Part 1 slides for public [Redacted]

NICE National Institute for Health and Care Excellence

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

- 2nd appraisal committee meeting

Chair's presentation

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Preview of key issues

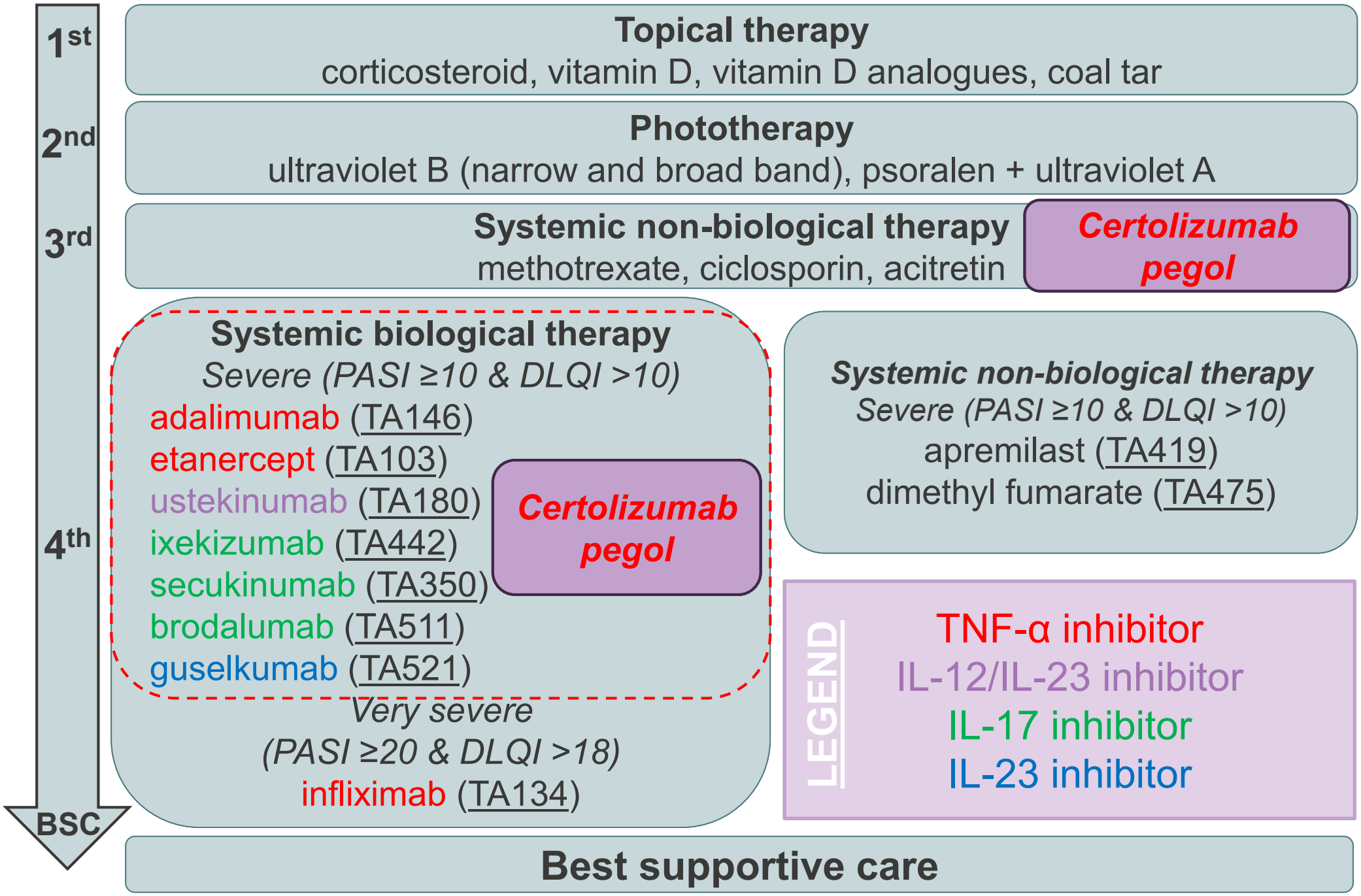
1. **New** analyses from company assessing the cost effectiveness of increasing dose of certolizumab pegol from 200 mg to 400 mg in patients with a partial or inadequate response to 200 mg dose after 16 weeks
   a. Additional scenarios comparing certolizumab pegol dose escalation strategy to switching to alternative treatments
   b. Additional analyses addressing potential bias due to choice of data used to model efficacy of dose escalation approaches

[redacted]

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. 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. *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 certolizumab pegol are provided free of charge

Treatment Pathway



Recommendation in Appraisal Consultation Document (ACD)

- Certolizumab pegol is recommended as an option for treating plaque psoriasis in adults, only if:
  - the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 and
  - **the disease has not responded to other systemic treatments**, including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet A radiation), or these options are contraindicated or not tolerated and
  - the company provides the drug according to the commercial arrangement.
- **Stop certolizumab pegol at 16 weeks** if the psoriasis has not responded adequately. An adequate response is defined as:
  - a 75% reduction in the PASI score (PASI 75) from when treatment started or
  - a 50% reduction in the PASI score (PASI 50) and a 5 point reduction in DLQI from when treatment started.

