences increase the risk of between study heterogeneity, which reduces the reliability of the NMA results. Heterogeneity was assessed for the studies included in the NMA using subgroup and sensitivity analyses for all PASI responses. Between-study standard deviation and total residual deviance were reviewed for subgroups and sensitivity models to determine whether inclusion of an effect modifier reduced heterogeneity or improved model fit. However, these were not detailed in the CS. Therefore, the ERG is uncertain whether the sensitivity adjustments made are appropriate. Furthermore, the NMA was only conducted in patients who were treated for an initial treatment period of 10 to 16 weeks, depending on the study. Therefore, the effect estimates only indicate the efficacy of initial treatment up to 16 weeks. Psoriasis is a chronic condition, with many patients being treated for much longer than 16 weeks. However, the NMA does not show long-term PASI response results.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 Critique of the NMA methods

The NMA results presented were PASI response rates (PASI 50, PASI 75 and PASI 90), which are appropriate outcomes for patients with moderate to severe psoriasis and consistent with previous NICE STA submissions for psoriasis therapies. However, NMAs undertaken for the development of the British Association of Dermatologists' (BAD) guidelines for biologic therapy for psoriasis, published in April 2017, also assessed PGA clear/almost clear and mean change in DLQI score and tolerability.[12]

The main analysis was conducted using a placebo-adjusted multinomial ordered probit model, where PASI response was treated like a categorical variable. This allows the model to simultaneously consider evidence from all PASI categories. However, the model makes a stronger proportional odds assumption than a standard binomial analysis, since it not only assumes the same relative treatment effect for each therapy but also assumes the same relative treatment effect for each PASI category. The proportional odds assumption can be checked informally by examining the relative treatment effects at the different PASI cut-offs in each trial and checking if they are approximately the same. The CS states that cross validation of the results from the binomial models with those predicted from the multinomial model indicated that the treatment effects of each therapy do not appear to be consistent for PASI 50, PASI 75 and PASI 90. Therefore, the results from the multinomial model may

not be fully reliable. However, the ERG considers that the multinomial logit model is the most appropriate, given the multiple PASI outcomes addressed.

Fixed-effects, random-effects and baseline risk-adjusted random effects approaches were explored. The baseline risk-adjusted (placebo adjusted) random-effects model was reported to provide the best model fit to the observed data based on statistical goodness of fit statistics (Deviance Information Criterion (DIC):2906.42 and between study standard deviation: 0.20) and previously published literature. A fixed effects model assumes negligible between-study heterogeneity while a random effects model allows for some between-study heterogeneity. Therefore, a random effects model appears more suitable for this analysis given the large number of RCTs (65) included in the NMA, which increases the likelihood of between-study heterogeneity. The DIC for the fixed effects model was 3091.64 (a between study standard deviation value was not reported). Thus, the choice concerning the fixed effects or random effects model to inform the economic model was done based on the DIC, i.e. the random effects model was chosen as it has a smaller DIC value.

The CS provided the WinBUGS code that was used to run the NMA analyses on page 56 of the Appendices. However, the ERG identified several problems with the code and noticed that the code did not appear to be correct for a NMA. In the points for clarification, the ERG requested all the files required to run the NMA analyses (fixed effects, random effects, with and without placebo adjustment) in WinBUGS (including data, model, and initial values for every chain). The company provided the same code that was originally provided in the Appendix, with no other files of input data. The CS reports that the approach used for the multinomial NMA has been adapted from the NICE Decision Support Unit (DSU) technical support document example in psoriasis (Example 6).[13] However, there is little similarity between the code used by the company and the example code in the DSU document. The code provided does not appear to be able to produce the results reported in the CS. First, there is no information about which trials were used for the baseline response. The trials used should be as specific as possible to the population of interest. It may be more reasonable to use only evidence from recent relevant trials. It is also uncertain from the code provided whether only placebo-controlled studies were used to assess baseline risk. Furthermore, the WinBUGS code is not consistent with the methods that are reported on page 50-54 of the Appendix. The company states that both fixed effects and random effects NMAs were considered. However, the WinBUGS code provided does not include code for a random effects or fixed effects model. In addition, the company state that the probit scale mean and precision values from the estimates of baseline risk in the NICE DSU example 6 (probit scale mean 1.097, precision 123) were used in their model.[13] The ERG does not consider that using mean and precision values given in an external example is an adequate method of building an NMA model. Mean and precision values of baseline risk should be individually

estimated for specific models using the current data available. Due to these issues and the incorrect code being presented, the ERG was unable to re-run the NMA. However, the results of the NMA appear to be consistent and similar to previous technology appraisal NMAs of biologics for psoriasis. Therefore, the ERG believes that the code provided was not the code used to produce the NMA results reported in the CS.

The CS assessed heterogeneity for the 65 studies included in the NMA. Inevitably the trials included in the NMA vary by design, prior medication (including prior use of systemic non-biologic and biologic therapies), comorbidities (psoriatic arthritis), average age and other relevant characteristics that are discussed in Section 4.2.1.3. All these variations contribute to differences in placebo response rates and, therefore, to differences in the relative efficacy of the intervention to placebo. The placebo-treated patients' estimates in the NMAs (baseline risk) were derived using pooled placebo estimates from studies identified in the SLR (from studies which compared a therapy of interest to placebo). Individual participant data (IPD) from RCTs included in the NMA would represent the gold standard, however the CS states that access to IPD was only available for 4/65 trials. The CS did not provide goodness of fit statistics (adjustment coefficient, total residual deviance or DIC) for the placebo unadjusted model, therefore the ERG is uncertain which is a better model fit for this analysis. The relative effects for each of the random effects, fixed effects and baseline risk-adjusted models for each intervention at each level of PASI response are reported in Table 18 of Appendix D.1.8 of the CS.

4.4.2 NMA results

Predicted probabilities of PASI responses for evaluated interventions (base case) for each PASI outcome are presented in Table 9 (adapted from Table 18 of Appendix D.1.8). The ERG requested the absolute PASI response rates for evaluated interventions in each of the trials included in the NMA (base case), which were not initially provided in the CS. These are presented in Appendix B of the points for clarification response. The forest plot of the primary analysis results for PASI 75 is presented in Figure 5 (Figure 19 of the CS). The forest plots for PASI 90 and PASI 50 are presented in Figure 20 and Figure 21 of the CS, respectively.

[redacted] The ERG checked the NMA results against those of a NMA undertaken by the guideline development group for the BAD guidelines for biologic therapy for psoriasis, published in April 2017.[12] The BAD NMA compared ixekizumab, secukinumab, infliximab, ustekinumab, adalimumab, etanercept, methotrexate and placebo. Interventions were ranked in order or efficacy. For the outcome PASI 75 at 3-4 months ixekizumab ranked best, followed by infliximab, secukinumab, ustekinumab, adalimumab, etanercept,

methotrexate and placebo, which is consistent with the certolizumab NMA results, for those particular therapies.

The ERG noticed that the results of the NMA imply that guselkumab has a PASI 75 response rate of [redacted]% at week 16. However, the VOYAGE 1[28] and VOYAGE 2 [29] trials, which are the primary phase III RCTs evaluating guselkumab, report PASI 75 response rates of 91.2% and 86.3%, respectively. In addition, the NMA also includes a phase II RCT evaluating guselkumab [30], which reports a PASI 75 response rate of 79.0%. In response to the ERG's points for clarification the company stated that this difference may be due to the multinomial model used in the NMA, which is discussed earlier in this section. The company also suggested reasons why this NMA has different effect estimates for guselkumab compared to other NMAs which included guselkumab. However, the company did not give any more details of why the effect estimates in this NMA were substantially smaller than the clinical trial data for guselkumab. The ERG is uncertain that the effect estimate of guselkumab produced by the network meta-analysis is reliable. The company compared the probability of response results for adalimumab and secukinumab between this NMA and the results in the ixekizumab NICE submission[31] as validation. The company stated that the PASI 50/75/90 results were comparable regarding adalimumab estimates. Although, the results are similar, the effect estimates for adalimumab are lower for each PASI outcome in this NMA compared to the ixekizumab NMA and the secukinumab estimates are also notably lower in this NMA.

[redacted] The CS states that [redacted]

[redacted]

[redacted]Similar results were seen for PASI 90 response rates. The CS positioned certolizumab earlier in the treatment pathway, for patients who were both non-biologic and biologic naïve. However, considering that the NMA shows that all biologic therapies are more effective than non-biologics and certolizumab has comparable efficacy to most other biologics, the ERG does not agree that certolizumab should be the only biologic available for use before non-biologic therapies. Therefore,

the ERG considers that the most relevant population for certolizumab is patients for whom systemic non-biologic therapy is inadequate, not tolerated or contraindicated.

Figure 5 Primary analysis (random effects placebo-adjusted multinomial model): absolute probabilities PASI 75 response (ITT population), Figure 19 of the CS

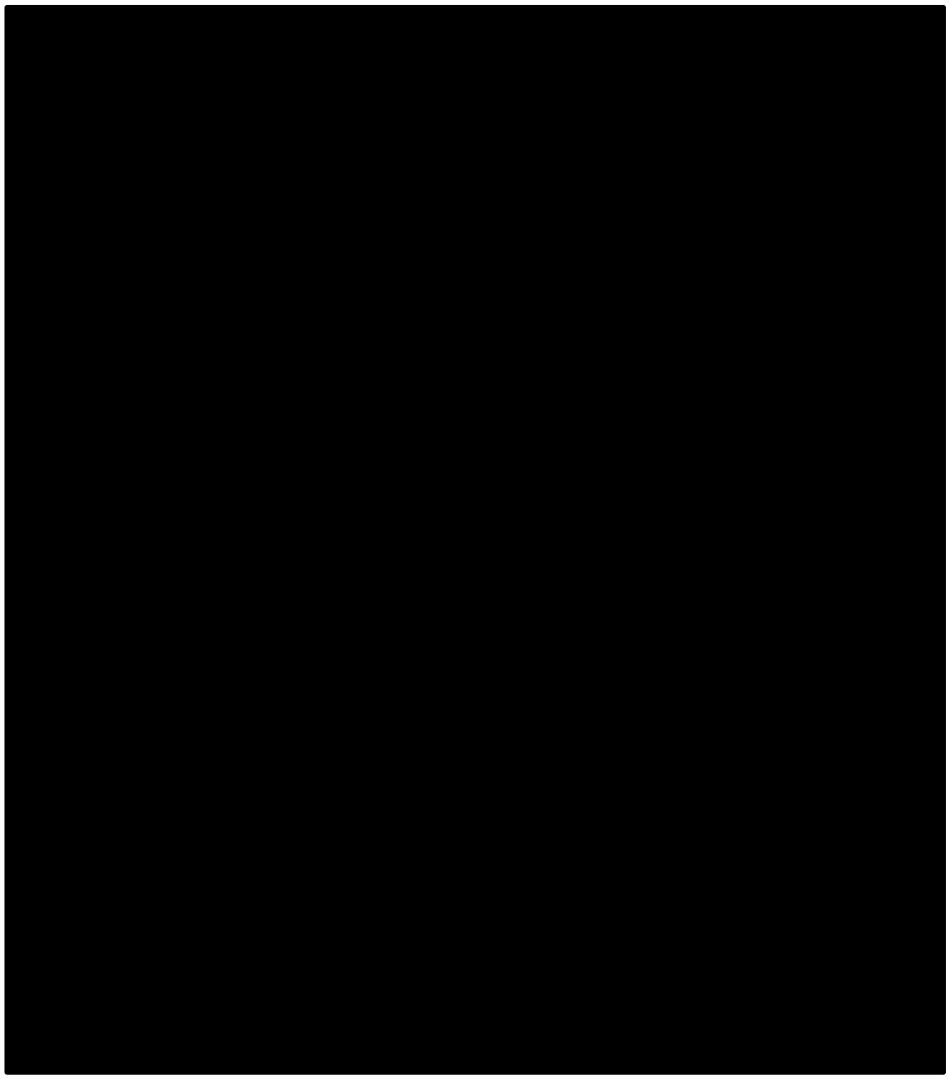


Table 9 Predicted probabilities of PASI responses for evaluated therapies for each PASI outcome (adapted from Table 18, page 74 of Appendix D.1.8

Treatment	Probability of PASI response (ITT population)									Ranking
	PASI 50			PASI 75			PASI 90			
	median	95% CrI		median	95% CrI		median	95% CrI		
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22
Ixekizumab (80 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1
Brodalumab (210 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2
Secukinumab (150mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10
Secukinumab (300 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5
Infliximab (5 mg/kg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4
CZP (200mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6
CZP (400 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3
Ustekinumab (45mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9
Ustekinumab (90 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7
Ustekinumab (45mg or90mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11
Guselkumab (100mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8
Tildrakizumab (100mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12
Adalimumab (40mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13
Etanercept (25mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15
Etanercept (50mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14
Dimethyl Fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17
Ciclosporin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18
Apremilast (30mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19
Acitretin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20
DIC	[redacted]			[redacted]			[redacted]			
Total residual deviance	[redacted]			[redacted]			[redacted]			

4.5 Conclusions of the clinical effectiveness section

The clinical evidence presented in the submission is based on three multicentre RCTs (CIMPASI-1, CIMPASI-2 and CIMPACT) comparing certolizumab to placebo and/or etanercept. An NMA was undertaken in order to compare certolizumab with the other therapies available at the same point in the treatment pathway, based on short-term efficacy data from individual trials.

All three certolizumab trials were reasonably good quality and the results are likely to be reliable. The three trials included non-biologic naïve patients, non-biologic non-responders and biologic exposed patients in the ITT population. Trial inclusion criteria appear to have been appropriate. However, patients were required to have a baseline PASI score ≥ 12 and there was no criteria for DLQI score, which is not entirely consistent with the threshold specified in the NICE pathway for patients to be considered for biologic therapies; PASI score ≥10 and DLQI score >10. However, the population in the trials is likely to be similar to the majority of patients eligible for biologic treatment in practice. Although all three trials excluded patients who had a history of primary failure (defined as no response within the first 12 weeks of treatment with the biologic) to any biologic or had received previous treatment with >2 biologics. This may exclude a proportion of the eligible population who are harder to treat and therefore less likely to achieve a response. Therefore, the results of the certolizumab trials may not be entirely generalisable to the proposed eligible population.

The trials demonstrated that certolizumab (200 mg Q2W and 400 mg Q2W) significantly reduced the severity of psoriasis and its impact on health-related quality of life, compared with placebo. A statistically significant difference was found between certolizumab (200 mg and 400 mg) and placebo for all of the outcomes reported at 16 weeks, including PASI 75 response (66.5-82.6% versus 3.8-11.6%), PASI 90 response (35.8-55.4% versus 0.3-4.5%), PGA score of 0 or 1 (47-71.6% versus 2-4.2%) and mean change in psoriasis percentage BSA affected (-16.3 to -20.5 versus -0.1 to -4.2). When results of the three trials were pooled, statistically significant improvements were observed for mean change from baseline in DLQI score in both the CZP 200 mg group (-9.1) and the CZP 400 mg group (-10.4) compared to the placebo group (-2.4) at week 16.

In CIMPASI-1 and CIMPASI-2, psoriasis severity at week 48 was assessed using the pooled results. The PASI 75 response rate was slightly higher at week 48 (83.6%) than in week 16 (82.0%) in the CZP 400 mg group. However, the PASI 75 response rate decreased at week 48 (70.7%) compared to week 16 (76.7%) in the CZP 200 mg group. In CIMPACT, PASI response was maintained through to week 48. The patients who were randomised to CZP 400 mg throughout the whole study had the highest PASI 75 (98.0%) and PASI 90 (87.8%) response rates compared to all other patients at week 48. Mean decreases from baseline in DLQI score were generally maintained through week 48 in patients receiving certolizumab in all three trials separately.

The ERG notes that the proportion of patients achieving PASI 75, PASI 90 and PASI 100 in both the CZP 200 mg and CZP 400 mg groups was greater in CIMPASI-2 than CIMPASI-1 and CIMPACT. However, the ERG is unclear about what is driving the difference between the study results. Therefore, the ERG is uncertain whether it is appropriate to pool results of all three trials, considering the heterogeneity between the results.

In the three certolizumab trials, [redacted]% to [redacted]% of patients in each of the treatment groups had not received any previous systemic therapy (including non-biologic). The ERG considers the biologic exposed and the systemic non-biologic therapy inadequate responders to be the most relevant populations, as they resemble the patients most likely to be treated with certolizumab in clinical practice. Subgroup analysis results are presented for non-biologic naïve patients, non-biologic inadequate responders and biologic exposed patients, which are assessed using the pooled study results. In non-biologic inadequate responders, the PASI response rates, PGA responses and DLQI change from baseline score for all three certolizumab trials pooled were similar to the pooled results for the ITT population at week 16. Subgroup results for the biologic exposed subgroup were also generally similar to the ITT pooled population at week 16. However, PASI 75, PASI 90 and PGA response rates were considerably lower at week 48 than at week 16 in the subgroup of biologic-exposed patients, compared with the biologic naïve patients, suggesting that certolizumab is poor at improving or maintaining response over time in biologic exposed patients. However, these results should be interpreted with caution, in view of the small numbers of patients in the subgroups.

During the 16-week initial treatment phase, the proportion of patients with an adverse event was higher in the CZP 400 mg group than the CZP 200 mg group. However, the rates are similar between the CZP 400 mg group and the placebo group ([redacted]% vs [redacted]%). The rate of adverse events increased from week 16 to week 144, suggesting that the risk of adverse events with certolizumab increases with longer exposure. In all three trials, the most common adverse events in the initial 16-week phase were infections and infestations (33.5%). The number of deaths due to adverse events was low in the maintenance phase, 0.3% in each treatment group.

The NMA appears to have included all relevant trials of certolizumab and the comparator therapies. Studies were assessed for quality, which suggested generally, the risk of bias for most studies was low. Inevitably the trials included in the NMA vary by design and patient characteristics. There was a substantial difference in the proportion of patients with psoriatic arthritis between the studies included (0% to 37%). There was also considerable variation in the time since diagnosis, ranging from 11 years to 24 years and mean baseline PASI score, which ranged from 15 to 33. All of these differences increase the risk of between study heterogeneity, which reduces the reliability of the NMA results.

The ERG identified several problems with the WinBUGS code used for the NMA. The CS reports that the approach used for the multinomial NMA has been adapted from the NICE Decision Support Unit (DSU) technical support document example in psoriasis (Example 6).[13] However, there is little similarity between the code used by the company and the example code in the DSU document. The code provided does not appear to be able to produce the results reported in the CS. Due to these issues, the ERG was unable to re-run the NMA.

[redacted] Similar results were seen for PASI 90 response rates. The results of the NMA, in terms of ranking order of effectiveness, were consistent with those of NMAs undertaken in other recent STAs of treatments for moderate to severe plaque psoriasis in adults and the NMA undertaken for the development of the BAD guidelines.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the electronic version of the economic model.

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Searches

The company undertook an SLR to identify published economic evaluations for individuals with moderate-to-severe plaque psoriasis. The review aimed to identify cost-effectiveness analyses, and cost and resource use data, for biologic therapies in the treatment of psoriasis. Full details of the search strategies are presented in Appendix G of the company submission.

Both SLRs searched the following electronic databases: MEDLINE, Embase, EconLit and NHS EED. An additional search of the grey literature (via Google Scholar and DuckDuckGo.com) was conducted to identify any further relevant studies.

The electronic database searches were performed in November 2016, with any studies published after this date identified through targeted literature searching.

The ERG considers that thorough searches of appropriate databases and conference proceedings were undertaken, albeit slightly out of date. The structure of the search strategies was appropriate. The strategies contained relevant subject headings, text word searches and synonyms and all search lines were combined correctly.

5.1.2 Inclusion/exclusion criteria used for study selection

The inclusion and exclusion criteria are provided in Table 27 in Appendix G.2.4 of the CS.

5.1.3 Studies included and excluded in the cost effectiveness review

The SLR identified 11 published economic evaluations, none of which assessed the cost-effectiveness of CZP. Four of these studies were based in a UK setting, but no details were provided on whether they were considered to provide relevant information to the current appraisal. Previous NICE TAs were summarised in section B.3.1 (Table 64), and described in further detail in Table 66 of the CS. Full details of the captured economic evaluations, as well as quality assessments for each study, are presented in Table 28 and Table 29 in Appendix G.4.

The ERG notes that the critical appraisal undertaken was generally a description of the models' features rather than a thorough analysis of the various modelling approaches, key assumptions and

data sources. However, the review provided useful contextual information and allowed the company to identify and justify any important differences in approaches.

5.1.4 Conclusions of the cost effectiveness review

The company's search identified no published cost-effectiveness studies of CZP. As such, the ERG considers that the *de novo* cost-effectiveness analysis reported in the company submission to be the most relevant source of evidence to inform the decision problem.

5.2 ERG's summary and critique of company's submitted economic evaluation

The company presented a *de novo* analysis based on a Markov model. The ERG notes that the model structure appears similar to the structure used in the economic evaluations identified in the cost-effectiveness review.

A summary of the company's economic evaluation is presented in Table 10 with justifications for key aspects and signposts to the relevant sections of the CS.

Table 10 Summary of the company's economic evaluation

Element of HTA	Approach	Source/Justification	Location in CS
Model Structure	A Markov model was employed for the cost-effectiveness analysis.	The use of a Markov model structure is appropriate when modelling sequences of treatments over an appropriate time horizon.	Section B.3.2.2 (p. 142 to 149)
Population	The eligible population is defined as patients with moderate to severe psoriasis, defined as a PASI score ≥12, who either are eligible for systemic non-biological therapy, or patients who have failed to respond to, or are unable to be treated with conventional systemic therapies.	In line with the NICE scope the company proposed that certolizumab be used as either as an alternative to systemic non-biological therapy or, consistent with the existing NICE pathway, following systemic non-biological therapies.	Section B.3.2.1 (p. 147)
Intervention and comparators	A number of different treatment sequences were considered, consisting of three lines of biologic treatment followed by BSC: A. Certolizumab-Ustekinumab-Infliximab-BSC B. Adalimumab-Ustekinumab- Infliximab -BSC C. Brodalumab – Ustekinumab- Infliximab -BSC D. Etanercept – Ustekinumab – Infliximab – BSC E. Guselkumab – Ustekinumab – Infliximab – BSC F. Ixekizumab – Ustekinumab – Infliximab – BSC G. Secukinumab – Ustekinumab – Infliximab – BSC H. Ustekinumab 45mg – Adalimumab – Infliximab – BSC I. Ustekinumab 90mg – Adalimumab – Infliximab – BSC	The comparators included in the model correspond to those recommended by NICE for the treatment of psoriasis after systemic non-biologic therapy has failed or was not tolerated. The positioning of biologics in the sequence was informed by the 2017 BAD guidelines, the CCG guidance on treatment sequencing in psoriasis and expert opinion from the company's advisory group.	Section B.3.2.3 and B.3.2.4 (p. 153 to 158)

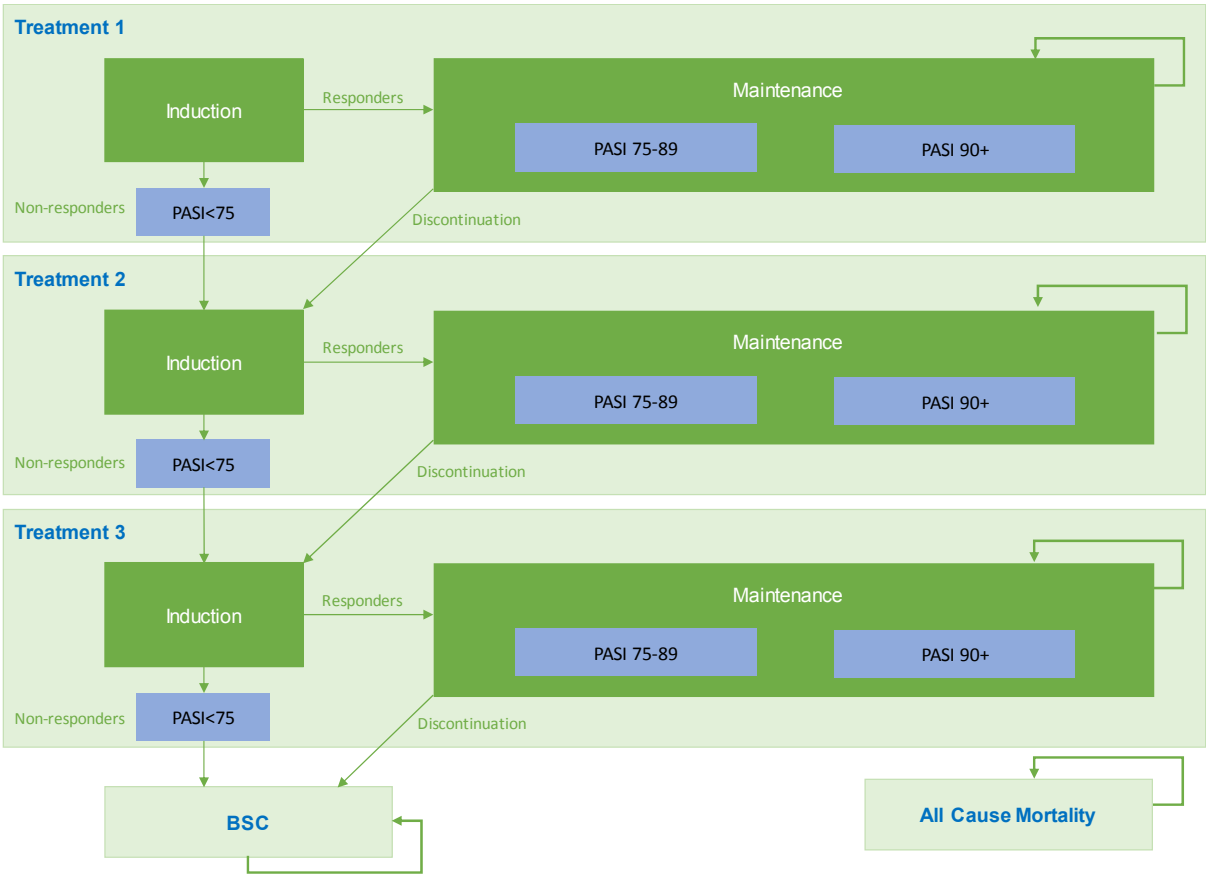
Perspective, time horizon and discounting	NHS and PSS perspective. A life-time horizon of 60 years was chosen and a discount rate of 3.5% was applied to both costs and QALYs	The perspective and discounting were considered consistent with the NICE reference case. A life-time horizon was considered sufficiently long to capture the incremental costs and benefits associated with the treatment sequence.	
Treatment effectiveness and extrapolation	Results from the NMA were used to inform the probability of response to treatment, by PASI category (0-49, 50-74, 75-89, 90-100), during the induction period of each treatment. Treatment continuation to the maintenance phase was dependent on PASI 75 response at the end of the induction period. Treatment discontinuation during the maintenance phase was fixed at a constant annual rate of 20% for all treatments. This incorporates withdrawal due to loss of response and adverse events.	Results from the NMA ensure all available evidence on the response to treatments is considered, addressing the lack of head-to-head trials comparing certolizumab relevant comparators. The same constant annual discontinuation rate was applied to all drugs and was justified as being consistent with evidence from the BADBIR registry. The discontinuation rate was derived from a UK-based registry (BADBIR) and matches the approach used previous NICE appraisals (TA146, TA350, TA442, TA511) [31-34]	Section B.3.3 (p. 158 to 161)
Health-related quality of life (HRQoL)	Estimated based on EQ-5D-3L data collected in the CIMPASI-1, CIMPASI-2 and CIMPACT trials. A GEE multivariate regression was used to identify the relationship between change in EQ-5D, PASI response at	The company justifies the use of EQ-5D data from CIMPASI-1, CIMPASI-2 and CIMPACT trials as providing the most relevant and robust source of utility data for certolizumab.	Section B.3.4 (p. 161 to 162), Table 76 (p.163)

	week 12, controlling for age, sex, BMI, base-line PASI score, previous biologic exposure, and treatment received.		
Resources and Costs	Costs and healthcare resource use considered included: • Drug Acquisition • Administration • Monitoring • Adverse Events • BSC	The identification and evaluation of resource use was justified as being consistent with previous NICE appraisals and current clinical guidelines.	Section B.3.5, (p. 164 to 169)
Adverse events	Adverse events, were not included in the analysis.	Adverse events we not included. The company noted this was consistent with previous HTA submissions.	Section B.3.4.3 (p. 170)
Subgroups	No clinically defined subgroup analysis is reported in the CS	As treatment response was reported to be consistent across clinically defined subgroups (previous use of systemic therapy, phototherapy and biological therapy, and disease severity), the company chose not to perform any subgroup analysis	
Sensitivity analysis	The company performed both one-way and probabilistic sensitivity analysis. A series of scenarios using alternative assumptions on key inputs were also presented	Justified based on the NICE reference case and the current methods guide.	Section B.3.8 (p. 174 to 205)

5.2.1 Model structure

The economic evaluation of certolizumab was conducted using a Markov state-transition model developed in Microsoft Excel. The use of a Markov approach was justified based on the need to model treatment sequences over a lifetime time horizon, considering separate treatment induction and maintenance phases for each treatment option. The ERG notes that the model structure is consistent with the most recent NICE technology appraisals of biologics for the treatment of psoriasis [31, 34]. The model structure is illustrated in Figure 6.

Figure 6 Schematic of company's economic model (CS Figure 23)



The model comprises four treatment-related health states (induction, maintenance, best supportive care and death) with patients being allocated to one of three PASI response categories (PASI <75, PASI 75-89, and PASI 90+). Patients were modelled to receive up to five lines of treatment, with the model allowing a comparison of any given sequence of treatments.

Each line of treatment in a sequence starts with an induction period which lasts between 10 and 16 weeks (see Table 12), reflecting the different response assessment times across treatments according to NICE treatment guidelines. For certolizumab, assessment of response was modelled to occur at 16 weeks after treatment initiation. At the end of the induction period, individuals are assigned to one of

the three PASI response categories based on the results generated by the NMA. Response to treatment was defined as achievement of a PASI 75 response, as this was the primary outcome used in the majority of the clinical trials of biologics in psoriasis and has been accepted by NICE as a clinically important marker of treatment response. Patients who achieved a response to treatment induction moved into the maintenance treatment phase and remained on the same therapy, while non-responders (PASI response <75) switched to a new therapy and re-entered the initial treatment phase.

During the maintenance period, individuals are assumed to continue to receive the same treatment and maintain their initial PASI response until treatment is discontinued due to loss of response and/or death. Unlike in previous appraisals, patients did not discontinue therapy due to adverse events [34]. Upon discontinuation due to loss of response, patients become eligible to receive the next treatment in the sequence, at this point PASI score is assumed to revert to baseline until the end of the treatment initiation period for the subsequent therapy. In line with a number of previous NICE appraisals, the company's base-case analysis assumes that patients discontinue treatment at a constant annual rate of 20% per annum across all treatments during the maintenance phase. Clinical advice to the ERG suggested this was not realistic, and based on BADBIR registry data it is more likely that we would see a sharp decrease in discontinuation over time [35, 36], with a significant proportion of patients remaining on a particular biologic without issues almost indefinitely.

In the company's base-case analysis, individuals who do not respond to the third line of treatment, or who discontinue during the maintenance phase, enter the best supportive care (BSC) state. Treatment within the BSC state comprises a blended comparator consisting of methotrexate, ciclosporin, and acitretin (in a ratio of 55:35:10). Patients are assumed to remain in the BSC state until the end of the model time horizon or death. A separate and common transition to death is assumed from all other states.

The structure of this model makes best supportive care state a key driver of relative cost-effectiveness, even when it is not a direct comparator. This is because patients spend a significant proportion of the time horizon of the model in this health state. This is a direct consequence of the use of a lifetime horizon and high treatment withdrawal rates. As discussed in detail in Section 5.2.4 the composition of BSC is unlikely to accurately represent clinical practice, particularly following previous biologic therapy. The uncertainty surrounding the composition, efficacy, and cost of best supportive care leads to distortion of the relative cost-effectiveness of biologics. In the model, this has the perverse effect of making those drugs with a lower response rate appear to be more cost-effective when viewed as single lines of therapy, as patients transition to BSC, a low-cost and relatively high-QALY state earlier and remain there for longer. Therefore, Section 6 presents several scenarios encompassing shorter time

horizons to more directly compare the cost-effectiveness of these biologics within the confines of the presented model structure.

A summary of the health states included in the model is presented in Table 11. Within each treatment state in the model, patients can be in a number of different health states, i.e. with a different level of PASI response associated with corresponding HRQoL and costs. This is described further in Sections 5.2.6 and 5.2.7.

Table 11 Summary of model states

State	Definition
Induction period	10-16 weeks (depending on the treatment), after which treatment response is assessed.
Maintenance period	Continued use of treatment if induction response is ≥ PASI 75 at the assessment point
BSC	Last treatment strategy for patients having failed all other treatment options.
Death	Absorbing state which can be reached from any state and at any time.

The model assumes that assessment of treatment response occurs at 16 weeks for certolizumab, reasoning that this is in line with recommendations in the as yet unpublished SmPC. This was also consistent with the timing of the response assessment in the CIMPASI-1-2, and CIMPACT trials.

The ERG notes that while the 16-week response assessment period for certolizumab is in line with the trial outcomes, and some other biologics, it may inflate the relative efficacy versus those drugs whose 10-12 week outcomes were used in the NMA (this is discussed further in Sections 4.3 and 4.4) Table 12 presents a summary of the response assessment periods for certolizumab and its comparators as implemented in the company's economic model.

Table 12 Summary of comparator response assessment periods

Drug	Duration	Source
Certolizumab pegol	16 weeks	Company assumption and SmPC
Guselkumab	16 weeks	NICE TA521[37]
Brodalumab	12 weeks	NICE TA 511[34]
Adalimumab	16 weeks	NICE TA 455[32]
Apremilast	16 weeks	NICE TA 368[38]
Dimethyl fumarate	16 weeks	NICE TA 475[39]
Etanercept	12 weeks	NICE TA 103[40]
Infliximab	10 weeks	NICE TA 134[41]
Ixekizumab	12 weeks	NICE TA 442[31]
Secukinumab	12 weeks	NICE TA 350[33]
Ustekinumab	16 weeks	NICE TA 180[42]

To account for the different assessment periods recommended by NICE for the initial response assessment, the model uses a cycle length of two weeks with a half-cycle correction. The ERG considers a two-week cycle length appropriate.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 13 summarises the ERG's assessment of whether the company's economic evaluation meets NICE's reference case and other methodological recommendations.

Table 13: NICE reference case checklist

Element of economic evaluation	NICE Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Defining the decision problem	As per NICE scope	Yes	The NICE scope refers to "*adults with moderate-to-severe plaque psoriasis"*, i.e. all patients covered under the licensed indication which includes patients conventional systemic treatments including both systemic non-biological and biological therapies.
Comparator(s)	As listed in the scope developed by NICE	Partially	The company states that the most appropriate comparators for certolizumab, given its proposed positioning are other biologic therapies, and BSC. A restricted set of 'all feasible' sequences were compared. Certolizumab was only evaluated as a

Element of economic evaluation	NICE Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
			first line treatment option within these sequences.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes	
Perspective on cost	NHS and PSS	Yes	
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes	
Time horizon	Long enough to reflect all of the important differences in costs or outcomes between the technologies being compared.	Yes	The base case includes a lifetime time horizon of 60 years, which is considered sufficiently long to account for all of the important differences between the comparator sequences.
Synthesis of evidence on health effect	Based on systematic review	Yes	A systematic review was undertaken to collect all available evidence on relevant health effects from published studies and previous submissions.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes	
Source of data for measurement of health-related quality of life	Reported directly by patients or carers	Yes	EQ-5D-3L collected alongside the CIMPACT trial
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes	Utilities were calculated using UK preference weights for EQ-5D-3L
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	All QALYs are given the same weight
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	

Element of economic evaluation	NICE Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes	

5.2.3 Population

Certolizumab is licensed for patients aged ≥18 years with moderate to severe plaque psoriasis, who are candidates for systemic therapy [2]. Moderate to severe plaque psoriasis is defined as a PASI score of 10 or greater, and a DLQI score of 10 or greater. The company presented this population in their economic analysis, using efficacy data for certolizumab drawn from three clinical trials where patients were required to have baseline PASI ≥12 to be eligible for enrolment.

The company considered the effectiveness of certolizumab in two patient populations: *(i)* those who are candidates for systemic biologic therapies, and *(ii)* for those who have an inadequate response, contraindication, or intolerance to other systemic non-biologic therapies (including ciclosporin, MTX or PUVA). The populations and the data from the clinical trials used to inform the efficacy in each population are summarised in Table 14. While the clinical data used to model candidates for systemic non-biologic therapy was based on a subgroup of those who were naïve to both non-biologic and biologic systemic therapy, the clinical data used to model inadequate responders to systemic non-biologic therapy was based on the overall patient population (i.e. including both systemic naïve and inadequate responders to systemic non-biologic therapy). It was not possible to restrict to this subgroup, as the necessary data were not available for all other biologic comparators.

Table 14 Patient populations considered in the economic analysis (CS Table 65, Page 148)

Analysis	Patient population
Systemic non-biologic therapy inadequate responders	Overall patient population: All patients captured in the CIMPASI-1, CIMPASI-2 and CIMPACT phase III clinical trials. This analysis informs the decision for the population who are eligible for current biologics, defined in the NICE scope as patients for whom conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated.
Candidates for systemic non-biologic therapy	Subgroup of the pooled CZP Phase III trials, where patients at the start of the trial were naïve to both non-biologic and biologic systematic therapy.
Abbreviations: CZP: certolizumab pegol; NICE: National Institute for Health and Care Excellence	

In the analysis of systemic non-biologic therapy inadequate responders**,** patients' starting characteristics in the model are assumed to be similar to the average baseline characteristics reported across the NMA studies. The mean age and weight of the cohort were assumed to be 44.9 years and 87.2kg, respectively. Approximately two-thirds (69.2%) of cohort were assumed to be male.

The starting characteristics of candidates for systemic non-biologic therapies were based on to the mean baseline characteristics reported for patients randomised to certolizumab 200mg and certolizumab 400mg in CIMPASI-1, CIMPASI-2 and CIMPACT.

Table 15 Starting patient characteristics (Table 72, CS, pg 158)

Model parameter	Value	Source
Systemic non-biologic inadequate responders		
Mean age, years	44.9 years	Pooled NMA data
Percentage male	69.2%	
Mean weight (kg)	87.2 kg	
Candidates for systemic non-biologic therapies		
Mean age, years	45.4 years	'All CZP' from Pool E1 candidates for systemic non-biologic subpopulation (see Appendix M)
Percentage male	63.4%	
Mean weight (kg)	91.8 kg	
Abbreviations: CZP: certolizumab pegol, NMA: network meta-analysis		

ERG comment

The population considered in the main analysis is largely representative of that in NHS clinical practice. However, the exclusion of patients with less severe disease at baseline, i.e. those with a PASI score of 10 or 11, may bias the trial results, or at least reduce their relevance for to the UK population. The ERG also notes that the candidates for systemic non-biologic therapies group is assumed to be older than the systemic non-biologic inadequate responders group, which is unrealistic given that the former are assumed to be at an early stage in the pathway. The impact of this discrepancy is, however, minor.

With regards to the population eligible for systemic non-biologic therapy, the clinical advisor to the ERG confirmed that although biologics such as certolizumab are licensed for use earlier in the pathway, in UK practice they would not be used before non-biologic systemic therapies. While the company argues this positioning reflects that set out in NICE's scope for this appraisal, this interpretation is inconsistent with the population considered in previous NICE assessments for other biologic treatments, which restricted use earlier in the pathway to those contraindicated to systemic non-biologic therapies despite similar wording of the scope. Therefore, the ERG considers it inappropriate to consider those patients eligible for systemic non-biologic therapy for treatment with certolizumab, in line with NICE's current clinical guidelines [14]. See Section 3.1 for further discussion.

5.2.4 Interventions and comparators

The comparators considered in the model were dependent upon the positioning of certolizumab and were modelled as a sequence of up to five therapies.

5.2.4.1 Candidates for systemic biologic therapy

The main intervention considered in the company's economic model is 200mg certolizumab Q2W after a 400mg loading dose (LD) at weeks 0, 2, and 4. Certolizumab is included in a first line position alongside the other biologics recommended by NICE for psoriasis patients who have failed to respond to conventional systemic therapies including methotrexate, ciclosporin, and acitretin, which comprise the most common best supportive care therapies. The comparator treatments included in the model are as follows:

- Adalimumab (80mg LD, 40mg Q2W)
- Brodalumab (210mg q1w for 3 weeks, then Q2W)
- Etanercept (including biosimilars) (25mg biw, or 50mg q1w)
- Guselkumab (100mg at weeks 0 and 4, followed by q8w)
- Ixekizumab (160mg week 0, then 80mg Q2W until week 12, then 80mg q4w)
- Secukinumab (300mg q1w for 5 doses, then 300mg every month)

- Ustekinumab (45mg weeks 0, 4, then 90mg q12w)
- Ustekinumab (90mg weeks 0, 4, then 90mg q12w)

The above therapies were modelled using nine different treatment sequences, each of which included three lines of active therapy, before patients move to non-biologic best supportive care. The company based this assumption on clinical opinion, which suggested that patients would receive up to three lines of biological therapy. As presented in Table 16**Error! Reference source not found.**, certolizumab and each of the comparator therapies listed above are assumed to be followed by a second- and third-line biologic therapy, each with a different mechanism of action to the preceding line. The company state that these sequences were selected to reflect clinical opinion and the most recent BAD guidelines, noting that BAD guidelines recommend that adalimumab and secukinumab should be used as first-line biologics for all patients regardless of concomitant psoriatic arthritis (PsA), and ustekinumab is given to those without PsA. The company also cites clinical opinion, previous NICE appraisals (TA511 and TA442), and prescribing data, to suggest that patients tend to switch to ustekinumab unless this has been used first-line.

Table 16 Treatment sequences included in the company base-case (CS Table 68, Page 156)

Sequence	1st line	2nd line	3rd line	4th line	5th line
A	CZP 200 mg	UST 90 mg	IFX	BSC	BSC
B	ADA	UST 90 mg	IFX	BSC	BSC
C	BROD	UST 90 mg	IFX	BSC	BSC
D	ETN	UST 90 mg	IFX	BSC	BSC
E	GUS	UST 90 mg	IFX	BSC	BSC
F	IXE	UST 90 mg	IFX	BSC	BSC
G	SEC	UST 90 mg	IFX	BSC	BSC
H	UST 45 mg	ADA	IFX	BSC	BSC
I	UST 90 mg	ADA	IFX	BSC	BSC

Abbreviations: ADA: adalimumab; BROD: brodalumab; BSC: best supportive care; CZP: certolizumab pegol; ETN, etanercept; GUS: guselkumab; IFX: infliximab; IXE: ixekizumab; SEC: secukinumab; UST: ustekinumab.