Candidates for non-biologic systemic therapy
Population excluded in previous appraisals
Not recommended

Candidates for biologic systemic therapy
200 mg dose recommended
Escalation to 400 mg dose not recommended

Committee's considerations – dose escalation

Issue	Committee's conclusions
Clinical effectiveness (ACD section 3.10)	• if no PASI 75 response after 16 weeks of treatment with 200 mg dose of certolizumab pegol every 2 weeks, there may be a response if this is increased to 400 mg every 2 weeks • trials did not compare efficacy of increasing the dose of certolizumab pegol with either placebo or another active treatment
Cost-effectiveness (ACD section 3.21)	• limited number of sequences explored in company analyses may bias cost-effectiveness results • appropriate to consider sequences involving switching from certolizumab pegol to another biologic in addition to company's approach of comparing increasing the dose of certolizumab pegol to increasing the dose of adalimumab • ICER for comparison to switching biologic greater than £500,000 per QALY gained → dose escalation not cost-effective

[redacted]

ACD consultation responses

- Consultee comments from:
  - UCB
  - Clinical expert
  - British Association of Dermatologists
  - Psoriasis and Psoriatic Arthritis Alliance

- Commentator comments from:
  - LEO Pharma

- Web comments from:
  - 4 x NHS professionals

[redacted]

Clinical expert and NHS professional comments

There is a proven benefit and clinical value with use of the 400 mg dose in initial non or inadequate responders. In patients where the psoriasis has not initially responded to the 200 mg dose, there is the opportunity to escalate to 400 mg if clinically appropriate - this is a unique feature of certolizumab.

With respect to the stopping rule, there should be opportunity to dose escalate to the 400 mg dose if there is an initial inadequate response […]

Ability to vary the dose is very helpful in practice in the absence of any data showing an increase in adverse events.

[Dose escalation] would be in line with the BAD guidelines which provide recommendations on when to increase the dose of biologic therapies as well as being within the marketing authorisation of certolizumab pegol in psoriasis.

British Association of Dermatologists guidelines:

Consider escalating the dose of biologic therapy in adults where this is feasible and funded and when an inadequate primary response may be due to insufficient drug dosing (e.g. in people who are obese or whose psoriasis relapses during the treatment cycle).

Commentator comment: apremilast and dimethyl fumarate as comparators

- *Apremilast and dimethyl fumarate positioned by NICE, for use in the same group of patients where the currently approved biologics are being used. As a result these treatments have been included in local guidelines for use as alternative to biologics in a number of areas.*
- *The most recent technology appraisal (brodalumab) included these treatments as comparators (guselkumab was a fast track appraisal so did not require comparison to all available treatments)*
- *The certolizumab pegol appraisal should incorporate them as well for completeness*
- *Alternatively, NICE should review the recommendations for dimethyl fumarate and apremilast to make it clear their use is only for patients who are severe but unsuitable for biologics*

1st committee meeting: company excluded apremilast and dimethyl fumarate as comparators as in clinical practice, these treatments would only be considered for use in patients unsuitable for biologic treatment or unwilling to receive biologic treatment

  - ERG noted that exclusion seemed appropriate

[redacted]

Definition of response at 16 weeks of treatment

- Adequate response defined in NICE guidance as:
  - a 75% reduction in the PASI score (PASI 75) from when treatment started or
  - a 50% reduction in the PASI score (PASI 50) and a 5 point reduction in DLQI from when treatment started.

- Inadequate response - do not have an adequate response
  - Non-responders
    - PASI <50
  - Partial responders
    - PASI ≥50 and <75

[redacted]

Company comments – certolizumab pegol dose escalation strategy

- Clear clinical desire for dose escalation strategy
- "*Analysis based on PASI75 non-responders and PASI 50-74 responders […] highly relevant [...] as reflects a group of patients who have achieved an inadequate response*"
- Concerned that evidence for clinical efficacy of dose escalation of certolizumab pegol in partial responders was not fully considered
  - Key model input for company's base case and scenario analyses
- Mixed sources of efficacy data potentially bias ERG analysis comparing certolizumab pegol dose escalation strategy with strategy of switching to alternative treatments in partial responders

[redacted]

Clinical efficacy of certolizumab pegol dose escalation strategy in partial and inadequate responders