The company note that numerous alternative approaches could have been taken when constructing the comparator sequences given the large number of available biologics, and highlights the effect of sequencing potentially non-cost-effective drugs at later therapeutic lines upon the apparent cost-effectiveness of a particular comparator. In justifying the selected sequences the company states that its aim was to compare certolizumab to those sequences most commonly used in practice and that it is their expectation that certolizumab will be used as a first line treatment option.

ERG comment

The ERG notes that the modelling of treatment sequences as opposed to the comparison of single lines of therapy followed by BSC more appropriately reflects clinical practice, and is consistent with the modelling approaches used in the most recent NICE appraisals (TA442, TA475, and TA511[31, 34, 39]). However, the ERG also notes that previous appraisals have also raised questions regarding whether the selected sequences (excluding a new therapy) are representative of current clinical practice and whether different positions have been assessed for a new therapy. In this regard, the ERG notes that the sequences proposed are unlikely to reflect current practice. Firstly because, as stated by the company, the majority of patients receive either adalimumab and secukinumab as their first line biologic therapy, with other biologics either used more rarely or further along a potentially longer sequence. Secondly, infliximab is unlikely to be used frequently in this population, as it is not funded on the NHS for those with moderate to severe disease. Infliximab would therefore be used only in those patients who have failed on all reasonable treatment options, and have more severe disease which requires management.

The ERG also questions positioning of certolizumab as first-line biologic therapy, which the ERG consider unlikely given the dominance of adalimumab and secukinumab and the imminent launch of adalimumab biosimilars. Expert clinical advice received by the ERG suggested that while certolizumab may be used in some patients as a first line biologic it was more likely to be used further along the pathway. Related to this, the ERG highlights that each biologic varies with regards to its relevance as a comparator for certolizumab. As previously discussed, treatments of different classes are used sequentially in clinical practice. Therefore, a more relevant comparison might be between anti-TNFα drugs, i.e. adalimumab, certolizumab, etanercept, and infliximab, while the others may not be considered strictly as alternatives at a particular point in the treatment pathway. Therefore it is worth noting certolizumab's relative cost-effectiveness compared to adalimumab in the analyses presented in this report, particularly given the current market share of adalimumab, and the significant anticipated reductions in price.

Further to the above, the ERG also notes concerns expressed by previous ERG groups and NICE committees that modelling selective sequences (as opposed to all feasible sequences) could provide misleading estimates of cost-effectiveness, particularly if there are treatments included in a sequence which are not cost-effective themselves (e.g. TA442 and TA475[31, 39]). The concept of treatment sequencing in the absence of real efficacy data is also highly problematic in itself, as the data does not (and cannot) demonstrate the efficacy of any particular sequence, with no evidence to suggest one is better than another. Sequencing as performed in this model essentially captures only the costs and naïve efficacy of each sequence, and it is uncertain whether this is an accurate proxy for real-world

efficacy. Thus, the impact of changing the ordering of drugs is primarily due to discounting and mortality, rather than any material difference in efficacy.

The use of best supportive care as an absorbing state after failure on a third biologic is also problematic given the high discontinuation rate applied by the company for biological therapies. This results in modelled patients spending a significant proportion of the modelled time horizon in the BSC state, which is unlikely to be the case in practice. As no comparators are cost-effective versus best supportive care, it is beneficial to the cost-effectiveness of a drug to remain in BSC for as long as possible, as the QALYs gained on BSC are cheaper. Thus, a sequence of drugs with lower response rates will appear more cost-effective, as patients get to BSC more quickly.

The residency time in the BSC state is particularly inappropriate in those with more severe or life-limiting disease, who, according to expert advice received by the ERG, would not receive sufficient symptom relief on BSC alone. Once patients are referred to a specialist centre, there would be no effective limit on the treatments (biologics or otherwise) offered, and after multiple failures of biological therapy would likely try small molecule therapies such as dimethyl fumarate and apremilast which can induce long-term symptom relief in some patients, and in others further biologics would be tried. However, this is unlikely to apply to the majority of patients, who are likely to be treated successfully over a long period with biologics.

In Section 6, the ERG proposes an alternative approach to inform the cost-effectiveness of alternative sequences based on net-benefit calculations in which a range of assumptions about sequencing are explored.

5.2.4.2 Dose escalation strategy

In line with the market authorisation, a treatment sequence was also explored where patients who did not achieve a PASI 75 response on the 200mg dose were escalated to 400mg Q2W.

This analysis compares this strategy to the adalimumab dose escalation strategy, which is a currently licensed alternative dose escalation strategy. The company assumed those patients who did not achieve a response on the adalimumab 40mg or certolizumab pegol 200mg dose within the induction period would be moved to an 80mg or 400mg dose respectively, and achieve a response in line with the data taken from the higher-dose trial arms (Table 17).

Table 17 Treatment sequences modelled for dose escalation strategies (CS Table 69, Page 157)

Sequence	1st line	2nd line	3rd line	4th line	5th line
K	CZP 200 mg	CZP 400 mg	UST 90 mg	IFX	BSC
L	ADA 40 mg	ADA 80 mg	UST 90 mg	IFX	BSC
Abbreviations: CZP: certolizumab, UST: ustekinumab, IFX: infliximab, BSC: best supportive care, ADA: adalimumab					

ERG comment

The ERG does not consider the sequences modelled by the company to be appropriate or informative. The ERG also notes the application of incorrect efficacy data in this scenario (further discussed in Section 5.2.6). The ERG considers the counterfactual to the proposed dose escalation strategy to certolizumab without dose escalation, to reflect that any recommendation for the use of certolizumab in the NHS should be based on the most cost-effective use of certolizumab. Under this counter factual the ERG's considers that the alternative to certolizumab escalation should be transition to the next biologic in the treatment pathway as per standard clinical practice. That is, is the best treatment option upon a 16-week non-response on 200mg certolizumab to increase the dose to 400mg, or switch to ustekinumab, the next treatment in the pathway. The ERG presents the results of an analysis of this decision in Section 6, in which the cost-effectiveness of CZP with, and without dose escalation is compared.

Further to above, with respect to the validity of the present comparison, clinical advice to the ERG suggests that while only adalimumab and etanercept are licensed for dose escalation, the 90mg ustekinumab dose is available at no extra charge and thus is generally the only drug for which dose escalation is used in practice, and typically only in those weighing >90kg. It is anticipated that given sufficient discount upon the release of adalimumab biosimilars, dose escalation may see increasing use in practice where all other treatment options have been exhausted or are inappropriate; however, this is dependent on local commissioning arrangements;

5.2.4.3 Candidates for systemic non-biologic therapy

The main comparator in the 'candidates for systemic non-biologic therapy' population was standard of care, which comprised best supportive care, followed by four lines of biological therapy. Although infliximab (5mg/kg weeks 0, 2, 6, then Q8W) is only recommended by NICE with patients with very severe psoriasis (defined as PASI≥20 and DLQI>18), this was included in the treatment sequence, but not compared directly to certolizumab pegol. Best supportive care comprised methotrexate, ciclosporin, or acitretin.

Table 18 Treatment sequences modelled for candidates for systemic non-biologic therapy (CS Table 70, Page 157)

Sequence	1st line	2nd line	3rd line	4th line	5th line
A	CZP 200 mg	UST 90 mg	IFX	BSC	BSC
M	SoC	ADA	UST 90 mg	IFX	BSC
Abbreviations: CZP: certolizumab, UST: ustekinumab, IFX: infliximab, BSC: best supportive care, ADA: adalimumab, SoC: standard of care					

This analysis treats the first therapeutic option in the sequence as one point earlier in the treatment pathway, and models certolizumab followed by ustekinumab 90mg, infliximab, and best supportive care, against standard of care, followed by adalimumab, ustekinumab 90mg, infliximab, and best supportive care.

ERG comment

The ERG do not consider the company to have presented sufficient evidence to support this earlier positioning of certolizumab. This sequence is unprecedented in previous guidance issued by NICE and does not accurately represent the outcome of an initial treatment decision, as it relies on accurate and representative treatment sequencing, which as previously discussed in Section 5.2.4.1 does not apply in this scenario. The cost-effectiveness of certolizumab at this point in the pathway also depends entirely upon its comparison against an already less cost-effective comparator, and not upon its positioning. This is demonstrated when the 2nd line treatment in sequence M above is changed from adalimumab to brodalumab, secukinumab, ixekizumab, or even certolizumab, in which case certolizumab in candidates for systemic non-biologics becomes cost-ineffective.

The company's base-case analysis uses pooled methotrexate and placebo response data at a 55:45 ratio, this is likely to underestimate the response rates of patients on systemic non-biologic therapies, as by definition these patients will be treated with methotrexate, ciclosporin, or acitretin. In the company's clarification response, an analysis was provided which used methotrexate data as a proxy for the first line standard of care, i.e. which was used in sequence M above, while BSC at 2nd or later line used the pooled response data as in the company's base case.

Current guidance suggests it is not appropriate to treat patients eligible for systemic non-biologic therapies with biologics, as conventional therapies can be used to successfully treat many patients at a fraction of the cost. A more plausible analysis would model a hypothetical change in NICE guidelines to allow earlier treatment with biologics, and compare certolizumab alongside all other available biologics.

5.2.5 Perspective, time horizon and discounting

Consistent with the NICE methods guide[43] the company's analysis used NHS and Personal Social Services (NHS & PSS) perspective and discounted costs and benefits at a rate of 3.5%.

A life time horizon of 60 years was chosen as it was considered sufficient to capture all relevant differences in costs and benefits between comparators. The impact of a shorter 5 year, 10 year and 15 year time horizons, in line with several previous NICE TAs, was also explored in a scenario analysis. The ERG considers that the shorter time horizons explored in the scenario analysis may be more appropriate. This is because of limitations in the model structure and available clinical data highlighted in section 5.2.1. In particular, the fact that patients spend a significant proportion of the time horizon of the model in the BSC health state, which is unlikely to reflect current practice. A shorter time horizon may therefore be more appropriate to mitigate the effect of these issues and the influence the BSC health state has on model outcomes. This would also align with a number of previous TAs, which have generally used time horizon of 5 to 10 years.[33, 37, 39, 41, 42]

5.2.6 Clinical effectiveness

5.2.6.1 Treatment effectiveness

Treatment effectiveness is measured in the model using the proportion of individuals achieving a specific threshold of PASI response relative to baseline. Relative change in PASI response is the most widely reported outcome in the clinical trials and has been used as the main outcome in previous models. At the end of each induction period patients are allocated to one of the following four health states:

- PASI 0-49: an improvement in their psoriasis less than 50%;
- PASI 50-74: an improvement in their psoriasis between 50 and 74%;
- PASI 75-89: an improvement in their psoriasis between 75 and 89%;
- PASI 90-100: an improvement in their psoriasis between 90% or greater.

The source of treatment effectiveness data used in the model was dependent upon the positioning of certolizumab.

Candidates for systemic biologic therapy

Where certolizumab is positioned as alternative to other biologic therapies the response rates for the majority of treatments included in the model were obtained from the company's NMA adjusted for placebo response. The exception to this is adalimumab 80 mg Q2W, which was not included within the NMA (due lack of appropriate data). PASI response rates for adalimumab 80 mg Q2W were estimated by multiplying the PASI 75 score for adalimumab 40 mg Q2W by a factor of 1.5. This multiplying

factor was derived from the CHAMPION 1 study[44]. The ERG considers that this assumption highly simplistic and that the resulting estimates of relative effectiveness for adalimumab 80 mg Q2W, are therefore subject to considerable uncertainty. Comparisons with adalimumab 80 mg Q2W are, however, only made in the dose escalation scenarios, which as stated in Section 5.2.4 have not used an appropriate counterfactual sequence. The implications of this assumption is therefore limited as in a more appropriately structured scenario this data would not be utilised.

Table 19: Proportion of patients in each PASI response category at the end of the induction period (CS Table 73)

	Response			
Treatment	**PASI <50**	**PASI 50 to <75**	**PASI 75 to <90**	**PASI 90+**
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]
ADA 80 mg*	[redacted]	[redacted]	[redacted]	[redacted]
BROD	[redacted]	[redacted]	[redacted]	[redacted]
BSC**	[redacted]	[redacted]	[redacted]	[redacted]
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]
CZP 400 mg	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]
GUS	[redacted]	[redacted]	[redacted]	[redacted]
IFX	[redacted]	[redacted]	[redacted]	[redacted]
IXE	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]
UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]
UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]

*ADA 80 mg derived from the CHAMPION study. **BSC is a mixture of placebo and MTX at a proportion of 45:55.
Key: PASI: psoriasis area and severity index; ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; IFX: infliximab; IXE: ixekizumab; SEC: secukinumab; UST: ustekinumab

In the base case analysis, the PASI 75 response rate was selected as the response threshold for treatment continuation beyond the induction period. The company justified this choice stating that this PASI 75 was "*the primary endpoint in the majority of psoriasis clinical trials and has been accepted by NICE in previous appraisals in psoriasis*" (CS, p. 147). The impact of using PASI 50 response rate an alternative cut-off was explored in a scenario analysis.

In the base-case analysis, it was assumed that prior biologic treatment did not modify treatment response and that the effectiveness of a drug was independent of its position in a sequence. The company did not justified this approach, but it is consistent with previous appraisals and the ERG

considers this acceptable given the availability of evidence to perform a robust NMA. Responders to treatment during the induction period were assumed to maintain their level of response during the maintenance phase until treatment discontinuation.

As discussed in Section 4.4, the ERG is generally satisfied with the approach taken by the company described in the CS and considers the use of a placebo adjusted model reasonable, and to provide somewhat better fit statistics compared with the unadjusted model. However, as noted in Section 4.4 the ERG is concerned about the WinBUGS code provided to the ERG, which does not reflect the code used to generate the results presented and has thus prevented the ERG from replicating the results of the NMA. It is therefore unclear whether the response rates generated are correct. Furthermore, the ERG is concerned about the significant range in response rates observed across the three phase 3 trials. This potentially suggests that the effectiveness of certolizumab is sensitive to the population in which it is used and a degree of uncertainty in the response rates that will be realised in practice. Because PASI response rate is a significant driver of cost-effectiveness, this uncertainty in the clinical data also impacts on the cost-effectiveness of certolizumab relative to other biologic therapies. To explore this uncertainty the ERG conducts additional scenario analysis using the response rates observed in each of the CIMPASI trials.

Candidates for systemic non-biologic therapy

In the scenario where certolizumab is considered as an alternative to non-biological systemic therapy, certolizumab and standard care PASI response scores are drawn from a subgroup analysis of the three phase 3 trials, using reported placebo response to represent standard care. The proportion of patients in each PASI category at the end of the induction period are summarised in Table 20. Because data for other biologic therapies is not available in this population, data were drawn from the NMA for other therapies.

Table 20 Proportion of patients in each PASI response category at the end of the induction period, candidates for systemic non-biological therapy population (CS Table 74, Page 160)

	Response			
Treatment	**PASI<50**	**PASI 50 to <75**	**PASI 75 to <90**	**PASI 90+**
Standard care	[redacted]	[redacted]	[redacted]	[redacted]
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]
CZP 400 mg	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: PASI, psoriasis area and severity index; CZP, certolizumab pegol				

As described in Section 5.2.4 the ERG has significant concerns about the appropriateness of positioning certolizumab as a comparator to non-biologic therapy. The ERG notes that the analysis presented in the CS use response rates observed in a pooled analysis of the three phase 3 trials to reflect the effectiveness of best supportive care. The ERG considers this inappropriate because patients in the placebo arm of the phase 3 trials were not permitted to receive any kind of systemic therapy, and therefore the PASI response rates observed in the placebo arm reflect the effectiveness of no therapy rather than standard care. Further, the ERG notes that the placebo response rates observed are substantially lower than the response rate predicted by the NMA for acitretin and methotrexate, which are routinely used non-biologic systemic therapies. Noting these issues the ERG therefore requested at the points for clarification stage for the company to justify the use of the placebo response data. The company in their response noted a lack of appropriate data to inform this analysis and that it was not possible to conduct a NMA in this population. The company therefore presented an additional scenario analysis using the response rate for methotrexate estimated in the NMA. The company's response highlighted that methotrexate is the cheapest systemic non-biologic, and in the NMA had the highest PASI response rates compared to acitretin and ciclosporin. The company therefore notes that the results of this analysis are an optimistic representation of standard care. The results of this additional analysis are presented in full in Section 5.2.9 and result in the ICER increasing to £18,145.34 per QALY.

5.2.6.2 Discontinuation

The rate of discontinuation in the induction phase of the model was determined for each therapy through a NMA of the clinical trial data, see Table 21 for the rate applied.

Table 21 Discontinuation rate per person week during the initial treatment phases (CS Table 75)

Treatment	Weekly discontinuation rate
ADA	[redacted]
BROD	[redacted]
BSC*	[redacted]
CZP 200 mg	[redacted]
CZP 400 mg	[redacted]
ETN	[redacted]
GUS	[redacted]
IFX	[redacted]
IXE	[redacted]
SEC	[redacted]
UST 45 mg	[redacted]
UST 90 mg	[redacted]

*BSC is a mixture of placebo and MTX at a proportion of 45:55.
Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; IFX: infliximab; IXE: ixekizumab; SEC: secukinumab; UST: ustekinumab

Long-term discontinuation data for each of the biologic therapies was not well reported in the clinical trials. Discontinuation rates during the maintenance phase of the model were therefore informed by the UK BADBIR register, which reports on the long-term drug survival rates of four biologics (adalimumab, etanercept, infliximab and ustekinumab).[45] Based on this data a constant annual discontinuation rate of 20.0% was applied in the maintenance period to all treatments (except BSC). This rate includes drop-outs for any reason (loss of response, adverse events, etc.). The rate applied is the same as that applied in a number of previous TAs submitted to NICE (TA146, TA350, TA442 and TA511)[31-34].

The company explores the possibility of differential discontinuation rates in a scenario analysis, noting that clinical expert opinion suggests certolizumab may have a particularly durable response. In this scenario the discontinuation rates of adalimumab was set to 18%, etanercept to 30% and all other biologic therapies including certolizumab to 9% per annum.

The ERG notes several issues and uncertainties regarding the scenario proposed by the company:

- As acknowledged by the company, the BADBIR registry does not include data specifically on certolizumab, and this scenario assumes the discontinuation rate for certolizumab aligns with that of ustekinumab. It is unclear why the discontinuation rate of certolizumab would be the same as ustekinumab given it is a different class of therapy (ustekinumab is an IL inhibitor) and it has a very different dosing frequency (every 12 weeks for ustekinumab compared with every 2 weeks for certolizumab).

- The limited long-term evidence presented on the duration of response suggests that a higher discontinuation rate may be appropriate for certolizumab; of the patients who achieved PASI 75 response at week 16, 89.5% continued to maintain that response at 48 weeks, suggesting loss of efficacy in 10.5% of patients.

- Evidence on the discontinuation rates of other anti-TNFs suggests a higher discontinuation rate and no biological explanation is put forward to support why certolizumab would have a substantially lower discontinuation rate than other anti-TNFα therapies.

The ERG considers that the assumptions applied in the base case analysis appear more justifiable than those considered by the scenario. However, the ERG recognises that there exists significant

uncertainty concerning both the rate of discontinuation and whether there are important treatment or class specific differences. Additional scenario analyses are presented in Section 6 exploring the potential for class-based effects.

5.2.6.3 Mortality

Mortality was based on general population mortality using age and sex adjusted rates. The company noted that there is a potential link between moderate to severe psoriasis and an increased risk of cardiovascular mortality, but also noted that moderate to severe psoriasis is also associated with obesity and therefore considers that there is a lack of robust evidence to support an additional mortality risk. This is in line with the majority of previous TA submissions, but the ERG notes that some recent appraisals, namely TA 511[34], have assumed an additional mortality risk. The impact of using alterative mortality rates is relatively small, given that they are applied to patients regardless of their response to therapy, and the ERG does not explore this further.

5.2.7 Health related quality of life

Outcomes of the model were expressed using quality adjusted life years (QALYs). The utility values used in the model were derived from EQ-5D-3L data (UK value set) collected in the CIMPASI-1, CIMPASI-2 and CIMPACT trials, using data reported from all patient arms and all time points. EQ-5D data were collected during patient visits at weeks 0, 8, 12, 16, 24, 32, and 48. The mean utility score at baseline in each trial was as follows: CIMPASI-1 was [redacted] (SD [redacted]), CIMPASI-2 was [redacted] (SD [redacted]), and CIMPACT was [redacted] (SD [redacted]).

The utility values in the model were based on the proportion of individuals in the different PASI response categories (<50, 50-75, 75-90, ≥90) and were assigned based on the PASI response category reached.

To estimate utility values for each level of response, the company developed a multivariable risk equation to predict utility values for each health state (PASI response, by category). The variables considered included age, sex and BMI in addition to baseline PASI score, and prior exposure to biologic treatment. The company used generalised estimating equations (GEE) approach to analyse EQ-5D data, in order to take into account the multiple observations per patient, which are more likely to be correlated than measurements from different individuals.

From inspection of the executable model, the ERG identified that a different set of utility values had been applied in the analysis where patients received CZP as first-line systemic therapy (i.e. the candidates for systemic therapy). This is due to the predictor of prior biologic use not being applied in

the model for these patients. In these patients, the predicted utility values were lower than those that were applied to non-biologic inadequate responder patients (Table 22).

In addition, a treatment variable was included in the final regression model, as this was reported to have a significant treatment effect on utility. The utilities estimated without the treatment effect were applied to BSC and to standard of care for the population who are candidates for systemic non-biologic therapy, and the utilities estimated with the treatment effect were applied to all biologics.

Table 22 Health state utility values

State	Prior biologics use		Candidates for systemic therapy	
	Utility value: BSC (difference from baseline)	Utility value: biologics (difference from baseline)	Utility value: BSC (difference from baseline)	Utility value: biologics (difference from baseline)
Baseline PASI	[redacted]	[redacted]	[redacted]	[redacted]
PASI <50	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50–75	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75–90	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90–100	[redacted]	[redacted]	[redacted]	[redacted]

PASI: psoriasis area and severity index, BSC: best supportive care
Note, these are corrected values that were supplied by the company in their response to the clarification questions by the ERG

The company did not model the impact of any treatment-related adverse events on quality of life, assuming the rate of these to be small and similar across treatments.

ERG comment

The ERG considers that the approach met the NICE reference case, but did not consider that the submission adequately justified the approach taken with the regression analysis, for example with the handling of missing data. However, the approach taken by the company seems unlikely to generate any important bias. No adjustment has been made for the impact of ageing in the model; however, in the absence of any differential mortality effect assumed between treatments, the ERG does not consider that this introduces any potential bias when comparing alternative sequences of equal length. The ERG is also satisfied with the approach regarding the exclusion of disutilities relating to adverse events, as these have not been demonstrated as being key drivers of the model in previous NICE appraisals [34] [31].

DLQI

The ERG noted that the CIMPASI and CIMPACT trials did not restrict the inclusion criteria based on DLQI score. However, patients with moderate to severe psoriasis, for whom certolizumab is licensed, are defined as those with DLQI greater than 10. The ERG requested that the company provided the mean utility values for the subset of the trial population who had DLQI≥10 (Table 31). As expected, these analyses provided lower utility values than that for the whole (DLQI unrestricted) population; however, the gain in utility with achieving each PASI response appears to be greater in the DLQI≥10 population. The ERG considers that these are more appropriate utility values to include in the analysis than those used in the base-case analysis, as they correspond to the subgroup of patients who are eligible treatment and appear to be more comparable to those estimated for other submissions of psoriasis (see Table 23 below). The impact of including these utility values is explored by the ERG in Section 6.

Table 23 Summary of utility values for DLQI≥10 (adapted from Table 42, points for clarification)

State	Prior biologics use	
	Utility value: BSC (difference from baseline)	**Utility value: biologics (difference from baseline)**
Baseline PASI	[redacted]	[redacted]
PASI <50	[redacted]	[redacted]
PASI 50–75	[redacted]	[redacted]
PASI 75–90	[redacted]	[redacted]
PASI 90–100	[redacted]	[redacted]
Abbreviations: PASI, psoriasis area and severity index; BSC, best supportive care		

Treatment effect on quality of life

In the company analysis, patients on best-supportive care or on non-biologic systemic therapy were assumed to have different quality of life than patients on biologic treatments, for a given PASI score. This was justified by the company on the basis that the mode of administration of systemic non-biologic therapies compared to biologics may result in a lower HRQL. Topical treatments, phototherapies, and systemic agents may be inconvenient and time-consuming to apply, compared with biologics, which are often self-administered, at less regular intervals. The ERG felt that it was unclear on whether these utility values would be applicable to patients who receive best supportive care after having failed treatment with all biologic treatment options, or to patients on first-line systemic therapy. The evidence supporting the quality of life in patients who did not receive biologic therapy was from the placebo arm of the certolizumab trials, which did not allow any active therapy

(systemic or topical) in the placebo arm. Therefore, it is not appropriate to use this data to reflect quality of life in patients who receive non-biologic systemic therapy. Previous appraisals have noted that a possible effect on HRQL associated with treatment with biologics over that of non-biologic systemic therapies may be plausible; however, minimal evidence has been provided to substantiate this and therefore previous appraisals have assumed a common utility set across both groups.

As such, the ERG considers that it may be more appropriate to apply a common set of utility values for all active therapy, and that this was not fully explored by the company. A scenario analysis exploring this, based on the analysis provided by the company for DLQI≥10, is presented in Section 6.

Differential utility values for biologic-experienced populations

The ERG did not consider it appropriate to differentiate HRQoL depending on whether a patient had prior treatment with biologic therapy in the analysis of patients who were candidates for systemic therapy (first line systemic therapy). Firstly, in the regression analysis this covariate was not found to be statistically significant, and secondly, the ERG did not consider it biologically plausible for this to be the case. The company also erroneously applied these utility values to patients on subsequent lines of therapy in this scenario, who would have had experience of treatment with biologic therapy at this point in the pathway. However, the ERG noted that this coefficient only made a small impact to the estimated utility value, and so did not explore this further or incorporate into any further analyses.

Comparison with other datasets

The company also undertook a systematic literature review to identify evidence for utility values reported in the published literature. The ERG considers that the company searches were adequate, albeit slightly out of date and missing a number of key sources of utility studies, and the structure of the search strategies was appropriate. In order to assess whether the utility values generated by the company are generalizable and comparable to those associated with other biologics (to which they are also applied to in this appraisal), the ERG compared the utility values to those reported by the ERG in the most recent NICE appraisals (Table 24).

Table 24 Comparison of utility values (DLQI≥10) (mean utility values and difference from baseline)

	Certolizumab	Brodalumab [a]	Secukinumab	Ixekizumab [b]
Baseline	[redacted]	0.521	0.642	0.660
PASI < 50	[redacted]	0.524 (0.004)	0.756 (0.114)	0.689 (0.029)
PASI 50–74	[redacted]	0.755 (0.234)	0.838 (0.196)	0.785 (0.125)

PASI 75–89	[redacted]	0.862 (0.341)	0.869 (0.227)	0.826 (0.166)
PASI 90–100	[redacted]	0.882 (0.361)*	0.908 (0.266)	0.844 (0.184)

[a] [redacted] (ERG-preferred utilities)

[b] Crosswalk values reported in Pickard (2017)

* PASI 90-99 (PASI 100 is increment of 0.3680)

There appears to be differences in utility scores estimated by each of the appraisals that are difficult to explain. Additionally, there appeared to be heterogeneity in baseline utility score between the certolizumab trials, where CIMPACT and CIMPASI-1 were broadly in agreement, and CIMPASI-2 was associated with a lower score. A similar pattern is observed between the three trials and PASI response rates, where CIMPASI-2 was associated with higher rates of PASI 75 than the other two trials, which were also similar in this regard (discussed in Section 4.2). The utility values for certolizumab, secukinumab and ixekizumab appear broadly comparable at baseline, although the magnitude of the utility benefit differed across appraisals. Notably, the brodalumab utilities are associated with a lower baseline value, and subsequently patients achieve higher utility gains with greater PASI responses.

These differences may indicate important differences in the trial populations, with individuals in the brodalumab trials appearing more severe in terms of their HRQoL at baseline. However, identifying differences between the trials is problematic, since the HRQoL data being compared are from the subgroups of individuals with DLQI≥10, for whom detailed information on baseline characteristics is not available. As such, the ERG cannot determine the reason for these differences.

The different baseline utility values are also a potentially important determinant of the HRQoL increments associated with the PASI response categories. There appear to be important differences across the studies, with the highest increments reported in the study with the lowest baseline EQ-5D. One potential explanation for the differences in the increments across the studies is that any ceiling effect of EQ-5D may be less evident in individuals with a lower baseline value.

Uncertainties remain regarding the generalisability of the company's utilities to the broader studies included in the NMA. A series of scenario analyses conducted by the company addressed these uncertainties, where the impact of applying utility values from the submissions for secukinumab, apremilast, and ixekizumab was explored. In all scenarios, certolizumab was associated with a higher ICER compared with the baseline comparator, etanercept (Table 102 and 103 of the CS).

5.2.8 Resources and costs

The CS (Section B 3.5, Page 163) describes the search strategies used to identify studies of resource use and treatment costs.

The costs included in the model comprised drug acquisition, administration, monitoring, and BSC. Unit costs were sourced from NHS reference costs and the Personal Social Services Research Unit (PSSRU).

5.2.8.1 Treatment acquisition costs

Drug costs were obtained from the British National Formulary (BNF) list prices, or where available, publicly available patient access scheme (PAS) information. The model also included the flat pricing scheme for ustekinumab, which makes the 90mg dose available at the same price as the 45mg dose. The acquisition costs for certolizumab also includes the agreed complex PAS, where the first 12 weeks of treatment are free. The CS does not include the confidential PAS schemes which have been approved for apremilast, ixekizumab, brodalumab, guselkumab, and secukinumab. Details of these confidential PAS schemes were made available to the ERG and have been incorporated into analysis presented in a confidential appendix.

Dosing of infliximab was based on patient body weight, estimated using the mean patient weight at baseline in the NMA (87.2 kg). The dose for methotrexate was based on 25% of patients receiving subcutaneous methotrexate, and 75% receiving oral methotrexate. This was based on clinical advice to the company. Table 25 and Table 26 present the treatment acquisition cost data and drug dosing schedules included in the company's base-case analysis (treatment induction and maintenance phases respectively). The company's model based per-cycle drug costs for both certolizumab regimes on 36 weeks of treatment costs spread over one year, significantly reducing per-cycle costs for certolizumab. The method used to calculate the number of annual doses was inconsistent between treatment phases and drugs. The corrected values were included in the ERG's cost corrections presented in Section 6. An important determinant of total cost for each drug is the different duration of induction for each drug, and the different dosing frequencies used during induction and throughout the maintenance phase.

Table 25 Drug acquisition costs during the treatment induction phase (CS Table 77, Page 165)

Treatment	Dosing schedule	Unit cost	No. vials/ syringes/ tablets	Total costs
Certolizumab pegol 200 mg	400mg LD week 0, 2, 4 then 200mg Q2W	£357.50	12	List price: £4,290.00 PAS price: £715.00*
Adalimumab 40 mg	80mg LD, 40mg Q2W	£352.14	10	£3,521.40
Brodalumab	210mg weeks 0, 3, 6, then 210mg Q2W	£640.00	8	£5,120.00
Etanercept (Enbrel)	25mg Q2W or 50mg q1w	£89.38	24	£2,145.12
Etanercept (Benepali)[a]	25mg Q2W or 50mg q1w	£82.00	24	£1,968.00
Etanercept (Erelzi)[a]	25mg Q2W or 50mg q1w	£80.44	24	£1,930.56
Guselkumab	100mg weeks 0, 4, 12	£2,250.00	3	£6,750.00
Infliximab (Remicade)	5 mg/kg weeks 0, 2, 4 ,8	£419.62	15	£6,294.30
Infliximab (Flixabi)[a]	5 mg/kg weeks 0, 2, 4 ,8	£377.00	15	£5,655.00
Ixekizumab	160mg LD week 0, then 80mg weeks 2, 4, 6, 7, 10, 12	£1,125.00	8	£9,000.00
Secukinumab	300mg weeks 1, 2, 3, 4, then q4w	£609.39	12	£7,312.68
Ustekinumab 45 mg	45mg weeks 0, 4, then q12w	£2,147.00	2	£4,294.00
Ustekinumab 90 mg	90mg weeks 0, 4, then q12w	£2,147.00	2	£4,294.00

*PAS for certolizumab pegol 400mg only applies if used as first-line dose

[a] denotes biosimilar

Abbreviations: LD, loading dose; PAS, patient access scheme; Q2W, every two weeks; SC, subcutaneous

Table 26 Maintenance phase drug acquisition costs (year 2) (CS Table 78, Page 166)

Treatment	Regimen	Unit cost	No. of units /year	Annual costs	Costs per cycle
Certolizumab pegol 200 mg	300mg Q2W	£357.50	26	£9,295.00	£356.28
Adalimumab 40 mg	40mg Q2W	£352.14	26.09	£9,187.08	£ 352.14
Brodalumab	210mg Q2W	£640.00	26.09	£16,697.14	£ 640.00
Etanercept (Enbrel)	25mg twice weekly	£89.38	104	£9,295.52	£ 352.30
Etanercept (Benepali)[a]	25mg twice weekly	£82.00	104	£8,557.52	£329.14
Etanercept (Erelzi)[a]	25mg twice weekly	£80.44	104	£8,394.72	£322.87
Infliximab (Remicade)	5mg/kg Q2W	£419.62	32.61	£13,684.48	£524.53
Infliximab (Flixabi)[a]	5mg/kg Q2W	£377.00	32.61	£12,441.00	£478.50
Ixekizumab	80mg q4w	£1,125.00	13	£14,625.00	£ 560.57
Secukinumab	300mg per month	£609.39	24	£14,625.00	£ 560.57

Ustekinumab 45 mg	45mg q12w	£2,147.00	4.33	£9,296.51	£ 356.33
Ustekinumab 90 mg	90mg w12w	£2,147.00	4.33	£9,296.51	£ 356.33
Guselkumab	100mg q8w	£357.50	7	£15,750	£ 603.70
* PAS for certolizumab pegol 400mg only applies if used as first-line dose [a] denotes biosimilar **Abbreviations**: PAS, patient access scheme; Q2W, every two weeks; SC, subcutaneous					

Biosimilars are used widely in UK practice and are often substantially cheaper than the originator products, however, the company's base-case did not use biosimilar costs where available. The company present a scenario analysis which includes biosimilar infliximab and etanercept at 20% and 40% uptake rates respectively. Expert advice to the ERG suggested these estimates of biosimilar uptake among UK clinicians are a significant underestimate. While clinicians are less likely to switch existing patients to a biosimilar product, they are almost exclusively used in new patients, providing they are licensed for psoriasis and are registered with BADBIR. By April 2017, the uptake of biosimilar infliximab across the NHS in England was 79.7% compared to 20% as suggested by the company. This has likely increased significantly since the release of the Biosimilar Medicines Commissioning Framework, which was published in order to 'embed the principles of switching to the best value biological medicine in commissioning and clinical practice' in advance of the release of biosimilar adalimumab in October 2018 [46]. There will be a number of biosimilar adalimumab products made available before the end of 2018, and it is anticipated that there will significant and co-ordinated movement towards biosimilar adalimumab upon the expiry of its patent, with clinical advice suggesting a reduction on the current list price of 30-40%. The company's model does not explore the availability of adalimumab biosimilars, the ERG therefore presents a scenario analysis assuming full uptake of biosimilars where available in Section 6.

The assumptions made by the company regarding the dosing for comparator products appears to be largely consistent with previous technology appraisals. However, the ERG notes some inconsistencies between the number of induction doses used in previous appraisals and the company's model. For a number of the biological therapies (adalimumab certolizumab pegol, brodalumab, etanercept, and ixekizumab), the final scheduled dose falls at the same time point as the response assessment applied in the model. In the previous appraisals TA442 and TA511[31, 34], the ERGs argued that as the last scheduled dose fell at the same time as response assessment, this dose, and subsequent doses, would only be given to individuals who were classed as responders at this time point.

The design of several of the comparator trials and the CIMPASI/CIMPACT studies is also supportive of a reduction in the number of doses administered during the induction period. The CIMPASI-1/-2 and CIMPACT trials assessed response at 16 weeks after 11 doses of treatment, i.e. the last dose

having been administered at 14 weeks. As certolizumab pegol is only available in two-dose packs, it is possible that the assumption of wastage of the final dose if a patient fails to respond as applied for brodalumab would apply.

5.2.8.2 Treatment administration costs

All subcutaneous treatments were assumed not to incur any administration costs; the cost of training patients to self-administer subcutaneous injections was included as a single one-hour training session with a nurse costing £36.00, and was applied once at the start of subcutaneous treatment. This is not consistent with previous submissions, NICE appraisals TA521 and TA442 included training costs during the induction period, consisting of 1-hour nurse training visits over the course of the first 2-3 doses, representing a total administration cost of £108.00. The ERG also notes that other competitors offer the self-injection training service to patients for free, while others also offer a free homecare service for those unable to self-inject. In the clarification response the company stated that patients would be offered up to [redacted] nurse visits for self-injection training.

Intravenous infusion costs of £101.54 were applied at each IV infusion visit.

5.2.8.3 Monitoring costs

Monitoring costs applied in the model are differentiated by the induction and maintenance periods, and during the induction period are further split by route of administration (SC injection, IV infusion), and are calculated per cycle. The unit costs are similar across treatment types, but costs are incurred more frequently in IV treatments during the initial treatment period. The modelled treatment monitoring costs are presented in Table 27. Unit costs were sourced from the 2016-17 NHS Reference Costs and an article published by Portsmouth CCG [47], and were largely in line with those used in previous appraisals.

As above, the model incorrectly calculated monitoring costs for all drugs across the initial and maintenance treatment periods, leading to a fourfold underestimation of costs. ERG-corrected results are presented in Section 6.

Table 27 Treatment monitoring costs during the initial and maintenance treatment phases (CS Table 80, Page 167)

Description	Data Source	Unit Cost	Frequency	Cost	Total cost
Initial treatment phase: SC injection					
Dermatologist	Consultant Led Outpatient Attendances service code 330 in Dermatology	£101.54	2	£203.08	£247.27
FBC	Currency Code: DAPS05 (Haematology)	£3.06	2	£6.12	
U&E	Currency Code: DAPS04 (Clinical Biochemistry)	£1.13	2	£2.26	
Chest x-ray	Portsmouth CCG	£27.00	1	£27.00	
Tuberculosis tests	Currency Code: DAPS06 (Immunology)	£6.55	1	£6.55	
LFT	Currency Code: DAPS04 (Clinical Biochemistry)	£1.13	2	£2.26	
Initial treatment phase: IV infusion					
Dermatologist	Consultant Led Outpatient Attendances service code 330 in Dermatology	£101.54	3	£304.62	£354.13
FBC	Currency Code: DAPS05 (Haematology)	£3.06	3	£9.18	
U&E	Currency Code: DAPS04 (Clinical Biochemistry)	£1.13	3	£3.39	
Chest x-ray	Portsmouth CCG	£27.00	1	£27.00	
Tuberculosis tests	Currency Code: DAPS06 (Immunology)	£6.55	1	£6.55	
LFT	Currency Code: DAPS04 (Clinical Biochemistry)	£1.13	3	£3.39	
Maintenance treatment phase: SC injection or IV infusion					
Dermatologist	Consultant Led Outpatient Attendances service code 330 in Dermatology	£101.54	2	£203.08	£213.72
FBC	Currency Code: DAPS05 (Haematology)	£3.06	2	£6.12	
U&E	Currency Code: DAPS04 (Clinical Biochemistry)	£1.13	2	£2.26	
Chest x-ray	Portsmouth CCG	£27.00	0	£0.00	
Tuberculosis tests	Currency Code: DAPS06 (Immunology)	£6.55	0	£0.00	
LFT	Currency Code: DAPS04 (Clinical Biochemistry)	£1.13	2	£2.26	

Abbreviations: FBC: full blood count; IV: intravenous; LFT: liver function tests; N/A: not applicable; SC: subcutaneous; U&E: urea and electrolytes.

5.2.8.4 Best supportive care costs

Resource use costs used for patients on BSC were derived from Fonia *et al*. (2010)[48], a retrospective observational study including 76 patients treated with biologics for at least 6 months at one UK site. This study has been used previously in numerous appraisals, and likely represents the best source of cost data for BSC.

Total costs of BSC consisted of drug acquisition costs and secondary care costs. Costs for systemic non-biologic therapies were taken from the BNF, The proportion of patients receiving each non-biologic systemic therapy was based on clinical advice to the company, with 55% receiving MTX, 35% ciclosporin, and 10% acitretin. These costs are presented in Table 28. Clinical opinion cited by the company stated that ~25% of patients on methotrexate received it subcutaneously, therefore methotrexate costs were weighted 25:75 between patients receiving it subcutaneously and orally.

Secondary care costs for patients on BSC were derived from Fonia *et al*. (2010)[48], and based upon 12 months before commencement of biologic therapy, inflated using HCHS to 2017 values.

The total annual costs associated with BSC were £3,671.66, or a cost per cycle of £140.73 (Table 29). This is far lower than the values used in previous appraisals; an annual cost of £5,283 was used in the recent TA511 (Brodalumab). This difference is driven by the drug acquisition costs; £183.06 in the present appraisal versus £1,570.29 in TA511. Previous appraisals have used the annual costs of BSC from NICE CG153 (based on Fonia *et al*.) or Fonia itself, whereas here the company uses BNF prices and mean duration of treatment per patient from Fonia *et al*. The ERG considered the estimates calculated by the company to be appropriate despite this difference, as a significant proportion (~41%) of the systemic therapy costs cited in the Fonia *et al.* study were from fumaric acid esters, which are not considered alongside BSC for this appraisal, and likely overestimates the cost of ciclosporin. The use of these lower costs for has a significant impact upon the cost-effectiveness of all biologics versus best supportive care, thus for consistency with previous appraisals the ERG explores implementing Fonia *et al.* drug acquisition costs in Section 6.

Table 28 Costs for systemic non-biologic therapies used in best supportive care (CS Table 82, Page 169)

	Unit	Cost per pack (BNF)	Units per pack	Unit cost	Dose	Cost per day
Acitretin	25 mg capsules	£43.00	60	£0.72	30 mg per day	£0.72
Ciclosporin	100 mg capsules	£48.89	30	£1.63	2.5 mg/kg/day (mean weight 87.2 kg)	£3.55
Methotrexate - oral	10 mg tablet	£38.00	100	£0.38	10 mg per week	£0.05
Methotrexate - SC	10 mg injection	£13.77	1	£13.77	10 mg per week	£1.97
Methotrexate weighted average (25% SC)				£3.73	10 mg per week	£0.53

Abbreviations: BNF, British National Formulary; SC, subcutaneous

Table 29 Costs for patients on BSC (CS Table 83, pg 169)

	Costs per annum	Costs per cycle
Systemic non-biologic therapy costs	£183.06	£7.02
Secondary care costs	£3,488.60	£133.72
Total per annum	£3,671.66	£140.73
Costs reported from Fonia (2010), inflated to 2016/17		

5.2.8.5 Non-responder costs

Modelled patients who are classed as non-responders or have discontinued treatment with biologics due to loss of response or AEs incur additional healthcare costs. This cost was calculated from the total systemic non-biologic and secondary care costs from Fonia *et al.* for the 12 months before commencement of biologic therapy, i.e. the modelled per-cycle cost for BSC (£140.74). The cost for non-responders is applied in the initial treatment period for each treatment in the sequence, except for when treated with BSC. The ERG considers this appropriate and in line with previous appraisals.

5.2.8.6 Adverse event costs

No adverse event costs associated with treatment are considered in the company submission. The company cites consistency with previous appraisals as justification for excluding costs associated with TRAEs, but adverse event costs were included in the base-case analysis for TA511, and have been included in some form in numerous others. Previous ERGs have generally considered the exclusion of adverse events optimistic or inappropriate.

While it may be reasonable to assume a similar net adverse event rate if certolizumab were to replace an existing biologic therapy within a sequence, this logic is unlikely to apply when adding an additional line of biologic therapy to the sequence, as the company propose in their 'patients eligible for treatment with non-biologic systemic therapy' analysis.

5.2.9 Cost effectiveness results

The company presented results for three base-case scenarios:

- In the population of inadequate responders to systemic non-biologic therapy,
- A dose escalation strategy in inadequate responders to systemic non-biologic therapy,
- In the population of candidates for systemic non-biologic therapy.

The results in this section are presented for the analyses when the PAS for certolizumab was applied. Additional comparators (secukinumab, apremilast, brodalumab, ixekizumab and guselkumab) have also approved by NICE conditional on the implementation of a confidential PAS: results for the company's base-case analysis with these PAS applied are presented in the confidential appendix to this report.

5.2.9.1 Base-case results

Systemic non-biologic therapy inadequate responders

For the analysis of systemic non-biologic therapy inadequate responders, the company reported the fully incremental cost-effectiveness ratios (ICERs) pairwise ICERs for the sequence associated with the lowest total costs compared to each comparator sequence. The least costly treatment sequence, with etanercept as first treatment in the sequence, was also associated with the lowest number of QALYs gained.

The fully incremental ICERs are calculated using the following process:

i) The sequences are ranked in terms of mean cost (from the least expensive to the most costly).

ii) If a sequence is more expensive and less effective than any previous sequence of lower cost, then this sequence is said to be dominated and is excluded from the calculation of the ICERs.

iii) After excluding any dominated sequences, the ICERs are calculated for each non-dominated sequence, from the cheapest to the most costly. If the ICER for a given

sequence is higher than that of any more effective strategy, then this sequence is ruled out on the basis of extended dominance.

iv) The final ICERs are then recalculated excluding any strategies that are ruled out by principles of dominance or extended dominance.

In the fully incremental ICER comparison, there were three non-dominated sequences. Of these, the least effective and lowest cost was the sequence starting with etanercept. The ICER of the certolizumab sequence was reported to be £11,471 per QALY compared to the etanercept sequence. The ICER of the other non-dominated sequence was £432,904, for the ixekizumab sequence. Four sequences were dominated by certolizumab (they were more costly and produced fewer QALYs than the certolizumab sequence). These included ustekinumab 45mg, adalimumab, ustekinumab 90mg, and guselkumab. Brodalumab was dominated by ixekizumab, and secukinumab was extendedly dominated. In the pairwise comparisons versus etanercept, the ICER ranged from £11,471 (versus the certolizumab sequence) to £164,664 (versus the guselkumab sequence).

All treatment sequences were associated with a total of [redacted] life years. This was identical for each sequence, since treatment or individual health states were assumed to not impact upon mortality rates.

Table 30 Base case fully incremental results for systemic non-biologic therapy inadequate responders – CZP with PAS (adapted from Table 43, company response to clarification questions)

1st Line Treatment in Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Fully incremental ICER (£/QALY)
ETN	[redacted]	[redacted]	-	-	-	-
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	£11,470.53	£11,470.53
UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	£51,528.43	Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	£45,655.86	Dominated
UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	£43,529.12	Dominated
GUS	[redacted]	[redacted]	[redacted]	[redacted]	£164,663.89	Dominated
SEC	[redacted]	[redacted]	[redacted]	[redacted]	£128,929.95	Extendedly dominated
IXE	[redacted]	[redacted]	[redacted]	[redacted]	£125,644.48	£432,904.41
BROD	[redacted]	[redacted]	[redacted]	[redacted]	£146,412.55	Dominated

Abbreviations: ADA: adalimumab; BROD: brodalumab; CZP: certolizumab pegol; ETN: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IFX: infliximab; IXE: ixekizumab; PAS: patient access scheme; QALYs: quality-adjusted life years; SEC: secukinumab; UST: ustekinumab.

Note that the results originally presented in the CS were updated by the company following the clarification stage, after correction of an error in the estimation of utility values

Dose escalation strategy

In the dose escalation strategy, certolizumab 200mg escalated to 400mg in non-responders was compared with adalimumab 40mg escalated to 80mg in non-responders. In this scenario, both certolizumab and adalimumab were associated with higher lifetime costs and higher lifetime QALYs compared with the matched comparator in the non-dose escalated scenario, as the dose-escalated comparator was essentially modelled as a fourth biologic treatment in addition to the three biologics. In this analysis, the ICER of dose-escalated certolizumab compared with dose-escalated adalimumab was estimated as £36,638 per QALY gained.

Similar to the analyses above, both sequences were associated with [redacted] life years gained.

Table 31 Base case results for systemic non-biologic therapy inadequate responders – CZP escalation strategy with PAS (adapted from Table 4, company response to clarification questions)

1st Line Treatment in Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	£36,637.86
ADA 40 mg	[redacted]	[redacted]	-	-	-

Abbreviations: ADA: adalimumab; CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio;; PAS: patient access scheme; QALYs: quality-adjusted life years

Note that the results originally presented in the CS were updated by the company following the clarification stage, after correction of an error in the estimation of utility values

Candidates for systemic non-biologic therapy

In this scenario, the ICER of certolizumab as first-line therapy compared with a sequence starting with standard care followed by adalimumab was estimated as £3,602 per QALY gained. Both treatment sequences were associated with [redacted] life years gained.

Certolizumab as first line systemic therapy was associated with similar lifetime costs compared with certolizumab as second-line systemic therapy, following failure with a standard systemic therapy (e.g. methotrexate). However, the treatment sequences generated fewer QALYs than the sequences for patients who were inadequate responders to non-biologic systemic therapy. This was partly due to the older age of patients entering the model in this analysis and the lower utility values applied to these patients (Section 5.2.7).

Table 32 Base case results for candidates for systemic non-biologic therapy – CZP with PAS (adapted from Table 45, company response to clarification questions)

1st Line Treatment in Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CZP 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	£3,601.54
SoC	[redacted]	[redacted]	-	-	-

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care

Note that the results originally presented in the CS were updated by the company following the clarification stage, after correction of an error in the estimation of utility values

The ERG had some concerns about the use of placebo response rates to represent effectiveness of first-line systemic therapy (Sections 5.2.4 and 5.2.6), since patients in the placebo arm of the certolizumab trials did not receive any systemic or topical therapy for the treatment of psoriasis. At the clarification stage, the company presented additional evidence on the cost-effectiveness of certolizumab, where the PASI response estimates of first-line supportive care was estimated for methotrexate from the NMA in the 'biologic-naïve' population subgroup. In this scenario, the ICER increased to £18,145 per QALY. The ERG felt that there was remaining uncertainty regarding the implementation of this scenario, and explored this further in Section 6.

Table 33 Base case results for candidates for systemic non-biologic therapy using biologic-naïve MTX data as a proxy for standard of care– CZP with PAS (Table 31, company response to clarification questions)

1st Line Treatment in Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CZP	[redacted]	[redacted]	[redacted]	[redacted]	£18,145.34
SoC	[redacted]	[redacted]	-	-	

Abbreviations: CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care

5.2.9.2 Sensitivity analysis

The company presented the uncertainty in the model in three ways: one-way deterministic sensitivity analyses (DSA), a probabilistic sensitivity analysis (PSA) and a series of scenario analyses.

Deterministic sensitivity analysis

One-way deterministic sensitivity analyses assessed the impact of single key variables on the base-case results. The DSA were conducted by varying selected key parameters, including those regarding PASI response, utility values, unit costs and resource use, by ±20%.

Tornado diagrams are presented in Figure 34 to Figure 43 in the CS, which display the impact on the incremental net benefit (INB) from varying each parameter. However, the ERG identified an error in their implementation in the executable model, and so these diagrams do not accurately depict the key drivers of the model. Updated tornado diagrams are provided in Appendix 10.1 of this report.

In the analysis of systemic non-biologic inadequate responders, the parameters that had the greatest influence were the acquisition cost of each comparator and the utility value for the patients with a PASI 75 response.

PASI response rates, utility values and the non-responder cost were also influential parameters in the analysis of candidates for systemic non-biologic therapy.

Probabilistic sensitivity analysis

The company reported incremental results from the probabilistic sensitivity analysis (based on 1,000 simulations). These were reported to be similar to the deterministic estimates, indicating that model appears relatively linear.

In the analysis of systemic non-biologic inadequate responders, the company reported that at a threshold of £20,000 per QALY, the certolizumab sequence had the highest probability of being cost-effective (89%), followed by the etanercept sequence (11%). At a £30,000 threshold, the certolizumab sequence was reported to have a 99% probability of being the most cost-effective of the sequences considered by the company.

Scenario analysis

Note that the CS presented the results of the scenario analyses in a different format to that of the base-case results, where ICERs are provided for each comparator versus certolizumab and for certolizumab versus each comparator, rather than the base-line sequence with the lowest treatment costs. A fully incremental analysis was not presented in the CS for these scenarios.

The scenarios suggested the cost-effectiveness of certolizumab was most sensitive to assumptions related to discontinuation rates in the maintenance phase (Table 98 and 99 in CS), utility values (Table 102 and 103 in CS) and inpatient costs (Table 113 and 114 in CS). The company estimated that the

certolizumab sequence remained cost-effective in the majority of scenarios. There was one exception: when health state utilities from the ixekizumab NICE submission were applied, certolizumab 200 mg was cost-effective against all treatment sequences apart from that starting with etanercept. The application of these utility values resulted in a substantial reduction in the number of QALYs gained across all treatments, as these utility values were much lower than those in other submissions. As a result, the ICER of certolizumab versus the baseline scenario (etanercept) increased to £50,653 per QALY. The utility values from the apremilast and the secukinumab submissions were more similar to that in the base-case of this appraisal, and their incorporation in the model were associated with only a small increase in QALYs.

When inpatient costs were reduced by 50%, the total costs of each sequence were reduced by approximately £15,000 compared with the base-case. This resulted in a small increase to the ICER of certolizumab versus the baseline scenario (etanercept).

Incorporating alternative maintenance phase discontinuation rates was associated with increased costs and QALYs across all sequences; however, certolizumab was associated with a similar estimate of cost-effectiveness as the base-case analysis.

The company also presented a scenario with [redacted] for certolizumab, which is of relevance to the dose escalation scenario (Table 93 in CS). [redacted] In this scenario, the total costs associated with the certolizumab sequence were reduced from [redacted] to [redacted] (Table 93 in CS, updated by the ERG following the correction of the executable model supplied at the clarification stage). This is lower than the total costs that the company estimated for the adalimumab dose escalation sequence ([redacted]), which resulted in a scenario where the certolizumab sequence dominated the adalimumab sequence.

[redacted]

5.2.9.3 Subgroup analysis

The company presented results for a subgroup of patients for patients who were biologic-naïve. The comparators in this analysis were restricted to those that provided biologic-naïve efficacy data for the NMA that informed this subgroup analysis, and included certolizumab 200mg, ustekinumab 45mg, ustekinumab 90mg and adalimumab.

Ustekinumab 90 mg and adalimumab were dominated by certolizumab in this subgroup. Certolizumab was cost-effective versus ustekinumab 45 mg (ICER of £2,630 per QALY, note that this was incorrectly reported in the text in the CS).

Table 34 Subgroup analysis results for systemic non-biologic therapy inadequate responders who are also biologic – CZP with PAS (adapted from Table 117, CS, pg 207)

1st Line Treatment in Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus CZP (£/QALY)	ICER CZP versus comparator
CZP 200 mg	[redacted]	[redacted]	-	-	-	-
UST 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	N/A	£2,597.43
UST 90 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant

Abbreviations: ADA: adalimumab; CZP: certolizumab pegol; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; UST: ustekinumab

Note that these have been updated by the ERG following the correction of the executable model supplied at the clarification stage

5.2.10 Model validation and face validity check

Validation undertaken by the company

The company reported that an internal (technical) validation and an external (face validity) validation was undertaken by health economics not directly involved in the project. The key inputs and assumptions used in the model were validated by a clinical expert, to ensure they reflect clinical practice in England and Wales. Where areas were identified that suggested that a source of data may not be directly relevant to clinical practice, the company performed sensitivity analysis to determine whether certolizumab was cost-effective across the range of possible values.

Validation undertaken by the ERG

In addition to the critique described above and consultation with an independent clinical expert, the ERG performed a series of model calculation checks, including pressure tests and formula auditing. The ERG felt that the executable model was not presented clearly, and contained a great deal of redundancy, in that it contained a large number of calculations, the formatting and labelling was poor, and there was not a particularly logical flow through the model. Given this lack of transparency in the calculations, the model was challenging to validate. A number of errors were identified as part of this

process, which have non-negligible impact on the results produced by the model. A description of the errors and the associated amendments made by the ERG is provided in Section 6.2.

5.3 Conclusions of the cost effectiveness section

The cost-effectiveness review carried out by the company did not identify any published evidence on the cost-effectiveness of certolizumab for psoriasis in the UK. Consequently, the company's model represents the most relevant source of existing evidence. The company's analysis is presented for two patient groups: *(i)* those who are candidates for systemic biologic therapies, and *(ii)* for those who have an inadequate response, contraindication, or intolerance to other systemic non-biologic therapies.

In the analysis of systemic non-biologic inadequate responders, the model included a total of nine treatment sequences which include three lines of active therapy, followed by BSC. Certolizumab was included in a first line position alongside other comparators recommended by NICE for psoriasis patients following failure on systemic therapies. A scenario was also explored in which patients who did not achieve a PASI 75 response on the certolizumab 200mg dose were escalated to certolizumab 400mg Q2W.

The company submission concludes that the certolizumab sequence is the most cost-effective in their base case analysis and is robust to a wide range of plausible alternative assumptions explored in sensitivity and scenario analyses. In the fully incremental ICER comparison, there were two non-dominated (dominance and extended dominance) sequences. Of the non-dominated sequences, the least effective and lowest cost was the sequence starting with etanercept. The deterministic ICER of the certolizumab sequence was reported to be £11,471 per QALY compared to the etanercept sequence. The ixekizumab sequence was the most effective and most costly of the non-dominated sequences. The ICER of the ixekizumab sequence versus the certolizumab sequence was £432,904 per QALY. In the pairwise comparisons versus etanercept, the ICER ranged from £11,471 (versus the certolizumab sequence) to £164,664 (versus the guselkumab sequence). None of the sequences were cost-effective versus best supportive care, with a pairwise ICER of £70,086 for certolizumab. Note these conclusions exclude PAS discounts for secukinumab, ixekizumab, guselkumab and brodalumab.

In the dose escalation analysis, dose-escalated certolizumab was compared with dose-escalated adalimumab. The ICER of dose-escalated certolizumab compared with dose-escalated adalimumab was estimated as £36,638 per QALY gained.

In the analysis of candidates for systemic biologic therapies, certolizumab was positioned as a direct comparator against standard care, comprising methotrexate, ciclosporin, and acitretin, followed by three lines of biologic therapy. The ICER of certolizumab as first-line therapy compared with a

sequence starting with standard care followed by adalimumab was estimated as £3,650 per QALY gained.

The ERG's critique has raised a number of issues and areas of uncertainty. The principal issues identified by the ERG are outlined in brief below.

(i) The ERG identified a significant number of calculation errors in the executable model. These related to the calculation of the costs of administration and training, the number of applications of administration costs, treatment monitoring costs across all treatment phases, and the calculation of year 1 per cycle certolizumab costs. A further error in the calculation of incremental QALYs was also identified and corrected by the ERG.

(ii) Scenarios presented by the company considering the cost-effectiveness of a certolizumab dose escalation do not consider an appropriate set of comparators, with the company comparing certolizumab to an adalimumab based dose escalation strategy. The ERG considers the most appropriate counterfactual to certolizumab with dose escalation to be certolizumab without dose escalation on the grounds that any recommendation for the use of certolizumab in the NHS should be based on the most cost-effective use of drug. Clinical advice to the ERG also suggests that while only adalimumab and etanercept are licensed for dose escalation, the 90mg ustekinumab dose is available at no extra charge and thus is generally the only drug for which dose escalation is used in practice, and typically only in those weighing >90kg.

(iii) In line with the NICE scope and licence for certolizumab, the company presents scenarios in which certolizumab is positioned as an alternative to systemics non-biological therapy. The ERG do not consider the company to have presented sufficient evidence to support this positioning of certolizumab. This sequence is unprecedented in previous guidance issued by NICE and relies on accurate and representative treatment sequencing, which is very difficult to do in the context of the available clinical data and structure of the economic model.

(iv) Biosimilars are used widely in UK practice and are often substantially cheaper than the originator products, however, the company's base-case did not use biosimilar costs where available. The company present a scenario analysis which includes the costs of biosimilar infliximab and etanercept. Expert advice to the ERG suggested the 20% and 40% uptake rates for biosimilar infliximab and etanercept among UK clinicians are a significant underestimate. The ERG also highlights that there will be a number of biosimilar adalimumab products made available before the end of 2018, and it is anticipated that there will significant and co-ordinated movement towards biosimilar adalimumab upon the expiry of its patent, with an expected reduction on the current list price of 30-40%.

(v) None of the biologic therapies are cost-effective versus best supportive care in the company's base-case. This has important consequences for interpreting the results of the economic model inflating the apparent cost-effectiveness of drugs with a lower response and leads to counter intuitive results in scenarios where differential rates of discontinuation are explored.

(vi) Resource use costs used for patients on BSC were derived from Fonia *et al.* (2010)[48], a retrospective observational study that has been used previously in numerous appraisals. Unlike previous appraisals, however, drug costs were drawn from the BNF rather than Fonia *et al.* itself. The consequence of this is that BSC is far cheaper than in previous appraisals. The ERG considered the estimates calculated by the company to be appropriate despite this difference, but notes that this has the consequence that no biologic therapy including certolizumab is cost-effective relative to BSC.

(vii) The of sequences evaluated by the company were restrictive in terms of the number of sequences included and the position of certolizumab within these, which focused on certolizumab as first-line biologic therapy. The ERG raised concerns about the clinical plausibility of this, given the entrenchment of similar efficacious alternatives including adalimumab, which will also potentially be significantly cheaper due to the imminent arrival adalimumab biosimilars. The ERG is also concerned that the modelling of selective sequences could provide misleading estimates of cost-effectiveness, particularly if there are treatments included in a sequence which are not cost-effective themselves.

(viii) The ERG considered that the utility regression model used in the company base-case should have limited to patients which a DLQI score ≥10. The ERG considers that these are more appropriate utility values to include in the analysis than those used in the base-case analysis, as they correspond to the subgroup of patients who are eligible treatment and appear to be more comparable to those estimated for other submissions of psoriasis, as these represent the population eligible for treatment with certolizumab.

(ix) In the company analysis, patients on best-supportive care or on non-biologic systemic therapy were assumed to have different quality of life than patients on biologic treatments, for a given PASI score. While the ERG considers this potentially plausible, the evidence used to support this assumption is based on a population who received no active therapy. This assumption is also inconsistent with previous appraisals. The ERG, therefore, considers that it may be more appropriate to apply a common set of utility values for all active therapy

In line with a number of previous appraisals, the company assumes a constant annual discontinuation rate of 20% in the maintenance period for all treatments (except BSC). The company, however, explore the possibility of differential discontinuation rates noting clinical expert opinion suggests certolizumab may have a particularly durable response. The ERG considers that the assumptions

applied in the base case analysis appear more justifiable than those considered by the scenario. However, the ERG recognises that there exists significant uncertainty concerning both the rate of discontinuation and whether there are important treatment or class specific differences.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

The ERG review identified a number of areas of uncertainty in the company's submission and economic model. Section 6 explores each of the following issues separately, and presents the effects of each upon the cost-effectiveness results.

1. Sequencing and head-to-head comparisons,
2. Assumptions regarding HRQoL and costs of BSC from TA511,
3. Time horizons,
4. Alternative HRQoL data sources,
5. Biosimilar costs and uptake,
6. Certolizumab trial data sources,
7. Dose escalation scenario,
8. Alternative positioning of biologics in the treatment pathway.

The ERG also proposes an alternative base-case, which draws upon some of these exploratory analyses.

A number of corrections to the executable model were made, which are further described in Section 6.2. This section also presents the impact of these changes upon the ICER and results.

The analyses presented by the ERG are based on deterministic results: no probabilistic alternative base-case results were produced as no variance covariance matrix was provided for the HRQoL data that the ERG received from the company. Note that the following results include only the patient access scheme (PAS) discount agreed for certolizumab; for results including all available PAS discounts for the comparator drugs, see the separate confidential appendix.

6.2 ERG corrections and adjustments to the company's base case model

A number of errors in the company's executable model were identified by the ERG. These were mostly calculation errors which led to the miscalculation of the cost of administration and training, the number of applications of administration costs, treatment monitoring costs across all treatment phases, and the calculation of Year 1 per-cycle certolizumab costs. A further error in the calculation of incremental QALYs was identified and corrected by the ERG.

Miscalculation of administration, training, and monitoring costs

The model incorrectly calculated per cycle administration, training, and monitoring costs in all treatment phases; total costs were divided by the number of weeks in the treatment period multiplied by the cycle length. The effect of this was a fourfold underestimation of per cycle costs in each of these categories, as the model divided each cost total by the number of weeks in a treatment period (e.g. 52 in maintenance year 2) multiplied by 2 (the cycle length). Thus, one year of cost was essentially spread over four years. This was applied equally over all treatments; however, the effect was most pronounced for infliximab due to its higher long-term administration costs. These errors were corrected, with the results presented in Table 35, Table 36, and Table 37 below.

Miscalculation of drug acquisition costs

The model miscalculated treatment acquisition costs for certolizumab in the first 36 weeks of maintenance treatment. In order to calculate per cycle treatment costs, the total acquisition costs for this period were divided by 26, i.e. the number of cycles in one year. Therefore only 69.3% of the total costs accrued during the first year were included. The number of unit doses per year was also calculated inconsistently between treatment periods and drugs, with a number using a 52 week year as a basis, rather than 52.179 as used for the majority. Patients were also assumed to receive 7 doses of guselkumab per year during the maintenance phase, rather than 6.52; i.e. every 8 weeks. The model was corrected to consistently use a 52.179 week year to calculate number of unit doses across treatments.

The model also assumed the number of vials/syringes/tablets used was equivalent to the number of times administration costs were incurred (i.e. four initial period administrations of infliximab cost £1,523, rather than £406), leading to a significant over-estimation of administration costs for infliximab.

Miscalculation of incremental QALYs

The company's model also miscalculated the incremental QALYs accrued on a number of treatment sequences, the corrected results presented below use the correct incremental QALYs which affects the ICERs and ranking of each drug.

Table 35, Table 36, and

Table 37 present the results of the ERG-corrected company base-case analyses, which incorporate corrections to the errors described above. This analysis includes only the PAS discount for certolizumab. All further scenario analysis conducted by the ERG in the following sections build upon the ERG-corrected company base-case analysis.

Table 35 Company base-case and ERG corrected results

First line therapy	Subsequent sequence	Total		Incremental		ICER vs BSC	CZP200 ICER vs comparator
		QALYs	Costs	QALYs	Costs		
Company base-case analysis results							
Best supportive care	BSC, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-	£70,086
Certolizumab pegol 200mg	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£70,086	-
Certolizumab pegol 400mg	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£100,788	£710,883
Etanercept	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£83,289	£11,471
Infliximab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£83,790	£36,171
Secukinumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£93,317	£598,382
Guselkumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£96,944	Dominant
Adalimumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£80,525	Dominant
Brodalumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£97,027	£720,462
Ustekinumab 90mg	ADA 40mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£68,027	Dominant
Ustekinumab 45mg	ADA 40mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£67,742	Dominant
Ixekizumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£95,529	£432,904
ERG-corrected company base-case analysis results							
Best supportive care	BSC, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-	£90,358
Certolizumab pegol 200mg	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£90,358	Equal
Certolizumab pegol 400mg	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£121,619	£742,834
Etanercept	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£108,495	£9,837
Infliximab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£91,220	£88,227
Secukinumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£110,312	£544,127
Guselkumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£113,685	Dominant
Adalimumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£103,032	Dominant

First line therapy	Subsequent sequence	Total		Incremental		ICER vs BSC	CZP200 ICER vs comparator
		QALYs	Costs	QALYs	Costs		
Brodalumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£114,812	£680,692
Ustekinumab 90mg	ADA 40mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£102,574	Dominant
Ustekinumab 45mg	ADA 40mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£104,303	Dominant
Ixekizumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£110,599	£406,911
Abbreviations: QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; BSC, best supportive care; CZP, certolizumab pegol; ADA, adalimumab; BROD, brodalumab; ETN, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; SEC, secukinumab; UST, ustekinumab							

Table 36 Company base-case (escalation strategy for inadequate responders) and ERG corrections

First line therapy	Subsequent sequence	Total		Incremental		ICER vs BSC	ICER
		QALYs	Costs	QALYs	Costs		
Company base-case analysis results (escalation strategy)							
Adalimumab 40mg	ADA80, UST90, INF, BSC	[redacted]	[redacted]	-	-	£98,035	-
Certolizumab pegol 200mg	CZP400, UST90, INF, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£87,125	£36,638
ERG-corrected company base-case analysis results (escalation strategy)							
Adalimumab 40mg	ADA80, UST90, INF, BSC	[redacted]	[redacted]	-	-	£103,185	-
Certolizumab pegol 200mg	CZP400, UST90, INF, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£100,607	£38,684
Abbreviations: ERG, evidence review group; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; BSC, best supportive care; CZP, certolizumab pegol; ADA, adalimumab; IFX, infliximab; UST, ustekinumab							

Table 37 Company base-case (candidates for systemic non-biologics) and ERG corrections

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
Company base-case analysis results (candidates for systemic non-biologics)						
Best supportive care	ADA40, UST90, INF, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	UST90, INF, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£3,602
ERG-corrected company base-case results (candidates for systemic non-biologics)						
Best supportive care	ADA40, UST90, INF, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	UST90, INF, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£6,757

Abbreviations: ERG, evidence review group; QALYS, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; BSC, best supportive care; CZP, certolizumab pegol; ADA, adalimumab; IFX, infliximab; UST, ustekinumab

6.3 Additional ERG analyses

6.3.1 Treatment sequencing and net-monetary benefit analysis

In Section 5.2.4, the ERG concluded that the treatment sequences considered in the company's primary analysis to be potentially misleading and unsuitable for decision making, given the lack of appropriate data to model treatment sequences, and difficulties associated with evaluating a large number of alternative sequences. The ERG therefore proposes an alternative approach to the assessment of the relative cost-effectiveness of certolizumab against biologics currently used in practice, which more fully addresses the issues discussed in Section 5. This is approach is consistent with the approach taken by the ERG in TA511[34], though with some modifications to account for the fact that in all company scenarios all biological therapies are not cost-effective versus best supportive care.

This approach comprises a number of steps. Firstly, this analysis no longer compares sequences of biologics, rather, each comparator is the only biologic in its sequence, and is compared to every other biologic, allowing a direct comparison of the costs and benefits associated with each option. Secondly, incremental net monetary benefit (NMB = λ x $\Delta E - \Delta C$) is presented for each comparator versus certolizumab, at a £20,000 and £30,000 per QALY threshold. Thirdly, and in contrast to TA511, this approach takes certolizumab as a baseline, and assesses the relative cost-effectiveness of all other biologics to certolizumab. This better accounts for the fact that none of the biologic therapies are costs-effective relative to BSC under the company's base-case assumptions. Using this approach if

an intervention has an incremental net monetary benefit (NMB)>0, then it would be considered more cost-effective than certolizumab.

Using the incremental net-benefit of each treatment versus certolizumab can be used as a basis for establishing whether certolizumab is a cost-effective treatment option versus other currently available biologics, and allows the ranking of cost-effectiveness without estimating fully incremental ICERs. The application of the net-benefit also has the specific advantage that it provides an unambiguous decision rule i.e. where NMB>0 implies a technology is cost-effective relative to certolizumab and avoids complications created by negative ICERs. This approach is taken in all subsequent scenario analyses unless otherwise stated (i.e. for the alternative populations.) The results of head-to-head comparisons of single lines of therapy are presented in Table 38, this analysis includes only the PAS for certolizumab, uses a lifetime time horizon and a discount rate of 3.5%. The top three ranked drugs at a cost-effectiveness threshold of £20,000 and £30,000 are highlighted in bold.

In this analysis, certolizumab ranks second at a cost-effectiveness threshold of £20,000, and first at a cost-effectiveness threshold of £30,000. A higher threshold used in this way places a greater value upon health benefits accrued, therefore the cost savings of etanercept become less important. While the lower ranking of ustekinumab 90mg vs ustekinumab 45mg at a £20,000 threshold may seem counterintuitive, the greater proportion of patients obtaining a response to 90mg at 16 weeks results in more patients remaining on ustekinumab, who accrue more additional cost than QALY value.

Table 38 ERG Scenario 1: single lines of therapy using incremental net-benefit and rankings

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 1: single-line head-to-head comparisons							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**2**	£0.00	**1**	£44,929
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,213.21	11	-£30,715.10	11	£130,128
Etanercept	[redacted]	[redacted]	£938.90	**1**	-£910.31	**2**	£76,290
Infliximab	[redacted]	[redacted]	-£25,508.50	10	-£24,971.28	10	£112,878
Secukinumab	[redacted]	[redacted]	-£20,665.94	7	-£20,232.41	7	£101,644
Guselkumab	[redacted]	[redacted]	-£17,876.89	6	-£18,065.74	6	£109,741
Adalimumab	[redacted]	[redacted]	-£828.98	**3**	-£2,012.85	**3**	£65,520
Brodalumab	[redacted]	[redacted]	-£24,352.29	9	-£23,948.28	9	£113,115
Ustekinumab 90mg	[redacted]	[redacted]	-£2,772.44	5	-£3,044.44	4	£57,486
Ustekinumab 45mg	[redacted]	[redacted]	-£2,735.91	4	-£3,162.66	5	£59,583
Ixekizumab	[redacted]	[redacted]	-£22,851.67	8	-£22,202.46	8	£102,802

Abbreviations: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit

6.3.2 Cost-effectiveness of BSC

While the approach outlined above has a number of important advantages, it does not address the underlying issue that none of the biologic therapies are cost-effective relative to BSC. As outlined in Sections 5.2.1, 5.2.4, and 5.2.6, this is important in determining the relative cost-effectiveness of individual therapies and will tend to favour less effective therapies, i.e. those which allow patients to progress to BSC the most quickly. To explore the impact of this issue on the ranking of therapies, Scenario 2 makes several plausible changes to the company base-case which make some biologic therapies cost-effective relative to BSC. These assumptions are drawn from TA511 and therefore have been accepted in a previous appraisal.

The changes to the company base-case in this scenario are as follows: i) consistent with previous appraisals, BSC drug acquisition costs are taken from Fonia *et al.* 2010 and inflated to 2018 values, ii) utility values are derived from TA511, iii) 40 year time horizon, iv) head-to-head single biologics. It is important to note the ERG does not necessarily consider these assumptions superior to those in the company's base-case, but presents these analyses for illustrative purposes only. Again note that this analysis does not include the PAS discounts available for brodalumab, guselkumab, ixekizumab, and secukinumab. Results incorporating these can be found in the confidential appendix.

As seen in Table 39, using the assumptions applied in TA511, certolizumab has the highest net monetary benefit at both thresholds, and has an ICER of £21,222 versus best supportive care. In this analysis, certolizumab and ustekinumab 90mg are cost-effective versus best supportive care, however, note that when the appropriate PAS discounts are applied, a number of other drugs become cost-effective versus BSC, and this has a non-negligible effect upon the rankings (see confidential appendix). The relative robustness in the ranking of certolizumab is supportive of the results presented in Scenario 1, and suggests that it is at least plausible that some of these drugs may be cost-effective.

Table 39 ERG Scenario 2: TA511 Assumptions applied

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 2: TA511 assumptions							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**1**	£0.00	**1**	£21,222
Certolizumab pegol 400mg	[redacted]	[redacted]	-£30,135.35	11	-£29,314.20	11	£75,215
Etanercept	[redacted]	[redacted]	-£3,172.91	**2**	-£6,242.46	5	£42,441
Infliximab	[redacted]	[redacted]	-£24,128.66	10	-£23,136.37	10	£63,091
Secukinumab	[redacted]	[redacted]	-£19,596.03	7	-£18,814.34	7	£56,528
Guselkumab	[redacted]	[redacted]	-£18,280.31	6	-£18,590.95	6	£62,563
Adalimumab	[redacted]	[redacted]	-£3,495.17	4	-£5,484.07	4	£34,802

Brodalumab	[redacted]	[redacted]	-£23,364.79	9	-£22,637.53	9	£63,783
Ustekinumab 90mg	[redacted]	[redacted]	-£3,393.64	**3**	-£3,851.64	**2**	£29,275
Ustekinumab 45mg	[redacted]	[redacted]	-£3,671.29	5	-£4,379.76	**3**	£30,539
Ixekizumab	[redacted]	[redacted]	-£21,368.58	8	-£20,248.23	8	£57,441
Key: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit							

6.3.3 Alternative time horizons

As discussed in Section 5.2.1, patients who fail three lines of biological therapy are assumed to move to best supportive care. As none of the comparators are cost-effective versus BSC, it benefits them to have a low response rate within this model structure, as patients will move to BSC sooner, and gain more cost-effective QALYs. Because of this, time spent on best supportive care (BSC) becomes a key driver of the model results, which is concerning given uncertainties surrounding the data used in this treatment option and the plausibility that patients will spend a significant proportion of their life on BSC.

The following analysis uses ERG Scenario 1 as a basis, i.e. head-to-head comparisons of a single biologic, but uses a 5, 10, and 15 year time horizon to focus the results on the short-term implications of choosing a particular biologic, rather than on the duration of BSC. Each treatment option is ranked by its NMB versus certolizumab, as described in Section 6.3.1.

In these scenarios the order of the top three biologics ranked by incremental net-monetary benefit remains the same across all time horizons. This is reassuring given the uncertainties discussed above, as it indicates the NMB ranking framework is not sensitive to the duration of BSC.

Table 40 ERG Scenarios 3, 4, and 5: alternative time horizons

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 3: 5 year time horizon							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**2**	£0.00	**1**	£51,747
Certolizumab pegol 400mg	[redacted]	[redacted]	-£23,527.72	11	-£23,220.87	11	£153,484
Etanercept	[redacted]	[redacted]	£716.21	**1**	-£395.76	**2**	£87,008
Infliximab	[redacted]	[redacted]	-£19,813.83	10	-£19,429.01	10	£132,765
Secukinumab	[redacted]	[redacted]	-£16,437.32	7	-£16,134.04	7	£121,664
Guselkumab	[redacted]	[redacted]	-£14,167.13	6	-£14,284.47	6	£132,854
Adalimumab	[redacted]	[redacted]	-£1,039.37	**3**	-£1,766.68	**3**	£80,058
Brodalumab	[redacted]	[redacted]	-£18,540.81	9	-£18,254.80	9	£132,042

Ustekinumab 90mg	[redacted]	[redacted]	-£2,800.84	5	-£2,966.07	4	£70,806
Ustekinumab 45mg	[redacted]	[redacted]	-£2,773.67	4	-£3,036.87	5	£73,664
Ixekizumab	[redacted]	[redacted]	-£18,397.16	8	-£17,957.11	8	£124,087
ERG Scenario 4: 10 year time horizon							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**2**	£0.00	**1**	£48,414
Certolizumab pegol 400mg	[redacted]	[redacted]	-£29,184.35	11	-£28,756.71	11	£140,528
Etanercept	[redacted]	[redacted]	£1,066.53	**1**	-£509.01	**2**	£81,420
Infliximab	[redacted]	[redacted]	-£24,008.45	10	-£23,527.65	10	£121,701
Secukinumab	[redacted]	[redacted]	-£19,555.91	7	-£19,170.42	7	£110,068
Guselkumab	[redacted]	[redacted]	-£16,857.19	6	-£17,019.76	6	£119,216
Adalimumab	[redacted]	[redacted]	-£769.96	**3**	-£1,784.50	**3**	£71,326
Brodalumab	[redacted]	[redacted]	-£22,811.09	9	-£22,450.41	9	£121,783
Ustekinumab 90mg	[redacted]	[redacted]	-£2,752.68	5	-£2,984.95	4	£62,774
Ustekinumab 45mg	[redacted]	[redacted]	-£2,705.32	4	-£3,071.70	5	£65,121
Ixekizumab	[redacted]	[redacted]	-£21,698.57	8	-£21,125.85	8	£111,502
ERG Scenario 5: 15 year time horizon							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**2**	£0.00	**1**	£46,206
Certolizumab pegol 400mg	[redacted]	[redacted]	-£30,690.05	11	-£30,214.69	11	£133,787
Etanercept	[redacted]	[redacted]	£1,017.45	**1**	-£743.15	**2**	£78,146
Infliximab	[redacted]	[redacted]	-£25,122.66	10	-£24,603.78	10	£115,985
Secukinumab	[redacted]	[redacted]	-£20,381.36	7	-£19,963.42	7	£104,569
Guselkumab	[redacted]	[redacted]	-£17,604.01	6	-£17,784.38	6	£113,003
Adalimumab	[redacted]	[redacted]	-£785.57	**3**	-£1,914.57	**3**	£67,510
Brodalumab	[redacted]	[redacted]	-£23,953.28	9	-£23,563.30	9	£116,192
Ustekinumab 90mg	[redacted]	[redacted]	-£2,760.68	5	-£3,019.80	4	£59,298
Ustekinumab 45mg	[redacted]	[redacted]	-£2,718.04	4	-£3,125.27	5	£61,473
Ixekizumab	[redacted]	[redacted]	-£22,560.07	8	-£21,935.53	8	£105,798

Key: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit

6.3.4 Alternative HRQoL data sources

As discussed in Section 5.2.7, the ERG considered it more appropriate to use the HRQoL values taken from those with a DLQI score >10, i.e. those defined as having moderate to severe psoriasis who are eligible for treatment with biologics. This analysis produces lower utility values, but with a greater utility gain for achieving each level of PASI response. The values generated with this approach are also more in line with those presented in previous appraisals.

The second scenario applies the same utilities across all treatment arms, that is, a particular PASI response produces the same utility score on biologics as on best supportive care. This is based on the regression analysis provided by the company for the DLQI≥10 population from the trials, weighted across the placebo and treatment arms by the proportion of patients across the three trials on which provided HRQoL data for the regression analysis who received treatment with a biologic therapy (85%). The values used in both these scenarios are presented in Table 41, with results presented in Table 42. As in previous scenarios, these are head-to-head comparisons of single biologics.

Table 41 Summary of utility values for DLQI≥10 (adapted from Table 42, points for clarification)

Health state	Utility value: Biologics	Utility value: BSC	Utility value: all patients
PASI <50	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	[redacted]	[redacted]
PASI: psoriasis area and severity index, BSC: best supportive care			

Certolizumab ranks the most cost-effective in terms of INB versus other biologics at both thresholds when the DLQI≥10 population HRQoL values were applied to biologics, but there remains a treatment effect for biologics. Certolizumab returns to second place at £20,000 and first at £30,000 when weighted utilities are applied equally across biologics and best supportive care based on the analysis described in Section 5.2.7.

Table 42 ERG Scenarios 6 and 7: Alternative HRQoL assumptions and sources

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 6: Population limited to DLQI≥10							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**1**	£0.00	**1**	£34,041
Certolizumab pegol 400mg	[redacted]	[redacted]	-£30,914.78	11	-£30,267.45	11	£98,809
Etanercept	[redacted]	[redacted]	-£198.09	**2**	-£2,615.78	**2**	£56,958
Infliximab	[redacted]	[redacted]	-£25,200.44	10	-£24,509.19	10	£85,850
Secukinumab	[redacted]	[redacted]	-£20,417.10	7	-£19,859.15	7	£77,255
Guselkumab	[redacted]	[redacted]	-£17,988.42	6	-£18,233.02	6	£83,045
Adalimumab	[redacted]	[redacted]	-£1,547.03	**3**	-£3,089.93	**3**	£49,244
Brodalumab	[redacted]	[redacted]	-£24,123.65	9	-£23,605.32	9	£85,988
Ustekinumab 90mg	[redacted]	[redacted]	-£2,940.40	4	-£3,296.38	4	£43,520
Ustekinumab 45mg	[redacted]	[redacted]	-£2,991.89	5	-£3,546.62	5	£45,032

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
Ixekizumab	[redacted]	[redacted]	-£22,480.38	8	-£21,645.53	8	£78,246
ERG Scenario 7: Equal utilities applied to biologics and BSC with population limited to DLQI≥10							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**2**	£0.00	**1**	£49,785
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,215.84	11	-£30,719.04	11	£142,079
Etanercept	[redacted]	[redacted]	£1,033.19	**1**	-£768.87	**2**	£96,741
Infliximab	[redacted]	[redacted]	-£25,406.85	10	-£24,818.80	10	£121,183
Secukinumab	[redacted]	[redacted]	-£20,595.22	7	-£20,126.34	7	£109,894
Guselkumab	[redacted]	[redacted]	-£17,880.86	6	-£18,071.69	6	£122,584
Adalimumab	[redacted]	[redacted]	-£814.28	**3**	-£1,990.81	**3**	£77,673
Brodalumab	[redacted]	[redacted]	-£24,276.29	9	-£23,834.29	9	£122,279
Ustekinumab 90mg	[redacted]	[redacted]	-£2,759.77	5	-£3,025.44	4	£64,224
Ustekinumab 45mg	[redacted]	[redacted]	-£2,735.41	4	-£3,161.92	5	£67,212
Ixekizumab	[redacted]	[redacted]	-£22,769.04	8	-£22,078.52	8	£110,425

Key: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit

6.3.5 Biosimilar costs and uptake

Section 5.2.8 argues that biosimilars would be used in practice where available, and given the steps taken by the NHS to ensure high uptake of biosimilar adalimumab upon the expiry of its patent in October 2018, it is reasonable to apply the anticipated cost of biosimilar adalimumab in the model. Table 43 presents a scenario in which all patients receive biosimilars infliximab, etanercept, and adalimumab, incurring relevant biosimilar costs. In this scenario, etanercept is substituted for Benepali®, at a unit cost of £82.00, infliximab for Flixabi®, costing £377.00, and a 20%, 30%, and 40% discount is applied to the £352.14 cost of adalimumab (Humira®), representing a range of anticipated prices for its biosimilars upon release. The use of biosimilar costs, assuming a discount between 20 and 40% for adalimumab, results in certolizumab ranking third in terms of its NMB, after adalimumab and etanercept.