Company has presented the following clinical evidence for certolizumab pegol dose escalation:

- pooled CIMPASI/CIMPACT results for **inadequate responders**: < PASI 75 response at 16 weeks
- CIMPACT data for **inadequate responders:** < PASI 75 response after 16 weeks
- CIMPACT data for **partial responders**: PASI 50-74 response after 16 weeks **(in model)**

CIMPACT: Inadequate responders
< PASI 75 response after 16 weeks

Responder rate, % (95% CI)	CZP 200 mg → CZP 400 mg at week 16 (n=[redacted])	
	Week 32	Week 48
PASI 75	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]
PASI 100	[redacted]	[redacted]

CIMPACT: Partial responders
PASI 50-74 response at 16 weeks

Responder rate, % (95% CI)	CZP 200 mg → CZP 400 mg at week 16 (n=[redacted])	
	Week 32	Week 48
PASI 75	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]
PASI 100	[redacted]	[redacted]

Note: n=165 patients in certolizumab pegol 200 mg arm of CIMPACT trial

⊙ ***In clinical practice, who would be considered for a higher dose of certolizumab pegol?***

Company's base case analysis

- Company: can compare certolizumab pegol dose escalation vs adalimumab dose escalation
  - Adalimumab is the only other option for clinicians who want to maintain existing therapy, rather than switching therapy, particularly for patients who have a partial response to initial treatment
- Company base case analysis (unchanged from 1st meeting) compares the following sequences:

CZP 200 → **CZP 400/UST** → UST → IFX → BSC

ADA 40 → **ADA 80** → UST → IFX → BSC

Efficacy based on weighted average of:

- Partial responders to CZP 200 mg (PASI 50-74) = CIMPACT results for CZP 400 mg
- Non-responders to CZP 200 mg (PASI <50) = network meta analysis (NMA) results for **ustekinumab**

Partial responders and non-responders (full inadequate response population) **all** escalate to ADA 80 mg.

Efficacy results based on NMA results for ADA 40 mg adjusted by multiplier of 1.5

- Company give new scenarios where:
  - subsequent treatments are best supportive care (i.e. head to head analyses)
  - alternative efficacy assumptions (see later slides)

ADA, adalimumab; BSC, best supportive care; CZP, certolizumab pegol; IFX, infliximab; UST, ustekinumab

ERG comments: company's base case analysis

- Identified several limitations of company's base case analysis:
  - PASI <50 responders to CZP do not receive escalated dose, whereas PASI <50 responders to ADA do
  - Non-responders to CZP 200 mg have ustekinumab at both 2nd and 3rd line → prefer head to head comparisons, where this does not occur
  - No trial data to support the efficacy of ADA 80 mg – efficacy either assumed to be equivalent to CZP 400 mg or adjusted from ADA 40 mg efficacy in network meta analysis → significant uncertainty in these analyses
  - No evidence provided on the use of ADA dose escalation to 80 mg in clinical practice – clinical advice to ERG stated dose escalation with ADA would only be commissioned if biosimilars were available at significantly reduced cost. Company present no additional analysis taking into account biosimilar prices (ERG present scenario with conservative discount)
- Switching to an alternative biologic is a more appropriate comparison

ADA, adalimumab; CZP, certolizumab pegol

Company's new scenario analyses: additional treatment switching comparisons

- Company present new scenario analyses for escalating to certolizumab pegol 400 mg in **partial responders**
  - present comparison to **switching** to alternative biologic (similar to previous ERG analysis)
  - as in base case **non-responders** to certolizumab 200 mg assumed to get ustekinumab

Head to head	**Treatment sequences**
CZP 200 → CZP 400/UST → BSC Versus CZP 200 → Switch → BSC	CZP 200 → CZP 400/UST → UST → IFX → BSC Versus CZP 200 → Switch → UST → IFX → BSC

Switch = **Ustekinumab*, ixekizumab or secukinumab**; *Head to head comparison only

- Guselkumab and brodalumab not considered as recently recommended and not currently standard clinical practice for second-line therapy
- Company present scenarios using alternative efficacy assumptions (see later slides)

BSC, best supportive care; CZP, certolizumab pegol; IFX, infliximab; UST, ustekinumab

ERG comments: additional treatment switching scenarios

- Considering alternative sequences is appropriate:
  - switching to ustekinumab reflects company's base case and clinical opinion to ERG
  - guselkumab and brodalumab may also have been appropriate comparisons

Head to head

CZP 200 → CZP 400/**UST** → BSC

Versus

CZP 200 → **Switch** → BSC

Treatment sequences

CZP 200 → CZP 400/**UST** → **UST** → IFX → BSC

Versus

CZP 200 → Switch → UST → IFX → BSC

Issues with non-responders pathway in escalation sequences:

CZP 200 → **UST** → BSC

Second-line treatment in non-responder pathway should be same as treatment being **switched** to in comparator sequence (e.g. if switch = IXE then compare with CZP 400/IXE) → presented in scenario analyses

CZP 200 → **UST** → **UST** → IFX → BSC

The use of treatment sequences results in non-responders receiving ustekinumab as both 2nd and 3rd line treatment (as seen previously for ADA sequence) – avoided using head to head comparisons

Company's updated analyses: source of efficacy data

- Company noted potential bias in ERG's analyses due to use of two different efficacy sources:
  - CIMPACT trial data for partial responders to certolizumab pegol
  - NMA results for alternative treatments assumed to apply when used at 2nd line
    - efficacy of alternative treatment assumed to be same as at 1st line → may bias results against certolizumab pegol as trial data reflects use of CZP at 2nd line
- It presented scenario analyses where efficacy for partial responders at 2nd line is either:
  - taken from the NMA results for that treatment, or
  - set to the efficacy of CZP 400 from CIMPACT for all treatments

ERG comments

- Using different sources of data justified but appropriate to explore using alternative sources
- Patients in CIMPACT and the NMA are both heterogeneous with respect to previous biological treatment → risk of bias may have been overstated
- Company scenario analyses using alternative sources **have small impact on ICERs** as these data are only applied to a small proportion of 2nd line patients

[redacted]

Dose escalation modelling approaches

Is the appropriate comparator for dose escalation of CZP:
- **Dose escalation of ADA (see below),**
- **Switching to an alternative biologic (see slide 21).**

How should partial and inadequate responders be modelled?

	Intervention		Comparator	
	Partial response (PASI 50-74)	**Non responders (PASI <50)**	**Partial response (PASI 50-74)**	**Non responders (PASI <50)**
1 (company base case)	CZP 400	UST	ADA 80	ADA 80
2	CZP 400	CZP 400	ADA 80	ADA 80
3	CZP 400	UST	ADA 80	UST

What source of efficacy data for CZP 400?
A – certolizumab pegol efficacy data from CIMPACT
B – certolizumab pegol data from NMA

Should treatment sequences be modelled?
X – subsequent therapies = ustekinumab → infliximab→ BSC
Y – head to head = next treatment is BSC

ADA, adalimumab; BSC, best supportive care; CZP, certolizumab pegol; UST, ustekinumab

Company analyses

	Intervention		Comparator		CZP400 efficacy data		Sequence or head to head		ICER
	Partial response	Non response	Partial response	Non response	CIMPACT	NMA	Sequence	Head to head	
1AX ★	CZP 400	UST	ADA 80	ADA 80	✓	✗	✓	✗	CZP dominates
2AX	CZP 400	CZP 400	ADA 80	ADA 80	✓	✗	✓	✗	CZP dominates
3AX	CZP400	UST	ADA 80	UST	✓	✗	✓	✗	£22,370
3AY	CZP400	UST	ADA 80	UST	✓	✗	✗	✓	£35,481
3BX	CZP400	UST	ADA 80	UST	✗	✓	✓	✗	£28,354
3BY	CZP400	UST	ADA 80	UST	✗	✓	✗	✓	£39,489

★ = company base case

Note: All scenarios based on cost of originator products, biosimilar prices for infliximab and adalimumab not considered

[redacted]

ERG analyses:
Biosimilar infliximab price, 20% adalimumab discount

- ERG presented equivalent scenarios using the costs of infliximab biosimilars and including a (conservative) discount of 20% for adalimumab biosimilars
  - ICER increases in all scenarios

	Intervention		Comparator		CZP400 efficacy data		Sequence or head to head		ICER
	Partial response	Non response	Partial response	Non response	CIMPACT	NMA	Sequence	Head to head	
1AX	CZP 400	UST	ADA 80	ADA 80	✓	✗	✓	✗	£56,112
3AX	CZP400	UST	ADA 80	UST	✓	✗	✓	✗	£79,587
3AY	CZP400	UST	ADA 80	UST	✓	✗	✗	✓	£82,620
3BX	CZP400	UST	ADA 80	UST	✗	✓	✓	✗	£67,610
3BY	CZP400	UST	ADA 80	UST	✗	✓	✗	✓	£72,133

[redacted]

Company and ERG scenarios: comparison with switching to alternative biologics

Cost-effectiveness results are confidential due to confidential patient access schemes for comparators so exact ICERs are not reported.

- **Comparisons to switching to ixekizumab, secukinumab and ustekinumab:** in all scenarios (company and ERG) where the certolizumab pegol escalation sequence is compared with a switching strategy the ICER is above the range at which NICE would consider certolizumab pegol cost-effective

[redacted]