Table 43 ERG Scenario 8, 9, and 10: Biosimilar costs applied for adalimumab, etanercept, and infliximab

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 8: Biosimilar costs for etanercept, infliximab, 20% discount for adalimumab							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**3**	£0.00	**3**	£44,929
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,213.21	11	-£30,715.10	11	£130,128
Etanercept	[redacted]	[redacted]	£2,096.88	**2**	£247.68	**2**	£66,397

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
Infliximab	[redacted]	[redacted]	-£21,074.10	8	-£20,536.88	8	£100,411
Secukinumab	[redacted]	[redacted]	-£20,665.94	7	-£20,232.41	7	£101,644
Guselkumab	[redacted]	[redacted]	-£17,876.89	6	-£18,065.74	6	£109,741
Adalimumab	[redacted]	[redacted]	£2,971.83	**1**	£1,787.96	**1**	£44,816
Brodalumab	[redacted]	[redacted]	-£24,352.29	10	-£23,948.28	10	£113,115
Ustekinumab 90mg	[redacted]	[redacted]	-£2,772.44	5	-£3,044.44	4	£57,486
Ustekinumab 45mg	[redacted]	[redacted]	-£2,735.91	4	-£3,162.66	5	£59,583
Ixekizumab	[redacted]	[redacted]	-£22,851.67	9	-£22,202.46	9	£102,802
ERG Scenario 9: Biosimilar costs for etanercept, infliximab, 30% discount for adalimumab							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**3**	£0.00	**3**	£44,929
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,213.21	11	-£30,715.10	11	£130,128
Etanercept	[redacted]	[redacted]	£2,096.88	**2**	£247.68	**2**	£66,397
Infliximab	[redacted]	[redacted]	-£21,074.10	8	-£20,536.88	8	£100,411
Secukinumab	[redacted]	[redacted]	-£20,665.94	7	-£20,232.41	7	£101,644
Guselkumab	[redacted]	[redacted]	-£17,876.89	6	-£18,065.74	6	£109,741
Adalimumab	[redacted]	[redacted]	£4,872.23	**1**	£3,688.36	**1**	£34,465
Brodalumab	[redacted]	[redacted]	-£24,352.29	10	-£23,948.28	10	£113,115
Ustekinumab 90mg	[redacted]	[redacted]	-£2,772.44	5	-£3,044.44	4	£57,486
Ustekinumab 45mg	[redacted]	[redacted]	-£2,735.91	4	-£3,162.66	5	£59,583
Ixekizumab	[redacted]	[redacted]	-£22,851.67	9	-£22,202.46	9	£102,802
ERG Scenario 10: Biosimilar costs for etanercept, infliximab, 40% discount for adalimumab							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**3**	£0.00	**3**	£44,929
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,213.21	11	-£30,715.10	11	£130,128
Etanercept	[redacted]	[redacted]	£2,096.88	**2**	£247.68	**2**	£66,397
Infliximab	[redacted]	[redacted]	-£21,074.10	8	-£20,536.88	8	£100,411
Secukinumab	[redacted]	[redacted]	-£20,665.94	7	-£20,232.41	7	£101,644
Guselkumab	[redacted]	[redacted]	-£17,876.89	6	-£18,065.74	6	£109,741
Adalimumab	[redacted]	[redacted]	£6,772.63	**1**	£5,588.76	**1**	£24,113
Brodalumab	[redacted]	[redacted]	-£24,352.29	10	-£23,948.28	10	£113,115
Ustekinumab 90mg	[redacted]	[redacted]	-£2,772.44	5	-£3,044.44	4	£57,486
Ustekinumab 45mg	[redacted]	[redacted]	-£2,735.91	4	-£3,162.66	5	£59,583
Ixekizumab	[redacted]	[redacted]	-£22,851.67	9	-£22,202.46	9	£102,802

Key: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit

6.3.6 Certolizumab pegol PASI response

The ERG noted a significant difference between the PASI response rates observed in the three certolizumab trials that could not be obviously explained by differences in the presented baseline characteristics. This suggests the cost-effectiveness of certolizumab may be sensitive to the population in which it is used, therefore there is uncertainty in the response rates that might be expected in clinical practice. These scenarios use the highest (CIMPASI-2) and lowest (CIMPASI-1) response rates observed in the certolizumab trials, which may be seen to represent the reasonable bounds of this treatment's relative cost effectiveness in practice. Note the naive values from the relevant trials are used, as the code used in the NMA was not available to the ERG despite it being requested at the points for clarification stage. Using the highest and lowest plausible response rates for certolizumab, its ranking does not change in head-to-head comparisons with the other biologics.

Table 44 ERG Scenarios 11 and 12: CIMPASI-1 and CIMPASI-2 PASI response rates

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 11: CIMPASI-1 PASI response rates for certolizumab pegol							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**2**	£0.00	**1**	£47,413
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,964.15	11	-£30,918.38	11	£130,128
Etanercept	[redacted]	[redacted]	£187.96	**1**	-£1,113.59	**2**	£76,290
Infliximab	[redacted]	[redacted]	-£26,259.45	10	-£25,174.57	10	£112,878
Secukinumab	[redacted]	[redacted]	-£21,416.88	7	-£20,435.70	7	£101,644
Guselkumab	[redacted]	[redacted]	-£18,627.83	6	-£18,269.02	6	£109,741
Adalimumab	[redacted]	[redacted]	-£1,579.92	**3**	-£2,216.13	**3**	£65,520
Brodalumab	[redacted]	[redacted]	-£25,103.23	9	-£24,151.57	9	£113,115
Ustekinumab 90mg	[redacted]	[redacted]	-£3,523.38	5	-£3,247.73	4	£57,486
Ustekinumab 45mg	[redacted]	[redacted]	-£3,486.85	4	-£3,365.95	5	£59,583
Ixekizumab	[redacted]	[redacted]	-£23,602.61	8	-£22,405.75	8	£102,802
ERG Scenario 12: CIMPASI-2 PASI response rates for certolizumab pegol							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**2**	£0.00	**1**	£42,566
Certolizumab pegol 400mg	[redacted]	[redacted]	-£30,501.54	11	-£30,635.01	11	£130,128
Etanercept	[redacted]	[redacted]	£1,650.56	**1**	-£830.22	**2**	£76,290
Infliximab	[redacted]	[redacted]	-£24,796.84	10	-£24,891.19	10	£112,878
Secukinumab	[redacted]	[redacted]	-£19,954.28	7	-£20,152.32	7	£101,644
Guselkumab	[redacted]	[redacted]	-£17,165.23	6	-£17,985.65	6	£109,741
Adalimumab	[redacted]	[redacted]	-£117.31	**3**	-£1,932.76	**3**	£65,520
Brodalumab	[redacted]	[redacted]	-£23,640.63	9	-£23,868.20	9	£113,115
Ustekinumab 90mg	[redacted]	[redacted]	-£2,060.78	5	-£2,964.35	4	£57,486

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
Ustekinumab 45mg	[redacted]	[redacted]	-£2,024.25	4	-£3,082.58	5	£59,583
Ixekizumab	[redacted]	[redacted]	-£22,140.01	8	-£22,122.37	8	£102,802

Abbreviations: PASI, psoriasis area severity index; BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit

6.3.7 Dose escalation scenario

The ERG did not consider the implementation of the company's dose escalation strategy to be appropriate, as previously discussed in Section 5.2.4. Table 45 presents the results of three scenarios exploring an alternative conceptualisation of the treatment escalation strategy. These scenarios treats escalation of certolizumab as a distinct decision in a patient's treatment strategy, and compares this to simply switching to a different biologic (ustekinumab). ICERs are produced for dose escalation with certolizumab compared with both switching to a new drug, i.e. not escalating, and other dose escalation strategies which could be used in practice.

The response data used in these three scenarios is based on data provided by the company in their response to Clarification Question B8. Scenario 13 uses 32 week response data from patients who escape to 400mg certolizumab arm after failing to achieve a PASI75 response at 16 weeks on 200mg certolizumab pegol. Scenario 14 replicates this, but restricts the analysis to only those patients who achieve a PASI50-74 response at week 16 and escape to 400mg certolizumab. Scenario 15 builds upon Scenario 14 further,

[redacted]

The results of these analyses show that dose escalation is never more cost-effective than switching to ustekinumab (at 45 or 90mg), except

[redacted]

and only partial responders may dose escalate.

Table 45 ERG Scenarios 13, 14, and 15: Dose escalation

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
ERG Scenario 13: Dose escalation (PASI<75 at 16w)						
Certolizumab pegol 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	CZP400, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ERG Scenario 14: Dose escalation (PASI50-74 at 16w)						
Certolizumab pegol 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	CZP400, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£469,793
ERG Scenario 15: Dose escalation (PASI50-74 at 16w) and [redacted]						
Certolizumab pegol 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	CZP400, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£22,618

Abbreviations: QALY, quality-adjusted life years; PASI, psoriasis area severity index; BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; UST, ustekinumab.

6.3.8 Alternative positioning of biologics in treatment pathway

Given the historic position of biologics and current NICE guidelines, the ERG has a number of concerns regarding the principle of considering certolizumab as an alternative to non-biologic therapy, which are typically given as first-line systemic therapy. As such, the ERG presents a series of analyses exploring the position of certolizumab further up the pathway, using a number of alternative assumptions which the ERG consider to be more appropriate than those presented by the company. Firstly, to more appropriately capture the effectiveness of non-biologic therapies, methotrexate response data is used as a proxy for standard of care (first-line) as presented by the company in response to clarification question B4. As outlined in Section 5.2.6 the ERG considers this more appropriate than using pooled placebo response data as is done in the company's base-case. Secondly, the ERG changed the sequence of therapies considered, so that the comparison reflects a choice between using certolizumab first-line or second line certolizumab following non-biologic therapy. Results of this comparison are presented in Scenario 17. For consistency with previously presented scenarios, a further scenario is also presented (Scenario 18) which compares certolizumab as a first-line treatment with certolizumab second-line, followed by best supportive care; i.e. removing further lines of biologic therapy.

For the reasons outlined in Section 5.2.4.3, the data available is inappropriate to make an informed decision on this positioning, and the response data derived from the systemic non-biologic therapy naïve group is unreliable due to its sample size and associated uncertainty. However, the results in Table 46 show that within the confines of the presented model structure, the alternative positioning of certolizumab prior to other biologics is not cost-effective.

Table 46 ERG Scenarios 16 and 17: Candidates for systemic non-biologics

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
ERG Scenario 16: Candidates for systemic non-biologics CZP 1st vs CZP 2nd line & sequencing						
Best supportive care	CZP200, UST90, INF, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	UST90, INF, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£402,644
ERG Scenario 17: Candidates for systemic non-biologics CZP alternate positioning only						
Certolizumab pegol 200mg	BSC, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Best supportive care	CZP200, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Abbreviations: QALY, quality-adjusted life years; BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; UST, ustekinumab; INF, infliximab.						

6.4 ERG alternative base-case

The ERG alternative base-case incorporates all of the ERG's corrections and a number of the above scenarios which were considered to represent the most plausible and useful results for the purposes of decision making.

6.4.1 Candidates for systemic biologic therapy

For the main position and population under consideration, the ERG alternative base-case includes assumptions from ERG Scenarios 1, 7, and 8 (without adalimumab price reduction).

As per Scenario 1, this analysis assesses each biologic against every other as a single line of therapy, using the incremental net-monetary benefit relative to certolizumab. As in Scenario 7, the utilities used are based on the population with DLQI ≥10 from both the certolizumab and placebo arms of the trials, with equal utility scores attached to each level of PASI response achieved on best supportive care and biologics. The ERG base-case also assumes all patients are given biosimilar versions of etanercept and infliximab, while this is as what was included in Scenario 8, this base-case does not speculate on biosimilar costs for adalimumab, and uses the current list price. The results can be found in Table 47.

Deterministic analyses are presented as insufficient data on the changes made to HRQoL were available to implement a probabilistic analysis.

Table 47 ERG Alternative base-case (candidates for biologics)

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Alternative base-case: Scenario 1+7+8							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**2**	£0.00	**2**	£49,785
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,215.84	11	-£30,719.04	11	£142,079
Etanercept	[redacted]	[redacted]	£2,191.17	**1**	£389.11	**1**	£84,196
Infliximab	[redacted]	[redacted]	-£20,972.45	8	-£20,384.40	8	£107,799
Secukinumab	[redacted]	[redacted]	-£20,595.22	7	-£20,126.34	7	£109,894
Guselkumab	[redacted]	[redacted]	-£17,880.86	6	-£18,071.69	6	£122,584
Adalimumab	[redacted]	[redacted]	-£814.28	**3**	-£1,990.81	**3**	£77,673
Brodalumab	[redacted]	[redacted]	-£24,276.29	10	-£23,834.29	10	£122,279
Ustekinumab 90mg	[redacted]	[redacted]	-£2,759.77	5	-£3,025.44	4	£64,224
Ustekinumab 45mg	[redacted]	[redacted]	-£2,735.41	4	-£3,161.92	5	£67,212
Ixekizumab	[redacted]	[redacted]	-£22,769.04	9	-£22,078.52	9	£110,425

Abbreviations: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit

To further explore the robustness of the above analyses, two further sets of exploratory analyses are presented relating to the cost-effectiveness of BSC and the future availability of adalimumab biosimilars.

Table 48 therefore presents results using the ERG base-case assumptions, and applying the assumptions used in Scenario 2, i.e. a 40 year time horizon, TA511 utilities, and BSC costs derived from Fonia *et al.* This scenario also uses the biosimilar costs as described in Scenario 8. Note that in this scenario, the ERG base-case assumptions regarding utilities superseded, thus this is Scenario 2 + 8. These results show that in contrast the alternative base-cases 3 and 4, certolizumab remains the highest-ranked of the biologics in terms of NMB, and also remains cost-effective versus BSC, albeit with a marginally higher ICER than adalimumab.

To address the imminent release of adalimumab biosimilars, Table 48 explores the impact of alternative discounts to the current Humira® list price of 20% and 40%. The results of this analysis show that when biosimilar discounts are taken into account certolizumab is ranked consistently below its potentially most relevant comparator adalimumab.

Table 48 Exploratory analysis on the ERG alternative base-case

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Alternative base-case 2: Scenario 2 + 8							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**2**	£0.00	**1**	£21,222
Certolizumab pegol 400mg	[redacted]	[redacted]	-£30,135.35	11	-£29,314.20	11	£75,215
Etanercept	[redacted]	[redacted]	-£2,014.94	**3**	-£5,084.49	5	£35,515
Infliximab	[redacted]	[redacted]	-£19,694.30	8	-£18,702.01	7	£55,358
Secukinumab	[redacted]	[redacted]	-£19,596.03	7	-£18,814.34	8	£56,528
Guselkumab	[redacted]	[redacted]	-£18,280.31	6	-£18,590.95	6	£62,563
Adalimumab	[redacted]	[redacted]	£305.60	**1**	-£1,683.31	**2**	£20,994
Brodalumab	[redacted]	[redacted]	-£23,364.79	10	-£22,637.53	10	£63,783
Ustekinumab 90mg	[redacted]	[redacted]	-£3,393.64	4	-£3,851.64	**3**	£29,275
Ustekinumab 45mg	[redacted]	[redacted]	-£3,671.29	5	-£4,379.76	4	£30,539
Ixekizumab	[redacted]	[redacted]	-£21,368.58	9	-£20,248.23	9	£57,441
ERG Alternative base-case 3: Scenario 1+7+8 (20% adalimumab discount)							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**3**	£0.00	**3**	£49,785
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,215.84	11	-£30,719.04	11	£142,079
Etanercept	[redacted]	[redacted]	£2,191.17	**2**	£389.11	**2**	£84,196
Infliximab	[redacted]	[redacted]	-£20,972.45	8	-£20,384.40	8	£107,799
Secukinumab	[redacted]	[redacted]	-£20,595.22	7	-£20,126.34	7	£109,894
Guselkumab	[redacted]	[redacted]	-£17,880.86	6	-£18,071.69	6	£122,584
Adalimumab	[redacted]	[redacted]	£2,986.52	**1**	£1,810.00	**1**	£53,129
Brodalumab	[redacted]	[redacted]	-£24,276.29	10	-£23,834.29	10	£122,279
Ustekinumab 90mg	[redacted]	[redacted]	-£2,759.77	5	-£3,025.44	4	£64,224
Ustekinumab 45mg	[redacted]	[redacted]	-£2,735.41	4	-£3,161.92	5	£67,212
Ixekizumab	[redacted]	[redacted]	-£22,769.04	9	-£22,078.52	9	£110,425
ERG Alternative base-case 4: Scenario 1+7+10 (40% adalimumab discount)							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	**3**	£0.00	**3**	£49,785
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,215.84	11	-£30,719.04	11	£142,079
Etanercept	[redacted]	[redacted]	£2,191.17	**2**	£389.11	**2**	£84,196
Infliximab	[redacted]	[redacted]	-£20,972.45	8	-£20,384.40	8	£107,799
Secukinumab	[redacted]	[redacted]	-£20,595.22	7	-£20,126.34	7	£109,894
Guselkumab	[redacted]	[redacted]	-£17,880.86	6	-£18,071.69	6	£122,584
Adalimumab	[redacted]	[redacted]	£6,787.32	**1**	£5,610.80	**1**	£28,585
Brodalumab	[redacted]	[redacted]	-£24,276.29	10	-£23,834.29	10	£122,279
Ustekinumab 90mg	[redacted]	[redacted]	-£2,759.77	5	-£3,025.44	4	£64,224
Ustekinumab 45mg	[redacted]	[redacted]	-£2,735.41	4	-£3,161.92	5	£67,212

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
Ixekizumab	[redacted]	[redacted]	-£22,769.04	9	-£22,078.52	9	£110,425
Abbreviations: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit							

6.4.2 Dose escalation strategy

For consistency with the ERG base-case presented above, Scenario 16 is updated to include assumptions regarding the utilities used in the model (Scenario 7). The dose escalation scenarios do not make use of the biosimilar and therefore Scenario 8 has no impact on the results of this analysis. The results of this analysis show that dose escalation with certolizumab is moderately more effective than switching to ustekinumab, but is substantially more costly due to the double number of vials required.

Table 49 ERG Alternative base-case (dose escalation)

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
ERG Alternative base-case (dose escalation): ERG Scenario 7 + 14						
Certolizumab pegol 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	CZP400, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£508,833
Abbreviations: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; UST, ustekinumab.						

6.4.3 Candidates for systemic non-biologic therapy

For consistency with the previously presented ERG base cases, Scenario 18 is updated to include the ERG's preferred utilities. As no biosimilar products are included in this scenario, these discounts are not applied in this scenario. Table 50 presents a comparison between certolizumab as a first line option, versus its use in its current position, i.e. after first-line systemic non-biologic therapy. This shows a small incremental difference in costs and QALYs, which results in certolizumab being dominated at this position in the pathway, versus certolizumab in its current position.

Table 50 ERG Alternative base-case (candidates for non-biologics)

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
ERG Alternative base-case (candidates for non-biologics): ERG Scenario 7 + 18						
Best supportive care	CZP200, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	BSC, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Abbreviations: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

6.5 Conclusions from ERG analyses

The key uncertainties discussed in Section 5 were assessed in the above scenario analyses by the ERG; however, the limitations of the model structure mean that these could not be fully addressed in some cases. The results of the scenarios for the primary population, i.e. non-biologic inadequate responders, are summarised in Table 51 below. This shows that at a £20,000 cost-effectiveness threshold, certolizumab was ranked 1st in 2 of the 16 scenarios, but was ranked in the top 3 by net monetary benefit across all scenarios at this threshold.

At a £30,000 threshold, certolizumab was ranked 1st in 10 of the 16 scenarios, the exceptions being when any discount was applied to the list price of adalimumab. The ERG considers certolizumab to be a cost-effective treatment option relative to currently available biologics, however, as an anti-TNFα it is most appropriate to compare certolizumab to adalimumab, which may become significantly cheaper, and therefore the most cost-effective option, upon the imminent launch and uptake of biosimilar products.

The key driver of changes to the rankings is the weighting of QALYs, i.e. the chosen cost-effectiveness threshold, and the availability of biosimilar products. The application of utilities from TA511 also has the effect of increasing the QALY gain of a PASI response, which improves the cost-effectiveness of these products relative to BSC. However, the cost-effectiveness of certolizumab versus BSC relies upon both using these utilities, and the treatment acquisition costs derived from Fonia *et al.,* which the ERG does not consider to be more appropriate than those proposed in the company's base-case analysis.

Table 51 NMB Rankings at £20,000 and £30,000 across ERG Scenarios and alternative base-cases

Treatment (single line)	Rank at £20,000 (by ERG scenario)												ERG alternative Base Case (20k)			
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**1**	**2**	**3**	**4**
Certolizumab pegol 200mg	**2**	1	**2**	**2**	**2**	**1**	**2**	**3**	**3**	**3**	**2**	**2**	**2**	**2**	**3**	**3**
Certolizumab pegol 400mg	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Etanercept	**1**	2	**1**	**1**	**1**	**2**	**1**	**2**	**2**	**2**	**1**	**1**	**1**	**3**	**2**	**2**
Infliximab	10	10	10	10	10	10	10	8	8	8	10	10	8	8	8	8
Secukinumab	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Guselkumab	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Adalimumab	**3**	4	**3**	**3**	**3**	**3**	**3**	**1**	**1**	**1**	**3**	**3**	**3**	**1**	**1**	**1**
Brodalumab	9	9	9	9	9	9	9	10	10	10	9	9	10	10	10	10
Ustekinumab 90mg	5	3	5	5	5	4	5	5	5	5	5	5	5	4	5	5
Ustekinumab 45mg	4	5	4	4	4	5	4	4	4	4	4	4	4	5	4	4
Ixekizumab	8	8	8	8	8	8	8	9	9	9	8	8	9	9	9	9
Treatment (single line)	**Rank at £30,000 (by ERG scenario)**												**ERG alternative Base Case (30k)**			
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**1**	**2**	**3**	**4**
Certolizumab pegol 200mg	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**3**	**3**	**3**	**1**	**1**	**2**	**1**	**3**	**3**
Certolizumab pegol 400mg	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Etanercept	**2**	5	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**1**	5	**2**	**2**
Infliximab	10	10	10	10	10	10	10	8	8	8	10	10	8	7	8	8
Secukinumab	7	7	7	7	7	7	7	7	7	7	7	7	7	8	7	7
Guselkumab	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Adalimumab	**3**	4	**3**	**3**	**3**	**3**	**3**	**1**	**1**	**1**	**3**	**3**	**3**	**2**	**1**	**1**
Brodalumab	9	9	9	9	9	9	9	10	10	10	9	9	10	10	10	10
Ustekinumab 90mg	4	**2**	4	4	4	4	4	4	4	4	4	4	4	**3**	4	4
Ustekinumab 45mg	5	**3**	5	5	5	5	5	5	5	5	5	5	5	4	5	5
Ixekizumab	8	8	8	8	8	8	8	9	9	9	8	8	9	9	9	9

Using the ERG's preferred assumptions for the two other treatment strategies proposed by the company, i.e. dose escalation and treating candidates for non-biologic systemic therapies, certolizumab was not found to be a cost-effective treatment option.

7 End of life

This intervention does not meet the end of life criteria published by NICE.

8 Overall conclusions

8.1 Clinical effectiveness

The CIMPASI-1, CIMPASI-2 and CIMPACT trials demonstrated that certolizumab (200 mg Q2W and 400 mg Q2W) significantly reduced the severity of psoriasis and its impact on health-related quality of life, compared with placebo. All three trials were relatively good quality RCTs and the results are likely to be reliable. However, the results may not be entirely generalisable to the proposed eligible population because inclusion criteria relating to disease severity were not the same as the threshold specified in the NICE treatment pathway and [redacted]% patients in the trials had not received previous systemic therapy. The ERG considers that the population most relevant to this submission is patients who have previously received systemic non-biologic therapy, as they resemble the patients most likely to be treated with certolizumab in clinical practice.

CIMPASI-2 had substantially higher PASI 75, PASI 90 and PASI 100 response rates than the CIMPASI-1 and CIMPACT trials. The baseline imbalances between the trials may partially explain the higher response rate in CIMPASI-2, however it is unclear what is driving the difference between the study results. Therefore, the ERG is uncertain whether it is appropriate to pool results of all three trials, considering the heterogeneity between the trial results.

The NMA appears to have included all relevant trials of certolizumab and the comparator therapies. However, there was considerable heterogeneity between the trials included in the NMA. They varied by design and patient characteristics, such as psoriatic arthritis, time since diagnosis, mean baseline PASI score, proportion of male patients and the time-point at which the primary outcome was assessed. All of these differences reduce the reliability of the NMA results.

[redacted]The results of the NMA, in terms of ranking order of effectiveness, were consistent with those of NMAs undertaken in other recent STAs of treatments for moderate to severe plaque psoriasis in adults and the NMA undertaken for the development of the BAD guidelines.

8.2 Cost-effectiveness

The economic evidence presented by the company primarily consisted of a *de novo* model. The company's model used a cohort state-transition approach which used the PASI response rates estimated from the NMA or from the CIMPASI and CIMPACT trials to determine the patient

transitions between the health states. The analysis considered the cost-effectiveness of certolizumab in two patient populations: *(i)* those who are candidates for systemic non-biologic therapies, and *(ii)* for those who have an inadequate response, are contraindicated, or intolerant to other systemic non-biologic therapies. The ERG considers the company's economic model to meet the requirements of the NICE reference case and addressed the decision problem specified in NICE's scope.

In the analysis of candidates for biologic therapy, there were three non-dominated sequences. Of the non-dominated sequences, the least effective and lowest cost was the sequence starting with etanercept. The deterministic ICER of the certolizumab sequence was reported to be £11,471 per QALY compared to the etanercept sequence. The ICER of dose-escalated certolizumab compared with dose-escalated adalimumab was estimated as £36,638 per QALY gained. In the analysis of candidates for systemic non-biologic therapy, the ICER of certolizumab as first-line therapy compared with a sequence starting with standard care followed by adalimumab was estimated as £3,650 per QALY gained. None of the sequences were cost-effective versus best supportive care, with a pairwise ICER of £70,086 for certolizumab.

The ERG identified several areas of uncertainty regarding inputs and assumptions, and a calculation error pertaining to the estimation of per-cycle costs. The ERG concludes that the restrictive nature of the sequences compared is an important limitation. The ERG proposes an alternative approach to inform the cost-effectiveness of alternative sequences based on net-benefit calculations and associated rankings of each individual treatment compared to BSC.

The ERG does not consider the company to have presented sufficient evidence to support the earlier positioning of certolizumab, in those who are candidates for systemic non-biologic therapy. This sequence is unprecedented in previous guidance issued by NICE and relies on accurate and representative treatment sequencing. The certolizumab dose escalation strategy did not consider an appropriate set of comparators, with the company comparing certolizumab to an adalimumab-based dose escalation strategy. The ERG considers the most appropriate counterfactual to certolizumab with dose escalation to be certolizumab without dose escalation.

The ERG carried out a number of analyses using assumptions and data inputs it believes are more plausible than those used in the company's base-case analysis; however, structural limitations in the model meant not all issues could be fully addressed. Across the ERG's scenario analyses and alternative base cases, certolizumab was consistently ranked in the top three biologics by net-monetary benefit at a £20,000 and £30,000 cost-effectiveness threshold. In those scenarios which applied a discount to the current list price of adalimumab in anticipation of the launch of biosimilars, adalimumab was ranked first in terms of NMB. However, the ERG consider the results to sufficiently

demonstrate that certolizumab is a cost-effective treatment option amongst currently used biologics at this point in the treatment pathway. Using the ERG's preferred assumptions for the two other treatment strategies proposed by the company, i.e. dose escalation and treating candidates for non-biologic systemic therapies, certolizumab was not found to be a cost-effective treatment option.

These results exclude the confidential PAS schemes for several comparators (brodalumab, guselkumab, ixekizumab, secukinumab). The impact of including these confidential PAS schemes is presented in a separate confidential appendix.

8.3 Implications for research

The lack of appropriate clinical evidence on the sequential use of biological therapies was considered to be one of the most important uncertainties supporting the cost-effectiveness analysis. In order to address this issue, evidence of the degradation of response to treatment associated with subsequent lines of treatment and the biologics treatment response in those who have had previous exposure to biologics would be required.

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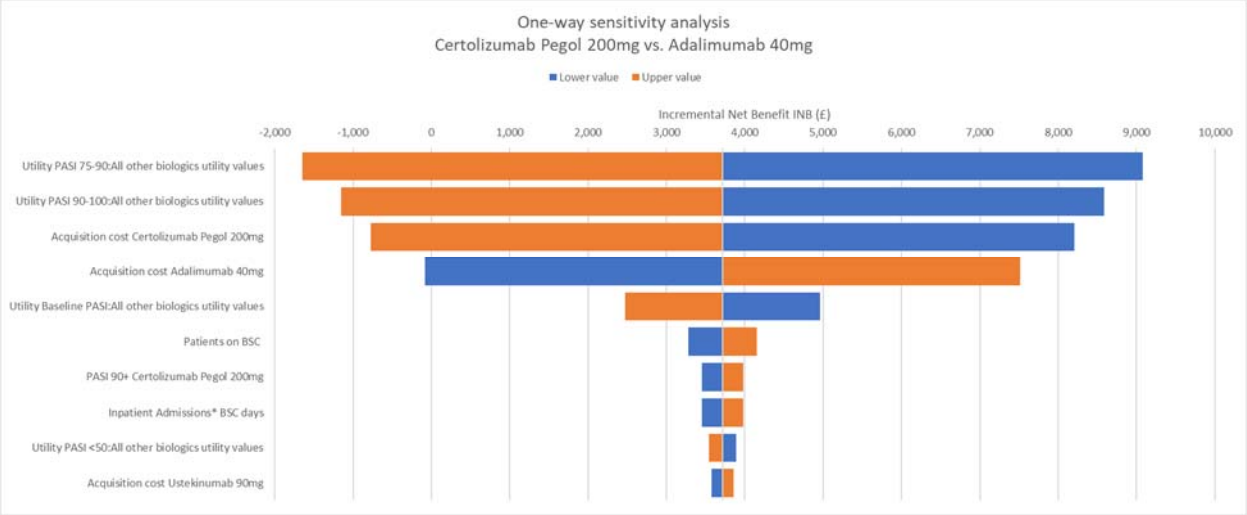
10 Appendices

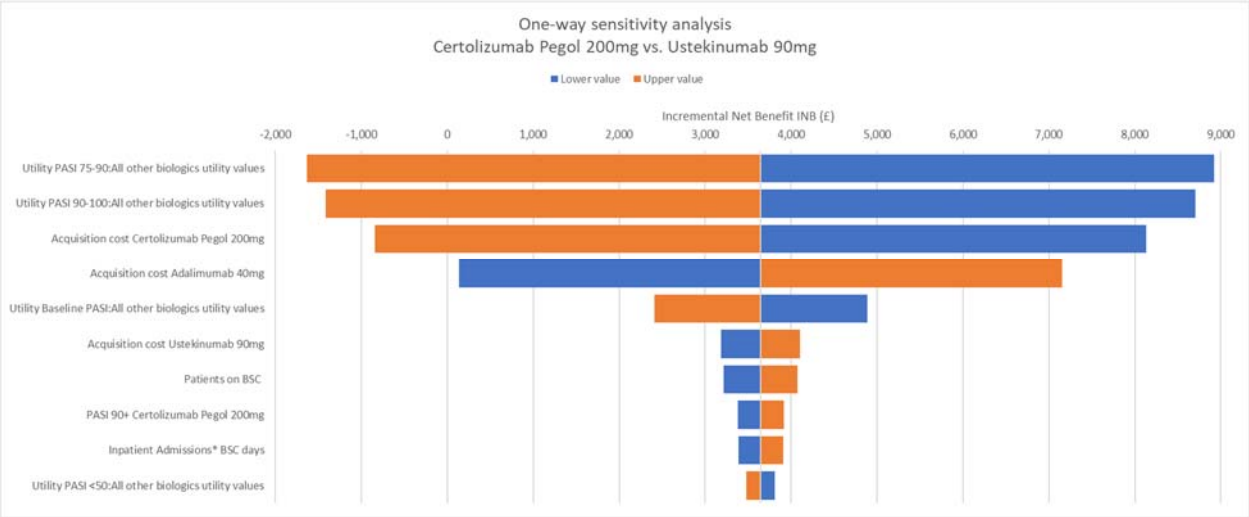
10.1 Tornado diagrams

The figures below present the tornado diagrams which were originally presented in Figure 34 to Figure 43 in the CS. These display the impact on the incremental net benefit (INB) from varying each parameter. These have been corrected by the ERG, as the original tornado diagrams did not include impact of changing utility values.

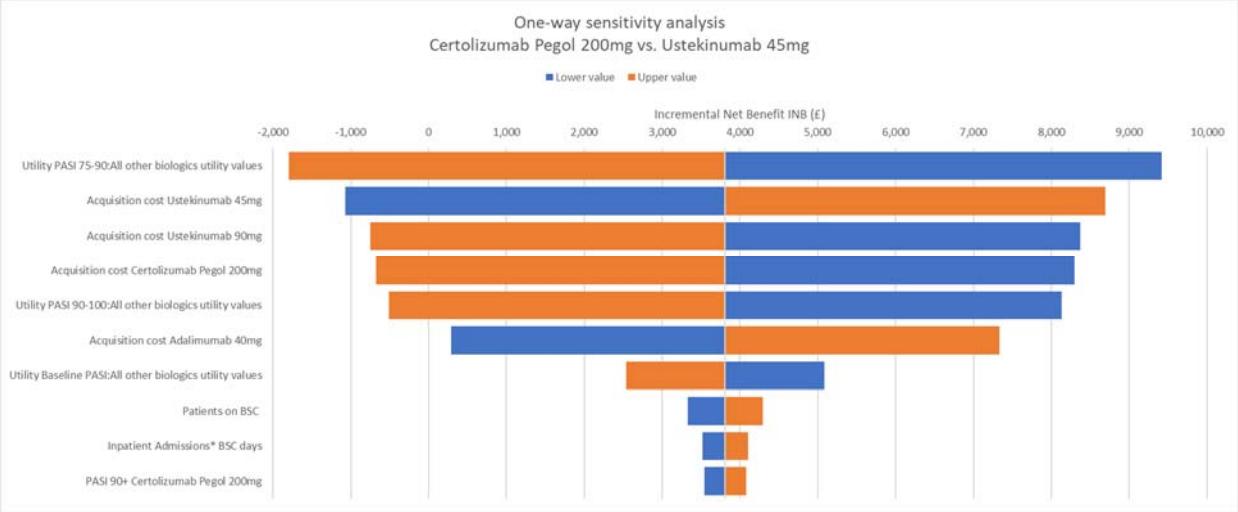
Tornado plot for systemic non-biologic therapy inadequate responders – CZP 200 mg versus ADA 40 mg (replaces Fig 34 in CS)



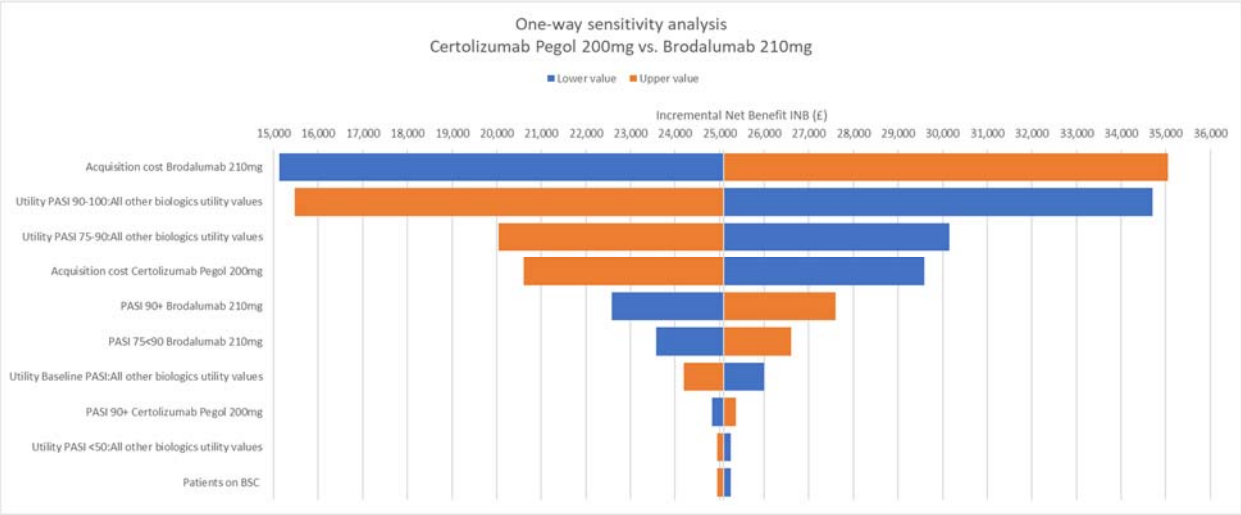
Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus UST 90 mg (replaces Fig 34 in CS)



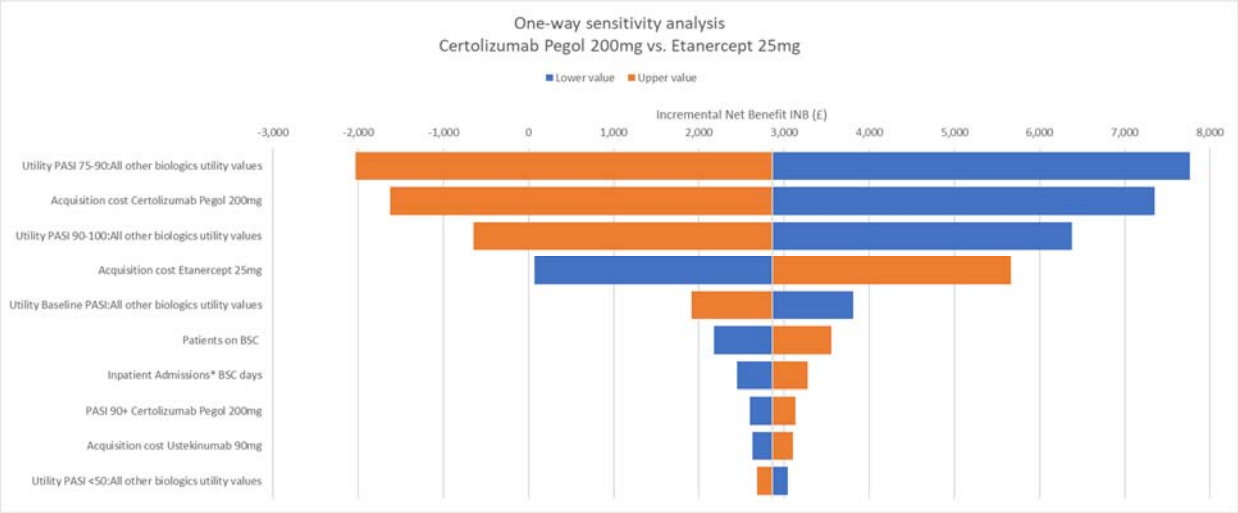
Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus UST 45 mg (replaces Fig 35 in CS)



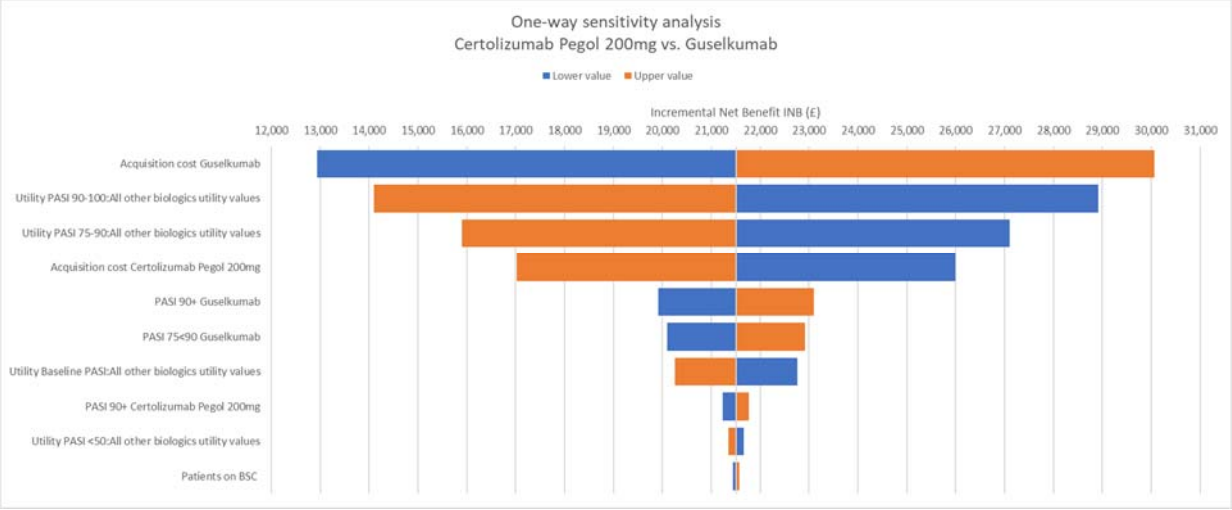
Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus BROD (replaces Fig 37 in CS)



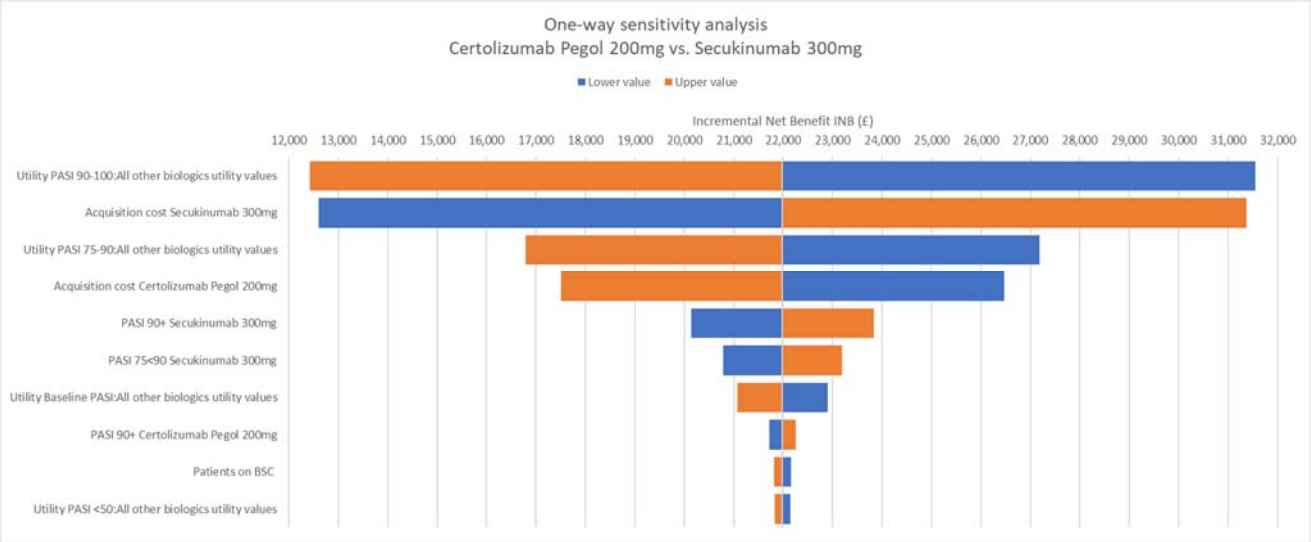
Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus ETN 25 mg (replaces Fig 38 in CS)



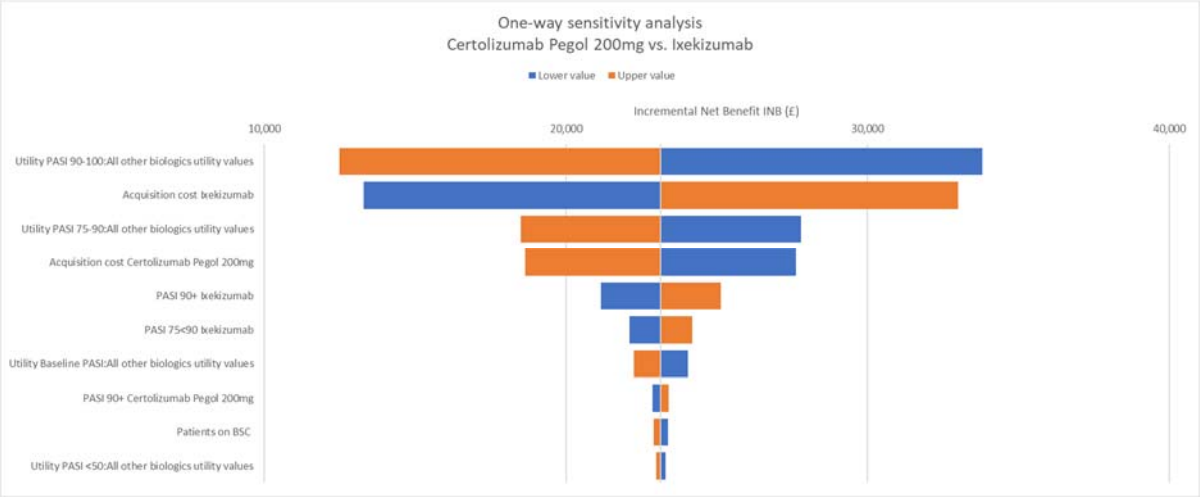
Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus GUS (replaces Fig 39 in CS)



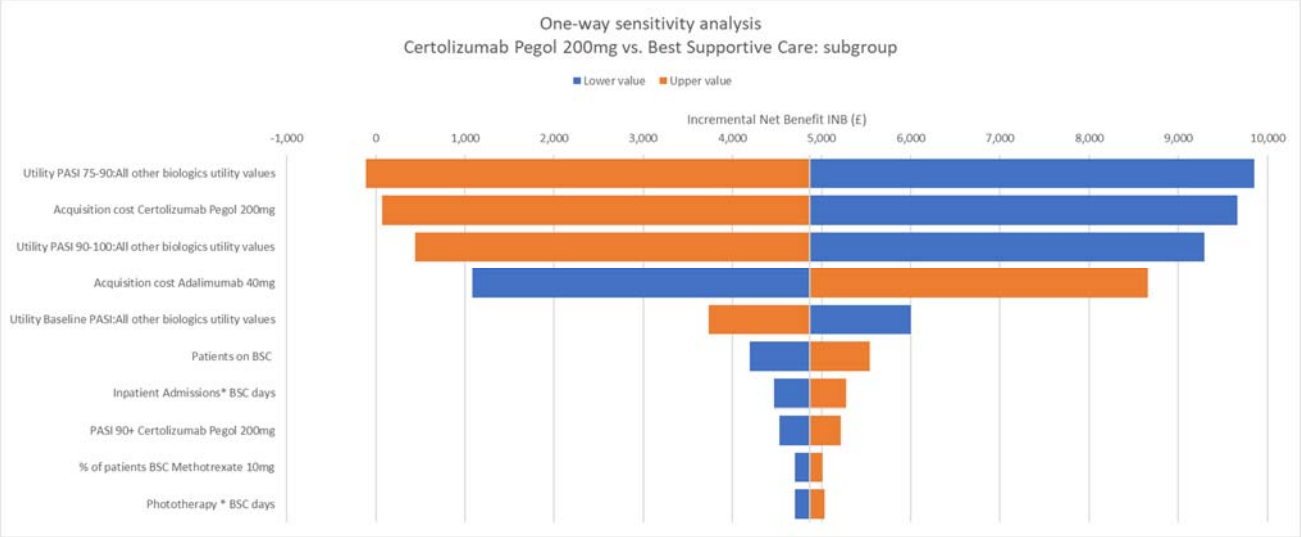
Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus SEC (replaces Fig 40 in CS)



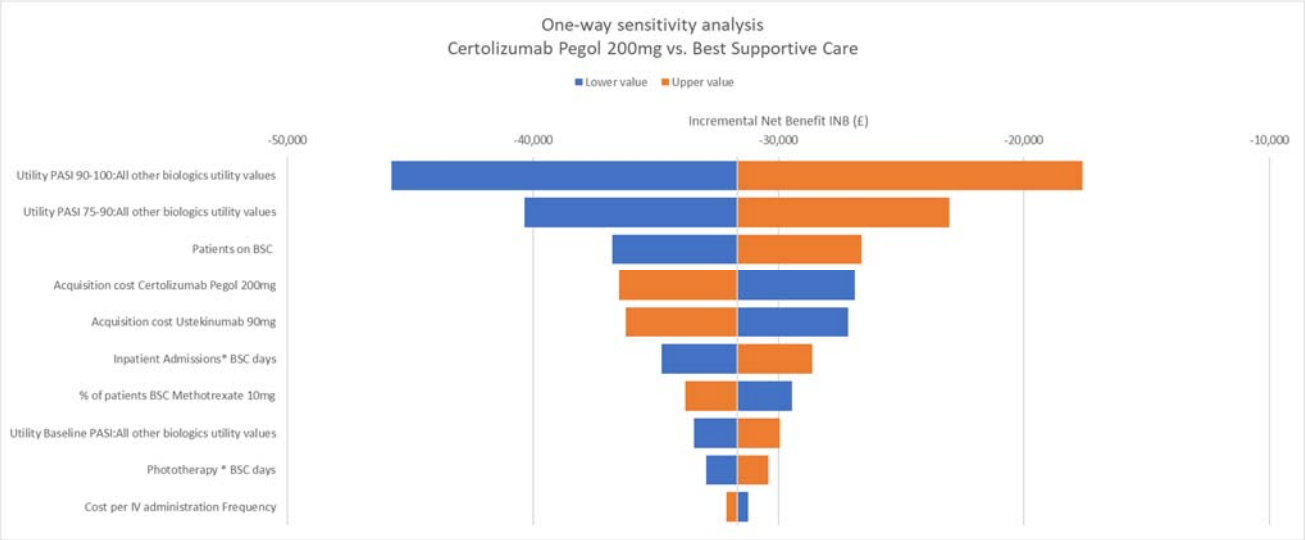
Tornado plot for systemic non-biologic therapy inadequate responders – CZP versus IXE (replaces Fig 41 in CS)



Tornado plot for systemic non-biologic inadequate responders - CZP escalation strategy with PAS vs ADA escalation strategy (replaces Fig 42 in CS)



Tornado plot for candidates for systemic non-biologic therapy – CZP 200 mg versus standard of care (replaces Fig 43 in CS)



ADDENDUM
Evidence Review Group's Report
Certolizumab pegol for treating moderate to severe plaque psoriasis

Amended clinical evidence provided by the company following the FAC and updated cost-effectiveness results

1 ERG commentary on the amended network meta-analysis

As part of the factual inaccuracy (FAC) pro-forma response to the ERG report, the company provided further exploration into the discrepancies in the PASI response rates for guselkumab predicted in their network meta-analysis and what was reported in the clinical trials for guselkumab. The revised NMA resulted in an increase in the estimated PASI 75 responder rate for guselkumab from [redacted] to [redacted] which is aligned with the PASI 75 responder rate observed in the clinical trials for guselkumab.

The company provided the corrected WinBugs code and data input (Table 3 in the FAC document). The ERG had identified several problems with the previous WinBugs code the company provided in the company submission and in the points for clarification response. The code did not appear to be correct and so the ERG was unable to reproduce the results reported in the company submission.

The ERG assessed the new WinBugs code, however there was still an essential part of the code missing (initial values and the centering constant), which were requested and provided a few days later. The ERG made some revisions to the updated WinBugs code. The duplicate line defining theta[i,k,j] with no regression was deleted and a redundant final bracket was removed. The duplicate line defining theta[i,k,j] with no regression was deleted and a correction to the definition of z in the linear predictor was made to conform with the TSU code corrected in September 2016 (now z[C[i,j+1]-1]). A correction for extreme values of the probabilities when zero events are observed was also added. In addition, a redundant final bracket was removed. The results obtained by running the corrected code are different to those reported in Figure 19, 20 and 22 of the CS, with slightly lower predicted absolute PASI responses for both doses of certolizumab and higher predicted absolute PASI responses for all other treatments. Therefore, the treatment ranking has changed from the original ranking presented in the CS. Ixekinumab, guselkumab, brodalumab, secukinumab (300 mg) and infliximab now have a higher PASI 75 response rate than certolizumab (200mg) and certolizumab (400 mg).

The company also provided revised WinBugs data as part of the pro-forma response (Table 4 in the FAC document), which the company state resolves the discrepancy of the lower guselkumab PASI 75 response rate reported in the submission compared to published guselkumab results. The revised WinBugs data includes only VOYAGE 1 and VOYAGE 2 trials for guselkumab. Whereas, previously the NMA also included the X-PLORE phase II RCT, which was not included in the guselkumab submission. The company also said the revised WinBugs data includes PASI 50 response estimates for guselkumab from VOYAGE 1 and VOYAGE 2 as identified in the guselkumab company submission. Whereas, previously the PASI 50 estimates for guselkumab from these studies were imputed as the data was not publically available. The company state that this revised data results in higher estimated PASI 75 response rates for guselkumab that are in line with the published estimates. However, the VOYAGE 1 and VOYAGE 2 PASI 50 input data provided in the factual inaccuracy

pro-forma response is identical to the original data, indicating that there has not been an update to the PASI 50 data. Nevertheless, the results obtained using the original data for guselkumab produced a PASI 75 response rate that was higher than the PASI 75 response rate presented in the CS ([redacted] vs [redacted], respectively). The updated guselkumab estimates are now in line with previously published estimates and are consistent with the clinical trial data for guselkumab.

Figure 1 Updated NMA: PASI 50 responder rates

Figure 2 Updated NMA: PASI 75 responder rates

Figure 3 Updated NMA: PASI 90 responder rates

2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Following the updated NMA provided by the company in their Factual Accuracy Check document, the ERG incorporated the results of the NMA provided by the company into the ERG-corrected model. This section presents the updated results reflecting the impact of this new information.

The results included in this document supersede those presented in Section 6 of the original ERG report. Note that the results presented here include only the complex PAS discount for certolizumab. A confidential appendix to this addendum presents the results with the confidential PAS applied for the comparator treatments (brodalumab, guselkumab, ixekizumab and secukinumab).

The sections of this addendum are as follows:

- Section 3 Corrections and adjustments to the company's base case model
- Section 4.1 Treatment sequencing and net-monetary benefit analysis
- Section 4.2 Cost-effectiveness of BSC
- Section 4.3 Alternative time-horizons
- Section 4.4 Alternative HRQoL data sources
- Section 4.5 Biosimilar costs and uptake
- Section 4.6 Certolizumab pegol PASI response
- Section 4.7 Dose escalation scenario
- Section 4.8 Alternative positioning of biologics in treatment pathway
- Section 5.1 ERG alternative base-case – candidates for systemic biologic therapy
- Section 5.2 Dose escalation strategy
- Section 5.3 Candidates for systemic non-biologic therapy

In the majority of scenarios, the rankings are very similar to those of the original analysis, the only difference being the rankings for secukinumab and guselkumab are inverted.

3 ERG corrections and adjustments to the company's base case model

Table 1 presents the results of the ERG-corrected company base-case, updating the results of Table 35 in the original ERG report. The largest differences in the results following the updates were to secukinumab, guselkumab, brodalumab and ixekizumab. The ICER for these treatments was lower in the updated analysis and guselkumab was no longer dominated by certolizumab, due to the higher number of QALYs generated by these sequences as a result of the higher PASI response rates predicted by the new NMA for these comparators (Figure 1 to Figure 3).

The results of the scenario for candidates for systemic non-biologics (Table 3) are the same as were presented in the ERG report, as this scenario was based on clinical data observed in the CZP trials and not the NMA.

Table 1 Company base-case and ERG corrected results (ERG Report Table 35)

First line therapy	Subsequent sequence	Total		Incremental		ICER vs BSC	CZP200 ICER vs comparator
		QALYs	Costs	QALYs	Costs		
Company base-case analysis results							
Best supportive care	BSC, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-	£70,086
Certolizumab pegol 200mg	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£70,086	-
Certolizumab pegol 400mg	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£100,788	£710,883
Etanercept	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£83,289	£11,471
Infliximab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£83,790	£36,171
Secukinumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£93,317	£598,382
Guselkumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£96,944	Dominant
Adalimumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£80,525	Dominant
Brodalumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£97,027	£720,462
Ustekinumab 90mg	ADA 40mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£68,027	Dominant
Ustekinumab 45mg	ADA 40mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£67,742	Dominant
Ixekizumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£95,529	£432,904
ERG-corrected company base-case analysis results							
Best supportive care	BSC, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-	£90,527

First line therapy	Subsequent sequence	Total		Incremental		ICER vs BSC	CZP200 ICER vs comparator
		QALYs	Costs	QALYs	Costs		
Certolizumab pegol 200mg	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Certolizumab pegol 400mg	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£731,555
Etanercept	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,943
Infliximab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£88,926
Secukinumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£452,740
Guselkumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£325,428
Adalimumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Brodalumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£555,547
Ustekinumab 90mg	ADA 40mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Ustekinumab 45mg	ADA 40mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Ixekizumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£354,577

Abbreviations: QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; BSC, best supportive care; CZP, certolizumab pegol; ADA, adalimumab; BROD, brodalumab; ETN, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; SEC, secukinumab; UST, ustekinumab

Table 2 Company base-case (escalation strategy for inadequate responders) and ERG corrections (ERG Report Table 36)

First line therapy	Subsequent sequence	Total		Incremental		ICER vs BSC	ICER
		QALYs	Costs	QALYs	Costs		
Company base-case analysis results (escalation strategy)							
Adalimumab 40mg	ADA80, UST90, INF, BSC	[redacted]	[redacted]	-	-	£98,035	-
Certolizumab pegol 200mg	CZP400, UST90, INF, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£87,125	£36,638
ERG-corrected company base-case analysis results (escalation strategy)							
Adalimumab 40mg	ADA80, UST90, INF, BSC	[redacted]	[redacted]	-	-	£110,051	-
Certolizumab pegol 200mg	CZP400, UST90, INF, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£100,757	£36,036

Abbreviations: ERG, evidence review group; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; BSC, best supportive care; CZP, certolizumab pegol; ADA, adalimumab; IFX, infliximab; UST, ustekinumab

Table 3 Company base-case (candidates for systemic non-biologics) and ERG corrections (ERG Report Table 37)

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
Company base-case analysis results (candidates for systemic non-biologics)						
Best supportive care	ADA40, UST90, INF, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	UST90, INF, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£3,602
ERG-corrected company base-case results (candidates for systemic non-biologics)						
Best supportive care	ADA40, UST90, INF, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	UST90, INF, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£6,757
Abbreviations: ERG, evidence review group; QALYS, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; BSC, best supportive care; CZP, certolizumab pegol; ADA, adalimumab; IFX, infliximab; UST, ustekinumab						

4 Additional ERG Analyses

4.1 Treatment sequencing and net-monetary benefit analysis

Table 4 presents the results of ERG Scenario 1, where single-line head-to-head comparisons between sequences were implemented. This updates the results of Table 35 in the original ERG report.

In this scenario, the rankings are very similar to those of the original analysis, the only difference being the rankings for secukinumab and guselkumab are inverted.

Table 4 ERG Scenario 1: single lines of therapy using incremental net-benefit and rankings (ERG Report Table 38)

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 1: single-line head-to-head comparisons							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	2	£0.00	1	£45,023
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,110.98	11	-£30,606.75	11	£130,304
Etanercept	[redacted]	[redacted]	£964.00	1	-£898.47	2	£77,637
Infliximab	[redacted]	[redacted]	-£25,563.60	10	-£24,994.44	10	£112,734
Secukinumab	[redacted]	[redacted]	-£21,008.50	6	-£20,473.53	6	£100,732
Guselkumab	[redacted]	[redacted]	-£22,023.95	7	-£21,217.60	7	£97,640
Adalimumab	[redacted]	[redacted]	-£1,310.60	3	-£2,089.07	3	£59,719
Brodalumab	[redacted]	[redacted]	-£24,815.01	9	-£24,304.45	9	£112,149
Ustekinumab 90mg	[redacted]	[redacted]	-£2,855.47	5	-£3,053.61	4	£57,002

Ustekinumab 45mg	[redacted]	[redacted]	-£2,805.02	4	-£3,171.65	5	£59,181
Ixekizumab	[redacted]	[redacted]	-£23,224.93	8	-£22,462.80	8	£101,749
Abbreviations: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit							

4.2 Cost-effectiveness of BSC

Table 5 presents the results of ERG Scenario 2, where assumptions regarding quality of life and cost of BSC were assumed to be consistent with those used in a previous NICE appraisal of brodalumab. This updates the results of Table 39 in the original ERG report.

In the updated scenarios, the rankings of certolizumab rankings remain the same. Adalimumab becomes more cost-effective at a £20,000 threshold (becomes the second most cost-effective treatment). Similar to Scenario 1, the rankings for secukinumab and guselkumab are inverted.

Table 5 ERG Scenario 2: TA511 Assumptions applied (ERG Report Table 39)

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 2: TA511 assumptions							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	1	£0.00	1	£21,287
Certolizumab pegol 400mg	[redacted]	[redacted]	-£30,018.87	11	-£29,187.26	11	£75,355
Etanercept	[redacted]	[redacted]	-£3,184.08	3	-£6,278.09	5	£43,583
Infliximab	[redacted]	[redacted]	-£24,116.95	10	-£23,072.71	10	£63,033
Secukinumab	[redacted]	[redacted]	-£19,725.38	6	-£18,778.37	6	£55,997
Guselkumab	[redacted]	[redacted]	-£20,329.01	7	-£19,015.33	7	£54,807
Adalimumab	[redacted]	[redacted]	-£3,045.61	2	-£4,346.94	4	£30,739
Brodalumab	[redacted]	[redacted]	-£23,603.73	9	-£22,702.86	9	£63,218
Ustekinumab 90mg	[redacted]	[redacted]	-£3,315.64	4	-£3,651.30	2	£28,981
Ustekinumab 45mg	[redacted]	[redacted]	-£3,607.78	5	-£4,216.15	3	£30,294
Ixekizumab	[redacted]	[redacted]	-£21,512.93	8	-£20,211.39	8	£56,849
Key: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit							

4.3 Alternative time-horizons

Table 6 presents the results of ERG Scenarios 3 to 5, where the time horizon of the analysis was altered. This updates the results of Table 40 in the original ERG report

While there are some small differences to the rankings (the rankings for secukinumab and guselkumab are inverted), the same conclusions can be made from the updated analysis, that the NMB ranking framework is not sensitive to the duration of BSC.

Table 6 ERG Scenarios 3, 4, and 5: alternative time horizons (ERG Report Table 40)

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 3: 5 year time horizon							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	2	£0.00	1	£51,846
Certolizumab pegol 400mg	[redacted]	[redacted]	-£23,456.43	11	-£23,145.83	11	£153,690
Etanercept	[redacted]	[redacted]	£738.47	1	-£381.65	2	£88,330
Infliximab	[redacted]	[redacted]	-£19,859.88	10	-£19,455.19	10	£132,585
Secukinumab	[redacted]	[redacted]	-£16,704.41	6	-£16,337.84	6	£120,533
Guselkumab	[redacted]	[redacted]	-£17,330.11	7	-£16,830.78	7	£117,572
Adalimumab	[redacted]	[redacted]	-£1,478.77	3	-£1,957.32	3	£73,038
Brodalumab	[redacted]	[redacted]	-£18,894.81	9	-£18,542.31	9	£130,906
Ustekinumab 90mg	[redacted]	[redacted]	-£2,876.49	5	-£2,996.13	4	£70,189
Ustekinumab 45mg	[redacted]	[redacted]	-£2,836.38	4	-£3,062.52	5	£73,152
Ixekizumab	[redacted]	[redacted]	-£18,688.05	8	-£18,177.26	8	£122,751
ERG Scenario 4: 10 year time horizon							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	2	£0.00	1	£48,512
Certolizumab pegol 400mg	[redacted]	[redacted]	-£29,091.09	11	-£28,658.22	11	£140,715
Etanercept	[redacted]	[redacted]	£1,092.31	1	-£494.53	2	£82,780
Infliximab	[redacted]	[redacted]	-£24,064.03	10	-£23,555.70	10	£121,541
Secukinumab	[redacted]	[redacted]	-£19,887.32	6	-£19,414.36	6	£109,070
Guselkumab	[redacted]	[redacted]	-£20,830.52	7	-£20,136.73	7	£105,951
Adalimumab	[redacted]	[redacted]	-£1,280.41	3	-£1,947.83	3	£65,084
Brodalumab	[redacted]	[redacted]	-£23,254.14	9	-£22,801.58	9	£120,739
Ustekinumab 90mg	[redacted]	[redacted]	-£2,840.73	5	-£3,009.57	4	£62,242
Ustekinumab 45mg	[redacted]	[redacted]	-£2,778.47	4	-£3,093.26	5	£64,680
Ixekizumab	[redacted]	[redacted]	-£22,059.57	8	-£21,389.29	8	£110,343
ERG Scenario 5: 15 year time horizon							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	2	£0.00	1	£46,302
Certolizumab pegol 400mg	[redacted]	[redacted]	-£30,590.33	11	-£30,109.14	11	£133,967
Etanercept	[redacted]	[redacted]	£1,043.08	1	-£730.14	2	£79,501
Infliximab	[redacted]	[redacted]	-£25,178.59	10	-£24,629.19	10	£115,835
Secukinumab	[redacted]	[redacted]	-£20,723.20	6	-£20,208.31	6	£103,627
Guselkumab	[redacted]	[redacted]	-£21,727.46	7	-£20,957.37	7	£100,518
Adalimumab	[redacted]	[redacted]	-£1,284.47	3	-£2,026.99	3	£61,564

Brodalumab	[redacted]	[redacted]	-£24,413.15	9	-£23,921.34	9	£115,199
Ustekinumab 90mg	[redacted]	[redacted]	-£2,846.72	5	-£3,035.35	4	£58,798
Ustekinumab 45mg	[redacted]	[redacted]	-£2,789.60	4	-£3,139.47	5	£61,059
Ixekizumab	[redacted]	[redacted]	-£22,932.50	8	-£22,199.96	8	£104,710
Key: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit							

4.4 Alternative HRQoL data sources

Table 7 presents the results of ERG Scenarios 6 and 7, where alternative assumptions regarding HRQoL were explored. This updates the results of Table 42 in the original ERG report

In this scenario, the rankings are very similar to those of the original analysis, the only difference being the rankings for secukinumab and guselkumab are inverted.

Table 7 ERG Scenarios 6 and 7: Alternative HRQoL assumptions and sources (ERG Report Table 42)

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 6: Population limited to DLQI≥10							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	1	£0.00	1	£34,111
Certolizumab pegol 400mg	[redacted]	[redacted]	-£30,808.79	11	-£30,153.47	11	£98,940
Etanercept	[redacted]	[redacted]	-£181.66	2	-£2,616.96	2	£57,929
Infliximab	[redacted]	[redacted]	-£25,236.71	10	-£24,504.10	10	£85,750
Secukinumab	[redacted]	[redacted]	-£20,699.76	6	-£20,010.42	6	£76,592
Guselkumab	[redacted]	[redacted]	-£21,547.17	7	-£20,502.43	7	£74,264
Adalimumab	[redacted]	[redacted]	-£1,781.31	3	-£2,795.13	3	£45,034
Brodalumab	[redacted]	[redacted]	-£24,523.47	9	-£23,867.14	9	£85,291
Ustekinumab 90mg	[redacted]	[redacted]	-£2,979.23	4	-£3,239.26	4	£43,168
Ustekinumab 45mg	[redacted]	[redacted]	-£3,024.86	5	-£3,501.43	5	£44,742
Ixekizumab	[redacted]	[redacted]	-£22,787.81	8	-£21,807.12	8	£77,482
ERG Scenario 7: Equal utilities applied to biologics and BSC with population limited to DLQI≥10							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	2	£0.00	1	£49,928
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,113.73	11	-£30,610.88	11	£142,326
Etanercept	[redacted]	[redacted]	£1,059.34	1	-£755.45	2	£99,227
Infliximab	[redacted]	[redacted]	-£25,461.49	10	-£24,841.26	10	£120,989
Secukinumab	[redacted]	[redacted]	-£20,936.46	6	-£20,365.48	6	£108,681
Guselkumab	[redacted]	[redacted]	-£22,015.92	7	-£21,205.55	7	£105,710
Adalimumab	[redacted]	[redacted]	-£1,302.18	3	-£2,076.43	3	£68,706
Brodalumab	[redacted]	[redacted]	-£24,737.61	9	-£24,188.35	9	£120,966

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
Ustekinumab 90mg	[redacted]	[redacted]	-£2,842.68	5	-£3,034.43	4	£63,540
Ustekinumab 45mg	[redacted]	[redacted]	-£2,804.65	4	-£3,171.10	5	£66,635
Ixekizumab	[redacted]	[redacted]	-£23,139.60	8	-£22,334.80	8	£109,051
Key: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit							

4.5 Biosimilar costs and uptake

Table 8 presents the results of ERG Scenarios 8 to 10, where biosimilar costs for adalimumab, etanercept, and infliximab were applied. This updates the results of Table 43 in the original ERG report

In this scenario, the rankings are very similar to those of the original analysis for the majority of comparator sequences. In these scenarios, secukinumab and infliximab became more cost-effective than guselkumab. Any discount over 20% to the originator list price of adalimumab places it first in the NMB rankings at 20k and 30k. At a discount of 60%, the pairwise ICER of adalimumab versus BSC is £2,229.

Table 8 ERG Scenario 8, 9, and 10: Biosimilar costs applied for adalimumab, etanercept, and infliximab (ERG Report Table 43)

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 8: Biosimilar costs for etanercept, infliximab, 20% discount for adalimumab							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	3	£0.00	3	£45,023
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,110.98	11	-£30,606.75	11	£130,304
Etanercept	[redacted]	[redacted]	£2,102.37	2	£239.90	2	£67,594
Infliximab	[redacted]	[redacted]	-£21,124.58	7	-£20,555.41	7	£100,283
Secukinumab	[redacted]	[redacted]	-£21,008.50	6	-£20,473.53	6	£100,732
Guselkumab	[redacted]	[redacted]	-£22,023.95	8	-£21,217.60	8	£97,640
Adalimumab	[redacted]	[redacted]	£2,938.71	1	£2,160.25	1	£40,555
Brodalumab	[redacted]	[redacted]	-£24,815.01	10	-£24,304.45	10	£112,149
Ustekinumab 90mg	[redacted]	[redacted]	-£2,855.47	5	-£3,053.61	4	£57,002
Ustekinumab 45mg	[redacted]	[redacted]	-£2,805.02	4	-£3,171.65	5	£59,181
Ixekizumab	[redacted]	[redacted]	-£23,224.93	9	-£22,462.80	9	£101,749
ERG Scenario 9: Biosimilar costs for etanercept, infliximab, 40% discount for adalimumab							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	3	£0.00	3	£45,023
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,110.98	11	-£30,606.75	11	£130,304

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
Etanercept	[redacted]	[redacted]	£2,102.37	2	£239.90	2	£67,594
Infliximab	[redacted]	[redacted]	-£21,124.58	7	-£20,555.41	7	£100,283
Secukinumab	[redacted]	[redacted]	-£21,008.50	6	-£20,473.53	6	£100,732
Guselkumab	[redacted]	[redacted]	-£22,023.95	8	-£21,217.60	8	£97,640
Adalimumab	[redacted]	[redacted]	£7,188.03	1	£6,409.56	1	£21,392
Brodalumab	[redacted]	[redacted]	-£24,815.01	10	-£24,304.45	10	£112,149
Ustekinumab 90mg	[redacted]	[redacted]	-£2,855.47	5	-£3,053.61	4	£57,002
Ustekinumab 45mg	[redacted]	[redacted]	-£2,805.02	4	-£3,171.65	5	£59,181
Ixekizumab	[redacted]	[redacted]	-£23,224.93	9	-£22,462.80	9	£101,749
Key: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit							

4.6 Certolizumab pegol PASI response

Table 9 presents the results of ERG Scenarios 11 and 12, where alternative PASI response rates for certolizumab were explored. This updates the results of Table 44 in the original ERG report

In this scenario, the rankings are very similar to those of the original analysis, the only difference being the rankings for secukinumab and guselkumab are inverted.

Table 9 ERG Scenarios 11 and 12: CIMPASI-1 and CIMPASI-2 PASI response rates (ERG Report Table 44)

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Scenario 11: CIMPASI-1 PASI response rates for certolizumab pegol							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	2	£0.00	1	£47,413
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,830.98	11	-£30,802.91	11	£130,304
Etanercept	[redacted]	[redacted]	£244.00	1	-£1,094.63	2	£77,637
Infliximab	[redacted]	[redacted]	-£26,283.61	10	-£25,190.60	10	£112,734
Secukinumab	[redacted]	[redacted]	-£21,728.50	6	-£20,669.69	6	£100,732
Guselkumab	[redacted]	[redacted]	-£22,743.95	7	-£21,413.76	7	£97,640
Adalimumab	[redacted]	[redacted]	-£2,030.61	3	-£2,285.23	3	£59,719
Brodalumab	[redacted]	[redacted]	-£25,535.01	9	-£24,500.61	9	£112,149
Ustekinumab 90mg	[redacted]	[redacted]	-£3,575.47	5	-£3,249.77	4	£57,002
Ustekinumab 45mg	[redacted]	[redacted]	-£3,525.02	4	-£3,367.81	5	£59,181
Ixekizumab	[redacted]	[redacted]	-£23,944.93	8	-£22,658.96	8	£101,749
ERG Scenario 12: CIMPASI-2 PASI response rates for certolizumab pegol							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	2	£0.00	1	£42,566

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
Certolizumab pegol 400mg	[redacted]	[redacted]	-£30,368.38	11	-£30,519.53	11	£130,304
Etanercept	[redacted]	[redacted]	£1,706.60	1	-£811.26	2	£77,637
Infliximab	[redacted]	[redacted]	-£24,821.00	10	-£24,907.22	10	£112,734
Secukinumab	[redacted]	[redacted]	-£20,265.89	6	-£20,386.31	6	£100,732
Guselkumab	[redacted]	[redacted]	-£21,281.35	7	-£21,130.39	7	£97,640
Adalimumab	[redacted]	[redacted]	-£568.00	3	-£2,001.85	3	£59,719
Brodalumab	[redacted]	[redacted]	-£24,072.41	9	-£24,217.24	9	£112,149
Ustekinumab 90mg	[redacted]	[redacted]	-£2,112.86	5	-£2,966.39	4	£57,002
Ustekinumab 45mg	[redacted]	[redacted]	-£2,062.42	4	-£3,084.44	5	£59,181
Ixekizumab	[redacted]	[redacted]	-£22,482.33	8	-£22,375.58	8	£101,749

Abbreviations: PASI, psoriasis area severity index; BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit

4.7 Dose escalation scenario

Table 10 presents the results of the ERG's dose escalation scenarios. This scenario updates Table 45 in the original ERG report. The results presented in Table 10 are very similar to those in the original analyses, as the PASI responses for certolizumab did not change a great deal after the NMA was amended. It should be noted that this is a comparison of two strategies – switching drug versus dose escalation. In the first strategy, patients are switched to ustekinumab upon partial or non-response on certolizumab 200mg at 16 weeks, this is compared to a strategy where these patients are switched to receive a higher dose (400mg q2w) dose of certolizumab instead.

Table 10 ERG Scenarios 13, 14, and 15: Dose escalation (ERG Report Table 45)

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
ERG Scenario 13: Dose escalation (PASI<75 at 16w)						
Certolizumab pegol 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	CZP400, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ERG Scenario 14: Dose escalation (PASI50-74 at 16w)						
Certolizumab pegol 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	CZP400, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£491,819
ERG Scenario 15: Dose escalation (PASI50-74 at 16w) and [redacted]						

Certolizumab pegol 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	CZP400, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£20,337
Abbreviations: QALY, quality-adjusted life years; PASI, psoriasis area severity index; BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; UST, ustekinumab.						

4.8 Alternative positioning of biologics in treatment pathway

In this scenario (corresponding to Table 46 in the original ERG report), the results are unchanged from the original analysis, as this scenario did not use clinical data drawn the NMA that was subsequently updated by the company.

Table 11 ERG Scenarios 16 and 17: Candidates for systemic non-biologics (ERG Report Table 46)

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
ERG Scenario 16: Candidates for systemic non-biologics CZP 1st vs CZP 2nd line & sequencing						
Best supportive care	CZP200, UST90, INF, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	UST90, INF, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£402,644
ERG Scenario 17: Candidates for systemic non-biologics CZP alternate positioning only						
Certolizumab pegol 200mg	BSC, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Best supportive care	CZP200, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Abbreviations: QALY, quality-adjusted life years; BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; UST, ustekinumab; INF, infliximab.						

5 ERG alternative base-case

5.1 Candidates for systemic biologic therapy

The NMB rankings of guselkumab and secukinumab switch following the inclusion of the corrected NMA results. The significant increase in PASI 75 response rates for guselkumab results in a substantial increase in total costs, which outweigh the greater benefits in the updated NMA.

A fully incremental analysis of the company's and ERG's preferred base-cases including all PAS discounts is presented in the accompanying confidential appendix.

Table 12 ERG Alternative base-case (candidates for biologics) (ERG Report Table 47)

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Alternative base-case: Scenario 1+7+8 (0% adalimumab discount)							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	2	£0.00	2	£49,928
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,113.73	11	-£30,610.88	11	£142,326
Etanercept	[redacted]	[redacted]	£2,197.72	1	£382.92	1	£86,390
Infliximab	[redacted]	[redacted]	-£21,022.46	7	-£20,402.24	7	£107,625
Secukinumab	[redacted]	[redacted]	-£20,936.46	6	-£20,365.48	6	£108,681
Guselkumab	[redacted]	[redacted]	-£22,015.92	8	-£21,205.55	8	£105,710
Adalimumab	[redacted]	[redacted]	-£1,302.18	3	-£2,076.43	3	£68,706
Brodalumab	[redacted]	[redacted]	-£24,737.61	10	-£24,188.35	10	£120,966
Ustekinumab 90mg	[redacted]	[redacted]	-£2,842.68	5	-£3,034.43	4	£63,540
Ustekinumab 45mg	[redacted]	[redacted]	-£2,804.65	4	-£3,171.10	5	£66,635
Ixekizumab	[redacted]	[redacted]	-£23,139.60	9	-£22,334.80	9	£109,051

Abbreviations: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit

The ERG's alternative base-case 2 as presented in Table 13 shows a similar drop in the ranking of guselkumab due to the aforementioned reasons, with infliximab now placed sixth rather than 8th/7th. The effect of a reduction in the list price of adalimumab between 20-60% is also presented, which again places certolizumab third in the ranking behind adalimumab and etanercept.

Table 13 Exploratory analysis on the ERG alternative base-case (ERG Report Table 48)

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Alternative base-case 2: Scenario 2 + 8							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	2	£0.00	1	£21,287
Certolizumab pegol 400mg	[redacted]	[redacted]	-£30,018.87	11	-£29,187.26	11	£75,355
Etanercept	[redacted]	[redacted]	-£2,045.72	3	-£5,139.73	5	£36,497
Infliximab	[redacted]	[redacted]	-£19,677.97	6	-£18,633.73	6	£55,306
Secukinumab	[redacted]	[redacted]	-£19,725.38	7	-£18,778.37	7	£55,997
Guselkumab	[redacted]	[redacted]	-£20,329.01	8	-£19,015.33	8	£54,807
Adalimumab	[redacted]	[redacted]	£1,203.66	1	-£97.67	2	£18,238
Brodalumab	[redacted]	[redacted]	-£23,603.73	10	-£22,702.86	10	£63,218
Ustekinumab 90mg	[redacted]	[redacted]	-£3,315.64	4	-£3,651.30	3	£28,981
Ustekinumab 45mg	[redacted]	[redacted]	-£3,607.78	5	-£4,216.15	4	£30,294
Ixekizumab	[redacted]	[redacted]	-£21,512.93	9	-£20,211.39	9	£56,849

Treatment (single line)	Inc. QALYs vs CZP	Inc. costs vs CZP	INB vs CZP at 20k	20k rank	INB vs CZP at 30k	30k rank	Pairwise ICER vs BSC
ERG Alternative base-case 3: Scenario 1+7+8 (20% adalimumab discount)							
Certolizumab pegol 200mg	[redacted]	[redacted]	£0.00	3	£0.00	3	£49,928
Certolizumab pegol 400mg	[redacted]	[redacted]	-£31,113.73	11	-£30,610.88	11	£142,326
Etanercept	[redacted]	[redacted]	£2,197.72	2	£382.92	2	£86,390
Infliximab	[redacted]	[redacted]	-£21,022.46	7	-£20,402.24	7	£107,625
Secukinumab	[redacted]	[redacted]	-£20,936.46	6	-£20,365.48	6	£108,681
Guselkumab	[redacted]	[redacted]	-£22,015.92	8	-£21,205.55	8	£105,710
Adalimumab	[redacted]	[redacted]	£2,947.14	1	£2,172.88	1	£46,659
Brodalumab	[redacted]	[redacted]	-£24,737.61	10	-£24,188.35	10	£120,966
Ustekinumab 90mg	[redacted]	[redacted]	-£2,842.68	5	-£3,034.43	4	£63,540
Ustekinumab 45mg	[redacted]	[redacted]	-£2,804.65	4	-£3,171.10	5	£66,635
Ixekizumab	[redacted]	[redacted]	-£23,139.60	9	-£22,334.80	9	£109,051

Abbreviations: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; INB, incremental net monetary benefit

5.2 Dose escalation strategy

As the update to the NMA had little effect upon the response rates for ustekinumab and certolizumab, the dose escalation strategy results are largely unchanged from the original ERG report. Table 14 includes an additional scenario that uses the ERG's preferred HRQoL data, and includes [redacted]

Table 14 ERG Alternative base-case (dose escalation) (ERG Report Table 49)

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
ERG Alternative base-case (dose escalation): ERG Scenario 7 + 14						
Certolizumab pegol 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	CZP400, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£533,154
ERG Alternative base-case (dose escalation): ERG Scenario 7 + 15 [redacted]						
Certolizumab pegol 200mg	UST90, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	CZP400, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£22,047

Abbreviations: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; UST, ustekinumab.

5.3 Candidates for systemic non-biologic therapy

As this scenario used trial-derived subgroup data for certolizumab pegol, the results are unchanged from those presented in Table 50 of the original ERG report.

Table 15 ERG Alternative base-case (candidates for non-biologics) (ERG Report Table 50)

First line therapy	Subsequent sequence	Total		Incremental		ICER
		QALYs	Costs	QALYs	Costs	
ERG Alternative base-case (candidates for non-biologics): ERG Scenario 7 + 17						
Best supportive care	CZP200, BSC, BSC, BSC	[redacted]	[redacted]	-	-	-
Certolizumab pegol 200mg	BSC, BSC, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Abbreviations: BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year						

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Certolizumab pegol for treating chronic plaque psoriasis [ID1232]

October 2018

UCB Response to ERG Report

File name	Version	Contains confidential information	Date
ID1232 certolizumab - Proforma Response_UCB final_2018-10-18	1.0	Yes Redacted	18.10.2018

Issue 1 Position of certolizumab pegol in the pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 87: **"**The ERG also questions positioning of certolizumab as first-line biologic therapy, which the ERG consider unlikely given the dominance of adalimumab and secukinumab and the imminent launch of adalimumab biosimilars.**"** "Related to this, the ERG highlights that each biologic varies with regards to its relevance as a comparator for certolizumab. As previously discussed, treatments of different classes are used sequentially in clinical practice. Therefore, a more relevant comparison might be between anti-TNFα drugs, i.e. adalimumab, certolizumab, etanercept, and infliximab, while the others may not be considered strictly as alternatives at a particular point in the treatment pathway."	UCB strongly requests amendment of these statements, which currently suggest that certolizumab pegol should be compared only to adalimumab and other anti-TNFs, rather than all treatment options available in psoriasis. UCB suggests the following deletions (text underlined): **"**The ERG also questions positioning of certolizumab as first-line biologic therapy~~, which the ERG consider unlikely given the dominance of adalimumab and secukinumab and the imminent launch of adalimumab biosimilars~~."** "Related to this, the ERG highlights that each biologic varies with regards to its relevance as a comparator for certolizumab. As previously discussed, treatments of different classes are used sequentially in	UCB believes that the statements are misleading and imply that the submitted evidence has deviated from the NICE final scope and the NICE reference case. To suggest that certolizumab pegol should be compared solely to adalimumab and anti-TNFs on the basis of a shared mechanism of action is inappropriate, goes against the final scope and remit of this appraisal and is not in line with previous technology appraisals in plaque psoriasis. UCB acknowledges the clinical expert input regarding the use of certolizumab pegol. However, its use in routine practice is a decision solely based on clinical and patient factors, and not on cost-effectiveness. The remit of this appraisal is to appraise the clinical and cost-effectiveness of certolizumab pegol within its marketing authorisation for treating moderate to severe plaque psoriasis. The relevant comparators defined in the final scope consisted of all biologic therapies approved by NICE, which represent biologics of varying mechanisms of action, including anti-TNFs, IL-17s, IL12/23 and IL23p19s. Although in clinical practice	Not a factual error, the ERG's critique was appropriately caveated.

	clinical practice. ~~Therefore, a more relevant comparison might be between anti-TNFα drugs, i.e. adalimumab, certolizumab, etanercept, and infliximab, while the others may not be considered strictly as alternatives at a particular point in the treatment pathway.~~"	mechanism of action may play some role in clinical decision-making on an individual patient level, there is no established and standardised sequencing order based on mechanism of action and there is no precedent from any prior NICE appraisals for new therapies for psoriasis to be evaluated only against other therapies that share their mechanism of action. Relevant comparators should represent all treatments – irrespective of mechanism of action – that constitute a part of current clinical care in the NHS for the patient population under consideration. Furthermore, the reference to infliximab as one of the most relevant comparators is inappropriate given that the NICE recommendation for infliximab restricts this therapy to use in the population of patients whose disease is "very severe", which is already acknowledged by the ERG in other sections of the report. Lastly, the reference to the dominance of secukinumab is not supported by any evidence and is contradictory to the evidence and discussions during the recent TA511, in which the use of secukinumab as third-line treatment option was acknowledged. UCB strongly requests amendments of these statements, which are misleading and bias the decision making in this appraisal.	

Issue 2 Reporting of trial data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1 Page 51: "The CZP 400 mg group has numerically higher but not statistically significantly different response rates to CZP 200 mg for PASI 75, PASI 90 and PGA." Page 61: "The difference in all PASI response rates between the 200 mg and 400 mg doses was not statistically significant."	UCB requests the below revisions to the statements, to accurately reflect the design of the clinical trials included in the UCB submission. The suggested amended text is underlined. Page 51 – current statement to be replaced with: "The CZP 400 mg group has numerically higher response rates to CZP 200 mg for PASI 75, PASI 90 and PGA" Page 61 – current statement to be replaced with: "The CZP 400 mg group has numerically higher response rates to CZP 200 mg in all PASI response rates."	UCB considers that the interpretation of the data is incorrect with regards to the differences between the CZP 200 mg Q2W and CZP 400 mg Q2W arms, and does not accurately reflect the clinical trial designs. The Phase III clinical trials evaluating the efficacy and safety of CZP in patients with moderate to severe plaque psoriasis were not designed to assess any statistical inference between the two CZP doses. Therefore, it is inaccurate to report that there was no statistically significant difference observed between the CZP arms given that the studies were not powered to compare between the two CZP doses.	Text amended: "The CZP 400 mg group has numerically higher response rates to CZP 200 mg for PASI 75, PASI 90 and PGA" "The CZP 400 mg group has numerically higher response rates to CZP 200 mg in all PASI response rates."
Point 2 - Page 51: "However, this maintenance cohort only includes patients who were PASI 50 responders (CZP 200/CZP 400); 176 patients in the CZP 200 mg arm and 166 patients in the CZP 400 mg arm.	UCB requests an amendment of the statement as follows, to accurately reflect the submitted evidence for psoriasis severity at Week 48. Furthermore, the last statement referring to PASI 75 placebo responders should be	UCB considers that the data for psoriasis severity at Week 48 is reported incorrectly and do not reflect the evidence submitted. The maintenance cohort included patients who were PASI 50 responders at Week 16. The number of patients in the CZP 200 mg arm and CZP 400 mg arm should be	Text amended: "However, this maintenance cohort only includes patients who were PASI 50 responders (CZP 200/CZP 400); 186 patients in the CZP 200 mg arm and 175 patients in the CZP 400 mg arm."

There were no PASI 75 (placebo) responders at week 16."	deleted, as it is not accurate. The current statement should be replaced with the below text (amended text is underlined). "However, this maintenance cohort only includes patients who were PASI 50 responders (CZP 200/CZP 400); 186 patients in the CZP 200 mg arm and 175 patients in the CZP 400 mg arm."	186 and 175, respectively. There were patients who were PASI 75 responders in the placebo arm at Week 16 (see Figure 5 in the company submission). Based on the above, UCB requests that the existing evidence included in the UCB submission is accurately reflected in the ERG report.	
Point 3 - Section 4.2.3 (paragraph 3 on page 56): "Whereas, patients in the CZP 400 mg group who were biologic naïve had higher PASI 75 and PASI 90 response rates than biologic exposed patients."	We request an amendment of the statement as follows, to accurately reflect the trial data in the biologic-naïve and biologic-exposed subgroups, which was included in the UCB submission. The suggested amended text is underlined. "Whereas, patients in the CZP 400 mg group who were biologic naïve had higher PASI 75 response rates than biologic exposed patients. The PASI 90 response rates were comparable between these subgroups."	UCB considers that the statement does not accurately reflect the evidence submitted. PASI 90 response rates between biologic-naïve and biologic-exposed patients are comparable, and the durability data in these patients has been reported incorrectly in the ERG report. The PASI 90 response rates were [redacted]% (CZP 400 mg Q2W bio-naïve) and [redacted]% (CZP 400 mg Q2W bio-experienced), which are comparable. Based on the above, UCB requests that the ERG report is updated to accurately reflect the evidence included in the UCB submission.	Text amended "Whereas, patients in the CZP 400 mg group who were biologic naïve had higher PASI 75 response rates than biologic exposed patients. The PASI 90 response rates were comparable between these subgroups."
Point 4 Section 4.2.3.1, page 56: "At week 48 biologic naïve patients had substantially higher	UCB requests an amendment of the statement as follows, to accurately reflect the submitted evidence. The suggested amended text (revisions and	UCB considers that the ERG report does not accurately reflect the evidence submitted. We assume that the ERG compared data	Text amended "At week 48 biologic naïve patients had higher PASI 75, PASI 90 and PGA 0/1 response rates than

PASI 75, PASI 90 and PGA 0/1 response rates than biologic exposed patients. In biologic exposed patients, PASI 75, PASI 90 and PGA 0/1 response rates were considerably lower at week 48 than at week 16." Section 4.2.5, page 62: "However, PASI 75, PASI 90 and PGA response rates were considerably lower at week 48 than at week 16 in the subgroup of biologic-exposed patients, compared with the biologic naïve patients, suggesting that certolizumab is poor at improving or maintaining response over time in biologic exposed patients."	deletions) is underlined. Page 56: "At week 48 biologic naïve patients had higher PASI 75, PASI 90 and PGA 0/1 response rates than biologic exposed patients in the CZP 400 mg Q2W arm. The response rates were comparable across both subgroups in the CZP 200 mg Q2W arm~~. In biologic exposed patients, PASI 75, PASI 90 and PGA 0/1 response rates were considerably lower at week 48 than at week 16~~." We request that the text on page 62 should be removed as the claim made by the ERG is unsubstantiated due to the reasons provided in the justification.	from Table 48 and Table 49 in the UCB submission. As indicated in the submission, the data for the initial treatment period at week 16 (Table 48) is based on Pool E1, which contains patients from all three CZP trials. The maintenance treatment period data at week 48 (Table 49) is based on Pool E3, which includes only CIMPASI-1 and CIMPASI-2. The data presented at week 16 and 48 is thus based on two different datasets and are therefore not comparable. Therefore, the statement made by the ERG for the maintenance treatment period is unsubstantiated. Based on the above, UCB requests that the ERG report is revised to avoid inaccurate conclusions.	biologic exposed patients in the CZP 400 mg Q2W arm. The response rates were comparable across both subgroups in the CZP 200 mg Q2W arm. ~~In biologic exposed patients, PASI 75, PASI 90 and PGA 0/1 response rates were considerably lower at week 48 than at week 16.~~" Text deleted: "However, PASI 75, PASI 90 and PGA response rates were considerably lower at week 48 than at week 16 in the subgroup of biologic-exposed patients, compared with the biologic naïve patients, suggesting that certolizumab is poor at improving or maintaining response over time in biologic exposed patients."

Issue 3 Cost-effectiveness: Adalimumab biosimilar as a comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response

Point 1 Page 87: "Therefore, it is worth noting certolizumab's relative cost-effectiveness compared to adalimumab in the analyses presented in this report, particularly given the current market share of adalimumab, and the significant anticipated reductions in price." Page 103, 116: "There will be a number of biosimilar adalimumab products made available before the end of 2018, and it is anticipated that there will significant and co-ordinated movement towards biosimilar adalimumab upon the expiry of its patent, with clinical advice suggesting a reduction on the current list price of 30-40%." Page 129: "Section 5.2.8 argues that biosimilars would be used in practice where available, and given the steps taken by the NHS to ensure high uptake of biosimilar adalimumab upon the expiry of its patent in October 2018, it is reasonable to apply the anticipated cost of biosimilar adalimumab in the model."	UCB suggest to clearly indicate in the report that adalimumab originator is the appropriate comparator to be used in the base case results (as opposed to adalimumab biosimilar)	As per the NICE guidance on Single Technology Appraisal processes, the scope of this appraisal is the evaluation of the clinical and cost-effectiveness of CZP within the context of the final appraisal remit and objectives, and not whether biosimilar adalimumab (or other products) should be preferentially positioned to CZP. Therefore, UCB strongly objects to the inclusion of statements on the positioning of adalimumab biosimilar as a relevant comparator to certolizumab pegol. UCB also believes the text relating to positioning of adalimumab biosimilar is contrary to the guidance provided by NICE's biosimilars position statement, which states that biosimilar products will usually be considered as interventions within the context of an MTA in parallel with their reference product in the indication under consideration, something not applicable to this Single Technology Appraisal. Adalimumab biosimilar does not constitute a part of routine clinical practice in the UK and therefore does not constitute a relevant comparator. Whilst, as the ERG note, the NHS have taken steps with the aim of ensuring high uptake of adalimumab biosimilar, at the current time there is neither evidence as to the extent of uptake of adalimumab biosimilar in the NHS, nor a guarantee that the desired uptake will be seen, and such evidence will not be available imminently. NHS experience of the arrival of previous biosimilars (for	Not a factual error – adalimumab biosimilars will be available by the date guidance for the present appraisal is released, therefore it is appropriate to consider biosimilar pricing here. High uptake is anticipated and the ERG understand that it will be enforced by many commissioning groups, given the significant cost savings involved.

Issue 4 Cost-effectiveness: ERG alternative approach (Incremental net monetary benefit)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1: Page 123: "In Section 5.2.4, the ERG concluded that the treatment sequences considered in the company's primary analysis to be potentially misleading and unsuitable for decision making, given the lack of appropriate data to model treatment sequences, and difficulties associated with evaluating a large number of alternative sequences. The ERG therefore proposes an alternative approach to the assessment of the relative cost-effectiveness of certolizumab against biologics currently used in practice, which more fully addresses the issues discussed in Section 5. This is approach is consistent with the approach taken by the ERG in TA51134, though with some modifications to account for the fact that in all company scenarios all biological therapies are not cost-effective versus best supportive care." Various pages: presentation of results in the form of incremental net	UCB request that results should be presented in the form of ICERs as the primary analysis, with any presentation of incremental net monetary benefit to be considered as a secondary analysis in order to aid NICE decision-making: results should not be presented in the form of incremental net monetary benefit only.	UCB acknowledge the academic validity and potential merits of expressing cost-effectiveness results in the form of incremental net monetary benefit, however implying that such approach should be used to inform decision making within this appraisal is inappropriate and misleading. We note that NICE have always quoted ICERs in their determination of the cost-effectiveness of biologic therapies for psoriasis. Further, although the NICE methods guide does state that expected net monetary or health benefits can be presented, the methods guide specifically states that this is in the context of being "in addition to ICERs".	Not a factual error. The most recent full STA in this indication (TA511) presented results using NMB, and explicitly did not present ICERs in the form suggested by the company. This approach was accepted by NICE, and the ERG considers it superior to the use of ICERs for the purposes of decision making, particularly given the issues specific to this appraisal.

monetary benefit.			

Issue 5 Cost-effectiveness: Dose-escalation strategy

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1: Page 89: "The ERG does not consider the sequences modelled by the company to be appropriate or informative." Page 89, 116: "The ERG considers the counterfactual to the proposed dose escalation strategy to certolizumab without dose escalation, to reflect that any recommendation for the use of certolizumab in the NHS should be based on the most cost-effective use of certolizumab. Under this counter factual the ERG's considers that the alternative to certolizumab escalation should be transition to the next biologic in the treatment pathway as per standard clinical practice. That is, is the best	UCB request that the ERG report acknowledges that adalimumab is has a licence that indicates dose escalation for patients and is therefore a relevant comparison in addition to strategies of switching to second-line biologics.	UCB disagrees that the sequences modelled for the dose escalation analysis are not appropriate or informative. The ERG reports implies that treatment with ADA does not allow dose escalation. UCB would like to note, that as per the EU SmPC, adalimumab is the only biologic other than certolizumab pegol, that allows increase in dose in case of inadequate response, therefore for patients initiating treatment with adalimumab as their first-line biologic dose escalation is a relevant potential strategy. As such a comparison to adalimumab dose escalation is reflective of one alternative therapy sequence in current clinical practice. UCB acknowledges the ERG's point that the analyses should consider the most cost-effective use of certolizumab pegol, which implies that treatment strategies of certolizumab pegol 200 mg followed by a second biologic also represent relevant comparators to the certolizumab pegol dose escalation strategy. Nevertheless,	Not a factual error.

treatment option upon a 16-week non-response on 200mg certolizumab to increase the dose to 400mg, or switch to ustekinumab, the next treatment in the pathway.”		in clinical practice, in case of a partial response, clinicians may prefer to escalate the dose of the biologic on which inadequate or partial response is achieved, where this is an option, rather than to switch to a different biologic therapy. Furthermore, updated economic analyses have been provided in appendix to this document, considering the ERG corrections, some assumptions and the original submitted approach. The conclusions of the updated cost-effectiveness analyses indicate that CZP dose escalation strategy is more effective vs ADA escalation strategy (as reflected through QALY’s) in all four scenarios, and is less costly in three out of four, leading to an ICER of £34,782.58 in one of the cases and to CZP dose escalation strategy dominating the ADA escalation strategy in the other three out of four scenarios. Furthermore, one of the scenario analysis [redacted] [redacted] [redacted]These updated economic analyses should be interpreted in the context of the [redacted] [redacted] [redacted], as explored in ERG scenario 15.	

Point 2 – Page 89: "Further to above, with respect to the validity of the present comparison, clinical advice to the ERG suggests that while only adalimumab and etanercept are licensed for dose escalation, the 90mg ustekinumab dose is available at no extra charge and thus is generally the only drug for which dose escalation is used in practice, and typically only in those weighing >90kg."	UCB requests an amendment to the statement to indicate that the two doses of ustekinumab are not routinely used as dose escalation, but rather body weight administrations and therefore would not be considered an appropriate comparator for the CZP dose escalation strategy.	UCB considers the statement that ustekinumab 90 mg is an escalation strategy, to inaccurately reflect the approved posology as per the ustekinumab EU SmPC. UCB would like to point out that although two doses of ustekinumab are available, the factor that determines which dose a patient receives is dependent of the patient body weight, rather than response to initial dose received, with the UST 90 mg being recommended only in patients with body weight > 100 kg. Therefore, stating that ustekinumab 90 mg represents a dose escalation strategy is misleading and inaccurately reflecting the approved posology.	Not a factual error. The text acknowledges this use of ustekinumab is unlicensed, but the ERG have been advised it is used in this way in clinical practice. Dose escalation with ustekinumab is also recommended in BAD guidelines.

Issue 6 Pooling of CIMPASI-1, CIMPASI-2 and CIMPACT

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1 – Pages 16, 23, 51, 62, 71, 141: "Therefore, the ERG is uncertain whether it is appropriate to pool results of all three trials, considering the heterogeneity between the trial results"	UCB suggests that the analysis adjusting for baseline gender and concomitant PsA should be acknowledged and that this shows that the efficacy of CZP is not affected by differences in baseline characteristics. We therefore request an amendment of the text as follows. The amended text is underlined. "Therefore, the ERG is uncertain whether it is appropriate to pool results of all three trials, considering the heterogeneity between the trial results. However, the company submitted several sensitivity analyses exploring the influence of differences in the baseline characteristics. The conclusion of these additional analyses indicate that these differences had no effect on the clinical efficacy outcomes observed across all three trials and the pooling."	The CIMPASI-1, CIMPASI-2 and CIMPACT studies were pooled in order to increase sample size, utilise all available relevant evidence and provide more precise estimates of the efficacy of treatment with certolizumab pegol. The baseline characteristics were validated by the clinical trial investigators as part of the internal study programme as being suitable to pool across the certolizumab pegol studies. UK clinical expert opinion further agreed that the small differences between the baseline characteristics of the trials would not affect outcomes. The pooled dataset of CIMPASI-1, CIMPASI-2 and CIMPACT (pool E1) was accepted by the European Medicines Agency in considering the marketing authorisation for certolizumab pegol in psoriasis and the European Public Assessment Report noted that "In Pool E1, baseline disease characteristics were generally well balanced across treatment groups". Although there are differences in baseline gender and concomitant PsA in the CIMPASI-2 study versus the other two studies, the company submission provided evidence supporting the notion that heterogeneity in these characteristics would	Not a factual error. The relevance of recorded baseline characteristics does not affect the ERG's concerns regarding the pooling of outcome data. Furthermore, after adjustment for baseline characteristics as performed by the company in their most recent analysis, the response estimates appear to diverge even further. The appropriateness of pooling the results of the trials is questionable, given these unexplained heterogeneity in results.

		not be expected to impact on the effect of certolizumab pegol observed in the three trials, in the form of subgroup analyses presented in Appendix E of the UCB original submission. Further to this, the differences between the proportion of males and patients with concomitant PsA have now been evaluated in a sensitivity analysis of the PASI responder rates at Week 16 across all three trials, where gender and PsA have been adjusted for in the logistic regression – an analysis requested by the ERG that could not be provided as part of the response to the ERG clarification questions due to time constraints. These additional analyses lead to similar results as those included in the original submission, for the individual studies and the pooling, indicating that these baseline characteristics are not the source of the differences in study results and do not impact the efficacy of CZP in the pooling. These analyses therefore support the appropriateness of pooling the CIMPASI-1, CIMPASI-2 and CIMPACT studies These detailed results have been provided in an appendix to this document In summary, the evidence presented, including the additional results provided in the appendix, support the appropriateness of pooling across all three trials, as differences in baseline characteristics do not account for the variation in PASI responder rates	

		observed across all three trials.	

Issue 7 Cost-effectiveness: submitted approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1 – Page 87: "In this regard, the ERG notes that the sequences proposed are unlikely to reflect current practice. Firstly because, as stated by the company, the majority of patients receive either adalimumab and secukinumab as their first line biologic therapy, with other biologics either used more rarely or further along a potentially longer sequence. Secondly, infliximab is unlikely to be used frequently in this population, as it is not funded on the NHS for those with moderate to severe disease"	We request the removal of this statement from the ERG report, as it is does not accurately reflect the wording used in the UCB submission. Suggested deletions are underlined "In this regard, the ERG notes that the sequences proposed are unlikely to reflect current practice. ~~Firstly because, as stated by the company, the BAD guideline the majority of patients receive either adalimumab and secukinumab as their first line biologic therapy, with other biologics either used more rarely or further along a potentially longer sequence~~. ~~Secondly, infliximab is unlikely to be used frequently in this population, as it is not funded on the NHS for those with moderate to severe disease~~"	UCB welcomes the ERG statement that the submitted approach to sequencing more appropriately reflects clinical practice and is consistent with the modelling approaches used in most recent technology appraisals. However, we believe it is inaccurate to state that the sequences proposed in the submission are unlikely to represent clinical practice. The comparator sequences for inadequate responders population were selected on the basis of expert clinical opinion and the latest BAD psoriasis treatment guidelines. According to BAD, within the context of biologic treatment, the recommended first-line therapies comprise adalimumab and secukinumab (regardless of whether patients also have PsA), and ustekinumab for patients without PsA. When patients fail to respond to the chosen first-line therapy, it is suggested that any of the currently licensed biologics may be tried. Based on prior NICE appraisals (TA511, TA442), prescribing data and clinical expert opinion, patients in the model switch to ustekinumab as their second-line biologic,	Not a factual error. The original text reflects the wording used in UCB's submission. The ERG report does not imply that infliximab is a direct comparator at first line.

		unless ustekinumab has been used first-line, in which case patients switch to adalimumab. The 90 mg dose of ustekinumab was used as the second-line biologic in the model, similarly to the approach in TA442. The UST 90 mg dose is priced the same as the UST 45 mg dose, and the 45 mg dose at second-line is investigated in scenario analysis. This approach was considered appropriate at the decision problem meeting of the current appraisal. The use of infliximab as the third-line treatment in the sequence reflects currently NICE guidance, as infliximab is not modelled as a direct comparator to CZP in the submission. UCB considers the ERG's statement misleading and does not accurately represent UCB's submission where infliximab was not considered a direct comparator. The treatment sequences selected for the UCB submission are consistent with the treatment sequences explored in the ixekizumab NICE appraisal (TA442). Although the Committee recognised that the treatment sequences presented did not cover all possible sequences, it concluded that the sequences included by the company in its economic model reasonably represented current NHS practice. Based on this, we consider it inaccurate for the ERG to conclude that the sequences proposed are unlikely to reflect clinical practice.	

Point 2 - Page 123: "In Section 5.2.4, the ERG concluded that the treatment sequences considered in the company's primary analysis to be potentially misleading and unsuitable for decision making, given the lack of appropriate data to model treatment sequences, and difficulties associated with evaluating a large number of alternative sequences."	We request the removal of this statement from the ERG report, as it is does not accurately reflect submitted approach and previous appraisals, as well as contradictory to the ERG statement on page 87.	UCB understand that modelling of treatment sequencing is an approach that comes with many challenges and acknowledge the ERG's legitimate concerns regarding the uncertainty introduced through the modelling of treatment sequences. However, UCB note that these limitations have been well-documented in previous appraisals and, in spite of this, analyses based on modelling of treatment sequences have informed Committee decision-making in each of the most recent NICE appraisals of biologics in psoriasis (excepting guselkumab, for which a cost minimisation analysis was presented). In both TA511 (brodalumab) and TA442 (ixekizumab), whilst analyses comparing each comparator alone (not in a sequence) against BSC were considered in decision-making, these analyses were considered alongside the cost-effectiveness analyses based on treatment sequences. The Final Appraisal Determination in TA511 (brodalumab) states that "The committee was aware that additional factors should be considered when comparing treatment sequences rather than individual treatments, such as the optimal ordering of treatments and the impact of including treatments that may not be cost-effective. The Committee agreed that, in principle, it was appropriate to compare treatment sequences in this appraisal…". This highlights that although the limitations and uncertainties associated with modelling of treatment sequences have been acknowledged by previous NICE	Not a factual error. As stated in the ERG report, the modelling of treatment sequences would be preferable in this context. However, due to the paucity of available data and the inappropriate construction of sequences in this submission, they are no more informative than head-to-head comparisons, and indeed their use may distort the cost-effectiveness results.

		Committees, cost-effectiveness analyses based on treatment sequences have been considered relevant for decision-making. Furthermore, the modelling of treatment sequences was a point of discussion at the decision problem meeting for this appraisal, and the UCB suggested approach of modelling treatment sequences similarly to previous appraisals (TA442 and TA551) was considered appropriate. UCB thus considers the statement to be misleading regarding the submitted approach and previous appraisals, as well as contradictory to the ERG statement on page 87. Lastly, given the above reason, cost-effectiveness analyses have been re-run, based on the ERG corrections and consideration of specific assumptions, while retaining the original approach of sequencing. The updated basecase results re-confirm the cost-effectiveness of CZP (details are provided in the appendix of this document.)	

Issue 8 Reporting of adverse event data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1 –Section 4.2.3 (first paragraph on page 60): "The rate of adverse events	We request an amendment to the statement as follows, to accurately reflect the serious	UCB believe the statement regarding the risk of adverse events increasing with longer exposure to certolizumab pegol is incorrect	Text deleted, however we cannot comment on the risk with longer exposure as there is no data at week

increased from week 16 to week 144, suggesting that the risk of adverse events with certolizumab increases with longer exposure."	adverse event data reported in the submission (page 122 of company submission). The amended text is underlined. "The exposure-adjusted TEAE incidence rates from Pool S3 (from baseline to Week 144) do not indicate an increase in risks with longer or higher exposure to CZP."	and needs to be amended to accurately reflect the serious adverse event data reported in the submission. It is not appropriate to compare the results in the initial treatment period up to Week 16 (Pool S1) to those reported up to Week 144 (Pool S3). The data reported in Pool S3 covers the initial, maintenance and open-label treatment periods and does not stratify the incidence of AEs at each timepoint. In addition, the patient numbers in each treatment arm in Pool S3 are considerably higher than those in Pool S1, as Pool S3 encompasses all patients from the phase II and phase III trials for CZP. Please also note that subjects receiving multiple dose levels of CZP have exposure included in both safety groups and therefore the number of subjects in each group will exceed the total number of subjects exposed to CZP. Based on the above, UCB requests that the serious adverse event evidence included in the submission is accurately reflected in the ERG report.	16 in pool S3 to compare it to.
Point 2 – Section 4.2.3 (first paragraph on page 60): "The number of deaths due to adverse events was low in the maintenance phase, [redacted]% in each treatment group."	We request an amendment to the statement as follows, to accurately reflect the serious adverse event data reported in the submission. The amended text is underlined. "The number of deaths due to adverse events was low up to Week 144, [redacted]% in each	UCB believe the phase reported for the number of deaths experienced is incorrect and needs to be amended to accurately reflect the serious adverse event data reported in the submission. The number of deaths was from baseline up until Week 144, not the maintenance treatment period. Based on the above, UCB requests that the serious adverse event evidence included in	Added: up to Week 144

	treatment group”	the submission is accurately reflected in the ERG report.	
Point 3 – Section 4.2.3 (first paragraph on page 60): “All of these were more frequent in the CZP 400 mg group than the CZP 200 mg group or placebo group, except for skin and subcutaneous tissue disorders, which were more frequent in the placebo group ([redacted]%) than the CZP 400 mg group ([redacted]%) and musculoskeletal and connective tissue disorders, which were also more common in the placebo group ([redacted]%) than the 400mg CZP group ([redacted]%).”	Please update “[redacted]%” to “[redacted]%”.	UCB believe the number of musculoskeletal and connective tissue disorders is reported incorrectly and needs to be amended to accurately reflect the serious adverse event data reported in the submission. The number for the placebo group should be [redacted]%. Based on the above, UCB requests that the serious adverse event evidence included in the submission is accurately reflected in the ERG report.	Updated [redacted]% to [redacted]%
Point 4 – Section 4.2.3 (first paragraph on page 60): “In the initial 16-week phase, the rate of serious adverse events across all three trials was [redacted]%. This increased to [redacted]% in the maintenance and open-label phase at 144 weeks.” This paragraph also reports the rate of patients reporting serious adverse events across the maintenance and open label period.	We request an amendment to the statement as follows, to accurately reflect the serious adverse event data reported in the submission. The amended text is <u>underlined</u>. “In the initial 16-week phase, the rate of serious adverse events across all three trials was [redacted]%. <u>The overall rate of serious adverse events from baseline to Week 144 in Pool S3 was [redacted]%. The most common serious adverse</u>	UCB believe the trial periods are reported incorrectly for serious adverse events and should be amended to accurately report the serious adverse event data in the submission. The number of patients reporting serious AEs and the rate of serious AEs presented at 144 weeks is from baseline to Week 144, and therefore should not be compared to the rate in Pool S1. In addition, results are not comparable across Pool S1 and Pool S3 due to the reasons outlined above. Based on the above, UCB requests that the serious adverse event evidence included in	Text amended: “<u>The overall rate of serious adverse events from baseline to Week 144 in Pool S3 was [redacted]%...Up to Week 144, the rate of patients reporting serious adverse events was higher in the CZP 400 mg group ([redacted]%) and the CZP 200 mg group ([redacted]%).</u>”

	events across the three studies were injury, poisoning and procedural complications, psychiatric disorders and musculoskeletal and connective tissue disorders. Up to Week 144, the rate of patients reporting serious adverse events was higher in the CZP 400 mg group (■%) and the CZP 200 mg group (■%).”	the submission is accurately reflected in the ERG report.	
Point 5 – Section 4.2.3 (first paragraph on page 60): “The rate of severe adverse events was comparable between the etanercept arm and the certolizumab arms but was lower in the etanercept arm than the placebo or certolizumab arm for any adverse event or serious adverse events.”	We request an amendment to the statement as follows, to accurately reflect the evidence submitted. The amended text is underlined. “The incidence of severe TEAEs was was similar between the two CZP doses and between the ETN and CZP 400 mg Q2W treatment groups, however the incidence of severe TEAEs was higher in the ETN group compared with the CZP 200 mg Q2W treatment group.”	UCB believes the statement does not accurately reflect the submitted evidence. When comparing the rate of serious adverse events in the etanercept arm to the ‘all CZP’ group (i.e. patients on both doses of CZP) then the rate of serious adverse events is higher in the etanercept arm. As per UCB submission (page 129), “The incidence of severe TEAEs was similar between the two CZP doses and between the ETN and CZP 400 mg Q2W treatment groups, however the incidence of severe TEAEs was higher in the ETN group compared with the CZP 200 mg Q2W treatment group.” Based on the above, UCB requests that the serious adverse event evidence submitted is accurately reflected in the ERG report.	Text amended: “The incidence of severe TEAEs was numerically higher in the etanercept arm compared with both the CZP 200 mg and CZP 400 mg treatment groups (CIMPACT trial).”

Issue 9 Company's submitted NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1 – Page 65: "However, the ERG identified several problems with the code and noticed that the code did not appear to be correct for a NMA." "However, there is little similarity between the code used by the company and the example code in the DSU document. The code provided does not appear to be able to produce the results reported in the CS." Page 93: "However, as noted in Section 4.4 the ERG is concerned about the WinBUGS code provided to the ERG, which does not reflect the code used to generate the results presented and has thus prevented the ERG from replicating the results of the NMA. It is therefore unclear whether the response rates generated are correct."	Please add the statement that the company provided the correct WinBUGS code alongside this pro forma. The new text is underlined. "The correct WinBUGS code has been provided by the company subsequent to the response to the clarification questions."	We thank the ERG for highlighting this issue and have now provided the WinBUGS code that matches the NMA results submitted in the appendix to this document. This code corresponds to both the original NMA from the company submission and the revised NMA results provided in the appendix to this document (see row below).	Not a factual inaccuracy.

Point 2 – Page 67: "The ERG noticed that the results of the NMA imply that guselkumab has a PASI 75 response rate of [redacted]% at week 16. However, the VOYAGE 1[28] and VOYAGE 2 [29] trials, which are the primary phase III RCTs evaluating guselkumab, report PASI 75 response rates of 91.2% and 86.3%, respectively. In addition, the NMA also includes a phase II RCT evaluating guselkumab 30, which reports a PASI 75 response rate of 79.0%. In response to the ERG's points for clarification the company stated that this difference may be due to the multinomial model used in the NMA, which is discussed earlier in this section. The company also suggested reasons why this NMA has different effect estimates for guselkumab compared to other NMAs which included guselkumab. However, the company did not give any more details of why the effect estimates in this NMA were substantially smaller than the clinical trial data for guselkumab. The ERG is uncertain that the effect	Please include acknowledgement of the revised NMA results provided as an appendix to this response, which now resolve the highlighted discrepancy in guselkumab PASI 75 responder rates. UCB requests the following text to be added: "Further exploratory analyses conducted by the company indicated that the difference in the guselkumab estimates were triggered by the lack of published peer-reviewed PASI 50 response rate data at the time the analysis was conducted. The NMA was re-run using only VOYAGE 1 and VOYAGE 2 trials for guselkumab and including the PASI 50 response estimates for guselkumab from these studies as identified in the guselkumab company submission in TA521. The results of this additional NMA were provided subsequently to the ERG clarification questions and provided results that were consistent with other recently undertaken NMAs in terms of the ranking order of therapies, and resulted in estimated PASI 75 response rates for guselkumab that were in line with the published estimates."	In response to ERG clarification question A25, UCB presented potential reasons for the discrepancy between the estimated PASI 75 responder rate for guselkumab from the submitted NMA and the PASI 75 responder rate observed in the VOYAGE 1 and 2 trials. Inclusion of the X-PLORE study (Gordon *et al*.) and lack of PASI 50 responder data inputs for guselkumab were both noted as potential considerations. However, at the time of submitting the response to the ERG clarification questions it had not been possible to clearly identify the source of the discrepancy. Further investigation of the source of the differences between the guselkumab estimated PASI 75 responder rates in the original NMA and the PASI 75 responder rates reported from the trials of guselkumab, indicated that this was a result of the lack of published peer-reviewed PASI 50 responder rate data for guselkumab at the time the NMA was originally run. PASI 50 responder rates for guselkumab from VOYAGE 1 and VOYAGE 2 have been identified as available in TA521 and the NMA has therefore been re-run with the inclusion of this PASI 50 data. This revised NMA also excludes the X-PLORE (Gordon *et al.*) study in order to make the NMA	Not a factual inaccuracy. New information received from the company will be included in an addendum to the original ERG report.

estimate of guselkumab produced by the network meta-analysis is reliable. The company compared the probability of response results for adalimumab and secukinumab between this NMA and the results in the ixekizumab NICE submission 31 as validation. The company stated that the PASI 50/75/90 results were comparable regarding adalimumab estimates. Although, the results are similar, the effect estimates for adalimumab are lower for each PASI outcome in this NMA compared to the ixekizumab NMA and the secukinumab estimates are also notably lower in this NMA."		more consistent with the NMA approach in previous appraisals (i.e. TA521), which did not include this study. It should be noted that exclusion of the X-PLORE (Gordon *et al.*) study had no impact on results. The revised NMA resulted in an increase in the estimated PASI 75 responder rate for guselkumab from [redacted]% to [redacted]%, which is aligned with the PASI 75 responder rate observed in the clinical trials for guselkumab and consistent with NMAs undertaken for other recent appraisals in terms of the ranking order of therapies. Details and results of this revised NMA are provided in the appendix to this document. The revised NMA has also been incorporated into an updated set of cost-effectiveness analyses, presented in the "Updated cost-effectiveness analyses" section of the appendix to this document.	

Issue 10 Misrepresentation of CZP mechanism of action

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1 – Summary, Section 1.1 (page 12): "Certolizumab pegol (Cimzia®,	We request an amendment of the statement as follows, to accurately reflect the currently existing clinical	UCB believes that the statement is misleading and needs to be amended to accurately reflect the existing clinical	Text amended: "Certolizumab pegol (Cimzia®, CZP) is a fragment-crystallizable-

CZP) is a fragment-crystallizable-(Fc)-free, PEGylated, anti-tumour necrosis factor (TNF). The CS states that it is not expected to undergo Fc receptor mediated transfer across the placenta."	evidence for CZP regarding placental transfer, which was included in the UCB submission. The amended text is underlined. "Certolizumab pegol (Cimzia®, CZP) is a fragment-crystallizable-(Fc)-free, PEGylated, anti-tumour necrosis factor (TNF). The CS states that, as CZP lacks an Fc region, it does not bind FcRn, and is thus not expected to undergo Fc receptor mediated transfer across the placenta. Data from the CRIB trial indicate that there was no to minimal placental transfer of CZP from mothers to infants, suggesting a lack of in utero foetal exposure during the third trimester.	evidence included in the UCB submission. The current statement misrepresents the difference in the mechanism of action of CZP vs other anti-TNFs and biologics, as well as the existing clinical evidence to support it. Furthermore, the statement implies that there is no clinical evidence supporting the lack of transfer across the placenta. Based on the above, UCB strongly requests that the existing evidence included in the UCB submission is accurately reflected in the ERG report.	(Fc)-free, PEGylated, anti-tumour necrosis factor (TNF). The CS states that, as CZP lacks an Fc region, it does not bind FcRn, and is thus not expected to undergo Fc receptor mediated transfer across the placenta. This statement does not imply that there is no clinical evidence supporting the lack of transfer across the placenta.
Point 2 – Background, Section 2.2 (page 26): "Active transport of Immunoglobulin G (IgG) across the placenta is mediated by the neonatal Fc receptor (FcRn), therefore, as certolizumab lacks an Fc region, it does not bind FcRn and is consequently not expected to undergo FcRn mediated transfer across the placenta."	We request an amendment of the statement as follows, to accurately reflect the currently existing clinical evidence for CZP regarding placental and breast milk transfer, which was included in the UCB submission. The amended text is underlined. "Active transport of Immunoglobulin G (IgG) across the placenta is mediated by the neonatal Fc receptor (FcRn), therefore, as certolizumab lacks an Fc region, it does not bind FcRn and is consequently not expected to undergo FcRn mediated transfer across the placenta. A clinical pharmacokinetic study in 16 women exposed to CIMZIA during the third trimester of pregnancy	UCB believes that the statement is misleading and needs to be amended to accurately reflect the existing clinical evidence, included in the UCB submission. In addition to placental transfer, FcRn is expressed in many different cell types across the body such as the epithelial cells of intestine (Israel *et al*., 1997; Dickinson *et al*., 1999) and transcytosis of IgGs from the intestinal lumen to the infant plasma is expected to be mediated by FcRn in intestinal cells (Challa D *et al*., 2014). Therefore, even if a small amount of CZP were to be consumed in breast	Not a factual inaccuracy.

	has shown no to minimal measurable levels of certolizumab pegol in infants' blood (LLoQ: 0.032 mcg/ml). The results of the CRADLE trial suggest that the level of CZP ingested by the suckling infant is minimal, indicating that continuation of CZP treatment is compatible with breastfeeding. Breast milk transfer of biologic molecules is driven by the size of the molecule and how lipophilic it is.[3] Although biologics generally have very low oral bioavailability due to their large molecular size and the proteolytic environment in the digestive system,[4] FcRn on human intestinal epithelial cells may promote uptake of undigested immunoglobulins. Physiologically, only minimal amounts of CZP are likely to cross into breast milk and be absorbed by the infant, due to its large molecule size and the replacement of the Fc portion with PEG.[3]"	milk by the infant, contrary to full IgGs that have been measured in the plasma of breast fed infants (Fritzsche *et al*., 2012), systemic absorption of CZP is even further unlikely. UCB believes that ignoring the information concerning breast milk transfer is misleading and needs to be amended to accurately reflect the existing clinical evidence, included in the UCB submission.	
Point 3 – Background, Section 2.2 (pages 26-27): "A recent analysis of prospective data on maternal certolizumab exposure and pregnancy outcomes (from the UCB Pharma safety database up to 6 March 2017; outcomes were known for 528/1137 prospectively reported	UCB requests an amendment of the statement as follows, to accurately reflect the currently existing clinical evidence for CZP regarding placental transfer and its conclusions, which were included in the UCB submission. The statement "(which has implications for the use of live vaccines)" should also be deleted.	The ERG have incorrectly omitted the clinical evidence from the CRIB trial, which provides evidence for the update to the EU SmPC on the use of live vaccines in infants. The omission of the trials results which have demonstrated that there was no to minimal placental transfer of CZP from mothers to infants, leads to inaccurate statements in the ERG report regarding	Not a factual inaccuracy.

pregnancies with maternal exposure to certolizumab) concluded that analysis of pregnancy outcomes does not indicate a teratogenic effect of certolizumab, compared to the general population, nor an increased risk of foetal death.[20] However, this paper only reported a limited range of outcomes and did not assess whether immunity was suppressed in the newborns (which has implications for the use of live vaccines)."	The amended text is underlined. "A recent analysis of prospective data on maternal certolizumab exposure and pregnancy outcomes (from the UCB Pharma safety database up to 6 March 2017; outcomes were known for 528/1137 prospectively reported pregnancies with maternal exposure to certolizumab) concluded that analysis of pregnancy outcomes does not indicate a teratogenic effect of certolizumab, compared to the general population, nor an increased risk of foetal death.[20] However, this paper only reported a limited range of outcomes and did not assess whether immunity was suppressed in the newborns" ~~(which has implications for the use of live vaccines)."~~ In the clinical pharmacokinetic study one infant had a measurable level of CIMZIA at birth, and no infants had measurable levels of CIMZIA at Week 4 and Week 8. There was no minimal placental transfer of CZP from mothers to infants. As a consequence, it is recommended to wait a minimum of 5 months following the mother's last Cimzia administration during pregnancy before administration of live or live-attenuated vaccines (e.g. BCG vaccine), unless the benefit of the vaccination clearly outweighs the theoretical risk of administration of live or live-attenuated vaccines to the	vaccinations.	

	infants.''		

Issue 11 Incorrect statements on trial design

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1 – Section 1.2 (paragraph 2 on page 13) and Section 3.5 (paragraph 2 on page 29): "The primary endpoints in all three clinical trials include psoriasis area and severity index (PASI) 75 and physician's global assessment (PGA) clear or almost clear"	We request an amendment of the statement as follows, to accurately report trial design. The amended text is underlined. "The co-primary endpoints in CIMPASI-1 and CIMPASI-2 were PASI 75 and PGA clear or almost clear; the primary endpoint in CIMPACT was PASI 75."	UCB believes the primary endpoints are reported incorrectly. PGA clear or almost clear is not a primary endpoint in CIMPACT. The statement made by the ERG implies that all three trials had the same primary endpoints, which is incorrect.	Text amended: "The co-primary endpoints in CIMPASI-1 and CIMPASI-2 were PASI 75 and PGA clear or almost clear; the primary endpoint in CIMPACT was PASI 75."
Point 2 – Section 1.2 (paragraph 2 on page 13): "The primary efficacy outcomes were the proportion of patients achieving a PASI 75 response and the proportion of patients achieving a PGA response at week 16."	We request an amendment of the statement as follows, to accurately report trial design. The amended text is underlined. "The primary efficacy outcomes in CIMPASI-1 and CIMPASI-2 were the proportion of patients achieving a PASI 75 response and the proportion of patients achieving a PGA response at week 16. The primary efficacy outcome for CIMPACT was the proportion of patients achieving a PASI75 response at Week 12."	UCB believe the primary efficacy outcome for CIMPACT is incorrectly reported. The primary efficacy outcome for CIMPACT was the proportion of patients achieving a PASI75 response at Week 12	Text amended: "The primary efficacy outcomes in CIMPASI-1 and CIMPASI-2,,.The primary efficacy outcome for CIMPACT was the proportion of patients achieving a PASI75 response at Week 12."

Point 3 – Section 4.2.1 (last paragraph on page 34): "Patients who did not achieve PASI 50 response at weeks 60, 72, 84, 96, 108, 120 or 132 were switched to receive CZP 400 mg Q2W for a minimum of 12 weeks, at the investigator's discretion."	We request an amendment of the statement as follows, to accurately report trial design. The amended text is underlined. "Patients who did not achieve PASI 50 response at weeks 60, 72, 84, 96, 108, 120 or 132 were switched to receive CZP 400 mg Q2W for a minimum of 12 weeks, at the investigator's discretion. This also applied to PASI 50 responders who did not achieve PASI 75."	UCB believe the maintenance treatment period for CIMPASI-1 and CIMPASI-2 is reported incorrectly and should be updated to accurately report the trial design. Patients who achieved a PASI 50 response but not a PASI 75 response also received CZP 400 mg Q2W based on investigator's discretion.	Text added: "This also applied to PASI 50 responders who did not achieve PASI 75."
Point 4 – Section 4.2.1 (bullet points on page 35): "Patients initially randomised to CZP 200 mg Q2W or CZP 400 mg Q2W were re-randomised (2:2:1) to receive either CZP 200 mg Q2W or CZP 400 mg Q2W or placebo"	We request an amendment of the statement as follows, to accurately report trial design. The amended text is underlined. "Patients initially randomised to CZP 200 mg Q2W were re-randomised (2:2:1) to receive either CZP 200 mg Q2W or CZP 400 mg Q4W or placebo. Patients initially randomised to CZP 400 mg Q2W were re-randomised (2:2:1) to receive either CZP 200 mg Q2W or CZP 400 mg Q2W or placebo."	UCB believe the patients re-randomised after Week 16 in CIMPACT is reported incorrectly and should be updated to accurately report the trial design. Patients initially randomised to CZP 200 mg Q2W were re-randomised (2:2:1) to receive either CZP 200 mg Q2W or CZP 400 mg Q4W or placebo (The difference is CZP 400 mg Q2W patients were re-randomised to CZP 200 mg Q2W, CZP 400 mg Q2W or placebo)	Text amended: "Patients initially randomised to CZP 200 mg Q2W were re-randomised (2:2:1) to receive either CZP 200 mg Q2W or CZP 400 mg Q4W or placebo. Patients initially randomised to CZP 400 mg Q2W were re-randomised (2:2:1) to receive either CZP 200 mg Q2W or CZP 400 mg Q2W or placebo."
Point 5 – Section 4.2.1.2 (paragraph 2 on page 36): "the primary endpoint was the proportion of patients achieving PASI 75 at week 16 and achieving a PGA clear or almost	We request an amendment of the statement as follows, to accurately report trial design. The amended text is underlined. "the co-primary endpoints were the proportion of patients achieving PASI	CIMPASI-1 and CIMPASI-2 co-primary endpoints reported incorrectly and should be changed to accurately report the trial design	Text amended: "the co-primary endpoints were"

clear response.”	75 at week 16 and achieving a PGA clear or almost clear response.”		
Point 6 – Section 4.2.3 (paragraph 3 on page 45): “Patients in the placebo group who did not achieve a PASI 75 also escaped to the open-label CZP 400 mg Q2W. Of those patients randomised to CZP 200 mg for the maintenance phase, 19.6% in CIMPASI-1 and 9.5% in CIMPASI-2 received escape therapy. Of those patients randomised to CZP 400 mg, 9.4% in CIMPASI-1 and 14.8% in CIMPASI-2 received escape therapy. Whereas, out of the patients randomised to placebo in the maintenance phase, 82.6% in CIMPASI-1 and 75.5% in CIMPASI-2 received escape therapy”	We request an amendment of the statement as follows, to accurately report trial design. The amended text is underlined. “Patients in the placebo group who did not achieve a PASI50 response escaped to CZP 400 mg Q2W. Patients in the placebo group who achieved a PASI50 response but not a PASI75 response moved to CZP 200 mg Q2W. Of those patients who received CZP 200 mg Q2W in the initial treatment period, 19.6% in CIMPASI-1 and 9.5% in CIMPASI-2 received escape therapy in the maintenance treatment period. Of those patients who received CZP 400 mg Q2W in the initial treatment period, 9.4% in CIMPASI-1 and 14.8% in CIMPASI-2 received escape therapy in the maintenance treatment phase. Whereas, out of the patients who received placebo in the initial treatment period, 82.6% in CIMAPSI-1 and 75.6% in CIMPASI-2 received escape therapy during the maintenance treatment phase”	UCB believe the escape therapy at Week 16 in CIMPASI-1 and CIMPASI-2 is reported incorrectly and should be updated to correctly report the trial designs for CIMPASI-1 and CIMPASI-2. CIMPASI-1 and CIMPASI-2 reported that patients in the placebo group who did not achieve a PASI50 response escaped to CZP 400 mg Q2W. Patients in the placebo group who achieved a PASI50 response but not a PASI75 response moved to CZP 200 mg Q2W. Of those patients who received CZP 200 mg Q2W in the initial treatment period, 19.6% in CIMPASI-1 and 9.5% in CIMPASI-2 received escape therapy in the maintenance treatment period. Of those patients who received CZP 400 mg Q2W in the initial treatment period, 9.4% in CIMPASI-1 and 14.8% in CIMPASI-2 received escape therapy in the maintenance treatment phase. Whereas, out of the patients who received placebo in the initial treatment period, 82.6% in CIMPASI-1 and 75.6% in CIMPASI-2 received escape therapy during the maintenance treatment phase	Text amended: “Patients in the placebo group who did not achieve a PASI 50 response escaped to CZP 400 mg Q2W. Patients in the placebo group who achieved a PASI 50 response but not a PASI 75 response moved to CZP 200 mg Q2W. Of those patients who received CZP 200 mg in the initial treatment period, 19.6% in CIMPASI-1 and 9.5% in CIMPASI-2 received escape therapy in the maintenance treatment period. Of those patients who received CZP 400 mg Q2W in the initial treatment period, 9.4% in CIMPASI-1 and 14.8% in CIMPASI-2 received escape therapy in the maintenance treatment phase. Whereas, out of the patients who received placebo in the initial treatment period, 82.6% in CIMPASI-1 and 75.6% in CIMPASI-2 received escape therapy during the maintenance treatment phase.”

Issue 12 Incorrect statements or numbers

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1 – The ERG makes inaccurate statements on pages 12, 27, 37: "the mean baseline DLQI scores for the different treatment groups across the trials ranged from 12.9 to 15.3"	We request an amendment of the data as follows, the amended text is underlined. "the mean baseline DLQI scores for the different treatment groups across the trials ranged from 12.8 to 15.3"	The baseline DLQI scores are reported incorrectly, and therefore UCB request that these are changed to accurately present the results. The lower value is 12.8.	Changed from 12.9 to 12.8
Point 2 – The ERG makes inaccurate statements on pages 16, 38, 62: "the ERG notes that the percentage of males is lower in the CIMPASI-2 trial (55.9%), compared to the CIMPASI-1 (69.2%) and CIMPACT trials (68.1%)"	We request an amendment of the data as follows, the amended text is underlined. "the ERG notes that the percentage of males is lower in the CIMPASI-2 trial (55.9%), compared to the CIMPASI-1 (69.2%) and CIMPACT trials (68.2%)"	The percentage of males in CIMPACT is reported incorrectly. The percentage of males in CIMPACT is 68.2%.	Changed from 68.1 to 68.2
Point 3 – The ERG makes inaccurate statements on pages 16, 38, 62: "The CIMPASI-2 trial also had a higher proportion of patients with psoriatic arthritis (25.1%) than the CIMPASI-1 trial (12.4%) and the CIMPACT trial (16.2%)."	We request an amendment of the data as follows, the amended text is underlined. "The CIMPASI-2 trial also had a higher proportion of patients with psoriatic arthritis (25.1%) than the CIMPASI-1 trial (12.4%) and the CIMPACT trial (16.1%)."	The proportion of patients with psoriatic arthritis in CIMPACT is reported incorrectly. The proportion of patients with psoriatic arthritis in CIMPACT is 16.1%	Changed from 16.2 to 16.1

Point 4 – The ERG makes inaccurate statements on page 16: "In the three certolizumab trials, [redacted]% to [redacted]% of patients had not received any previous systemic therapy (including non-biologic)" On page 38: "In the three certolizumab trials, [redacted]% to [redacted]% of patients had not received any previous systemic therapy (including non-biologic)"	Please change "[redacted]% to [redacted]%" to "[redacted]% to [redacted]%"	The proportion of patients who have not received any previous systemic therapy is not accurately reported and should be updated. It does not specify here that the range of numbers here is for each treatment arm and not overall for each trial. When considering the proportions for all patients in each trial the range should be [redacted]% to [redacted]%.	Text amended: "In the three certolizumab trials, the proportion of patients who had not received any previous systemic therapy (including non-biologic) ranged from [redacted]% to [redacted]%"
Point 5 – The ERG makes an inaccurate statement on page 29: "The outcomes reported in the CS included severity of psoriasis, psoriasis symptoms on the nails, relapse rate, adverse events, HRQoL and work productivity and social activities."	We request an amendment of the statement as follows, the amended text is <u>underlined.</u> "The outcomes reported in the CS included severity of psoriasis, psoriasis symptoms on the nails, relapse rate, adverse events, HRQoL and work productivity and <u>activity impairment</u>."	The outcomes reported are not accurate. Social activities should be replaced by activity impairment.	Not a factual inaccuracy. The term 'work productivity and social activities' is consistent with Table 1 of the submission.
Point 6 – The ERG makes an inaccurate statement on page 42: "The proportion of missing values imputed was small for the PASI response and PGA outcomes at week 16 (ranging from [redacted]% to [redacted]%). Whereas, these were higher at week 48,	Please change "[redacted]% to [redacted]%" to "[redacted]% to [redacted]%", and "[redacted]%-[redacted]%" to "[redacted]%-[redacted]%"	The proportion of missing input values is incorrect and should be updated to accurately report the proportion of patients missing input values The proportion of missing values should be: At Week 16: [redacted]% to [redacted]%	<u>Amended: [redacted]% to [redacted]% to [redacted]% to [redacted]%, and [redacted]%-[redacted]% to [redacted]%-[redacted]%.</u>

ranging from [redacted]%-[redacted]%."		At Week 48: [redacted]% to [redacted]%	
Point 7 – The ERG makes an inaccurate statement on page 44: "The proportion of males was higher in the CIMPASI-2 trial than CIMPASI-1 and CIMPACT (Table 1)"	We request an amendment of the statement as follows, the amended text is underlined. "The proportion of males was lower in the CIMPASI-2 trial than CIMPASI-1 and CIMPACT"	The proportion of males in CIMPASI-2 is reported incorrectly and should be amended to correctly report the proportion of males in each trial. The proportion of males in CIMPASI-2 is lower than CIMPASI-1 and CIMPACT	Text amended: "The proportion of males was lower in the CIMPASI-2 trial than CIMPASI-1 and CIMPACT"
Point 8 – The ERG makes an inaccurate statement on page 45: "DLQI results at week 16 were only presented for the pooled data, rather than each individual trial (presented in Table 6 below)."	We request an amendment of the statement as follows, the amended text is underlined. "DLQI results at week 16 were presented for the pooled data in the main submission, with each individual trial presented in the appendices"	The results for the individual trials were presented in the appendices, therefore UCB believe the statement should be amended to correctly report the outcomes provided in the company submission	Text amended: "DLQI results at week 16 were presented for the pooled data in the main submission, with each individual trial presented in the appendices"
Point 9 – The ERG makes an inaccurate statement on page 45: "In CIMPASI-1 and CIMPASI-2, greater reductions from baseline in SF-36 were reported for patients in both CZP treatment groups compared to placebo at week 16."	We request an amendment of the statement as follows, the amended text is underlined. "In CIMPASI-1 and CIMPASI-2, greater improvements from baseline in SF-36 were reported for patients in both CZP treatment groups compared to placebo at week 16"	The change from baseline in SF-36 is reported incorrectly. SF-36 scores increased from baseline in the trials	Text amended: "In CIMPASI-1 and CIMPASI-2, greater improvements from baseline in SF-36 were reported for patients in both CZP treatment groups compared to placebo at week 16"
Point 10 – The ERG makes an inaccurate statement on page 46: "PASI 75, PASI 90, PASI 100 and PGA response were significantly higher in both the	We request an update the response to include the p-values for PASI100, ensuring that these are highlighted yellow and underlined to be marked as	The p value reported for PASI responder rates in CIMPACT is incorrect. The value reported is true for PASI75, PASI90 and PGA, however the PASI100 results for CZP 200 mg Q2W and CZP 400mg Q2W	Text added: "The PASI 100 results for CZP 200 mg and CZP 400 mg compared to placebo were

CZP 200 mg and CZP 400 mg groups than the placebo group at week 16 (p[redacted]).”	academic in confidence.	were associated with p values of [redacted] and [redacted] vs placebo.	associated with p-values of [redacted] and [redacted], respectively.”
Point 11 – The ERG makes an inaccurate statement on page 46: “Of those patients randomised to CZP 200 mg for the maintenance phase, 30.8% received escape therapy and of those randomised to CZP 400 mg, 22.5% received escape therapy. A much larger percentage of patients randomised to ETN (53.5%) and placebo (96.3 %) received escape therapy.”	We request an amendment of the statement as follows, the amended text is underlined. “Of the patients who received CZP 200 mg Q2W in the initial treatment period, 30.8% escaped in the maintenance treatment phase to CZP 400 mg Q2W and of the patients who received CZP 400 mg Q2W in the initial treatment period, 22.5% received escape therapy in the maintenance treatment phase. A much larger percentage of patients randomised to ETN and placebo in the initial treatment period then received escape therapy in the maintenance treatment period (96.4%).”	Escape therapy at Week 16 is reported incorrectly for CIMPACT. In CIMPACT, of the patients who received CZP 200 mg Q2W in the initial treatment period, 30.8% escaped in the maintenance treatment phase to CZP 400 mg Q2W and of the patients who received CZP 400 mg Q2W in the initial treatment period, 22.5% received escape therapy in the maintenance treatment phase. A much larger percentage of patients randomised to ETN and placebo in the initial treatment period then received escape therapy in the maintenance treatment period (96.4%).	Amended: “Of the patients who received CZP 200 mg Q2W in the initial treatment period, 30.8% escaped in the maintenance treatment phase to CZP 400 mg Q2W and of the patients who received CZP 400 mg Q2W in the initial treatment period, 22.5% received escape therapy in the maintenance treatment phase. A much larger percentage of patients randomised to ETN (53.5%) and placebo in the initial treatment period then received escape therapy in the maintenance treatment period (96.4%).”
Point 12 – The ERG makes an inaccurate statement in Table 3, one of the treatment groups considered is CZP 200 mg/CZP 400 mg.	We request the addition of a footnote noting that the frequency for this treatment group is CZP 400 mg Q4W.	The dose for CZP 400 is incorrectly labelled in Table 3. It is not noted that the frequency of CZP 400 mg here is Q4W, as opposed to Q2W when mentioned in the rest of the table.	Added footnote: frequency for this treatment group is Q4W.
Point 13 – The ERG makes an inaccurate statement in Table 3: “Adjusted p value (vs placebo) <	We request that the p value is updated to <0.0001	The adjusted p-value reported in Table 3 is incorrect. This should be p<0.0001	Amended p-value to <0.0001.

0.001”			
Point 14 – The ERG makes an inaccurate statement in Table 4: the p values for PASI 100 response in the CZP 200 mg and CZP 400 mg treatment groups at Week 16 are reported as <0.001.	We request that p values for PASI 100 response in CZP 200 mg and CZP 400 mg treatment groups at Week 16 are updated to [redacted] and [redacted], respectively. The adjusted p value should be updated to <0.0001	The p values in Table 4 are reported incorrectly. The p values in the CZP 200 mg and CZP 400 mg treatment groups at Week 16 should be 0.0043 and 0.0070, respectively. The adjusted p value reported for the rest of the treatment arms is <0.001. This is incorrect. The p value should be <0.0001	Amended p-value to <0.0001 and added [redacted] and [redacted] for PASI 100.
Point 15 – The ERG makes an inaccurate statement in Table 5: the p values for PASI 100 response in the CZP 200 mg and CZP 400 mg treatment groups at Week 16 are reported as <0.001. The adjusted p value reported for the rest of the treatment arms is <0.001. This is incorrect. The p value should be <0.0001	We request that p values for PASI 100 response in CZP 200 mg and CZP 400 mg treatment groups at Week 16 are updated to [redacted] and [redacted], respectively. The adjusted p value should be updated to <0.0001	The p values in Table 5 are reported incorrectly. The p values for PASI 100 response in the CZP 200 mg and CZP 400 mg treatment groups at Week 16 should be [redacted] and [redacted], respectively. The adjusted p value reported for the rest of the treatment arms is incorrect. The p value should be <0.0001	Amended p-value to <0.0001 and added [redacted] and [redacted] for PASI 100.
Point 16 – The ERG makes an inaccurate statement in Table 4 and Table 5, The footnote states: “Patients who received CZP 200 mg or 400 mg until week 16, had a PASI 75 response at week 16 and were re-randomised to placebo, CZP 200 mg or CZP 400 mg.”	We request an amendment of the statement as follows, the amended text is <u>underlined.</u> “Patients who received CZP 200 mg or 400 mg until week 16, <u>had a PASI 50 response at week 16 and continued receiving the treatment to which they had been randomised in the initial treatment period</u>”	The footnotes in Table 4 and Table 5 are incorrect. The data reported at Week 48 is for patients who had a PASI 50 response at Week 16 and continued receiving the treatment to which they had been randomised in the initial treatment period.	Amended text: “Patients who received CZP 200 mg or 400 mg until week 16, <u>had a PASI 50 response at week 16 and continued receiving the treatment to which they had been randomised in the initial treatment period</u>”

Point 17 – The ERG makes an inaccurate statement on page 52: "In the CZP 200 mg arm, [redacted]% of patients who had nail disease at baseline were missing data and in the CZP 400 mg arm, [redacted]% of patients who had nail disease at baseline were missing data at week 48."	Please change "[redacted]%" to "[redacted]%"	The missing data in nail disease patients at Week 48 is reported incorrectly. The proportion of patients in the CZP 400 mg arm with missing data should be [redacted]%.	Changed [redacted]% to [redacted]%.
Point 18 – An inaccurate statement is made on page 55: "In response to the ERG's points for clarification, the company state that no treatment by subgroup interaction terms of [redacted] were observed for these subgroups"	We request an amendment of the statement as follows, the amended text is underlined. "In response to the ERG's points for clarification, the company state that no treatment by subgroup interaction terms of [redacted] were observed for these subgroups. The company further clarified this point by stating that [redacted] interaction term applies to: PGA responder rate subgroup analysis at Week 16 (Pool E1): - Any prior systemic therapy used for psoriasis PGA responder rate subgroup analysis at Week 16 (Pool E3): - Geographical region PASI75 responder rate subgroup analysis at Week 16 (Pool E1): Geographical region"	We noticed that there was an error in the response to the ERG clarification questions. Please update based on the additional information provided below. We have noticed that this was incorrectly reported in the response to the clarification questions. The [redacted] interaction term applies to: PGA responder rate subgroup analysis at Week 16 (Pool E1): - Any prior systemic therapy used for psoriasis PGA responder rate subgroup analysis at Week 16 (Pool E3): - Geographical region PASI75 responder rate subgroup analysis at Week 16 (Pool E1): - Geographical region	Not a factual inaccuracy, this is the information we received in response to the ERG's points for clarification.

Point 18 – The ERG makes an inaccurate statement on page 58: "The 48-week maintenance phase was completed by 93% of patients in CIMPASI-1 and 90% in CIMPACT."	We request an amendment of the statement as follows, the amended text is underlined. "The 48-week maintenance phase was completed by 94% of patients in CIMPASI-1 and 95% in CIMPACT."	The proportion of patients who completed the maintenance phase is reported incorrectly. The proportion of patients in CIMPASI-1 should be 94%. The proportion of patients in CIMPACT should be 95% if the figure is to be calculated in the same approach as those for CIMPASI-1 and CIMPASI-2 (using the blinded maintenance group only).	93% changed to 94% and 90% changed to 95%.
Point 19 – The ERG makes an inaccurate statement on page 104: "As certolizumab pegol is available in single-unit packs, the assumption of wastage of the final dose if a patient fails to respond as applied for brodalumab would not apply"	We request an amendment of the statement as follows, the amended text is underlined. "As certolizumab pegol is only available in packets with two doses, it is possible the assumption of wastage of the final dose if a patient fails to respond as applied for brodalumab, might apply"	Certolizumab pegol is not available in single-unit packs. CZP is currently only available in packs of two doses	Amendment made as suggested by the company.
Point 20 – The ERG makes an inaccurate statement on page 110: "In this scenario, the ICER of certolizumab as first-line therapy compared with a sequence starting with standard care followed by adalimumab was estimated as £3,650 per QALY gained."	We request an amendment of the statement as follows, the amended text is underlined. "In this scenario, the ICER of certolizumab as first-line therapy compared with a sequence starting with standard care followed by adalimumab was estimated as £3,601.54 per QALY gained	The ICER for the candidates for systemic non-biologic therapy is reported incorrectly. The ICER should be £3,601.54	Amendment made.
Point 21 – The ERG makes an inaccurate statement on page 116: "The company present a scenario analysis which	We request an amendment of the statement as follows, the amended text is underlined.	The statement on the proportion of patients on biosimilars in this scenario is incorrect and therefore the results could be misinterpreted. The scenario analysis	Amendment made as suggested, text changed to reflect the provenance of the

includes biosimilar infliximab and etanercept at 20% and 40% uptake rates respectively."	"The company present a scenario analysis which includes the costs of biosimilar infliximab and etanercept"	assumes all patients on etanercept or infliximab receive the biosimilar (cost for all patients is biosimilar cost)	company's estimates.
Point 22 – mis-reporting of the Marketing Authorisation Page 26 "This is in line with its amended marketing authorisation (received 8 June 2018)."	We request the bellow amendment (text underlined) "This is in line with its granted marketing authorisation (received 8 June 2018)."	The statement is inaccurate as it implies that there was a change in the marketing authorisation for CZP, for the treatment of moderate to severe plaque psoriasis, during the regulatory process. We think the statement should have read "granted".	Amendment made - 'Amended' removed.
Point 22 – Page 80: "The model assumes that assessment of treatment response occurs at 16 weeks for certolizumab, reasoning that this is in line with recommendations in the as yet unpublished SmPC"	We request the bellow amendment (text underlined) "The model assumes that assessment of treatment response occurs at 16 weeks for certolizumab, reasoning that this is in line with approved regulatory recommendations. ~~in the as yet unpublished SmPC~~""	The statement is inaccurate as it implies that the model was based on off label information. We would like to note that the evidence submitted, including the model were in line with CHMP Positive Opinion and the EC decision, which were available at the time of the submission.	Not a factual error.
Point 23 – page 116 "In line with the NICE scope and anticipated licence for certolizumab, the company presents scenarios in which certolizumab is positioned as an alternative to systemic non-biological therapy."	We request the deletion of "anticipated" from the mentioned statement.	The statement is inaccurate as it implies that at the time of the submission, CZP did not yet have a marketing authorisation. As per the company submission (Table 2), CZP received the European Marketing Authorisation on 8 June 2018.	Amendment made.
Point 24 – on page 62: "Systematic searches were	Please change the year to 2017.	The dates for the SLR are mis-reported. The databases were searched until	Amendment made.

carried out in MEDLINE, Embase and CENTRAL-indexed databases for RCTs that were published until December 11th 2011."		December 11th 2017.	
Point 25 – page 29: "The CS states that psoriasis symptoms in the joints was an outcome listed in the decision problem and included in the submission, however it is not reported."	We suggest revisions to the ERG report to indicate that this evidence was included in the original submission.	This evidence has been included in the original submission (section B 2.1.3, pages 135-136)	Not a factual inaccuracy. Results relating to psoriasis symptoms in the joints were not presented for the three trials included in the submission.

Issue 13 Confidential Marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1 - Section 4.2.1 (first paragraph on page 37): "The mean DLQI scores for the CIMPASI-1, CIMPASI-2 and CIMPACT trials ranged from [redacted]".	Please remove AIC marking	The mean DLQI scores are not AIC	Removed AIC marking.
Point 2 – Page 37, 60: "Across the three certolizumab trials, [redacted] patients had a DLQI score <10"	Please mark [redacted] as yellow and underlined, to mark as academic in confidence	The number of patients with DLQI<10 is AIC	AIC marking updated.
Point 3 - Section 4.2.1 (paragraph 3 on page 37): "In response to the ERG's points for clarification	Please mark [redacted] as yellow and underlined, to mark as academic in confidence	The number of patients from the UK in CIMPACT is AIC	AIC marking updated.

the company stated that in the CIMPACT trial [redacted] patients were from the UK"			
Point 4 – Section 4.2.1 (paragraph 3 on page 45): "From week 16, patients in the CZP 200 mg and CZP 400 mg groups who did not achieve a PASI 50 response to certolizumab escaped to open-label CZP 400 mg Q2W. Patients in the placebo group who did not achieve a PASI 75 also escaped to the open-label CZP 400 mg Q2W. Of those patients randomised to CZP 200 mg for the maintenance phase, [redacted]% in CIMPASI-1 and [redacted]% in CIMPASI-2 received escape therapy. Of those patients ran domised to CZP 400 mg, [redacted]% in CIMPASI-1 and [redacted]% in CIMPASI-2 received escape therapy. Whereas, out of the patients randomised to placebo in the maintenance phase, [redacted]% in CIMPASI-1 and [redacted]% in CIMPASI-2 received escape therapy."	Please underline and highlight yellow the values reported in the text to mark as academic in confidence	The values reported here should be AIC as they are not yet in the public domain	AIC marking updated.
Point 5 – Section 4.2.3 (first paragraph on page 54): "The CS presented another pooled data set, E5, which includes [redacted] patients in CIMPASI-1, CIMPASI-2 and CIMPACT randomised to CZP 200 mg or CZP 400 mg, who responded to treatment and stayed on the same dose of certolizumab until week 48."	Please underline and highlight yellow the number of patients in Pool E5 to report this value as academic in confidence	The number of patients in Pool E5 should be marked as AIC	AIC marking updated.
Point 6 – Section 4.2.3 (first paragraph on page 55: "The PASI 75 response rate stays the same in the CZP 200 mg group from week 16 to week	Please underline and highlight yellow the response rates as these should be academic in confidence	The responder rates in the non-biologic inadequate responders population should be AIC	AIC marking updated.

48 ([redacted]%). However, the PASI 75 response rate decreases slightly from week 16 to week 48 in the CZP 400 mg group ([redacted]%)."			
Point 7 – Section 4.2.3: In Table 7, the n numbers are reported for each treatment arm.	Please underline and highlight yellow the n numbers for each treatment arm in the non-biologic therapy inadequate responders and candidates for non-biologic systemic therapy subgroups	The n numbers in Table 7 should be marked as AIC for the non-biologic therapy inadequate responders and candidates for non-biologic systemic therapy	AIC marking updated.
Point 8 – Section 4.2.3: In Table 8, the n numbers for each treatment arm in Pool S1 are reported	Please underline and highlight yellow the n numbers for each treatment arm in the initial treatment period	The n numbers in Table 8 should be AIC for the initial treatment period	AIC marking updated.
Point 9 – Section 4.2.5 (paragraph 2 on page 61): "However, there were more female patients in the placebo group ([redacted] %) compared to the CZP 200 mg group ([redacted]%) and the CZP 400 mg group ([redacted]%)."	Please underline and highlight yellow the proportion of females in each treatment arm. Please also make the correction to the proportion of patients in the placebo group	The proportion of females in the subgroup of systemic non-biologic therapy inadequate responders should be marked as AIC as these have not yet been published. The proportion in the placebo group should be updated to [redacted]%.	AIC marking updated and changed [redacted] to [redacted].
Point 10 – Section 5.2.7 (paragraph 3 on page 96): "The mean utility score at baseline in each trial was as follows: CIMPASI-1 was [redacted] (SD [redacted]), CIMPASI-2 was [redacted] (SD [redacted]), and CIMPACT was [redacted] (SD [redacted])."	Please underline and highlight yellow the mean utility scores (and SD) for each trial	The mean utility score at baseline for each trial should be marked as AIC as this has not yet been published	AIC marking updated.
Point 11 – Section 5.2.9.2 (page 113) "The company also presented a scenario with [redacted] for certolizumab, which is of relevance to the dose escalation scenario (Table 93 in	Please underline and highlight blue the text as this is commercial in confidence.	The information should be marked as CIC as this is commercial in confidence.	CIC marking updated.

CS)."			

Issue 14 Risk of performance bias in the CIMPACT study

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.2. (paragraph 2 on page 41): "All patients, outcome assessors and care providers in the certolizumab arms were blinded in the CIMPACT trial until the end of the maintenance phase. However, patients in the CIMPACT trial receiving etanercept were unblinded as etanercept could only be produced in a commercial presentation. Placebo and etanercept were also provided by unblinded personnel. This introduces a potential risk of performance bias as patients and investigators may have been able to distinguish treatment allocation between etanercept and the other treatment arms." .	We request an amendment of the statement as follows, to accurately reflect the blinding of the CIMPACT study, which was included in the UCB submission. The amended text is underlined. "All outcome assessors were blinded in the CIMPACT trial until the end of the maintenance phase. In the certolizumab and placebo arms, patients were also blinded until the end of the maintenance phase. However, patients in the CIMPACT trial receiving etanercept were unblinded as etanercept could only be produced in a commercial presentation. Placebo and etanercept were also provided by unblinded personnel. This introduces a potential risk of performance bias as patients and administrators of etanercept may have been able to distinguish treatment allocation between etanercept and the other treatment arms."	UCB believe the ERG report's use of the term "investigators" is potentially misleading as this could be interpreted as either the treatment administrators and/or the outcome assessors. The ERG report text should be updated to clarify that "patients and administrators of etanercept may have been able to distinguish treatment allocation….". Furthermore, by referring only to blinding of outcome assessors "in the certolizumab arms", the ERG report has the potential to mislead readers into thinking that, by implication, outcome assessors were not blinded for the etanercept and placebo arms and patients were not blinded for the placebo arm. The ERG report should make it clear that outcome assessors were blinded across the study as a whole and that the only unblinded element of the placebo arm was the care provider. This is to avoid the reader incorrectly interpreting that the study outcome assessors were unblinded and that patients receiving placebo were not blinded.	Text amended: "All outcome assessors were blinded in the CIMPACT trial until the end of the maintenance phase. In the certolizumab and placebo arms, patients were also blinded until the end of the maintenance phase. However, patients in the CIMPACT trial receiving etanercept were unblinded as etanercept could only be produced in a commercial presentation. Placebo and etanercept were also provided by unblinded personnel. This introduces a potential risk of performance bias as patients and administrators of etanercept may have been able to distinguish treatment allocation between etanercept and the other treatment arms."

Issue 15 Definition of primary failures

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Point 1 – Pages 12, 27, 37, 60, 70: In multiple places, the ERG report makes inquorate statements that the three trials excluded patients who had a history of primary failure to any biologic.	UCB request an amendment of the statement, to include the specific definition of primary failures as per the design of the submitted trials. An example for revisions on page 12 are provided below, and these should be applied to all relevant paragraphs in the ERG report. The amended text is underlined. Page 12 - statement to be replace with the below: "However, all three trials excluded patients who were primary failures to any biologic therapy (primary failure defined as no response within the first 12 weeks of treatment with the biologic) or been exposed to >2 biologics." Furthermore, the wording on page 25 should be adjusted to no longer include "(primary failure)" in brackets after referring to a definition of primary failure ("do not respond adequately to a first biological drug") that is inconsistent with the use of the term primary failure when later discussing the certolizumab pegol trials. Alternatively, it should be made	UCB believe the ERG report presents incomplete information regarding the exclusion criteria for the CZP trials relating to primary failure. As per the clinical trial inclusion/exclusion criteria of each of the CIMPASI 1, CIMPASI 2 and CIMPACT studies the primary definition was specified as: "primary failure defined as no response within the first 12 weeks of treatment with the biologic". The term 'primary failure' may be used with varying definitions in clinical practice and the literature, and it is therefore not necessarily the case that all primary failures as per other potential definitions were excluded from the trials. For example, pg 25 of the ERG report, in referring to NICE CG 153, defines a primary failure as a patient who does "not respond adequately to a first biological drug". There may be a difference between not responding adequately to a first biologic and having no response within the first 12 weeks of a biologic, and therefore it is possible that the CIMPASI 1, CIMPASI 2 and CIMPACT trials might have included some patients meeting the definition of	Added "(primary failure defined as no response within the first 12 weeks of treatment with the biologic)" to page 12, 27, 37, 63 and 72. Regarding the wording on page 25, this is not a factual inaccuracy - it is clear that this definition of primary failure is from NICE guidance.

	clear that this definition of primary failure is as per the specific source, but that definitions of primary failure can vary in practice and across clinical trials.	primary failure as described on page 25 of the ERG report. To ensure accurate reflection of the design of the CIMPASI1; CIMPASI 2 and CIMPACT studies, the ERG report should clearly indicate the definition used for primary responders in these trials.	
Point 2 – Section 4.2.1.3, page 37: "The CIMPASI-1, CIMPASI-2 and CIMPACT trials excluded patients who had a history of primary failure to any biologic or had previous treatment with >2 biologics. This may exclude a proportion of the eligible population who are harder to treat and therefore, less likely to achieve a response. Therefore, the results of the included trials may not be generalisable to these more difficult to treat patients in practice." Similar statements in section 4.2.5 (pages 60-61), section 4.5 (page 70).	UCB requests the following amendment, to ensure accurate reflection of the existing evidence. We also suggest the deletion of the last statement implying that such evidence does not exist. The amended text is underlined. "The CIMPASI-1, CIMPASI-2 and CIMPACT trials excluded patients who had a history of primary failure to any biologic or had previous treatment with >2 biologics. This may exclude a proportion of the eligible population who are harder to treat and therefore, less likely to achieve a response. However, in the CIMPACT trial provides relevant data on the efficacy of CZP in primary nonresponders. ~~Therefore, the results of the included trials may not be generalisable to these more difficult to treat patients in practice~~."	UCB believe that the statements are inaccurately reflecting the evidence submitted, by omitting the fact that the CIMPACT study does provide evidence for primary failures. In the CIMPACT study, patients in the etanercept (ETN) arm who did not achieve a PASI 75 response at Week 16 were re-randomised (2:1) to either certolizumab pegol (loading dose of 400 mg at Weeks 16, 18 and 20 followed by 200 mg 2QW) or placebo. Given that [redacted] of patients initially randomised to etanercept had never used prior biologic therapy, the CIMPACT study provides evidence of CZP efficacy in primary failures to ETN (where primary failure is defined as no PASI 75 response to etanercept at Week 16). This evidence should be acknowledged in the ERG report, which currently indirectly implies that such evidence for CZP does not exist.	Not a factual inaccuracy.

Appendix

Issue 6 Pooling of CIMPASI-1, CIMPASI-2 and CIMPACT

The ERG report raises concerns regarding the appropriateness of pooling results from the CIMPASI-1, CIMPASI-2 and CIMPACT trials based on baseline imbalances between the trials and the observation that the PASI response rates in CIMPASI-2 are higher than in the other two trials.

The ERG note uncertainty over what is driving the difference between these study results, but highlight baseline differences in gender and the proportion of patients with psoriatic arthritis between trials as potential causes. The ERG report notes that it would have been helpful to receive analyses of PASI 50, PASI 75 and PASI 90 response rates for these pooled study results with an adjustment for gender and psoriatic arthritis in the logistic regression. Re-analysis of the PASI response rates including these factors could not be completed in the timeframe of responding to the ERG clarification questions. However, analyses adjusting for PsA and gender in the logistic regression have been conducted subsequently and are now available for each of the CIMPASI-1, CIMPASI-2 and CIMPACT studies alone, as well as the pooling (Pool E1). These results are summarised in Table 1 and Figure 1 to Figure 3.

The adjusted analysis result in similar conclusions to the submitted analysis and demonstrate that the differences in these baseline characteristics is not the source of the differences in study results and do not affect the efficacy of CZP in the pooling of the three trials. These analyses therefore support the appropriateness of pooling the CIMPASI-1, CIMPASI-2 and CIMPACT studies despite observed differences in gender and concomitant PsA at baseline between studies.

Table 1: PASI50, PASI75 and PASI90 responder rates adjusted by PsA and gender at Week 16 in CIMPASI-1, CIMPASI-2 and CIMPACT, and Pool E1 (new evidence)

	CIMPASI-1			CIMPASI-2			CIMPACT			Pool E1		
Responder rate, %	**Placebo (n=51)**	**CZP 200 mg Q2W (n=95)**	**CZP 400 mg Q2W (n=88)**	**Placebo (n=49)**	**CZP 200 mg Q2W (n=91)**	**CZP 400 mg Q2W (n=87)**	**Placebo (n=57)**	**CZP 200 mg Q2W (n=165)**	**CZP 400 mg Q2W (n=167)**	**Placebo (n=157)**	**CZP 200 mg Q2W (n=351)**	**CZP 400 mg Q2W (n=342)**
PASI50	***	***	***	***	***	***	***	***	***	***	***	***
PASI75	***	***	***	***	***	***	***	***	***	***	***	***
PASI90	***	***	***	***	***	***	***	***	***	***	***	***

Abbreviations: CZP: certolizumab pegol; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; Q2W: every two weeks.
Estimates of responder rate and p-values are based on a logistic regression model with factors for treatment, region, study (pooled data only), prior biologic exposure (yes/no), study*region (pooled data only), study*prior biologic exposure (yes/no) (pooled data only) sex and concomitant PsA on the multiply imputed data sets using MCMC method for multiple imputation.
The responder rates are the adjusted predicted probabilities from the logistic regression model (pooled data only).
Source: UCB data on file (2018).[5]

Figure 1: PASI50 response at Week 16, adjusted additionally by gender and PsA, in CIMPASI-1, CIMPASI-2, CIMPACT and Pool E1 (new evidence)

Abbreviations: CZP: certolizumab pegol; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks.
Estimates of responder rate and p-values are based on a logistic regression model with factors for treatment, region, study (pooled data only), prior biologic exposure (yes/no), study*region (pooled data only), study*prior biologic exposure (yes/no) (pooled data only) sex and concomitant PsA on the multiply imputed data sets using MCMC method for multiple imputation.
The responder rates are the adjusted predicted probabilities from the logistic regression model (pooled data only).
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).
Source: UCB data on file (2018).[5]

Figure 2: PASI75 response at Week 16, adjusted additionally by gender and PsA, in CIMPASI-1, CIMPASI-2, CIMPACT and Pool E1 (new evidence)

Abbreviations: CZP: certolizumab pegol; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks.
Estimates of responder rate and p-values are based on a logistic regression model with factors for treatment, region, study (pooled data only), prior biologic exposure (yes/no), study*region (pooled data only), study*prior biologic exposure (yes/no) (pooled data only) sex and concomitant PsA on the multiply imputed data sets using MCMC method for multiple imputation.
The responder rates are the adjusted predicted probabilities from the logistic regression model (pooled data only).
Pooled data is from CIMPASI-1, CIMPASI-2 and CIMPACT (Pool E1).
Source: UCB data on file (2018).[5]

Figure 3: PASI90 response at Week 16, adjusted additionally by gender and PsA, in CIMPASI-1, CIMPASI-2, CIMPACT and Pool E1 (new evidence)

Abbreviations: CZP: certolizumab pegol; PASI: Psoriasis Area and Severity Index; Q2W: every two weeks.
Estimates of responder rate and p-values are based on a logistic regression model with factors for treatment, region, study (pooled data only), prior biologic exposure (yes/no), study*region (pooled data only), study*prior biologic exposure (yes/no) (pooled data only) sex and concomitant PsA on the multiply imputed data sets using MCMC method for multiple imputation.
The responder rates are the adjusted predicted probabilities from the logistic regression model (pooled data only).
Source: UCB data on file (2018).[5]

Issue 9 Company's submitted NMA

1 Revised NMA incorporating PASI 50 responder rates from VOYAGE 1 and VOYAGE 2 and excluding the X-PLORE (Gordon et al.) study

As noted in the proforma Issue 2, ERG clarification question A25 highlighted a discrepancy between the PASI 75 responder rates reported in the clinical literature for guselkumab and those being estimated by the NMA submitted by UCB. In UCB's response to the ERG clarification questions we noted that time constraints had not permitted the source of this discrepancy to be identified and appropriately resolved. Following the response to the ERG clarification questions, further exploratory analyses have been conducted to determine the difference in the guslkumab estimates. Two sensitivity analyses have been conducted as detailed below:

- Assesment of the impact of X-PLORE study (Gordon *et al*.)
- Assessment of impact of lack of published peer-reviewed PASI 50 response rates for guselkumab

The first sensitivity analysis indicated that the exclusion of X-PLORE study (Gordon *et al*.) has no impact on the originally submitted NMA results. Given the conclusion of the first sensitivity analysis and in order to compare to the NMA estimates from the guselkumab submission (TA521), the second sensitivity analysis has also excluded the X-PLORE (Gordon *et al*.) study. PASI 50 responder rates from VOYAGE 1 and VOYAGE 2 have been identified as available in TA521 and the NMA has therefore been re-run with the inclusion of this PASI 50 data for guselkumab. Of note, as indicted in the response to the ERG clarification questions, the published peer-reviewed PASI 50 response rates for guselkumab were not available at the time the NMA was originally run.

The revised NMA resulted in an increase in the estimated PASI 75 responder rate for guselkumab from [redacted]% to [redacted]%, which is aligned with the PASI 75 responder rate observed in the clinical trials for guselkumab. The conclusions of this revised NMA are consistent with NMAs undertaken for other recent appraisals in terms of the ranking order of therapies.

Figure 4: Updated NMA: PASI 50 responder rates

Figure 5: Updated NMA: PASI 75 responder rates

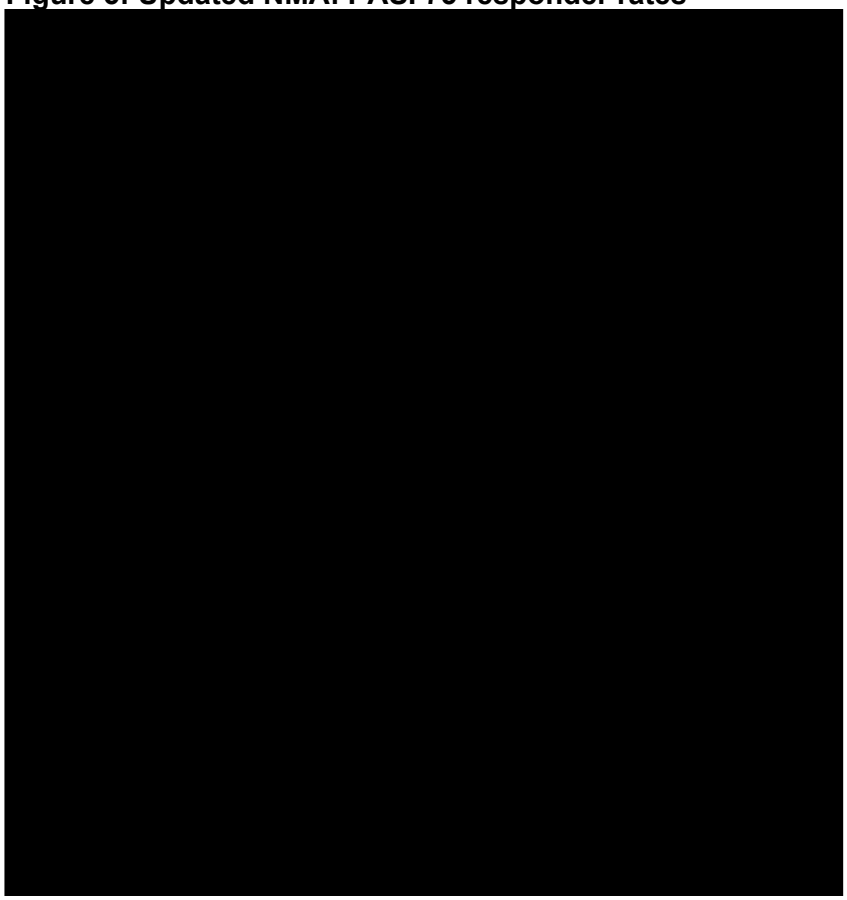
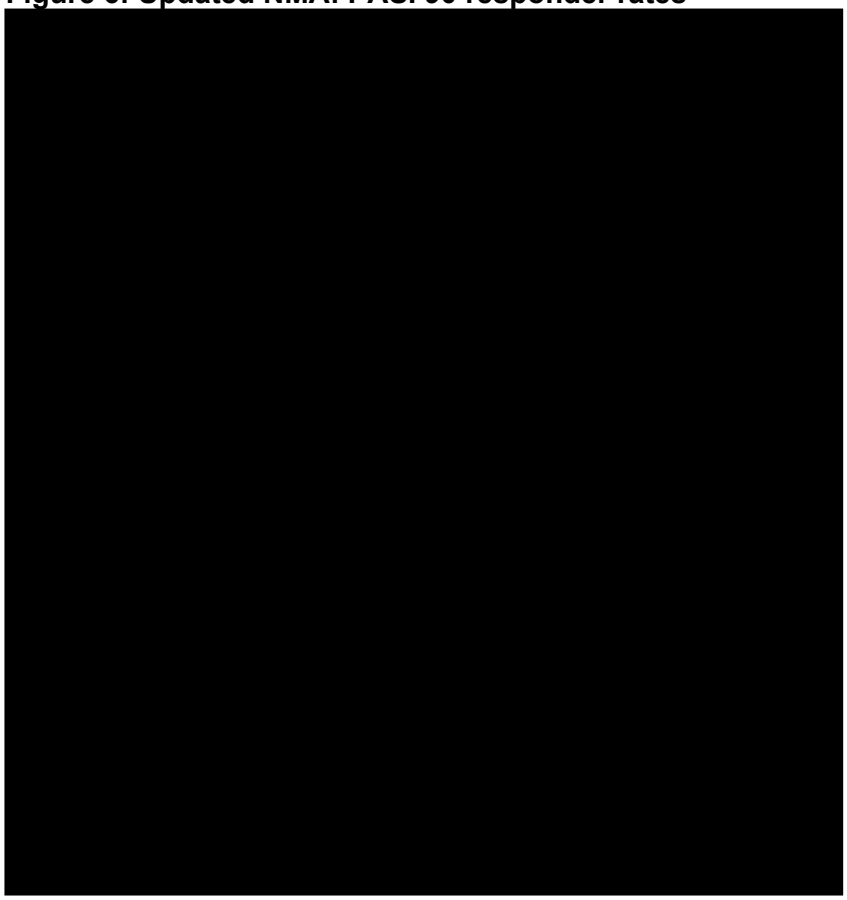


Figure 6: Updated NMA: PASI 90 responder rates



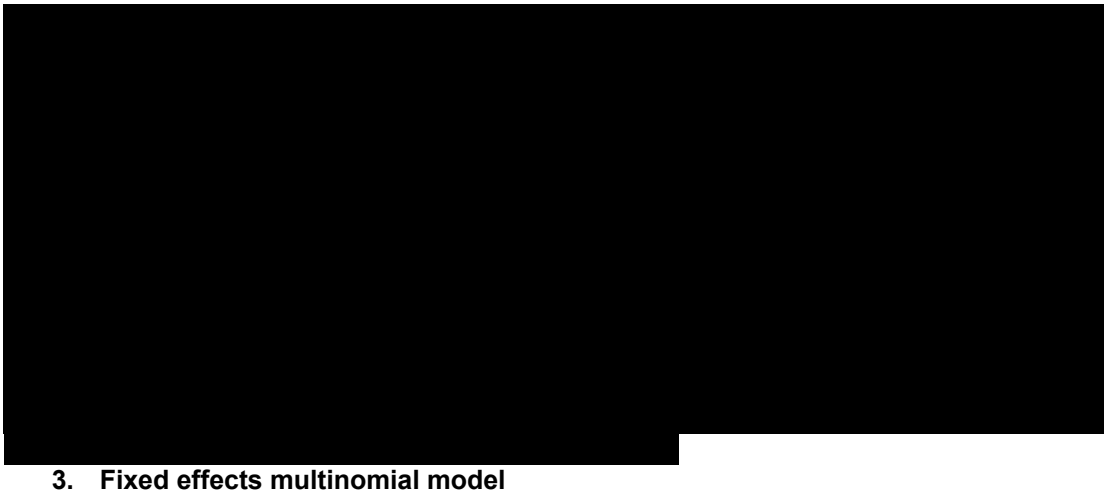
2 WinBUGS code

The ERG report noted that the WinBUGS code for the NMA provided alongside the submission was incorrect. The correct WinBUGS code that was used to run the original NMA is included below for the ERG. Three sets of code are provided:

1. Random effects multinomial model, baseline risk adjusted – representing the NMA model used in the originally submitted NMA and for the revised NMA presented later in this appendix
2. Random effects multinomial model – for completeness
3. Fixed effects multinomial model – for completeness

1. Random effects multinomial model, baseline risk adjusted

2. **Random effects multinomial model**



3. **Fixed effects multinomial model**

3 NMA datasets

The data tables informing the original NMA are presented in Table 3. The data tables informing this revised NMA are provided in Table 3 below.

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Table 2: Data Set: Original Multinomial model for ITT

	Tx 1	Tx 2	Tx 3	Tx 4	Number of arms	Number of cut points	Cut point 1	Cut point 2	Cut point 3	Cut point 4	n, Tx=1, PASI 50	N, Tx=1, PASI 50	n, Tx=1, PASI 75	N, Tx=1, PASI 75	n, Tx=1, PASI 90	N, Tx=1, PASI 90	n, Tx=2, PASI 50	N, Tx=2, PASI 50	n, Tx=2, PASI 75	N, Tx=2, PASI 75	n, Tx=2, PASI 90	N, Tx=2, PASI 90	n, Tx=3, PASI 50	N, Tx=3, PASI 50	n, Tx=3, PASI 75	N, Tx=3, PASI 75	n, Tx=3, PASI 90	N, Tx=3, PASI 90	n, Tx=4, PASI 50	N, Tx=4, PASI 50	n, Tx=4, PASI 75	N, Tx=4, PASI 75	n, Tx=4, PASI 90	N, Tx=4, PASI 90
Study	t[,1]	t[,2]	t[,3]	t[,4]	na[]	nc[]	C[,1]	C[,2]	C[,3]	C[,4]	r[,1,1]	n[,1,1]	r[,1,2]	n[,1,2]	r[,1,3]	n[,1,3]	r[,2,1]	n[,2,1]	r[,2,2]	n[,2,2]	r[,2,3]	n[,2,3]	r[,3,1]	n[,3,1]	r[,3,2]	n[,3,2]	r[,3,3]	n[,3,3]	r[,4,1]	n[,4,1]	r[,4,2]	n[,4,2]	r[,4,3]	n[,4,3]
AMAGINE 1	1	5	NA	NA	2	3	1	3	4	NA	214	220	4	6	2	2	37	222	29	185	156	156	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
AMAGINE 2	1	5	21	NA	3	3	1	3	4	NA	284	309	19	25	6	6	84	612	100	528	428	428	90	300	69	210	141	141	NA	NA	NA	NA	NA	NA
AMAGINE 3	1	21	5	NA	3	3	1	3	4	NA	296	315	13	19	6	6	96	313	67	217	150	150	93	624	100	531	431	431	NA	NA	NA	NA	NA	NA
Asahina	1	3	NA	NA	2	4	1	2	3	4	37	46	7	9	2	2	8	43	8	35	26	27	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bachelez	1	11	NA	NA	2	4	1	2	3	4	85	107	16	22	5	6	66	335	72	269	89	197	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
BRIDGE	1	9	NA	NA	2	4	1	2	3	4	93	131	18	38	14	20	124	267	43	143	51	100	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cai	1	3	NA	NA	2	3	1	3	4	NA	76	86	7	10	3	3	74	333	71	259	188	188	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CHAMPION	1	15	3	NA	3	4	1	2	3	4	37	53	6	16	4	10	42	110	29	68	24	39	13	108	9	95	31	86	NA	NA	NA	NA	NA	NA
Chaudhari	1	13	NA	NA	2	2	1	3	NA	NA	9	11	2	2	NA	NA	2	11	9	9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CIMPACT	[redacted]																																	
CIMPASI 1	[redacted]																																	
CIMPASI 2	[redacted]																																	
CORE	1	4	NA	NA	2	4	1	2	3	4	66	88	17	22	4	5	35	88	17	53	26	36	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ERASURE	1	17	18	NA	3	3	1	3	4	NA	237	248	8	11	3	3	67	234	76	167	91	91	45	245	55	200	145	145	NA	NA	NA	NA	NA	NA
ESTEEM 1	1	4	NA	NA	2	4	1	2	3	4	234	282	33	48	14	15	232	562	144	330	131	186	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ESTEEM 2	1	4	NA	NA	2	4	1	2	3	4	110	137	19	27	6	8	122	274	73	152	55	79	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EXPRESS	1	13	NA	NA	2	4	1	2	3	4	71	77	4	6	1	2	27	301	32	274	70	242	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	Tx 1	Tx 2	Tx 3	Tx 4	Number of arms	Number of cut points	Cut point 1	Cut point 2	Cut point 3	Cut point 4	n, Tx=1, PASI 50	N, Tx=1, PASI 50	n, Tx=1, PASI 75	N, Tx=1, PASI 75	n, Tx=1, PASI 90	N, Tx=1, PASI 90	n, Tx=2, PASI 50	N, Tx=2, PASI 50	n, Tx=2, PASI 75	N, Tx=2, PASI 75	n, Tx=2, PASI 90	N, Tx=2, PASI 90	n, Tx=3, PASI 50	N, Tx=3, PASI 50	n, Tx=3, PASI 75	N, Tx=3, PASI 75	n, Tx=3, PASI 90	N, Tx=3, PASI 90	n, Tx=4, PASI 50	N, Tx=4, PASI 50	n, Tx=4, PASI 75	N, Tx=4, PASI 75	n, Tx=4, PASI 90	N, Tx=4, PASI 90
EXPRESS II	1	13	NA	NA	2	3	1	3	4	NA	204	208	2	4	2	2	71	314	101	243	142	142	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FEATURE	1	18	NA	NA	2	2	1	2	NA	NA	59	59	0	0	NA	NA	18	59	5	41	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FIXTURE	1	11	18	17	4	3	1	3	4	NA	308	324	11	16	5	5	181	323	75	142	67	67	74	323	74	249	175	175	108	327	85	219	134	134
Gottlieb-A	1	10	NA	NA	2	4	1	2	3	4	49	55	5	6	1	1	17	57	23	40	11	17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gottlieb-B	1	11	NA	NA	2	2	1	3	NA	NA	63	68	5	5	NA	NA	62	141	79	79	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Igarashi	1	20	22	NA	3	4	1	2	3	4	27	31	2	4	1	2	11	64	15	53	17	38	10	62	10	52	15	42	NA	NA	NA	NA	NA	NA
JUNCTURE	1	18	17	NA	3	2	1	3	NA	NA	59	61	2	2	NA	NA	8	60	19	52	NA	NA	17	61	NA	44	NA	NA	NA	NA	NA	NA	NA	NA
Krueger	1	20	22	NA	3	4	1	2	3	4	57	64	6	7	0	1	16	64	15	48	18	33	5	64	7	59	19	52	NA	NA	NA	NA	NA	NA
Leonardi	1	11	10	NA	3	4	1	2	3	4	142	166	18	24	5	6	43	164	40	121	76	81	68	162	39	94	36	55	NA	NA	NA	NA	NA	NA
LIBERATE	1	4	11	NA	3	4	1	2	3	4	56	84	18	28	7	10	31	83	21	52	20	32	14	83	30	69	23	40	NA	NA	NA	NA	NA	NA
LOTUS	1	20	NA	NA	2	4	1	2	3	4	130	162	14	32	13	18	14	160	14	146	25	132	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
M05- 258	1	3	NA	NA	2	2	1	3	NA	NA	50	52	2	2	NA	NA	21	45	24	24	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Meffert	1	6	NA	NA	2	3	1	2	3	NA	32	39	3	7	4	4	17	41	12	24	12	12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
METOP	1	15	NA	NA	2	4	1	2	3	4	20	29	6	9	3	3	31	91	23	60	21	37	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nakagawa	1	5	NA	NA	2	2	1	3	NA	NA	35	38	2	3	NA	NA	2	37	1	35	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ohtsuki	1	4	NA	NA	2	4	1	2	3	4	66	84	12	18	5	6	42	85	19	43	12	24	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Papp-B	1	10	11	NA	3	4	1	2	3	4	175	193	12	18	5	6	70	196	59	126	46	67	44	194	54	150	56	96	NA	NA	NA	NA	NA	NA
PEARL	1	20	NA	NA	2	4	1	2	3	4	52	60	5	8	2	3	10	61	10	51	11	41	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PHOENIX 1	1	20	22	NA	3	3	1	3	4	NA	247	255	3	8	5	5	84	255	64	171	107	107	87	256	74	169	95	95	NA	NA	NA	NA	NA	NA
PHOENIX 2	1	20	22	NA	3	3	1	3	4	NA	395	410	12	15	3	3	136	409	100	273	173	173	100	411	102	311	209	209	NA	NA	NA	NA	NA	NA
Reich	1	7	8	NA	3	4	1	2	3	4	52	59	3	7	3	4	8	59	7	51	21	44	4	58	6	54	21	48	NA	NA	NA	NA	NA	NA

	Tx 1	Tx 2	Tx 3	Tx 4	Number of arms	Number of cut points	Cut point 1	Cut point 2	Cut point 3	Cut point 4	n, Tx=1, PASI 50	N, Tx=1, PASI 50	n, Tx=1, PASI 75	N, Tx=1, PASI 75	n, Tx=1, PASI 90	N, Tx=1, PASI 90	n, Tx=2, PASI 50	N, Tx=2, PASI 50	n, Tx=2, PASI 75	N, Tx=2, PASI 75	n, Tx=2, PASI 90	N, Tx=2, PASI 90	n, Tx=3, PASI 50	N, Tx=3, PASI 50	n, Tx=3, PASI 75	N, Tx=3, PASI 75	n, Tx=3, PASI 90	N, Tx=3, PASI 90	n, Tx=4, PASI 50	N, Tx=4, PASI 50	n, Tx=4, PASI 75	N, Tx=4, PASI 75	n, Tx=4, PASI 90	N, Tx=4, PASI 90
reSURFACE 1	1	19	NA	NA	2	3	1	3	4	NA	145	154	5	9	4	4	112	309	90	197	107	107	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
reSURFACE 2	1	11	19	NA	3	3	1	3	4	NA	147	156	7	9	2	2	162	313	84	151	67	67	119	307	69	188	119	119	107	314	169	207	38	38
REVEAL	1	3	NA	NA	2	3	1	3	4	NA	372	398	18	26	8	8	236	814	212	578	366	366	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SPIRIT	1	13	NA	NA	2	4	1	2	3	4	40	51	8	11	2	3	3	99	9	96	30	87	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Strober	1	11	NA	NA	2	3	1	3	4	NA	67	72	2	5	3	3	84	139	36	55	19	19	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Torri	1	13	NA	NA	2	2	1	2	NA	NA	16	19	3	3	NA	NA	5	35	4	30	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tyring	1	11	NA	NA	2	4	1	2	3	4	263	306	28	43	11	15	82	311	82	229	82	147	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ultIMMa-1	1	21	16	NA	3	2	1	4	NA	NA	97	102	5	5	NA	NA	58	100	42	42	NA	NA	76	304	228	228	NA	NA	NA	NA	NA	NA	NA	NA
ultIMMa-2	1	16	21	NA	3	2	1	4	NA	NA	96	98	2	2	NA	NA	74	294	221	221	NA	NA	51	99	48	48	NA	NA	NA	NA	NA	NA	NA	NA
UNCOVER 1	1	14	NA	NA	2	3	1	3	4	NA	414	431	15	17	2	2	47	433	79	386	307	307	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
UNCOVER 2	1	14	11	NA	3	3	1	3	4	NA	164	168	3	4	1	1	36	351	67	315	248	248	209	358	82	149	67	67	NA	NA	NA	NA	NA	NA
UNCOVER 3	1	14	11	NA	3	3	1	3	4	NA	179	193	8	14	6	6	49	385	74	336	262	262	178	382	106	204	98	98	NA	NA	NA	NA	NA	NA
Van de Kerkhof	1	11	NA	NA	2	4	1	2	3	4	42	46	3	4	0	1	30	96	30	66	23	36	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
VOYAGE 1	1	3	12	NA	3	3	1	3	4	NA	164	174	5	174	5	5	90	334	78	334	166	166	29	329	59	329	241	241	NA	NA	NA	NA	NA	NA
VOYAGE 2	1	12	3	NA	3	3	1	3	4	NA	228	248	14	248	6	6	68	496	81	496	347	347	78	248	54	248	116	116	NA	NA	NA	NA	NA	NA
X-PLORE	1	3	12	NA	3	3	1	3	4	NA	40	42	1	2	1	1	13	43	11	30	19	19	9	42	7	33	26	26	NA	NA	NA	NA	NA	NA
Yang	1	13	NA	NA	2	4	1	2	3	4	39	45	5	6	1	1	5	84	11	79	20	68	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Papp-D	1	19	NA	NA	2	3	1	3	4	NA	43	45	0	2	NA	NA	22	86	32	66	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	Tx 1	Tx 2	Tx 3	Tx 4	Number of arms	Number of cut points	Cut point 1	Cut point 2	Cut point 3	Cut point 4	n, Tx=1, PASI 50	N, Tx=1, PASI 50	n, Tx=1, PASI 75	N, Tx=1, PASI 75	n, Tx=1, PASI 90	N, Tx=1, PASI 90	n, Tx=2, PASI 50	N, Tx=2, PASI 50	n, Tx=2, PASI 75	N, Tx=2, PASI 75	n, Tx=2, PASI 90	N, Tx=2, PASI 90	n, Tx=3, PASI 50	N, Tx=3, PASI 50	n, Tx=3, PASI 75	N, Tx=3, PASI 75	n, Tx=3, PASI 90	N, Tx=3, PASI 90	n, Tx=4, PASI 50	N, Tx=4, PASI 50	n, Tx=4, PASI 75	N, Tx=4, PASI 75	n, Tx=4, PASI 90	N, Tx=4, PASI 90
Goldminz	15	3	NA	NA	2	2	1	3	NA	NA	11	15	4	4	NA	NA	14	15	1	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
RESTORE 1	15	13	NA	NA	2	4	1	2	3	4	85	215	40	130	49	90	86	653	59	567	152	508	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gisondi	2	10	NA	NA	2	3	1	2	3	NA	15	20	3	5	2	2	13	22	5	9	4	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
IMMvent	3	16	NA	NA	2	2	1	4	NA	NA	161	304	143	143	NA	NA	84	301	217	217	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ACCEPT	11	22	20	NA	3	3	1	3	4	NA	150	347	117	209	80	80	91	347	101	347	155	155	68	209	65	209	76	76	NA	NA	NA	NA	NA	NA
PIECE	11	13	NA	NA	2	4	1	2	3	4	9	23	9	14	5	5	1	25	5	24	14	19	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
IXORA-S	14	21	NA	NA	2	2	1	3	NA	NA	16	136	21	120	NA	NA	52	166	44	114	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CLEAR	18	20	NA	NA	2	3	1	3	4	NA	23	334	47	311	264	264	58	335	84	277	193	193	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Papp-C	1	5	NA	NA	2	3	1	2	3	NA	32	38	6	6	NA	NA	4	40	7	36	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Footnote: Tx represents treatment, N represents total number of patients, n represents number of events.

Table 3: Data Set: Multinomial Analysis with updated VOYAGE 1 and VOYAGE 2 studies (includes PASI 50) data without Gordon 2015

Treatment 1	Treatment 2	Treatment 3	Treatment 4	Number of arms	Number of cut points	Cut point 1	Cut point 2	Cut point 3	Cut point 4	Events, Tx=1, PASI 50	N, Tx=1, PASI 50	Events, Tx=1, PASI 75	N, Tx=1, PASI 75	Events, Tx=1, PASI 90	N, Tx=1, PASI 90	Events, Tx=2, PASI 50	N, Tx=2, PASI 50	Events, Tx=2, PASI 75	N, Tx=2, PASI 75	Events, Tx=2, PASI 90	N, Tx=2, PASI 90	Events, Tx=3, PASI 50	N, Tx=3, PASI 50	Events, Tx=3, PASI 75	N, Tx=3, PASI 75	Events, Tx=3, PASI 90	N, Tx=3, PASI 90	Events, Tx=4, PASI 50	N, Tx=4, PASI 50	Events, Tx=4, PASI 75	N, Tx=4, PASI 75	Events, Tx=4, PASI 90	N, Tx=4, PASI 90	
t[,1]	t[,2]	t[,3]	t[,4]	na[]	nc[]	C[,1]	C[,2]	C[,3]	C[,4]	r[,1,1]	n[,1,1]	r[,1,2]	n[,1,2]	r[,1,3]	n[,1,3]	r[,2,1]	n[,2,1]	r[,2,2]	n[,2,2]	r[,2,3]	n[,2,3]	r[,3,1]	n[,3,1]	r[,3,2]	n[,3,2]	r[,3,3]	n[,3,3]	r[,4,1]	n[,4,1]	r[,4,2]	n[,4,2]	r[,4,3]	n[,4,3]	Trial
1	5	NA	NA	2	3	1	3	4	NA	214	220	4	6	2	2	37	222	29	185	156	156	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	AMAGINE 1
1	5	21	NA	3	3	1	3	4	NA	284	309	19	25	6	6	84	612	100	528	428	428	90	300	69	210	141	141	NA	NA	NA	NA	NA	NA	AMAGINE 2
1	21	5	NA	3	3	1	3	4	NA	296	315	13	19	6	6	96	313	67	217	150	150	93	624	100	531	431	431	NA	NA	NA	NA	NA	NA	AMAGINE 3
1	3	NA	NA	2	4	1	2	3	4	37	46	7	9	2	2	8	43	8	35	26	27	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Asahina
1	11	NA	NA	2	4	1	2	3	4	85	107	16	22	5	6	66	335	72	269	89	197	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Bachelez
1	9	NA	NA	2	4	1	2	3	4	93	131	18	38	14	20	124	267	43	143	51	100	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	BRIDGE

1	3	NA	NA	2	3	1	3	4	NA	76	86	7	10	3	3	74	333	71	259	188	188	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Cai
1	15	3	NA	3	4	1	2	3	4	37	53	6	16	4	10	42	110	29	68	24	39	13	108	9	95	31	86	NA	NA	NA	NA	CHAMPION
1	13	NA	NA	2	2	1	3	NA	NA	9	11	2	2	NA	NA	2	11	9	9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Chaudhari
[redacted]																																CIMPACT
[redacted]																																CIMPASI 1
[redacted]																																CIMPASI 2
1	4	NA	NA	2	4	1	2	3	4	66	88	17	22	4	5	35	88	17	53	26	36	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	CORE
1	17	18	NA	3	3	1	3	4	NA	237	248	8	11	3	3	67	234	76	167	91	91	45	245	55	200	145	145	NA	NA	NA	NA	ERASURE
1	4	NA	NA	2	4	1	2	3	4	234	282	33	48	14	15	232	562	144	330	131	186	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	ESTEEM 1
1	4	NA	NA	2	4	1	2	3	4	110	137	19	27	6	8	122	274	73	152	55	79	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	ESTEEM 2
1	13	NA	NA	2	4	1	2	3	4	71	77	4	6	1	2	27	301	32	274	70	242	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	EXPRESS
1	13	NA	NA	2	3	1	3	4	NA	204	208	2	4	2	2	71	314	101	243	142	142	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	EXPRESS II
1	18	NA	NA	2	2	1	2	NA	NA	59	59	0	0	NA	NA	18	59	5	41	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	FEATURE
1	11	18	17	4	3	1	3	4	NA	308	324	11	16	5	5	181	323	75	142	67	67	74	323	74	249	175	175	108	327	85	219	134	134	FIXTURE
1	10	NA	NA	2	4	1	2	3	4	49	55	5	6	1	1	17	57	23	40	11	17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Gottlieb-A
1	11	NA	NA	2	2	1	3	NA	NA	63	68	5	5	NA	NA	62	141	79	79	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Gottlieb-B
1	20	22	NA	3	4	1	2	3	4	27	31	2	4	1	2	11	64	15	53	17	38	10	62	10	52	15	42	NA	NA	NA	NA	Igarashi
1	18	NA	NA	2	2	1	3	NA	NA	59	61	2	2	NA	NA	8	60	19	52	NA	NA	17	61	NA	NA	NA	NA	NA	NA	NA	NA	JUNCTURE
1	20	22	NA	3	4	1	2	3	4	57	64	6	7	0	1	16	64	15	48	18	33	5	64	7	59	19	52	NA	NA	NA	NA	Krueger
1	11	10	NA	3	4	1	2	3	4	142	166	18	24	5	6	43	164	40	121	76	81	68	162	39	94	36	55	NA	NA	NA	NA	Leonardi
1	4	11	NA	3	4	1	2	3	4	56	84	18	28	7	10	31	83	21	52	20	32	14	83	30	69	23	40	NA	NA	NA	NA	LIBERATE
1	20	NA	NA	2	4	1	2	3	4	130	162	14	32	13	18	14	160	14	146	25	132	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	LOTUS

1	3	NA	NA	2	2	1	3	NA	NA	50	52	2	2	NA	NA	21	45	24	24	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	M05-258
1	6	NA	NA	2	3	1	2	3	NA	32	39	3	7	4	4	17	41	12	24	12	12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Meffert
1	15	NA	NA	2	4	1	2	3	4	20	29	6	9	3	3	31	91	23	60	21	37	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	METOP
1	5	NA	NA	2	2	1	3	NA	NA	35	38	2	3	NA	NA	2	37	1	35	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Nakagawa
1	4	NA	NA	2	4	1	2	3	4	66	84	12	18	5	6	42	85	19	43	12	24	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Ohtsuki
1	10	11	NA	3	4	1	2	3	4	175	193	12	18	5	6	70	196	59	126	46	67	44	194	54	150	56	96	NA	NA	NA	NA	Papp-B
1	20	NA	NA	2	4	1	2	3	4	52	60	5	8	2	3	10	61	10	51	11	41	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	PEARL
1	20	22	NA	3	3	1	3	4	NA	247	255	3	8	5	5	84	255	64	171	107	107	87	256	74	169	95	95	NA	NA	NA	NA	PHOENIX1
1	20	22	NA	3	3	1	3	4	NA	395	410	12	15	3	3	136	409	100	273	173	173	100	411	102	311	209	209	NA	NA	NA	NA	PHOENIX2
1	7	8	NA	3	4	1	2	3	4	52	59	3	7	3	4	8	59	7	51	21	44	4	58	6	54	21	48	NA	NA	NA	NA	Reich
1	19	NA	NA	2	3	1	3	4	NA	145	154	5	9	4	4	112	309	90	197	107	107	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	reSURFACE1
1	11	19	NA	3	3	1	3	4	NA	147	156	7	9	2	2	162	313	84	151	67	67	119	307	69	188	119	119	107	314	169	207	38	38	reSURFACE2
1	3	NA	NA	2	3	1	3	4	NA	372	398	18	26	8	8	236	814	212	578	366	366	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	REVEAL
1	13	NA	NA	2	4	1	2	3	4	40	51	8	11	2	3	3	99	9	96	30	87	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SPIRIT
1	11	NA	NA	2	3	1	3	4	NA	67	72	2	5	3	3	84	139	36	55	19	19	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Strober
1	13	NA	NA	2	2	1	2	NA	NA	16	19	3	3	NA	NA	5	35	4	30	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Tori
1	11	NA	NA	2	4	1	2	3	4	263	306	28	43	11	15	82	311	82	229	82	147	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Tyring
1	21	16	NA	3	2	1	4	NA	NA	97	102	5	5	NA	NA	58	100	42	42	NA	NA	76	304	228	228	NA	NA	NA	NA	NA	NA	ultIMMa-1
1	16	21	NA	3	2	1	4	NA	NA	96	98	2	2	NA	NA	74	294	221	221	NA	NA	51	99	48	48	NA	NA	NA	NA	NA	NA	ultIMMa-2
1	14	NA	NA	2	3	1	3	4	NA	414	431	15	17	2	2	47	433	79	386	307	307	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	UNCOVER1
1	14	11	NA	3	3	1	3	4	NA	164	168	3	4	1	1	36	351	67	315	248	248	209	358	82	149	67	67	NA	NA	NA	NA	UNCOVER2

1	14	11	NA	3	3	1	3	4	NA	179	193	8	14	6	6	49	385	74	336	262	262	178	382	106	204	98	98	NA	NA	NA	NA	NA	NA	UNCOVER 3
1	11	NA	NA	2	4	1	2	3	4	42	46	3	4	0	1	30	96	30	66	23	36	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Van de Kerkhof
1	3	12	NA	3	3	1	3	4	NA	164	174	5	174	5	5	90	334	78	334	166	166	29	329	59	329	241	241	NA	NA	NA	NA	NA	NA	VOYAGE 1
1	12	3	NA	3	3	1	3	4	NA	228	248	14	248	6	6	68	496	81	496	347	347	78	248	54	248	116	116	NA	NA	NA	NA	NA	NA	VOYAGE 2
1	13	NA	NA	2	4	1	2	3	4	39	45	5	6	1	1	5	84	11	79	20	68	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yang
1	19	NA	NA	2	3	1	3	4	NA	43	45	0	2	NA	NA	22	86	32	66	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Papp-D
15	3	NA	NA	2	2	1	3	NA	NA	11	15	4	4	NA	NA	14	15	1	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Goldminz
15	13	NA	NA	2	4	1	2	3	4	85	215	40	130	49	90	86	653	59	567	152	508	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	RESTORE 1
2	10	NA	NA	2	3	1	2	3	NA	15	20	3	5	2	2	13	22	5	9	4	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Gisondi
3	16	NA	NA	2	2	1	4	NA	NA	161	304	143	143	NA	NA	84	301	217	217	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	IM Mvent
11	22	20	NA	3	3	1	3	4	NA	150	347	117	209	80	80	91	347	101	347	155	155	68	209	65	209	76	76	NA	NA	NA	NA	NA	NA	ACCEPT
11	13	NA	NA	2	4	1	2	3	4	9	23	9	14	5	5	1	25	5	24	14	19	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	PIECE
14	21	NA	NA	2	2	1	3	NA	NA	16	136	21	120	NA	NA	52	166	44	114	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	IXORA-S
18	20	NA	NA	2	3	1	3	4	NA	23	334	47	311	264	264	58	335	84	277	193	193	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	CLEAR
1	5	NA	NA	2	3	1	2	3	NA	32	38	6	6	NA	NA	4	40	7	36	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Papp-C

Issue 5 and 7 Updated cost-effectiveness analyses

In their report, the ERG presented an alternative base case, which incorporated identified technical corrections to the model and the ERG's preferred approach as detailed for ERG scenarios 1, 7 and 8:

- *Scenario 1* removed treatment sequencing and essentially modelled each biologic (certolizumab pegol and each comparator biologic) as the only biologic in its sequence. Scenario 1 also presented results in terms of the incremental net monetary benefit for each comparator versus certolizumab pegol at a £20,000 and £30,000 per QALY gained threshold
- *Scenario 7* assumed equal utilities for biologics and BSC (i.e. no differences in health state utilities across treatment arms), and used the utilities for the analysis of the population limited to DLQI >10
- *Scenario 8* incorporate biosimilar costs for all patients receiving etanercept and infliximab, and a 20% discount for adalimumab. However, the ERG notes that in their ERG alternative base case the discount for adalimumab was not assumed and hence the ERG alternative base case only applies the biosimilar costs for all patients receiving etanercept and infliximab.

As part of this response, UCB have provided results of an updated NMA (see Appendix – Issue 9), in response to the ERG clarification question A25, which highlighted a discrepancy between the PASI response rates reported in the clinical literature for guselkumab and those being estimated by the submitted NMA. In UCB's response to the ERG clarification questions we noted that time constraints had not permitted the source of this discrepancy to be identified and appropriately resolved, which has now been done as per Appendix – Issue 9 of this document. Following the revised NMA, we consider that it would be valuable to provide the results of the economic analyses that incorporate this new NMA evidence available for the NICE decision-making at the Committee meeting.

As such, the updated economic analysis is presented below. This updated basecase analysis is based on:

- the ERG alternative base case and therefore incorporates all technical corrections to the model;
- the new evidence provided by the updated NMA as described above.
- the ERG's approach to utility values as per Scenario 7, and incorporates biosimilar costs for etanercept and infliximab as per scenario 8, in order to limit differences between this analysis and the ERG alternative base case for ease of comparison.

However, this updated UCB basecase analysis differs from the ERG alternative base case (corrected model plus scenario 1, 7 and 8) in that it does not incorporate the changes proposed in ERG scenario 1. More specifically, the two main differences are:

- the UCB updated base case analysis retains the use of treatment sequences as presented in the original submission. Although we acknowledge the ERG's concerns regarding the uncertainty introduced through the modelling of treatment sequences, UCB note that analyses based on modelling of treatment sequences have informed Committee decision-making in each of the most recent NICE appraisals of biologics in psoriasis (excepting guselkumab, for which a cost minimisation analysis was presented). For example, in both TA511 (brodalumab) and TA442 (ixekizumab), whilst analyses comparing each comparator alone (not in a sequence) against BSC were considered in decision-making, these analyses were considered alongside the cost-effectiveness analyses based on treatment sequences. Indeed, in TA511 (brodalumab) the Final Appraisal Determination states that "The committee was aware that additional factors should be considered when comparing treatment sequences rather than individual treatments, such as the optimal ordering of treatments and the impact of including treatments that may not be cost-effective. The Committee agreed that, in principle, it was appropriate to compare treatment sequences in this appraisal….". This highlights that although the limitations and uncertainties associated with modelling of treatment sequences have been acknowledged by previous NICE Committees, cost-effectiveness analyses based on treatment sequences have still been considered relevant for decision-making.
- Our UCB updated base case analysis presents results in terms of ICERs as opposed to incremental net monetary benefit. Although UCB acknowledge the academic validity and merits of expressing cost-effectiveness results in the form of incremental net monetary benefit, we note that NICE always quote ICERs in their final guidance documents and that although the NICE methods guide does state that expected net monetary or health benefits can be presented, this is in the context of being "in addition to ICERs".

The results of the updated basecase analysis, as described above, for the inadequate responders population are presented in Table 4. The conclusions of the updated basecase analysis indicate that CZP is cost-effective at a £20,000 per QALY threshold, which is consistent with the previously submitted basecase (original submission and in response to the ERG clarifications).

Table 4: Updated basecase fully incremental results for systemic non-biologic therapy inadequate responders – CZP with PAS

First line therapy	Subsequent sequence	Total		Incremental		ICER vs baseline (£/QALY)	Fully incremental ICER (£/QALY)	CZP ICER vs comparator
		QALYs	Costs	QALYs	Costs			
Company updated basecase analysis								
Etanercept	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	-	-	-		£10,021.84
Certolizumab pegol	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,021.84	£10,021.84	-
Ustekinumab 45mg	ADA 40mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£32,031.78	CZP Dominates	CZP Dominates
Adalimumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£29,042.21	CZP Dominates	CZP Dominates
Ustekinumab 90mg	ADA 40mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£28,316.08	CZP Dominates	CZP Dominates
Secukinumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£112,252.35	Extendedly dominated	£415,708.59*
Guselkumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£7,285.63	£319,704.91	£319,704.91*
Ixekizumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,472.83	GUS Dominates	£329,545.14*
Brodalumab	UST 90mg, INF 100mg, BSC, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£131,983.44	GUS dominates	£507,019.45*

Abbreviations: QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; BSC, best supportive care; CZP, certolizumab pegol; ADA, adalimumab; BROD, brodalumab; ETN, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; SEC, secukinumab; UST, ustekinumab
*Indicates south-west ICER and should be interpreted as the ICER for the comparator versus CZP

Dose escalation

In addition to the above analyses, the analysis for the dose escalation scenario has also been updated. Consistent with the above approach, the updated basecase analysis is based on:

- the ERG corrected model
- the ERG utilities as per ERG scenario 7, consistent with the ERG alternative base case for the escalation strategy and the approach taken in the updated analysis for the inadequate responders population above
- Incorporates biosimilar costs for etanercept and infliximab where relevant, consistent with the approach taken in the updated analysis for the inadequate responders population above

The ERG report refers in various places to ustekinumb 90 mg as a dose escalation strategy. However, ustekinumab 90 mg represents a weight-based dosing approach, whereby the 90 mg dose (as opposed to the 45 mg dose) may be considered appropriate for patients weighing over 100 kg. Therefore UCB considers that ustekinumab 90 mg is not an escalation strategy. UCB do not consider the ERG's alternative base case for the dose escalation, whereby escalation from CZP 200 mg to CZP 400 mg is compared to escalation of certolizumab pegol 200 mg to ustekinumab 90 mg, as appropriate. As such, the UCB updated analysis for the dose escalation strategy is presented for certolizumab pegol dose escalation versus adalimumab dose escalation.

In addition to the above analyses, we note that the ERG also conducted a dose escalation scenario based on data provided by UCB in their response to the ERG clarification questions, considering PASI response rates for (1) patients who escape to CZP 400 mg after failing to achieve a PASI 75 at 16 weeks; 2) patients who escape to CZP 400 mg after failing to achieve a PASI 50-74 response at 16 weeks.

UCB have therefore also explored the updated model described above for these scenarios, with results presented below in **Error! Reference source not found.**. UCB considers the analysis based on PASI75 non-responders and PASI 50-74 responders conducted by the ERG to be a highly relevant scenario as it reflects a group of patients who have achieved an inadequate response and therefore a group of patients for whom the therapy has demonstrated some benefit. In clinical practice, such patients are likely to be candidates for dose escalation. Given the demonstration of an inadequate or partial response, clinicians may prefer to escalate the dose of the biologic on which inadequate or partial response is achieved, where this is an option, rather than to switch to a different biologic therapy. For this reason, in this subgroup UCB considers that the comparison to the adalimumab dose escalation strategy is particularly relevant as a comparator.

It should be noted that a further analysis incorporating a [redacted], had also been considered.

The conclusions of updated cost-effectiveness analyses indicate that CZP dose escalation strategy is more effective vs ADA escalation strategy (as reflected through QALY's) in all four scenarios, and is less costly in three out of four, leading to an ICER of £34,782.58 in one of the cases and to CZP dose escalation strategy dominating the ADA escalation strategy in the other three out of four scenarios.

Table 5: Updated base case results for systemic non-biologic therapy inadequate responders – CZP escalation strategy with PAS

First line therapy	Subsequent sequence	Total		Incremental (CZP escalation vs comparator)		ICER CZP escalation versus comparator
		QALYs	Costs	QALYs	Costs	
Efficacy assumptions based on the updated NMA						
CZP 200mg	CZP 400mg, UST, IFX, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, UST, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,782.58
Efficacy assumptions for CZP (PASI<75 at week 16)						
CZP 200mg	CZP 400mg, UST, IFX, BSC	[redacted]	[redacted]			
ADA 40mg	ADA 80mg, UST, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates
Efficacy assumptions for CZP (PASI 50-74 response at week 16)						
CZP 200mg	CZP 400mg, UST, IFX, BSC	[redacted]	[redacted]			
ADA 40 mg	ADA 80mg, UST, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates
Efficacy assumptions for CZP (PASI 50-74 response at week 16) and [redacted]						
CZP 200mg	CZP 400mg, UST, IFX, BSC	[redacted]	[redacted]			
ADA 40 mg	ADA 80mg, UST, IFX, BSC	[redacted]	[redacted]	[redacted]	[redacted]	CZP dominates

Abbreviations: ADA, adalimumab; BSC, best supportive care; CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; IFX, infliximab; UST, ustekinumab.

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